SPANDIDOS PUBLICATIONS

ONCOLOGY REPORTS 45: 26, 2021

Neoadjuvant therapy for pancreatic cancer: Limitations and advances of response assessment (Review)

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Received April 5, 2020; Accepted December 7, 2020

DOI: 10.3892/or.2021.7977

Abstract. Neoadjuvant therapy (NAT) has been widely recommended for managing patients with borderline resectable pancreatic cancer and resectable tumors with high risk factors. Accurate evaluation of the response after NAT is crucial to decide surgery, which then improves the rate of R0 resection and avoids meaningless surgery. The response to NAT is currently evaluated by conventional radiological examination and changes of serum CA19-9 levels. However, these assessments cannot accurately reflect the response to NAT. This article describes the limitations and advances of NAT response evaluation in pancreatic cancer. The values of some traditional imaging techniques, including positron emission tomography, endoscopic ultrasound, and diffusion weighted magnetic resonance imaging, are discussed, as well as novel imaging modalities or biomarkers, such as radiomics, dual energy computed tomography and liquid biopsy.

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Key words: pancreatic cancer, neoadjuvant therapy, response evaluation, imaging techniques, biomarkers

1. Introduction

Neoadjuvant therapy (NAT) has become common practice in managing patients with localized pancreatic cancer (PC). Multimodal NAT strategies have been developed, such as chemotherapy and/or chemoradiotherapy (CRT). The benefits of NAT include increased feasibility of R0 resection, elimination of micrometastases, and identifying aggressive tumors to avoid futile surgery (1). Accurate evaluation of response after NAT is therefore a prerequisite for patients to achieve these benefits from NAT. However, the evaluation of response to NAT is particularly difficult in PC. Consensus and recommendations are still lacking. Conventional radiological examination is one of the most common assessment methods, but this strategy has been identified as unsuitable to evaluate NAT response in PC (2). Another method is monitoring the levels of serum carbohydrate antigen 19-9 (CA19-9); however, the cut-off value of decreased CA19-9 for diagnosing NAT responders remains controversial (3,4). Therefore, it is crucial to identify novel imaging tools or biomarkers. This review presents the challenges and new developments for NAT response evaluation in PC.

2. Limitations of restage after NAT by conventional radiological images

The decision for further operation after NAT traditionally depends on radiologic imaging, especially contrast enhanced computed tomography (CT). However, radiologic imaging no longer predicts unresectability after NAT for patients with locally advanced PC (LAPC) and borderline resectable PC (BRPC) (5). Response Evaluation Criteria in Solid Tumors (RECIST) are not effective criteria for patients with BRPC (6). Katz *et al* (6) evaluated the restage values of RECIST for BRPC. Among the 122 patients with BPRC who completed NAT (gemcitabine-based chemotherapy followed by planned chemoradiation or chemoradiation alone) and were restaged, 69% patients had stable disease, 12% had a partial response, and 19% had progressive disease. Although only one patient downstaged to resectable status after NAT, 85 patients (66%) underwent surgical resection. Of that, 81 patients achieved R0 resection. Significant downstaging of PC after NAT is rare; yet, even a minimal radiological response of imaging resulted in a R0 resection of 76.3% (7).

Histological response cannot be reflected by conventional radiological images. The A021101 trial was a prospective, multicenter, single-arm clinical trial, which was designed as patients received modified FOLFIRINOX treatment for four cycles followed by 5.5 weeks of external-beam radiation with capecitabine (orally twice daily) prior to pancreatectomy. In total, 22 patients initiated modified FOLFIRINOX treatment. Results indicated that only 27% of patients with BRPC had a radiologic partial or complete response after NAT, and yet R0 resection and less than 5% residual cancer cells on histopathology were achieved in 93 and 33% of patients, respectively (8). Similarly, Xia *et al* (7) showed that one-fourth of patients who underwent NAT with gemcitabine-based systemic chemotherapy for BRPC did not have a radiologic response but had an Even's grade IIB or greater pathologic response.

Furthermore, radiologic response was not prognostic with regard to overall survival. Patients with positive radiological response had no differences in overall survival compared with patients without radiological response (6,7).

