

## Updated therapeutic outcome for patients with periampullary and pancreatic cancer related to recent translational research

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### Abstract

Chemotherapy with improved effect in patients

with metastatic pancreatic cancer has recently been established, launching a new era for patients with this very aggressive disease. FOLFIRINOX and gemcitabine plus nab-paclitaxel are different regimens, both capable of stabilizing the disease, thus increasing the number of patients who can reach second line and even third line of treatment. Concurrently, new windows of opportunity open for nutritional support and other therapeutic interventions, improving quality of life. Also pancreatic surgery has changed significantly during the latest years. Extended operations, including vascular/multivisceral resections are frequently performed in specialized centers, pushing borders of resectability. Potentially curative treatment including neoadjuvant and adjuvant chemotherapy is offered new patient groups. Translational research is the basis for the essential understanding of the ongoing development. Even though biomarkers for clinical management of patients with periampullary tumors have almost been lacking, biomarker driven trials are now in progress. New insight is constantly made available for clinicians; one recent example is selection of patients for gemcitabine treatment based on the expression level of the human equilibrium nucleoside transporter 1. An example of new diagnostic tools is identification of early pancreatic cancer patients by a three-biomarker panel in urine: The proteins lymphatic vessel endothelial hyaluronan receptor 1, regenerating gene 1 alpha and translation elongation factor 1 alpha. Requirement of treatment guideline revisions is intensifying, as combined chemotherapy regimens result in unexpected advantages. The European Study Group for Pancreatic Cancer 4 trial outcome is an illustration: Addition of capecitabine in the adjuvant setting improved overall survival more than expected from the effect in advanced disease. Rapid implementation of new treatment options is mandatory when progress finally extends to patients with this serious disease.

**Key words:** Chemotherapy; Clinical outcome; Evidence-

based medicine; Molecular expression profiling; Pancreatic cancer; Periampullary tumor; Prognostic markers; Survival

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**Core tip:** More effective chemotherapy and reorganized care for patients with periampullary carcinoma has opened windows of opportunity for improved surgical performance. Combined with neoadjuvant and adjuvant chemotherapy new patient groups can therefore be offered potentially curative treatment. A biomarkers can predict gemcitabine sensitivity, thus improving patient selection. A three-biomarker panel in urine can identify patients with early pancreatic adenocarcinoma. Clinical implementation of new diagnostic and therapeutic options is mandatory.

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## INTRODUCTION

The different prognosis of pancreatic ductal adenocarcinoma (PDAC) and other periampullary carcinomas generates from profound biological diversities, increasingly explained by recent translational research<sup>[1]</sup>. Most details from whole genome analysis of the mutational landscape<sup>[2]</sup> generate knowledge that cannot be directly translated into clinical applications. Nevertheless, accumulative genetic and molecular biological information constantly increase the basis for clinical studies, and together with well-designed randomized controlled trials (RCT), the scientific development is accelerated. Outcome from recent trials are summarized in this review, related to relevant translational research which is rapidly generating new windows of diagnostic and therapeutic opportunity.

### **Molecular expression profiling in histological subtypes**

The different prognosis for periampullary carcinomas, arising from pancreatic duct cells, distal bile duct cells or the mucosa of the ampulla or duodenum is documented by numerous authors<sup>[3-6]</sup>. Intestinal or pancreaticobiliary differentiation have been shown to be prognostically more important than anatomic site of origin<sup>[7]</sup>, and an integrative platform, enabling profiling of micro(mi)RNA, mRNA and proteins have recently been published<sup>[8]</sup>. Utilizing this platform, the molecular profiles of 85 periampullary adenocarcinomas, resected by pancreaticoduodenectomy (PD, or Whipple-procedure), was characterized by mRNA and

miRNA expressions, comparing tumors from different anatomical sites of origin as well as different histological subtypes<sup>[9]</sup>. Six miRNA families were downregulated and four were upregulated in the pancreaticobiliary type as compared to the intestinal type. miRNA and mRNAs associated with improved survival for both histopathological subtypes were identified. The genes 3-phosphoinositide dependent protein kinase 1 (PDPK1), phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2), glucose 6-phosphatase alpha (G6PC) and miRNAs miR-127-3p and miR-377 were linked to enriched pathways and identified as prognostic markers for future clinical investigation.

