ORIGINAL PAPER

# Diffusion Weighted Magnetic Resonance Sequences do not Improve Pathologic Response Prediction after Neoadjuvant Therapy for Pancreatic Cancer

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**ABSTRACT**

**Background** Pre-operative neoadjuvant chemotherapy (NAC) is routinely used for pancreatic ductal adenocarcinoma (PDAC), however there are no validated tools for evaluating pathologic response in these patients. This study compared changes in imaging characteristics to determine if pathologic response after NAC can be predicted. **Methods** 36 patients with histologically confirmed PDAC, who underwent pancreaticoduodenectomy, with pre-operative NAC and pre and post therapy diffusion weighted MRI (DW-MRI) between 2016 and 2018 were included. Response to NAC was determined using tumor size changes, RECIST criteria and DW-MRI (changes in apparent diffusion coefficient (ADC)). Pathologic response on final histology was used as reference. **Results** 25 (69%) patients demonstrated pathologic response to NAC. Reduction in size was noted in 31 patients. ADC values increased on restaging MRI in 15 cases. Reduction in size alone predicted pathologic response with 92% sensitivity and 27% specificity compared to increased ADCs, 48% sensitivity and 73% specificity. **Discussion** Reduction in tumor size alone correlated with pathologic response to NAC. DW sequences alone had poor sensitivity but better specificity of predicting response. Caution is urged in using ADC values from DW-MRI to determine responses after NAC. Traditional size criteria should continue to be used for predicting pathologic response after NAC.

## Introduction

Pancreatic adenocarcinoma is the fourth leading cause of death in the United States [1]. Approximately 30% of all pancreatic cancer patients have surgically resectable disease at the time of diagnosis and about 40% of patients present with locally advanced disease [2, 3]. Neo-adjuvant chemotherapy (NAC) is routinely used for locally advanced disease with the goal of reducing tumor burden to get patients to curative intent surgery[1]. Currently, pathologic response to neoadjuvant therapy is assessed based on tumor size reduction measured by anatomical imaging modalities, such as CT or MRI. Other characteristics, such as reduction in vessel encroachment are also routinely used as surrogates for response. These characteristics are not only used to determine response but also define resectable versus border resectable tumors [4].

Current imaging modalities are limited in their evaluation of response prediction after chemotherapy [5]. Response Evaluation Criteria in Solid Tumors (RECIST), which was developed in the 2000s based on criteria set by the World Health Organization is routinely used for response assessment [6]. The RECIST criteria determines response as either complete with disappearance of all target lesions, partial with at least 30% decrease in the sum of diameters of target lesions, progressive disease with at least 20% increase in the sum of diameters or stable disease with neither sufficient shrinkage nor increase in size [5]. This evaluation criterion does not incorporate microscopic and cellular changes that would otherwise represent NAC response at the histological level. In order to capture the microstructural changes that occur post therapy and may define response better, diffusion weighted magnetic resonance imaging (DW-MRI) has been recently used in the evaluation of tumor characteristics [7]. DW-MRI relies on the difference of Brownian motion of water molecules into biological tissues, reflecting changes in water mobility

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based on cellular volume and density [8][1]. Based on these characteristics, diffusion of water molecules is restricted in malignant lesions, given the higher density of cells and hyper-cellularity [6]. Restricted diffusion results in a decrease in the apparent diffusion coefficient (ADC) and hyper-intense signals on DW-MRI. In contrast, benign lesions have expanded extracellular space with easier diffusion of water, which results in a high ADC and hypo-intense signals on DW-MRI [9, 10] **(Figure 1)**.

Some studies have reported that an increased ADC value during treatment corresponds to response in colorectal cancers, though this finding has not been systematically studied or correlated to pathologic response [6, 11, 12]. Although, the usefulness of DW-MRI in evaluating disease progression has been studied, there is still a need to tailor these findings to individual tumor types, anatomic sites and therapies. We used the differences between imaging characteristics on DW-MRI to determine if pathologic response could be predicted pre-operatively after NAC in patients with pancreatic adenocarcinoma who subsequently undergo pancreaticoduodenectomy (PD).