3. Reasons for poor evaluation performance of conventional radiological imaging

NAT, especially CRT, causes tumor necrosis, fibrosis, or inflammatory changes, which results in an increase of fibrosis within the lesion and a decrease of cancer cells (9). However, the currently available radiological imaging technology cannot distinguish tissue desmoplastic reactions after NAT and the viable tumor. The sensitivity and specificity of CT and magnetic resonance imaging (MRI) in predicting the presence of viable cancer cells at vessel interfaces after NAT were 71 and 58%, respectively (10). Therefore, the histological response cannot truly be reflected by RECIST that depends on tumor morphology. Tumor size reductions were replaced by intra-tumoral fibrosis (5,11).

Although downstaging or radiological response is not observed, clinically significant cytotoxic activity may occur at the peripheral tumor-vessel interface (6). In the study by Katz *et al* (6), CT images revealed a close relationship between the tumor and mesenteric vasculature in all patients after NAT, but only one patient had a positive superior mesenteric artery margin. Dholakia *et al* (12) reported that both tumor volume and degree of tumor-vessel involvement did not significantly change in cases that underwent resection after NAT (induction chemotherapy followed by chemoradiation or upfront chemoradiation). Successful resection is common for patients with BRPC who had no radiographic downstaging or even improvement of tumor-vessel involvement (12).

Artery invasion is a major factor in the staging of PC, which means an aggressive disease with adverse prognosis. The higher morbidity and mortality of arterial resection and reconstruction make surgeons give up radical resections. Of note, conventional radiological images cannot accurately assess artery invasion or infiltration, which might lead to an overestimation of grade of artery invasion, especially for cases that underwent NAT (13). Some cases that were classified as artery invasion or encasement by conventional radiological images could be resected radically without arterial resection and reconstruction by sharp dissection under an artery sheath or on the adventitial layer of a suspected artery (13,14). Hackert and colleagues (13) reported 15 LAPC cases with arterial-sparing resection after NAT with FOLFIRINOX or gemcitabine plus abraxane. All cases were exploration by an 'artery first' maneuver. The arterial level of the suspected attachment or encasement was exposed. The adventitial layer was then opened longitudinally and tissues were obtained for frozen section examination. Only cases without viable tumor underwent further resection. R0 resection was achieved in 6 out of 15 patients and the other 9 cases were R1 resections with positive sites located at the peripancreatic soft tissue margins.

4. Evaluation of NAT response using CA19-9

CA19-9, also known as sialyl Lewis-A, is an indicator of aberrant glycosylation of PC and is widely used as a treatment biomarker. Theoretically, a greater CA19-9 reduction could reflect at least a partial response (7). However, the precise value and cutoff for this diagnosis remain to be elucidated.

First, the exact cut-off value of decreased CA19-9 for diagnosing NAT responders remains controversial. Tsai *et al* (3) found that normalization of CA19-9 following NAT rather than the magnitude of change was the strongest prognostic marker for long-term survival. Failure to normalize CA19-9 after NAT was associated with a 2.77-fold increased risk of death. Murakami *et al* (15) showed that patients with arterial contact who achieved normalization of serum CA19-9 or Dupan-2 after NAT are potentially good candidates for tumor resection. By contrast, some studies showed that a decrease in CA19-9 of >50% after NAT treatment was associated with R0 resection rate, histopathologic response, and survival in patients with BRPC (4,16).

Furthermore, pretreatment levels of CA19-9 could influence its application in patient selection. Combs *et al* (17) showed that pretreatment levels of CA19-9 significantly influenced OS using different cut-off values. With the increase of CA19-9 after NAT, the possibility of surgical resection after NAT decreased from 46% in patients with CA19-9 levels below 90 U/ml to 31% in the group with CA19-9 levels higher than 269 U/ml.

Finally, the value of CA19-9 in patients with negative expression of Lewis antigen (that is critical for CA19-9 biosynthesis) is unclear. Luo *et al* (18) indicated that CA19-9 could be used as a biomarker in patients with Lewis (-). Authors of that study showed that 8.4% of patients with PC (n=1482) were Lewis (-), but only 41.9% of those cases had CA19-9 values ≤2 U/ml, and 27.4% of cases had elevated levels (>37 U/ml). The area under the receiver operating characteristic curve for CA19-9 as a diagnostic biomarker was 0.842 in Lewis (-) patients with PC, which was similar to that of CA19-9 applied in all of the patients with PC (0.898). Those results mean investigating the values of CA19-9 in monitoring chemotherapy efficiency further.