In lung cancer patients a serum specific miRNA signature have been identified and validated in a study on 1115 high risk individuals for lung cancer, enrolled in a screening protocol. Overall accuracy, sensitivity and specificity were found above 70%, area under the curve (AUC) in the (receiver operating characteristics) ROC-analysis was 0.85<sup>[10]</sup>. In another report on circulating miRNA as biomarker of lung cancer, a panel of 24 miRNAs with optimal classification performance was identified<sup>[11]</sup>, enabling earlier detection of patients with lung cancer. Also in breast cancer circulating cell-free miRNAs have been found to be a biomarker for diagnostic and possibly targeted therapeutic utilization<sup>[12]</sup>. A similar development is foreseeable for patients with periampullary tumors. A feasibility study on 46 patients with early stage PDAC, 29 patients with chronic pancreatitis and 26 healthy controls, investigated the discriminant ability of the combination of miR-143 and miR-30e in urine samples. Sensitivity above 80%, specificity above 90% and AUC 0.923 in the ROC analysis was recently published<sup>[13]</sup>. Also proteomics of 18 urine samples were analyzed in 192 patients with PDAC and 87 healthy controls. A three-biomarker panel was identified, able to differentiate patients with early stage pancreatic cancer from healthy controls by urine specimens<sup>[14]</sup>. The discriminant ability of the proteins lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), regenerating gene 1 alpha (REG1A) and (translation elongation factor 1 alpha) TEF1 increased further when combined with serum Ca19-9 value, resulting in AUC 0.97 in the ROC analysis. Accordingly, improved diagnosis of patients with localized *i.e.*, resectable periampullary tumors is achievable, based on recent translational research. Epigenetic downregulation of miRNA 192 expression has recently been found to promote pancreatic cancer progression<sup>[15]</sup>, explaining the early metastatic behavior of PDAC. Thrombospondin-1 (TSP-1) was found to decrease preclinical, even 24 mo prior to the diagnosis of PDAC, and the combination of TSP-1 and serum Ca19-9 achieved significant diagnostic yield: AUC 0.86 in ROC analysis<sup>[16]</sup>. A circulating miRNA profile has also been found to predict disease progression in patients with metastatic pancreatic cancer, receiving second line treatment<sup>[17]</sup>, illustrating that monitoring of treatment

outcome is becoming possible, based on miRNA as biomarker.

## RESECTION MARGIN ASSESSMENT

A standardized protocol for PD specimen examination, defining R1 status as tumor cells within 1 mm distance from the resection margin (RM), introduced by Verbeke<sup>[18]</sup>, have profoundly influenced reporting on R0/R1 status. This is illustrated by numerous reports, for example from the European Study Group for Pancreatic Cancer (ESPAC). In the ESPAC 1 study (inclusion 1994-2000), R1 status was reported in 18%<sup>[19]</sup>, ESPAC 3 (inclusion 2000-2008) reported R1 in 16%<sup>[20]</sup>, but in ESPAC 4 (inclusion 2009-2014) the frequency of R1 resections was 60%. Traditionally, R0 status was considered the only satisfactory outcome of PD<sup>[21]</sup>, as no clinical benefit was supposed to result from R1 resection. High rates of R0 status was conceived as an important indicator of good surgical performance. However, the ESPAC data and numerous other reports leave little doubt that historical differences in R1 rates result from divergence in pathology examination, more than quality of surgery<sup>[22]</sup>. This opinion is supported by recent reports from the US<sup>[23]</sup> and France<sup>[24]</sup>, underlining the importance of focused attention on standardized pathology reports in order to increase comparability of published data. In the center of Heidelberg, R0 status was not a prognostic indicator until the new standard was introduced<sup>[25]</sup>.

Tumor growth is more dispersed in pancreatic head cancers than in rectal cancer, ampullary cancer and distal bile duct cancer<sup>[26]</sup>. The implication is that even R0 status according to the standardized pathology protocol, does not completely exclude the possibility of residual tumor cells in the operation field. The necessity of adjuvant chemotherapy is very well documented, and is compatible with this hypothesis.