## METHODS

### Data Collection

This was an observational, retrospective study of all patients who underwent PD for pancreatic ductal adenocarcinoma (PDAC) at the Emory University Hospital between January 1, 2016 and January 31, 2018. The study population was selected based on the following inclusion criteria: (a) DW-MRI sequences performed pre and post neoadjuvant therapy during the period mentioned above; (b) pathologic diagnosis of pancreatic ductal adenocarcinoma; and (c) a history of pre-operative neoadjuvant therapy, either chemotherapy or chemoradiation. There were 224 patients who underwent a whipple procedure, of which 112 were histologically proven to be PDAC and 42 received preoperative chemotherapy. Of these 42 patients 36 patients meet all inclusion criteria **(Figure 2)**. Electronic medical records were analyzed for patient demographics, operative data, overall survival. and reviewing imaging studies. Additionally, archived histology specimens were re-assessed for characterizing pathologic response. The study was performed with institutional IRB approval (IRB00096336).

### MRI

All patients with pancreatic masses undergo standardized pancreas protocol MR imaging at the authors institution. MR images were obtained using a whole-body 3.0 T scanner (Philips Achieva 3.0- T TX MR; Philips Medical Systems, Best, The Netherlands) with standard quadrature body coil and phased-array 16- channel sensitivity encoding abdominal coil. Patients were placed in a supine position. Using a respiratory-triggered turbo spin-echo sequence, axial T2W were obtained (repetition time,1210–1220 milliseconds [ms]/echo time, 70 ms; matrix, 256 × 198; section thickness, 4 mm; gap, 1 mm; number of sections, 32–36; field of view, 36 cm; number of signal averaged, 1). Axial DW images were performed using a respiratory triggered spin-echo, single-echo echo-planar sequence with chemical shift-selective fat-suppression techniques (*b* was 0 and 1000 seconds/mm$^2$; repetition time, 2280–3600 ms/echo time, 40–50 ms; matrix, 236 × 186; section thickness, 4 mm; gap, 1 mm; field of view, 38 cm; number of sections, 32–36; number of signal averaged, 3). DW gradients were done with three orthogonal directions.

All imaging data was transferred to an analysis workstation, which generated the ADC maps for each patient and their corresponding images. Using these ADC maps the regions of interest (ROI) were created in order to determine the ADC of the primary tumor. Tumor size was

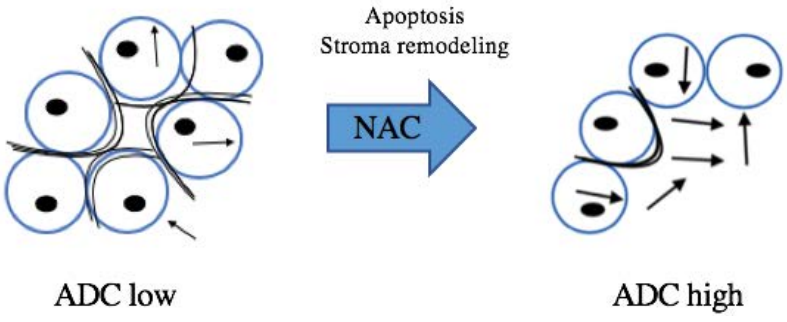


**Figure 1.** Model of tumor cellular changes and ADC after NAC. ADC is low with higher cellular numbers and decreased extracellular space leading to decreased water motion/diffusion. After NAC, ADC is high secondary to apoptosis and stromal remodeling leading to decreased number of cells and increased extracellular space allowing higher water motion/diffusion.