5. Advances in the evaluation of response to NAT

Evaluation of responses to NAT by RECIST criteria based on conventional CT/MRI has become challenging, and therefore novel assessment tools are needed. Some conventional imaging techniques have been explored and show potentially

favorable values, such as positron emission tomography (PET), endoscopic ultrasound (EUS), and diffusion weighted MRI. Novel imaging modalities or biomarkers have been developed and have shown encouraging results. Advances in the last five years are presented in Table I (3,19-54). In addition, considering the limitations of CT that might miss more than 30% of occult metastases in patients with BRPC or LAPC, which would result in an underestimated pretreatment staging and overestimated restaging after NAT treatment, the value of laparoscopic examination before NAT treatment is also discussed in this section.

^{18}F-fluorodeoxyglucose (FDG)-PET and post-treatment staging. FDG-PET is widely used to diagnose malignant tumors, detect distant metastases, and monitor tumor progression (55), which has also been used in the field of NAT in the assessment of therapeutic efficacy. FDG uptake is closely associated with tumor burden and viability (47), and changes in standard uptake values (SUVs) can reflect the metabolic response of cancer to chemotherapy. Therefore, FDG-PET/CT is used to assess the efficacy of NAT in various solid tumors, such as esophageal adenocarcinoma (56) and triple-negative breast cancer (57). The predictive values of FDG-PET/CT on NAT in PC have been described by only a few reports. A randomized phase III trial examined the feasibility of PET in evaluating the efficacy of nab-paclitaxel plus gemcitabine for the treatment of patients with metastatic PC and showed that patients with higher metabolic response had a longer survival (58). Akita *et al* (47) showed that FDG-PET could predict the efficacy of neoadjuvant chemoradiotherapy (NACRT) for resectable PC (RPC) and BRPC. The maximum SUVs and tumor size were significantly decreased compared with pretreatment values. However, both the maximum SUV and the percentage of SUV decline (that is, regression index) were significantly related to Evans grade III/IV (59), which grades the pathological response of PC, while only the regression index predicted NACRT efficacy. The AUC of the regression index for the detection of grade III/IV was 0.822 using 50% as the threshold, with a sensitivity and specificity of 92.9 and 62.3%, respectively.

Although declined SUV after NAT showed a good pathological response and prognostic value, there are some limitations of FDG-PET/CT in evaluating the efficacy of NAT using SUV. For example, SUVs are mainly influenced by tumor burden and aggressiveness. However, the physiologic uptake and inflammation in the surrounding non-cancerous tissue can also influence the SUV (55). Many factors cause peripancreatic inflammation, including blockage of the pancreatic duct by the tumor, endoscopic retrograde biliary drainage, radiotherapy, and EUS biopsy (47,55,60,61). Tissues with inflammation show an overlap uptake such as malignant tumors (55), which can lead to falsely elevated SUVs (47). Additionally, the presence of inflammatory cells including macrophages, neutrophils, and fibroblasts can cause high uptake of FDG (55). As we known, PC tissues contain massive stroma, of that, infiltration of inflammatory cells including macrophages, neutrophils, is one of the pathological features of cancer. NAT can induce the infiltration of inflammatory cells and fibrosis even further, and therefore post-therapy SUV might not reflect the real pathological response.

The right timing of FDG-PET/CT examination after NAT is important for improving its predictive value. Ramanathan *et al* reported that metabolic response rates at week 8 after NAT with nab-paclitaxel plus gemcitabine or gemcitabine alone were similar to the best metabolic response in a randomized phase III trial (58). Akita *et al* (47) found that 8 weeks after radiotherapy is a good time for FDG-PET/CT examination. No inflammatory changes in the peripancreatic tissues were observed at that time through pathological examination of the resected specimens. A higher specificity (62.9%) was shown compared with previously reported values (47,56).