## MORPHOLOGICAL HETEROGENEITY

High levels of morphological heterogeneity is common in PDAC<sup>[27]</sup> and desmoplastic stroma is also predominant. Both characteristics are supposed to be obstacles to effective chemotherapeutic treatment. This hypothesis is supported by a report, classifying PDAC as classical, quasi mesenchymal and exocrine-like with different therapeutic outcome<sup>[28]</sup>. Genetic heterogeneity is contributing to therapeutic failure<sup>[29]</sup>, and whole-genome sequencing of 100 PDACs have recently redefined the mutational landscape<sup>[2]</sup>. Further genome-wide investigation of copy number aberrations revealed significant prognostic implications. Deletion in the genes RAB12 and COLEC12 are associated with increased and amplification with decreased postoperative survival after PD<sup>[30]</sup>. Also the stromal compartment provides stimulatory signals to the cancer cells, and the interaction has therapeutic relevance<sup>[31]</sup>. Investigation of miRNA expression profiling of carcino-

matous and stromal components in twenty periampullary adenocarcinomas, identified miRNA mediated interactions between carcinoma and stroma cells<sup>[32]</sup> which may be utilized as future therapeutic targets. These data has potential for clinical utilization in the near future.

## PERSONALIZED MEDICINE - NEW

### CLINICALLY APPLICABLE BIOMARKERS

Based on microarrays from patients randomized to chemotherapy in the ESPAC 3 trial plus controls from the ESPAC 1 trial, expression of the human equilibrium nucleoside transporter 1 (hENT1) levels were determined<sup>[33]</sup>. Survival was compared between patients with high and low hENT1 expression in the gemcitabine and 5-fluorouraci (5-FU) arms. There was no difference in the 5-FU arm, whereas gemcitabine treated patients with high hENT1 expression lived median 26.2 mo vs 17.1 mo if hENT1 expression was low ( $P = 0.002$ ). Patients with Gemcitabine sensitive tumors can thus be selected, resulting in higher response rates in future, biomarker driven trials. There has recently been an explosion of available biomarkers for PDAC which need clinical validation<sup>[34,35]</sup>. Exosomes are extracellular vesicles, containing proteins and nucleic acids, secreted by all cells, circulating in the blood. Identification of cancer cell derived exosomes has until recently not been possible, but a cell surface proteoglycan, glypican-1 (GPC1), specially enriched on cancer cell derived exosomes, was recently described, and GPC1 positive circulating exosomes (GPC1<sup>+</sup>crExos) were isolated from serum in PDAC-patients<sup>[36]</sup>. Levels of GPC1<sup>+</sup>crExos were also found to correlate with tumor burden in the same patient series. Exosomes have even been shown to initiate pre-metastatic niche formation in the liver<sup>[37]</sup>, supporting the hypothesis proposed by Heiler *et al*<sup>[38]</sup> that cancer stem cells gain the capacity for cell to cell crosstalk from generation, loading and delivery of exosomes. Utilization of exosomes as diagnostic biomarker as well as staging instrument is probably shortly upcoming opportunities.

## CHEMOTHERAPY

The development of effective oncological regimens has been slow, due to the chemoresistant character of PDAC. Table 1 shows key information from important clinical trials in first line therapy of metastatic disease, illustrating that gemcitabine became standard of care for fourteen years after Burris publication<sup>[39]</sup>. Even though S1 (tegafur, prodrug of 5-FU) could increase response rate, overall survival (OS) was no longer<sup>[40]</sup>. The addition of erlotinib to gemcitabine<sup>[41]</sup> resulted in a significant but small increase in OS. FOLFIRINOX represented a breakthrough in 2011, increasing response rate  $\times 3$ , and median survival almost  $\times 2$ , from 6.8 mo in the gemcitabine group to 11.1 mo<sup>[42]</sup>. In

**Table 1 Important clinical trials in metastatic pancreatic ductal adenocarcinoma**

Ref.	Year published	Investigated drugs	Clinical outcome	
			OS	ORR
Burris <i>et al</i> <sup>[39]</sup>	1997	Gemcitabine vs 5-FU	5.65 mo vs 4.4 mo	5.4% vs 0.0%
Ueno <i>et al</i> <sup>[40]</sup>	2005	S-1 (quasi mesenchymal and oteracil)	5.6 mo	21.1%
Moore <i>et al</i> <sup>[41]</sup>	2007	Gemcitabine vs erlotinib	5.91 mo vs 6.24 mo	8.0% vs 8.6%
Conroy <i>et al</i> <sup>[42]</sup>	2011	Gemcitabine vs Oxaliplatin + irinotecan + leucovorin + 5-FU (FOLFIRINOX)	6.80 mo vs 11.10 mo	9.4% vs 31.6%
Von Hoff <i>et al</i> <sup>[43]</sup>	2013	Gemcitabine vs gemcitabine + nab-paclitaxel	6.70 mo vs 8.50 mo	7.0% vs 23.0%

OS: Overall survival; ORR: Overall response rate; 5-FU: 5-Fluorouraci.