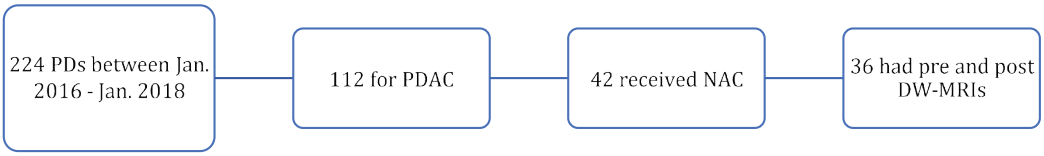


**Figure 2.** Patient population. 224 patients underwent a pancreatiduodenectomies (PDs) between Jan. 2016 and Jan. 2018. Only 36 patients met all inclusion criteria for the study, which included having pre and post NAC DW-MRIs in order to asses response. All patients required the procedure for pancreatic ductal adenocarcinoma (PDAC).

measured using the greatest diameter of the lesion on MR images. ROI was defined as either tumor center or tumor periphery. A single experienced abdominal MR radiologist (PM interpreted all images and generated the ROI and subsequent ADC values. The radiologist was blinded to all clinical information, including final pathological findings and prognosis.

### Pathology

Stained tissue sections were pulled from archives for all 36 patients. All pathology specimens were analyzed at the same lab by an expert pancreatic pathologist (AK). The pathologist was blinded to all clinical information, including extent, staging of the cancer, as well as all imaging findings. Histopathologic response after neoadjuvant therapy was assessed using the criteria suggested by the College of American Pathologists, which focuses on determining the number of viable tumor cells and fibrosis present in the tissue after NAC therapy [13]. AK reviewed at least 8 slides from each pancreatic tumor sample and assessed for response using the grading scheme shown in **Supplemental Figure 1**.

### Data Analysis

Pathologic findings were used as reference to define either neoadjuvant therapy response or no response. Response to therapy based on DW-MRI findings was assessed comparing mean ADC values pre and post neoadjuvant therapy using paired t-tests; a higher ADC value post therapy compared to pre-therapy meant response while a decrease in tumor size between pre and post neoadjuvant therapy meant response according to tumor size changes. Tumor size changes post therapy were categorized as any decrease, decrease greater than 0.5 cm, and decrease greater than 1.0 cm. Response was also assessed using the RECIST criteria by calculating the percentage of reduction in size for each tumor. In addition, changes in vessel encroachment were analyzed as a separate variable. Sensitivity and specificity for detecting response with tumor size changes, RECIST criteria, vessel encroachment and DW- MRI mean ADC value changes were calculated and then compared to sensitivity and specificity utilizing pairs of criteria. All statistical computations were performed by using the Statistical Package for the Social Sciences 16.0 (SPSS, Inc. Emory) for Windows. Statistical significance was determined at a $p < 0.05$.

## RESULTS

### Pathology

Patient characteristics are summarized in **Table 1.** All patients were treated with pre-operative chemotherapy; 19 patients were treated with FOLFIRINOX, of which 4 also received neoadjuvant radiation, and 17 patients were treated with Gemcitabine and Abraxane, of which 3 also received radiation. Based on UICC TNM classification, 1 patient was in stage IA, 1 in stage IB, 18 were in stage IIA, and 13 were in stage IIB. Overall, pathologic response to NAC was observed in 25 patients, while 11 patients were unresponsive. Of note, those patients with pathologic response had a longer overall survival compared to those with no pathologic response, although not significantly different (p=0.089) **(Supplemental Figure 2)**.

### Imaging Characteristics

Thirty-one tumors showed a decrease in size. Of these 19 showed a decrease greater than 0.5 cm, and 9 showed a decrease greater than 1.0 cm. Tumor response based on RECIST criteria identified only 9 cases as having partial response and all others as stable disease. 29 patients presented with vessel encroachment, out of which 10 showed improvement post NAC. Mean ADCs increased in 15 patients and remained unchanged in 21. Response by imaging was compared to pathologic results; true responders were those patients who showed response to NAC on imaging with a corresponding response on histologic data. Of the 31 patients with any decrease in size, 23 (74%) were true responders. Based on RECIST criteria, 8 (89%) of the 9 patients categorized as partial responders were true responders. However, using the same criteria, of the 27 patients categorized as stable disease, 17 (63%) of them were true responders. Of those patients showing vessel interface improvement, 8 (80%) of them were true responders while 11 (58%) out of the 19 showing no interface improvement were true responders. Of the 15 patients showing DW-MRI response with increased ADCs, 12 (80%) of them were true responders, while 13 (58%) of the 21 with unchanged ADCs were true responders. Sensitivities and specificities calculated in this study are shown in **Table 2**. A decrease in size in tumor size had 92% sensitivity and 27% specificity. RECIST criteria and vessel interface improvement both had a sensitivity of 32% while a specificity of 91% and 82%, respectively. Lastly, sensitivity for increased mean ADCs was 48% with 73% specificity.