Compared with traditional RECIST, the metabolic response detected by PET represents a functional measure of tumor response by evaluating metabolic activity and shows a higher accuracy. More patients experienced a metabolic response than a RECIST-defined response in a randomized phase III trial (58). Although the predictive value of PET has some limitations, the correct timing of examination may improve the accuracy. Taken together, these findings indicate that the application of PET in NAT should be further investigated.

Endoscopic ultrasound (EUS). EUS is rarely used to evaluate NAT response in PC (62). Tumor stiffness on EUS elastography could reflect the abundance of cancer stroma (63), which is the theoretical basis of EUS for response evaluation. For cases that underwent treatment with agents targeting the stroma, such as nab-paclitaxel and gemcitabine, elastography could monitor stromal changes with treatment and show potential value for response evaluation. Alvarez *et al* (64) indicated that tumor stiffness on EUS elastography was significantly reduced after NAT with nab-paclitaxel and gemcitabine, and the ratio value was decreased from 36 to 18 after treatment. A reduction of tumor stiffness was positively correlated with a decrease of serum CA19-9 levels and resectability.

However, the value of elastography for conventional chemotherapy and radiation therapy was uncertain due to the weak influence of stroma (64). Bettini *et al* (65) found that the information provided by EUS was not reliable for patient selection for further surgery among those who underwent NAT with radiotherapy combined with 5-fluorouracil and cisplatin chemotherapy.

Diffusion-weighted magnetic resonance imaging (DWI). DWI is a functional MRI technique that can recognize tissue diffusivity characteristics and perform quantitative and qualitative evaluation of a tumor (66). The utility of DWI in evaluating the responses of PC to NAT has been previously investigated. A pilot study indicated that pretreatment apparent diffusion coefficient (ADC) values differed significantly between responders and non-responders and could be used in the prediction of gemcitabine-based NARCT response (67). The sensitivity, specificity, and accuracy for predicting NAT responders were 100, 75, and 83%, respectively (48). Although DWI had improved performance compared to conventional MRI or CT to assess NAT response in PC (68), the data are limited and obtained from small samples. Further investigation is needed to evaluate the utility of this technique.

Artificial intelligence and radiomics. Artificial intelligence (AI) can be applied to automatically quantify radiographic patterns

Table I. Advances in the evaluation of response to neoadjuvant therapy in the last five years.

Author/(Refs.)/Year	Disease	NAT regimens	Tools	Index	Results
Truty *et al* (28) 2019	BRPC LAPC	FOLFIRINOX GEM plus nab-paclitaxel CRT	PET	SUV CA19-9	Complete metabolic response correlated with major pathologic response. CA19-9 response associated with prolonged survival.
Sherman *et al* (42) 2018	LAPC	GEM Docetaxel Capecitabine CRT	PET	SUV; CA 19-9; Tumor size; Degree of vascular involvement	No presenting parameter could predict the success of NAT.
Sakane *et al* (45) 2017	T1-3 N0-1 M0	CRT	PET	SUV MTV TLG	Higher post-treatment SUVpeak and positive MTV/TLG predicted the unfavorable histopathological effects.
Akita *et al* (47) 2017	RPC BRPC	GEM-based CRT	PET	SUV; Percentage of SUV decline (regression index)	The post SUV-max and regression index were related to pathological response. The sensitivity and specificity of regression index for the detection of Evans grade III/IV were 92.9 and 62.3%.
Mellon *et al* (50) 2017	BRPC LAPC	GEM FOLFIRINOX Other	PET	SUV CA19-9	Tumor regression grade was correlated with CA19-9 or SUVmax.
Nasief *et al* (19) 2020	BRPC LAPC	CRT	CT	DR CA19-9	DRF correlated to CA19-9. DRFs-CA19-9 combination predicts treatment response.
Borhani *et al* (23) 2020	RPC BRPC	-	CT	Texture analysis	Patients with higher MPP at pretreatment CT have favorable histologic response.
Kim *et al* (34) 2019	-	CRT	CT	Texture analysis	Higher subtracted entropy and lower subtracted grey level co-occurrence matrices entropy are important parameters for prediction of longer OS.
Amer *et al* (38) 2018	Stage I/II/IV	-	CT	Tumor/parenchyma interface	Change at the PDAC/parenchyma interface was an early predictor of response to therapy.
Wagner *et al* (49) 2017	BRPC LAPC	FOLFIRINOX	CT	Largest axis; P3A; Arterial/venous involvement	The largest axis/P3A variations were higher in case of complete pathological response.
Klaassen *et al* (35) 2018	PDAC	-	MRI	Six DW-MRI models	All models could identify individual treatment effects.
Dalah *et al* (37) 2018	RPC BRPC	-	MRI	ADC	ADC values after NAT were correlated with pathological responses.
Trajkovic-Arsic *et al* (41) 2017	LAPC Metastatic	GEM-based FOLFIRINOX	MRI	ADC	ADC could be an early response monitoring tool.