**Table 2 Important clinical trials evaluating adjuvant chemotherapy in pancreatic ductal adenocarcinoma**

Ref.	Year published	Investigated drugs	Number of patients	Clinical outcome	
				Median survival (mo)	5-year survival (%)
Neoptolemos <i>et al</i> <sup>[19,52]</sup> (ESPAC 1)	2001 and 2004	5-FU/FA vs No chemotherapy	149/143	20.1/15.5	21.0/8.0
Oettle <i>et al</i> <sup>[53]</sup>	2007	Gemcitabine vs No chemotherapy	179/175	22.1/20.2	22.5/11.5
Neoptolemos <i>et al</i> <sup>[20]</sup> (ESPAC 3)	2010	Gemcitabine vs 5-FU/FA	539/551	23.6/23.0	17.5/15.9
Neoptolemos <i>et al</i> <sup>[20]</sup> (ESPAC 4)	2016	Gemcitabine vs Gemcitabine + Capecitabine	366/364	25.5/28.0	16.3/28.8
Uesaka <i>et al</i> <sup>[55]</sup>	2016	Gemcitabine vs S1	193/192	24.5/46.5	24.4/44.1

5-FU: 5-Fluorouraci; FA: Folinic acid; ESPAC: European Study Group for Pancreatic Cancer.

2013 gemcitabine plus nab-paclitaxel was also shown to stabilize metastatic disease<sup>[43]</sup>. This has opened new windows of opportunity for maintenance treatment in case of intolerable toxicity<sup>[44]</sup>, second line chemotherapy in cases of progression during first line treatment<sup>[45-47]</sup> and even third line chemotherapy, even though no evidence for this is available yet. Regimen of second line chemotherapy should be chosen related to first line<sup>[48]</sup>. Nanoliposomal irinotecan with 5-FU/folinic acid (FA) increased OS to median 6.2 mo in a recently published RCT on gemcitabine refractory metastatic PDAC<sup>[49]</sup>. The American Society of Clinical Oncology (ASCO) has recently published guidelines, incorporating this new insight, for treatment of patients with locally advanced<sup>[50]</sup> and metastatic<sup>[51]</sup> PDAC, recommending practical answers to key clinical questions for each patient group.

Adjuvant chemotherapy has been evaluated in numerous RCTs, published during the last 15 years, as illustrated in Table 2. The necessity of adjuvant treatment was first documented by Neoptolemos in the ESPAC 1 trial<sup>[19,52]</sup>, later verified by Oettle<sup>[53]</sup>. Median and 5 year survival have increased during the following decennium. In a western patient population, gemcitabine plus capecitabine is now standard of care, resulting in median 28 mo and close to 30% five year survival after upfront surgery<sup>[54]</sup>. A recent report from Japan<sup>[55]</sup>, suggests that even better outcome is achievable with adjuvant S1.

## SURGERY

The concept that upfront surgery is the best treatment option for patients with resectable tumors, is widely accepted<sup>[1,56-58]</sup>. Nationwide centralization of PD in

the Netherlands resulted in decreased postoperative in-hospital mortality from 9.8% in 2004 to 5.1% in 2009<sup>[59]</sup>, and the importance of volume-outcome relationship is increasingly emphasized<sup>[60]</sup>. The reorganization of care for patients with periampullary cancer, based on multidisciplinary management, is widely supported<sup>[48,61]</sup>, and it has resulted in significant change in surgical practice during recent years. Extended operations including vascular/multivisceral resections are now frequently performed, and borders of resectability are continuously being pushed<sup>[62]</sup>. The outcome value of multivisceral resections has been assessed<sup>[63]</sup>, criteria for clinical evaluations are defined<sup>[64]</sup> and the basis for perfected surgical practice is continuously improving. Better handling of surgical complications is an important element of this development and a reason for reduced failure to rescue in case of serious complications<sup>[65-67]</sup>. The improvement of outcome related to patient volume continues after 40 procedures/year at one hospital<sup>[68]</sup>. Nevertheless, postoperative complications is a major problem after pancreatic surgery, precluding adjuvant chemotherapy and thus decreasing OS<sup>[69,70]</sup>. The focus on improved surgical performance is therefore increasing, generating comprehensive evaluation of new technical details<sup>[71]</sup>.