## DISCUSSION

### Assessing Response after NAC using Conventional Imaging Criteria

Currently size changes are evaluated based on RECIST, which has stringent definitions. In the current study, using RECIST and comparing it to pathologic response resulted in a low sensitivity of 32%. Therefore, it is possible that RECIST may not be the best predictor of response to NAC. Treatment response is also evaluated using changes in overall tumor size [4]. When evaluating response based on tumor size decrease alone without RECIST categorization, the best sensitivity (92%) to detect response was in those tumors with any decrease in size **(Table 2)**. Therefore, minor changes in the size of the tumor correspond to response to NAC at the histologic level. Of note, when analyzing the significance of vessel encroachment improvement pre and post NAC, sensitivity to assess response was the same as RECIST, 32% **(Table 2)**. Of the tumors showing no improvement in vessel encroachment post-treatment, 58% had actual pathologic response on final histology suggesting that this criterion

**Table 1.** Analysis of patient demographic characteristics based on pathologic response. Pathologic response classification based on final scoring by expert pathologist (AK). Total number of patients included was 36. ADC (Apparent diffusion coefficient); NAC (Neoadjuvant chemotherapy).

| Variable | Total (n) | Pathologic Responders (n=25) | | Pathologic Non-Responders (n=11) | | p-value |
|---|---|---|---|---|---|---|
| **Age, median** | | 67 | (54-84) | 69 | (47-83) | 0.248 |
| **Sex, female, n (%)** | 13 | 9 | -69.20% | 4 | -30.80% | 0.983 |
| **Race, n (%)** | | | | | | 0.761 |
| African American | 4 | 3 | -75.00% | 1 | -25.00% | |
| White | 23 | 15 | -65.20% | 8 | -34.80% | |
| Other | 9 | 7 | -77.80% | 2 | -22.20% | |
| **Pre-Operative chemotherapy, n (%)** | | | | | | 0.86 |
| FOLFIRINOX | 19 | 14 | -73.70% | 5 | -26.30% | |
| Gemcitabine + Abraxane | 17 | 11 | -64.70% | 6 | -35.30% | |
| Pre-Operative radiation, n (%) | 7 | 7 | -100.00% | 0 | 0.00% | 0.051* |
| **Pathologic Characteristics** | | | | | | |
| Size, cm, median (range) | | 2.2 | (0.7-7.0) | 3.6 | (2-4.9) | 0.284 |
| Tumor histologic grade, n (%) | | | | | | 0.109 |
| 1 | 3 | 3 | -100.00% | 0 | 0.00% | |
| 2 | 22 | 12 | -54.50% | 10 | -45.50% | |
| 3 | 10 | 9 | -90% | 1 | -10% | |
| Lymphovascular invasion, n (%) | 24 | 15 | -62.50% | 9 | -37.50% | 0.201 |
| Perineural invasion, n (%) | 29 | 19 | -65.50% | 10 | -34.50% | 0.298 |
| Involved lymph nodes | | 0 | (0-5) | 3.5 | (0-31) | 0.020* |
| Margin positivity | 9 | 7 | -77.80% | 2 | -22.20% | 0.531 |
| yPT | | | | | | 0.576 |
| 1 | 3 | 3 | -100.00% | 0 | 0.00% | |
| 2 | 3 | 2 | -66.70% | 1 | -33.30% | |
| 3 | 29 | 19 | -65.50% | 10 | -34.50% | |
| 4 | 1 | 1 | -100.00% | 0 | 0.00% | |
| yPN, 1, n (%) | 20 | 11 | -55.00% | 9 | -45.00% | 0.035* |
| **Stage** | | | | | | 0.146 |
| IA | 1 | 1 | -100.00% | 0 | 0.00% | |
| IB | 1 | 1 | -100.00% | 0 | 0% | |
| IIA | 18 | 9 | -50.00% | 9 | -50.00% | |
| IIB | 13 | 11 | -84.60% | 2 | -15.40% | |
| **Tumor Response to Therapy on Imaging, n (%)** | | | | | | |
| Any size change | 31 | 23 | -74.20% | 8 | -25.80% | 0.123 |
| Size decrease >0.5cm | 19 | 15 | -78.90% | 4 | -21.10% | 0.191 |
| Size Decrease >1.0cm | 9 | 7 | -77.80% | 2 | -22.20% | 0.531 |
| **Vessel-tumor Interface on Imaging, n (%)** | | | | | | |
| Pre-NAC | 27 | 17 | -63.00% | 10 | -37.00% | 0.144 |
| Post-NAC | 30 | 20 | -66.70% | 10 | -33.30% | 0.418 |
| Interface improvement post-NAC | 10 | 8 | -80.00% | 2 | -20.00% | 0.394 |
| **ADC Value Changes on DWI, n (%)** | | | | | | 0.076 |
| Increased ADC post NAC | 15 | 12 | -80.00% | 3 | -20.00% | |
| Unchanged ADC post NAC | 21 | 13 | -62.00% | 8 | -38.00% | |
| Decreased ADC post NAC | 0 | 0 | 0.00% | 0 | 0.00% | |

