

ORIGINAL ARTICLE

Added value of CA19-9 response in predicting resectability of locally advanced pancreatic cancer following induction chemotherapy

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Abstract

Background: Determining the resectability of locally advanced pancreatic cancer (LAPC) after induction chemotherapy is complex since CT-imaging cannot accurately portray tumor response. We hypothesized that CA19-9 response adds to RECIST-staging in predicting resectability of LAPC.

Methods: Post-hoc analysis within a prospective study on LAPC (>90° arterial or >270° venous involvement). CA19-9 response was determined after induction chemotherapy. Surgical exploration was performed in RECIST-stable or -regressive disease. The relation between CA19-9 response, resectability and survival was assessed.

Results: Restaging in 54 patients with LAPC after induction chemotherapy (mostly FOLFIRINOX) identified 6 RECIST-regressive, 32 RECIST-stable, and 16 patients with RECIST-progressive disease. The resection rate was 20.3% (11/54 patients). Sensitivity and specificity of RECIST-regression for resection were 40% and 87% whereas the positive predictive value (PPV) and negative predictive value (NPV) were 67% and 68%. Using a 30% decrease of CA19-9 as cut-off, 9/10 patients were correctly classified as resectable (90% sensitivity, PPV 43%) and 3/15 as unresectable (20% specificity, NPV 75%). In the total cohort, a CA19-9 decrease $\geq 30\%$ was associated with improved survival (22.4 vs. 12.7 months, $p = 0.02$).

Conclusion: Adding CA19-9 response after induction chemotherapy seems useful in determining which patients with RECIST non-progressive LAPC should undergo exploratory surgery.

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Introduction

The prognosis of patients with pancreatic cancer is dismal.¹ Upon diagnosis, only 20% of patients can undergo a surgical resection with curative intent, whereas 40% of patients present with metastatic disease and 40% with locally advanced pancreatic cancer (LAPC), in which a resection is prohibited due to perivascular tumor infiltration.^{1,2}

Novel chemotherapy regimen, mostly FOLFIRINOX, consisting of 5-fluorouracil, leucovorin, irinotecan and

oxaliplatin, have resulted in a significant prolonged survival in patients with LAPC and metastatic pancreatic cancer.^{3,4} Additionally, FOLFIRINOX can result in down-staging of LAPC, ultimately even rendering 20–25% of patients resectable, which is associated with improved survival.⁵ LAPC definitions and resectability criteria, however, vary greatly, with resectability rates in LAPC following induction FOLFIRINOX ranging from 0 to 60%.^{6,7}

Following induction chemotherapy, treatment response is usually assessed on CT-imaging with the Response Evaluation Criteria in Solid Tumours (RECIST1.1).⁸ According to RECIST, tumor progression requires at least 20% increase in the sum of the tumor diameters in 3 directions (and an absolute increase >5 mm) or the occurrence of new lesions. Regression requires

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tumor shrinkage of at least 30%. RECIST-stable disease is defined by the absence of progression and regression and therefore seen in the majority of patients after induction FOLFIRINOX.

Although these definitions seem clear, current CT-imaging techniques are inadequate to discriminate between fibrotic tissue or viable tumor tissue following (FOLFIRINOX) induction chemotherapy,⁹ with a 58% specificity and 71% sensitivity of CT-imaging for resectability of pancreatic cancer.¹⁰ As a result, patients with RECIST-stable disease are in many centers worldwide not surgically explored. Some high-volume expert centers, however, proceed nearly routinely to surgery in these patients based on their experience that a radical resection is often possible.^{7,9} Since a negative surgical exploration in pancreatic cancer is associated with worse short term outcomes,¹¹ we are in clear need of more accurate predictive tools to better select patients for surgery.

Carbohydrate Antigen 19-9 (CA19-9) is a non-specific tumor marker for pancreatic carcinoma which has previously been correlated with disease stage and survival.^{12–14} Low pre-operative serum levels of CA19-9 in patients with pancreatic cancer are associated with resectability¹⁵ and high values of the tumor marker predict unresectability.¹⁶ However, little is known on the predictive value of CA19-9 response following induction chemotherapy to predict resectability in LAPC.

The aim of this study was therefore to determine the diagnostic accuracy of serum CA19-9 response in combination with RECIST-response on CT-imaging in patients with LAPC following induction chemotherapy to detect resectability.

Methods

This study follows the Standards for Reporting Diagnostic Accuracy (STARD) guideline for diagnostic studies.¹⁷

Patient selection

Post-hoc analysis in the prospective IMPALA cohort study on multimodality treatment of LAPC (Netherlands Trial Registry number NTR4230), which included 132 consecutive patients with LAPC, included between December 1st, 2013 and May 31st, 2015.¹⁸

From the original cohort, patients diagnosed with LAPC as defined by the consensus criteria of the Dutch Pancreatic Cancer Group (>90° arterial and/or >270° venous involvement)¹⁹ were identified and retrieved based on the following inclusion criteria: pathology proof, non-metastatic LAPC receiving induction chemotherapy, or borderline resectable pancreatic cancer patients who were considered as having LAPC during a previous exploration.

In the IMPALA-study, all patients were offered 3 months of induction chemotherapy followed by CT-restaging.¹⁸ FOLFIRINOX was offered to patients with a WHO score of 0–1 and gemcitabine to others. Patients with RECIST non-progressive (i.e. stable or regression) disease after 3 months of induction

chemotherapy, underwent exploratory laparotomy for either resection or, if resection was not feasible, ablative treatment with irreversible electroporation (IRE). CA19-9 levels were not presented during the multidisciplinary meeting and therefore not taken into account during the decision-making process.

Included in this study were patients who completed 3 months of induction therapy, in whom pre- and post-chemotherapy CA19-9 serum values and adequate CT-imaging was available. CA19-9 was only considered if serum bilirubin levels at the time of evaluation were <20 μmol/L. A flow-chart of the study protocol is shown in [Supplement 1](#).

Radiological assessment of disease progression

Restaging of patients was performed according to the RECIST1.1 criteria comparing the last CT prior to chemotherapy with the first CT after 3 months induction chemotherapy.⁸

Disease response was scored according to the following criteria: Regressive Disease: minimum of 30% decrease in the sum of diameters of target lesions, taking baseline sum diameters as reference. Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered as progression. Stable Disease: Neither sufficient shrinkage to qualify for regression nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

The radiologist performing restaging of patients was blinded for patient details, CA19-9 levels and treatment.

Statistical analysis

Continuous data are presented as mean and standard deviation in case of a normal distribution or as median and interquartile range (IQR) in case of a non-normal distribution, while dichotomous data are presented as proportions. Categorical (binary, ordinal or nominal) data are presented as frequencies and percentages. Correlations between CA19-9, RECIST and resectability were analysed for diagnostic accuracy based on sensitivity, specificity and PPV/NPV. The cut-off value for a significant decrease in CA19-9 serum values was based on limiting the number of false-negatives and optimizing sensitivity, aided by a Receiver Operating Characteristic (ROC) curve and sensitivity analysis. Patients with non-elevated CA19-9 levels (i.e. <34 UI/L) were censored from the analyses. Survival was analysed using Kaplan–Meier curves and were compared between sub-groups using a log-rank test. Patients alive at follow-up were censored. To detect potential selection bias, survival was compared for the patients included in this study with the patients who were excluded based on unavailability of CA19-9. Statistical analyses were performed using IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Orchard Road Armonk, New York, US) and STATA version 14.1 (StataCorp LP, College Station, Texas, US).

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