Patients with borderline resectable PDAC was primarily described by Katz *et al*<sup>[72]</sup> as those with localized disease with tumor or patients characteristics precluding immediate surgery. After neoadjuvant chemotherapy, chemoradiation or both in 125 of these patients, 66 (41%) underwent pancreatic resections, 18 (27%) with vascular resection/reconstruction. Median postoperative survival was 40 mo. Subsequently, the borderline concept is defined in detail<sup>[73]</sup>. Management and treatment outcome in patients with borderline

resectable tumors is an area of intense scrutiny.

Neoadjuvant treatment, also in patients with resectable tumors, is widely accepted in the United States<sup>[74,75]</sup>, whereas upfront surgery is still considered standard of care in influential European centers<sup>[76]</sup>. Clinical and preclinical data support the concept that PDAC metastases appear early in the pathogenesis, even before the tumor can be identified<sup>[77]</sup>, favoring neoadjuvant chemotherapy. A meta-analysis focusing outcome in patients with resectable and unresectable tumors<sup>[78]</sup>, found that resection frequencies and survival after neoadjuvant therapy in resectable patients was similar to patients undergoing upfront surgery and adjuvant chemotherapy. In patients with unresectable tumors, approximately one third became resectable after restaging. In another meta-analysis of neoadjuvant chemotherapy in patients with borderline resectable PDAC, primary outcome measures were proportion of complete or partial response, stable or progressive disease as well as percentages of exploration and resection, and these results were also similar<sup>[79]</sup>. This evidence seems to support recommendation of neoadjuvant chemotherapy in borderline resectable PDAC, as resection rates and survival can be raised to the same level as patients with resectable tumors. A report from the National Cancer Data base on patients with PDAC stage I and II, who underwent PD between 2006 and 2012<sup>[80]</sup>, found increased rates of neoadjuvant treatment from 12.0% in 2006 to 20.2% in 2012. Patients who complete all intended neoadjuvant therapy, including surgery and adjuvant chemotherapy are by some authors supposed to experience increased OS, compared to patients undergoing upfront surgery<sup>[81]</sup>. However, evidence from well conducted RCTs is lacking, and the putative benefit of neoadjuvant treatment can be a by-product of selection bias, as patients with rapid disease progression never undergo surgery. Therefore, the real benefit or harm of neoadjuvant chemotherapy in patients with resectable PDAC still requires systematic evaluation. The International Study Group for Pancreatic Cancer recommendations is still upfront surgery for resectable and borderline resectable tumors<sup>[64,82,83]</sup>.

## DISTAL CHOLANGIOCARCINOMA, AMPULLARY AND DUODENAL ADENOCARCINOMA

Patients with periampullary adenocarcinomas undergo the same surgical resectional procedure as patients with PDAC, and postoperative survival is longer<sup>[84-88]</sup>. However, some data are contradictory: similar survival for patients with distal cholangiocarcinoma and PDAC was recently reported<sup>[89]</sup>, as well as comparable prognosis for ampullary and extra-ampullary duodenal carcinomas<sup>[90]</sup>. Even ampullary carcinoma with the same median postoperative survival as PDAC has been described from Denmark<sup>[91]</sup>. Routine histopathology from 207 PD specimens were recently re-evaluated

by two independent experienced pancreatic pathologists, and 53% of distal cholangiocarcinoma were misdiagnosed as PDAC<sup>[92]</sup>. A comprehensive assessment of tumor origin in pancreatic head cancer documented inaccurate and inconsistent distinctions between pancreatic, ampullary and distal bile duct cancer<sup>[6]</sup>. This divergence in pathology assessment may explain some of the contradictory data on prognosis in periampullary carcinomas. Ampullary carcinoma can be of pancreaticobiliary- or intestinal type, and the molecular signatures of mRNA and miRNA, linked to specific intracellular pathways, correlate to subtype above anatomical origin in periampullary tumors<sup>[9]</sup>. Histological subtype is a predictor of survival, and have also recently been found to influence response to adjuvant gemcitabine<sup>[93]</sup>.