**Table 2.** Sensitivity and specificity for all criteria for response, including multiple combinations analyzed during the study. Increased ADC was considered response to NAC, while unchanged ADV was considered no response.

| Imaging Criteria | Sensitivity | Specificity |
|---|---|---|
| Any Decrease | 92% | 27% |
| Decrease >0.5cm | 60% | 64% |
| Decrease >1.0cm | 28% | 82% |
| RECIST – Partial Response | 32% | 91% |
| Vessel interface Improvement | 32% | 82% |
| Increased mean ADCs | 48% | 73% |
| **Combinations** | **Sensitivity** | **Specificity** |
| Increased ADC **OR** Decrease in Size | 100% | 27% |
| Increased ADC **AND** Decrease in Size | 46% | 73% |
| Unchanged ADC **AND** Decrease in Size | 71% | 45% |
| Unchanged ADC **AND** Unchanged/ Increase in Size | 16% | 100% |

may also not be clinically valuable in assessing response. Vessel encroachment although important when assessing resection options should not be used as a factor to assess NAC response. One possible reason for this finding could be that desmoplastic stroma undergoes treatment fibrosis and this cannot be differentiated from the malignant process on conventional imaging.

### DW-MR Imaging for Assessment of Pathologic Response

There is conflicting data regarding the utility of ADC as a predictor of response to chemotherapy and overall prognostic factor. Fukukura *et al*. described that there is no association observed between ADC and PDAC tumor differentiation, concluding that ADC has no potential for prediction of prognosis in these patients. This study concluded that TNM staging determined with current CT or MRI should be the tool utilized for treatment planning and predicting survival. On the other hand, Niwa *et al*. [12], showed that those patient with pancreatic adenocarcinoma with lower ADC values can predict a higher or earlier progression in chemotherapy-treated patients. However, this study looked at progression only rather than response to NAC. Even when looking at other types of tumors, data is also conflicting. For instance, Dzik-Jurasz *et al*. showed that when looking at ADC values correlating to response to NAC in rectal cancer, a decrease in ADC predicted response rather than an increase. Whereas, when looking at colorectal cancer with metastasis to the liver, an increase in ADC was observed in those patients with response to NAC [14]. The same is observed with brain tumors where an increase in ADC values was observed after initiation of treatment [15].

The results from the current study demonstrated that although 80% of tumors showing an increase in ADC post NAC treatment were true pathologic responders, sensitivity of predicting response was only 48%, which compared to any decrease in size alone is much lower **(Table 2)**. Nevertheless, compared to tumor size change alone, the specificity of an increase in ADC was higher at 73% compared to 27%, respectively. DW-MRI changes alone should not be used to predict pathologic response to neoadjuvant treatment. Our data supports the findings of Fukukura *et al*. [7], with DW-MRI characteristics alone not being a prognostic tool in NAC for PDAC. In comparison to those studies showing the utility of ADC as factor to predict response, our results differ given the difference in tumor location, tumor behavior, and could also be secondary to the difference in neoadjuvant therapy [16].