Table I. Continued.

Author/(Refs.)/Year	Disease	NAT regimens	Tools	Index	Results
Okada *et al* (48) 2017	BRPC	FOLFIRINOX Nab-paclitaxel plus GEM CRT	MRI	ADC	The sensitivity, specificity, accuracy of ADC for discriminating between nonresponders and responders were 100, 75 and 83%.
Ehrlich *et al* (22) 2019	BRPC LAPC	-	EUS	EUS-FNA for periarterial soft tissue	Sensitivity, specificity and accuracy of EUS-FNA for determining resectability were 80, 100 and 92.9%.
Payen *et al* (20) 2019	Brca2-mutant mouse model of PDAC	Cisplatin	Harmonic motion imaging	Stiffness	Tissue stiffness decreases when tumors respond successfully to chemotherapy.
Heger *et al* (26) 2019	Unresectability	GEM-based FOLFIRINOX	Biomarker (blood)	CA19-9	CA 19-9 levels below 91.8 U/ml as well as a reduction to <40.7% after NAT predict tumor resectability.
Aoki *et al* (29) 2019	-	-	Biomarker (blood)	CA19-9	Decreased CA19-9 levels (≤103 U/ml) after NAT predicts a better prognosis.
Michelakos *et al* (40) 2019	BRPC LAPC	FOLFIRINOX	Biomarker (blood)	CA19-9 Tumor size	Preoperative CA 19-9 >100 U/ml and tumor size (>3.0 cm on CT) predicted decreased OS
Tsai *et al* (3) 2018	Localized PC	-	Biomarker (blood)	CA19-9	Normalization of CA19-9 after NAT, rather than the magnitude of change, is the strongest prognostic marker for long-term survival
Van Veldhuisen *et al* (36) 2018	LAPC	FOLFIRINOX	Biomarker (blood)	CA19-9	A CA19-9 decrease ≥30% after NAT was associated with improved survival
Williams *et al* (54) 2016	BRPC LAPC	-	Biomarker (blood)	CA19-9	Pre-operative CA19-9 decrease could guide treatment duration
Aldakkak *et al* (52) 2015	Localized PC	GEM-based CRT	Biomarker (blood)	CA19-9	Pre-treatment CA19-9 could not predict OS. Normalization of post-treatment CA19-9 in response to NAT was highly prognostic.
Bernard *et al* (31) 2019	Potentially resectable tumors	-	Biomarker (blood)	Liquid biopsy (plasma exoDNA and ctDNA)	An increase in exoDNA level after NAT was associated with disease progression. MAFs ≥5% in exoDNA were a significant predictor of PFS An MAF peak above 1% in exoDNA was associated with radiologic progression.
Gemenetzis *et al* (32) 2018	-	-	Biomarker (blood)	Liquid biopsy (CTCs)	Patients received NAT had lower total CTCs Preoperative numbers of CTCs were predictors of early recurrence in post-NAT patients.

Table I. Continued.