## IS ADJUVANT CHEMOTHERAPY INDICATED FOR PERIAMPULLARY CARCINOMA?

A single center study from Johns Hopkins Hospital found that adjuvant chemoradiation did not improve survival<sup>[94]</sup>. The only well conducted RCT, investigating this question, is the ESPAC 3 trial, in which 297 patients with ampullary carcinoma, 96 with distal cholangiocarcinoma and 35 other carcinoma were randomized between 5-FU/FA, Gemcitabine or observation only. Median survival was 35.2 mo in the observation group vs 43.1 mo in the two chemotherapy groups, but the difference was not significant in the primary analysis. After multivariate analysis, adjusting for prognostic variables, statistically significant survival benefit was found after adjuvant chemotherapy<sup>[95]</sup>. The authors underline that distal cholangiocarcinoma should be analyzed separately, *i.e.*, not together with tumors with other sites of origin, as periampullary adenocarcinoma is not a separate tumor entity. As documented above<sup>[9]</sup>, site of tumor origin influence expected survival and pancreaticobiliary and intestinal subtypes respond differently to adjuvant gemcitabine<sup>[93]</sup>. Accordingly, the probable survival benefit from adjuvant chemotherapy, shown in the ESPAC 3 trial, should be further investigated by evaluation of combination chemotherapies in a modified study design.

## CONCLUSION

Lack of biomarkers, applicable as diagnostic tools and/or therapeutic targets has been a major hindrance for development of personalized treatment in patients with periampullary tumors. This is now rapidly changing<sup>[1,96]</sup>. A practical example is selection of patients for gemcitabine treatment guided by hENT1 expression<sup>[33]</sup>. Clinical implementation of new micromolecular markers is presently a major issue. Subsequently, treatment guidelines need revision. Surgical treatment of metastatic PDAC has been evaluated<sup>[97]</sup>, resulting in median

postoperative survival 13.8 mo, estimated one year survival 58.9%. In an earlier study of 40 patients with metastases from periampullary carcinoma undergoing curative intent surgery, median survival for the pancreaticobiliary subtype was 13 mo, intestinal 23 mo<sup>[98]</sup>. Metastatic disease is therefore conceived as a palliative condition, without clinical benefit from resectional surgery<sup>[58]</sup>. However, in a recent report from Milan<sup>[99]</sup>, 127 patients with metastatic PDAC were treated by the new chemotherapeutic regimens, and 11 patients with radiological and biochemical response (Ca19-9 normalization) underwent resection of the pancreatic primary tumor plus liver or lung metastases. Postoperative median survival was 39 mo vs 12 mo for the 116 patients without surgical resection. One year and three year survival were 100% vs 42% and 57% vs 5% respectively. The difference is obviously caused by better chemoresponse in the resected group, possibly also by additional benefit from resectional surgery. When new biomarkers enable personalized chemotherapeutic treatment and selection of patients for surgery based on improved knowledge about the malignancy potential of the tumor, cure seems achievable also for some patients with metastatic PDAC in the near future. Clarification of the role of surgery, related to chemotherapy is associated with severe methodological difficulties, as numerous patients deny inclusion in randomized trials, evaluating neoadjuvant chemotherapy. Low response rates of neoadjuvant and corresponding high risk of ending up with unresectable tumors are frequent patient concerns. These issues goes beyond the scope of this paper, but solid evidence, clarifying benefit/harm of neoadjuvant chemotherapy in pancreatic cancer will be major future scientific achievements.

A major problem for numerous patients with periampullary carcinoma is that they suffer severely during most of their residual lifetime, and palliative interventions, improving their quality of life, are important. Appropriate instruments for measuring patient reported outcome (PRO) has been lacking, but a brief, disease specific instrument has recently been developed, the PANcreatic Cancer DIsease (PACADI) score<sup>[100]</sup>. This is a brief, eight item, patient derived instrument, feasible also for patients with severe fatigue during late disease course. The future holds opportunities of well-designed interventional outcome-studies with survival and PRO as endpoints, increasing the rate of therapeutic intervention improvement.

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