### Combining Conventional Imaging Criteria with DW Criteria to Assess Response

There are no definitive studies that have combined conventional response criteria with changes in DW-MRI characteristics to assess NAC response. The results from this study show that using ADC value changes in combination with changes in size leads to increased sensitivity and specificity. When combining increase in ADC or decrease in size, sensitivity increased to 100% and an unchanged ADC and unchanged size had a 100% specificity **(Table 2)**. Therefore, in combination with tumor size changes, DW-MRI changes marginally improves sensitivity in response prediction and can reliably predict non-responders to NAC.

### Pathologic Response

Pre-operative chemotherapy ± radiation have improved outcomes of locally advanced and borderline resectable PDAC compared to previous treatment options [12]. In this study the authors used pathologic response to neoadjuvant therapy as the gold standard for response prediction. Patients with response after pre-operative treatment have generally improved long-term outcomes, including a prolonged survival that can be up to 60 months in patients with complete response [12, 13, 17, 18, 19]. In this study, 69% of the patient population had a pathologic response, and these patients had an overall longer survival **(Supplemental Figure 2)**.

## LIMITATIONS

Though all patients underwent a standardized pancreas protocol MRI in this study there was some variability in the DW portion of this imaging. This study has as small sample size. In addition, neoadjuvant treatment was not standardized and therefore the patient population had two different chemotherapy regimens and some with

additional radiation treatment. Lastly, this study did not assess for response in non-resectable tumors.

## CONCLUSION

The date from the current study suggest that conventional size criteria focused on tumor size reduction alone is the best available predictor of pathologic response to NAC. DW-MRI sequences alone have very poor sensitivity but better specificity than tumor size changes when predicting response. In combination the specificity increases to 100%, making it reliable in predicting non-responders to neoadjuvant treatment though the poor sensitivity (16%) renders this finding rather meaningless from a clinical standpoint. Regardless of the improved specificity in non-responders with the use of DW-MRI sequences, the authors conclude that traditional size criteria alone should continue to be the definitive guide for predicting pathologic response after NAC in patients with PDAC.

## Conflict of Interest

Authors declared that no conflict of interest.