Author/(Refs.)/Year	Disease	NAT regimens	Tools	Index	Results
Liang *et al* (44) 2017	-	-	Biomarker (blood)	Liquid biopsy (tumor-derived extracellular vesicles EphA2-EV)	Levels change of plasma EphA2-EV was associated with treatment response.
Murthy *et al* (24) 20196	RPC	GEM-based 5FU-based Both Other	Biomarker (blood)	Systemic immune inflammatory markers	Elevated post-NAT SII was an independent, negative predictor of OS. An 80% reduction in SII predicted a CA 19-9 response after NAT.
Kawai *et al* (30) 2019	BRPC CRT	FOLFIRINOX	Biomarker (blood)	Systemic immune inflammatory markers	A low lymphocyte-to-monocyte ratio is useful prognostic factor
Hasegawa *et al* (53) 2016	PDAC	GEM-based Chemotherapy	Biomarker (blood)	Systemic immune inflammatory markers	Pre-treatment NLR was a predictive indicator of pathological response
Felix *et al* (43) 2018	PDAC (Stage I/II-IV)	-	Biomarker (blood)	S-TK	The S-TK activity in the NAT group was higher than that in the group not receiving NAT. S-TK activity may be used for monitoring NAT efficacy.
Kuwabara *et al* (27) 2019	PDAC	-	Biomarker (tissue)	TLO	TLO/tumor ratio was an independent predictive prognostic factor.
Tsai *et al* (33) 2018	RPC BRPC	-	Biomarker (tissue)	Molecular profiling (6 biomarkers)	Molecular profiling may improve the efficacy of chemotherapy
Kurahara *et al* (39) 2018	PDAC	CRT	Biomarker (tissue)	GLUT-1	Patients with low GLUT-1 expression displayed a better response to NAT. GLUT-1 expression was significantly increased after NAT treatment.
Yabushita *et al* (46) 2017	BRPC	GEM plus S-1 CRT	Biomarker (tissue)	hENT1; TS; DPD	The presence of three markers was associated with improved partial response rates to NAT
Capello *et al* (51) 2015	LPC, BRPC LAPC	FOLFIRINOX	Biomarker (tissue)	CES2	High CES2 expression was associated with longer OS.
Farren *et al* (21) 2020	PDAC	FOLFIRINOX Radiotherapy	Biomarker (tissue)	Immunologic microenvironment	NAT modulate tumor, immune, and stromal components of the tumor microenvironment.
Mota *et al* (25) 2020	BRPC LAPC	-	Biomarker (tissue)	Immunologic microenvironment	The degree of antitumor immune remodeling correlates to the degree of histopathologic response to NAT

ADC, apparent diffusion coefficient; BRPC, borderline resectable pancreatic cancer; CES2, carboxylesterase 2; CRT, chemoradiotherapy; CT, computed tomography; CTCs, circulating tumor cells; DPD, dihydropyrimidine dehydrogenase; DR, delta-radiomics; DRF, delta-radiomics features; DW, diffusion-weighted; EUS, endoscopic ultrasound; FNA, fine needle aspiration; GEM, gemcitabine; GLUT-1, glucose transporter type 1; hENT1, equilibrative nucleoside transporter 1; LAPC, locally advanced pancreatic cancer; MAF, mutant allele fraction; MPP, mean positive pixel; MRI, magnetic resonance imaging; MTV, metabolic tumor volume; NAT, neoadjuvant therapy; NLR, neutrophil to lymphocyte ratio; OS, overall survival; P3A, product of the three axes; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PET, positron emission tomography; PFS, progression-free survival; SII, systemic immune-inflammation index; S-TK, serum thymidine kinase 1; SUV, standard uptake value; TLG, total lesion glycolysis; TLO, tertiary lymphoid organs; TS, thymidylate synthase.

in medical imaging data (69,70). Compared with human assessment, AI can perform precise volumetric delineation of tumor size, convert intratumoral phenotypic nuances to genotype implications, and recognize complex patterns in images (69,70), which is effective in cancer detection and characterization (71,72). AI can also dynamically monitor a tumor (69), including evaluation of responses to treatment.

Radiomics has been developed based on AI and is widely used in many different precision medicine applications. Unlike traditional radiological images that assess a tumor depending on largely qualitative features, including tumor density, pattern of enhancement, tumor margins, anatomic relationship to the surrounding tissues, and intratumoral composition (69), radiomics is the conversion of digital radiological images into mineable quantitative data (73), including tumor intensity, shape, size or volume, and texture features images are computed and quantified (74,75). Radiomics can reflect a tumor panorama by a non-invasive examination compared with conventional biopsy-based assays that represent only a sample of the tumor (76). This is particularly useful in PC, in which different lesions can exist in different microenvironments due to the excessive stroma and heterogeneous (77-79).