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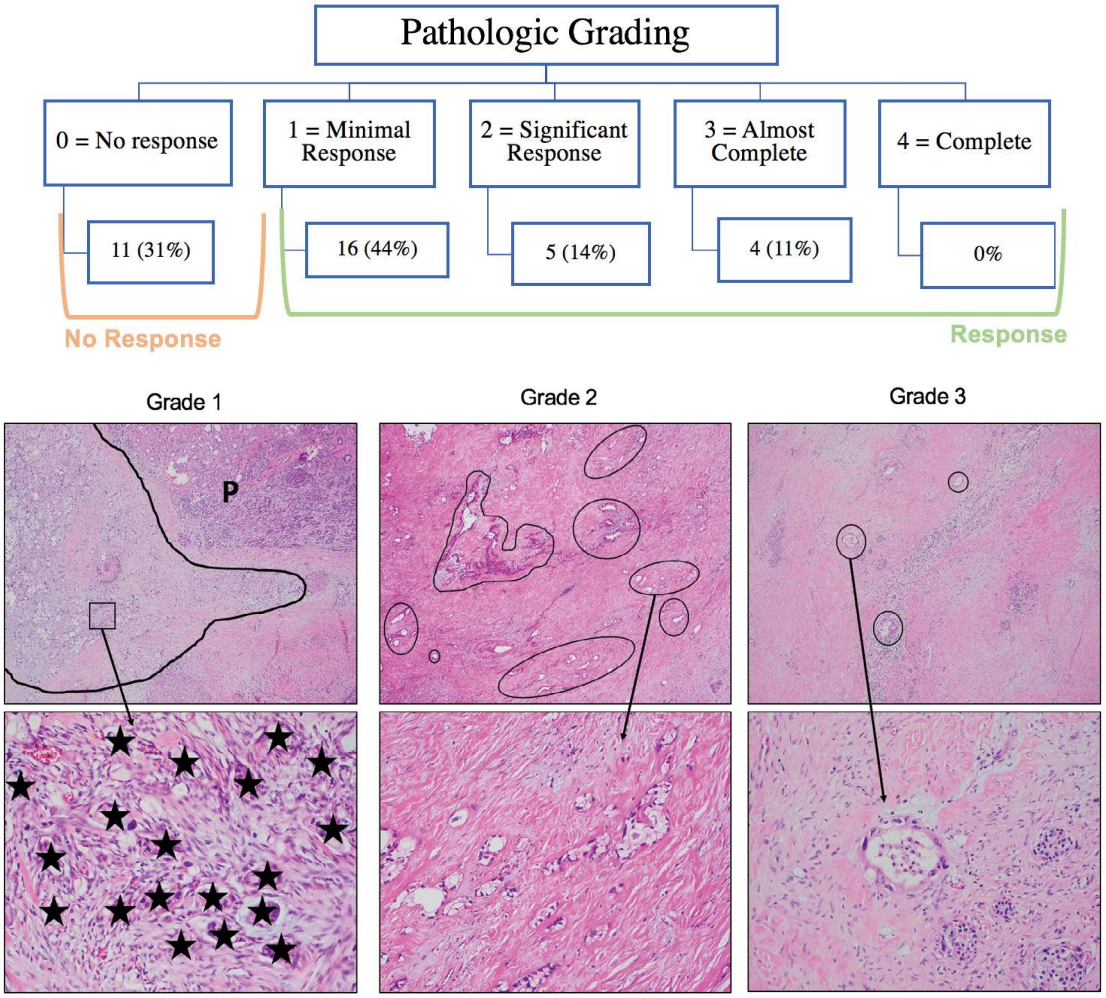
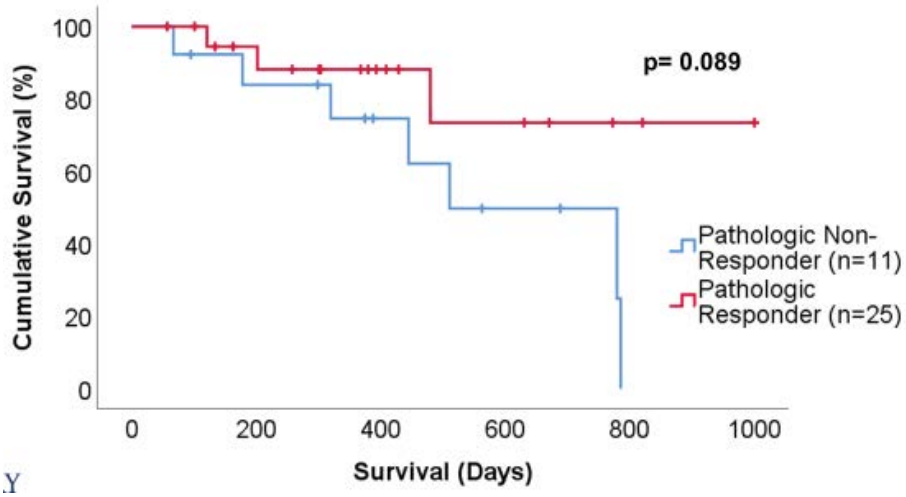
## Supplemental Figure




**Supplemental Figure 1.** Grading system utilized to categorize response to NAC. The images at the bottom are histologic slides as examples, with the bottom row being the same slide at a higher magnification. Zero represented no response to NAC. One was minimal response with most of the tissue being tumor cells after treatment; the stars on the corresponding picture at the bottom represent tumor. Two representing significant response; all circled areas on histologic slide representing remaining areas of tumor cells. Three representing almost complete response, with very few areas of remaining tumor cells, as seen on the corresponding slide. Response meant decreased number of viable tumor cells, necrosis or fibrosis.




**Supplemental Figure 2.** Survival of patients with PDAC based on pathologic response versus no response after NAC. Although there is no significant difference between the two groups (p = 0.089), there is an overall longer survival for those patients who had pathologic response after NAC.