Radiomics is beneficial for patient selection. Trebeschi *et al* (76) found that radiomics may function as a non-invasive biomarker for response to immunotherapy for patients with metastatic melanoma and non-small cell lung cancer and potentially benefit patient stratification in both neoadjuvant and palliative settings. Radiomics can also predict the responses to treatment. A combined intratumoral and peritumoral radiomic feature could successfully predict the pathological complete response of breast cancer to NAT from pretreatment dynamic contrast-enhanced MRI (80). Texture analysis of T2-weighted MR images could predict the efficacy of NACRT in rectal cancer (81). Radiomics based on FDG-PET scans indicated that convolutional neural networks achieve an average 80.7% sensitivity and 81.6% specificity in predicting non-responders of patients with esophageal cancer who underwent NAT (82).

The predictive roles of radiomics in evaluating NAT responses in PC are unclear. Chakraborty *et al* (83) quantified the heterogeneity of PC by texture analysis and showed that radiomics analysis based on tumor texture could quantify the heterogeneity of PC and optimize patient selection for therapy. In sum, a combination of AI and radiomics presents better values in evaluating NAT responses than traditional radiological images, which is a promising technique in PC.

Dual energy CT (DECT). DECT enables the differentiation of tumor compositions by simultaneous scanning with different levels of energy and has been used to assess NAT response in gastric and rectal cancer with potential values (84,85). One dilemma of conventional CT/MRI in evaluating NAT response is the difficulty in identifying fibrosis caused by treatment. DECT showed a good performance in the differential diagnosis of PC and chronic mass-forming chronic pancreatitis (86). Considering the features of pathological changes after treatment in PC, quantitative DECT may be useful for monitoring the treatment effects in patients with PC (87). Iodine concentration during DECT could differentiate responders with PC after first-line chemotherapy from non-responders with sensitivity, specificity, and AUC of 97.7, 70.6, and 0.889, respectively (88). Furthermore, low-energy monoenergetic decompositions from DECT may detect an early radiation therapy response because of the increase in soft tissue contrast and the magnitude of radiation-induced changes (89).

New biomarkers. Although serum CA19-9 is generally used to monitor the response to NAT, only moderate predictive values were observed with this marker, and the significance of decreased CA19-9 levels after NAT has not been well clarified (3,29). Serum CA19-9 is also not applicable for patients with negative expression of Lewis antigen (18,90). Therefore, more sensitive and specific biomarkers are needed to assess the response of NAT.

Liquid biopsy includes detection of circulating free deoxyribonucleic acid (cfDNA), circulating tumor cells (CTCs), and exosomes, which displays encouraging value in monitoring the therapeutic response (91). Gemenetzis *et al* (32) identified two major CTC subtypes, including epithelial CTCs (eCTCs) and epithelial/mesenchymal CTCs (mCTCs). Patients who received NAT had significantly lower levels of both of these CTC subtypes compared with patients with upfront resection. Furthermore, NAT resulted in a significant decrease of CTCs, indicating that CTCs dynamics reflected the response to treatment. Bernard *et al* (31) showed that an increase in exosome DNA levels after NAT was significantly associated with disease progression. KRAS mutant allele fraction peak in exosome DNA above 1% was significantly associated with radiologic progression. Liang and colleagues reported that levels changes of ephrin type-A receptor 2 in tumor-derived extracellular vesicles (EphA2-EV) were associated with the treatment response. Plasma EphA2-EV levels were significantly decreased in patients with good or partial therapy responses, but not in those with poor response after NAT (44).

Other biomarkers have also been investigated. For patients with BRPC, the presence of three favorable factors (positive expression of human equilibrative nucleoside transporter 1 with negative expression of thymidylate synthase and dihydropyrimidine dehydrogenase) was strongly associated with improved partial response rates to NAT (gemcitabine and S-1 followed by radiotherapy) (46). Serum thymidine kinase (TK) activities in preoperative samples in PC patients who had received NAT were significantly higher than those in patients who had not received NAT. Patients who underwent complete NAT with preoperative serum TK levels <80 Du/l showed a longer OS compared with patients with serum TK levels >80 Du/l (43). Abnormal preoperative glycated haemoglobin A1c (HbA1c) was associated with a 2.74-fold increased odds of metastatic progression during NAT (93). Increased neutrophil-to-lymphocyte ratio after NAT was associated with poor survival after resection of BRPC (93). Tissue expression levels of miRNA-10b are predictive of response to NAT and outcomes in PC (94). Biomarkers from metabolomics analysis are promising. Although few effective metabolic biomarkers have been reported in PC, metabolomics has been used to predict the responses of NAT in breast and rectal cancer (95-97).

The above mentioned biomarkers showed potential predictive values in evaluating the responses to NAT. However, almost all studies were preclinical and thus large prospective studies are required to validate these results.

Laparoscopy staging and whether it should be routinely performed. Laparoscopic examination can identify hepatic metastases, peritoneal and serosal implants that may be missed by CT scan then improves the accuracy of cancer staging and avoids unnecessary laparotomy (98). A systematic review and meta-analysis assessed the role of staging laparoscopy in RPC and BRPC and included 1,756 patients with RPC after standard imaging extracted from 12 studies and 242 patients with locally advanced disease from 3 studies. The results showed that 350 of 1,756 cases (20%) were then staged as non-resectable cancer after laparoscopic examination. In addition, 86 of 242 cases (36%) were restaged as metastatic disease (99).

However, the value of laparoscopic staging prior to NAT is unclear. Peng *et al* (100) evaluated 116 patients with BRPC, including 75 patients who underwent staging diagnostic laparoscopy prior to NAT. There was no difference in overall treatment cost, oncologic treatment, and remaining surgical treatment for patients who underwent laparoscopic examination compared with those who did not. A total of 19 (25%) patients were found with occult abdominal metastases and had a lower overall cost compared with those with negative laparoscopic examination due to avoiding further surgery, radiation, and aggressive chemotherapy (100). Ta *et al* showed that staging laparoscopy could more accurately select patients for neoadjuvant protocols (99).

The question is which subgroup of patients with PC would benefit from a laparoscopic examination. Slaar *et al* (101) showed that laparoscopic examination could be performed on selected patients who had a higher chance of metastasis at exploration, such as patients with a tumor ≥3 cm and severe weight loss (≥10 kg) or in patients with a tumor ≥4 cm and moderate weight loss (≥5 kg). National Comprehensive Cancer Network (NCCN) panels recommend laparoscopic examination for resectable PC with high-risk factors (102). Laparoscopic staging should be considered for patients with BRPC prior to NAT. Intraoperative ultrasound is useful during laparoscopic examination to further evaluate the liver, tumor, and vascular involvement.

As an invasive examination, the risks of laparoscopy should be considered, as they may promote trocar-site implantation and peritoneal implant progression. Additionally, there is no clear exploring pathway during laparoscopic staging. Some surgeons merely examine the visible liver and peritoneal surfaces without mobilization and with or without washing for cytology (100). Other surgeons perform extended exploration, including the posterior liver surface, mobilization of the duodenum, evaluation of the proximal jejunal mesentery, and visualization of the lesser sac (103). However, whether extended exploration increases the incidence of tumor implantation remains unknown.

6. Conclusions and future perspectives

Currently, restaging after NAT in PC mainly depends on conventional radiological examination and changes of serum CA19-9 levels. However, the responses to NAT cannot be accurately reflected by these assessment tools. Several novel imaging modalities or biomarkers have been developed and show promise, but further validation in large samples is needed. In consideration of the histopathological characteristics of PC, novel evaluation techniques that reflect the metabolic response or recognize components of the tumor stroma should be developed in future studies.

Acknowledgements

We would like to thank Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Funding

This work was supported by the China Postdoctoral Science Foundation (2018M632681), the Natural Science Foundation of China (81502051), and the Shandong Provincial Natural Science Foundation, China (ZR2015HQ010, ZR2017MH032).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JX, SH, and LW proposed and designed the study. LW and JX wrote the draft. JX, HZ, and FL collected and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. HZ, SH, and LW revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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