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Treatment of localized pancreatic cancer

Towards innovative and personalized treatment strategies

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SUMMARY AND DISCUSSION

ENGLISH SUMMARY

This thesis addresses optimization of the interpretation and applicability of tumor markers such as carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) in various stages of localized pancreatic ductal adenocarcinoma (PDAC). Furthermore, this thesis explores the impact as well as the optimal applicability of intraoperative ultrasound (IOUS) and stereotactic ablative radiation therapy (SABR) in the treatment of localized PDAC. Overall, the results of this thesis contribute to new insights and better patient selection in the treatment of localized PDAC.

In **Chapter 2**, we assessed the impact of neoadjuvant therapy based on the baseline value of CA19-9 in 179 patients with primary resectable (PR) and borderline resectable (BR) PDAC from two randomized controlled trials. Herein, patients were randomized between neoadjuvant chemoradiotherapy (CRT) and upfront surgery. The neoadjuvant CRT group had a better overall survival (OS) compared to the upfront surgery group: 20.9 versus 15.6 months (p=0.019). Patients with a CA19-9 level <500 U/ml had a better overall survival (OS) following neoadjuvant CRT compared to upfront surgery, whereas among patients with CA19-9 >500 U/ml this difference was not significant, probably due to lack of statistical power in this group. Strikingly, despite lower overall resection rates among patients who received CRT, this group had better survival outcomes when analyzed by intention to treat. Contrary to what is advised by international recommendations, these findings suggest that the decision regarding neoadjuvant CRT in PR- and BR-PDAC should not be dependent on the level of baseline CA19-9.

In **Chapter 3** we aimed to define the optimal response of serum CA19-9 to induction chemotherapy in 212 patients with locally advanced PDAC (LAPC) and identify independent prognostic factors for survival in this patient category. A decline of ≥40% was associated with a median OS benefit (19.6 vs. 12.7 months, p=0.03). Among patients with elevated CA19-9 at baseline, a decline of ≥60% was the optimal cut-off and associated with prolonged median OS compared to <60% decline or an increase of CA19-9 (21.7 vs. 14.0 vs. 12.6 months, p<0.001). These cut offs may be helpful when assessing treatment response and enhance appropriate patient selection for specific treatment strategies. Other independent factors that were associated with prolonged OS were longer duration of chemotherapy, treatment with stereotactic ablative radiation therapy (SABR), and a surgical resection.

In **Chapter 4**, we investigated whether serum CEA could function as an alternative marker for response evaluation following treatment with (m)FOLFIRINOX in patients with localized PDAC but non-elevated CA19-9 levels. Among 277 patients with localized PDAC from 5 referral centers with non-elevated CA19-9, 33% had elevated levels of CEA (above 5 ng/ml) prior to induction chemotherapy (baseline). Compared to normal CEA values, we found that both elevated CEA at baseline as well as elevated CEA at restaging showed significant worse OS, 21 vs. 24 months and 20 vs. 29 months respectively. Also, both elevated CEA at baseline and at restaging had a higher proportion of patients with radiologically based metastases and lower proportion of patient that received a surgical resection. Among other potential predictors for survival, only elevated baseline CEA was independently associated with a poor OS. Normalization of CEA at time of restaging showed a survival difference of 14 months (p=0.088), but investigation in a larger cohort is necessary confirm an association.

Chapter 5 describes the outcomes of the ULTRAPANC study, which investigated the impact of intra-operative ultrasonography (IOUS) during surgical exploration in 85 patients with any extent of vascular involvement on preoperative imaging. All patients underwent an assessment with IOUS at the start of the surgical exploration via laparotomy. Based on IOUS, the resectability status changed in 38% of patients (32/85), of which 94% (n=30) were downstaged, predominantly from BR-PDAC to PR-PDAC (69%, n=22). Downstaging was mainly based on the absence of arterial involvement on IOUS images compared to preoperative imaging. Among 71% (20/28) of the patients with presumptive SMA involvement on preoperative imaging, no SMA involvement was determined with IOUS. Among these patients, 75% (n=15) had a surgical resection, all with a radical (i.e. R0) SMA resection margin upon pathological analysis. Furthermore, IOUS showed ≤180° PV/SMV involvement in 50% of patients with presumed >180° PV/VMS involvement prior to surgery. Considering our results and the fact that surgical explorations for localized PDAC will be increasingly performed, IOUS has the potential to increase the accuracy of determination of the local resectability status and may guide and speed up the surgical exploration.

To enhance patient selection for SABR in LAPC, **Chapter 6** describes the search for potential predictive factors for OS in 74 prospectively included patients with unresectable localized PDAC, treated with palliative chemotherapy followed by treatment with SABR. SABR was delivered in 5 fractions of 8 Gy within two weeks using magnetic resonance guided radiotherapy. Median OS in the entire cohort from start of SABR was 12.1 months, and 19.6 months from pathologically confirmed diagnosis, and at one-year the local control rate was 90%. Grade 3 toxicity occurred in 2.7% (n=3) of patients, consisting of grade 3 fatigue (n=1) or gastro-intestinal complications (n=2). Among patients with pain prior to SABR, 83.3% (n=30/36) had either disappearance or relief of pain allowing reduction of pain medication. We identified that a Karnofsky Performance Score (KPS) ≥90, age <70, and absence of pain prior to treatment, were independently associated with better OS. We identified an unfavorable subgroup (n=31) with 0-1 favorable factors, and a favorable subgroup (n=43) with 2-3 favorable factors. From start of SABR, median OS for

the unfavorable subgroup was 6.6 months versus 17.3 months in the favorable subgroup, p<0.001. This median OS difference of almost one year addresses the need for definite clinical parameters to select patients for the appropriate treatment and dose delivery.

Chapter 7 describes a systematic review including eight studies with 317 patients, that investigated SABR as single therapy in patients with primary localized PDAC whom would otherwise be treated with best supportive care. We sought to find out if SABR has an acceptable toxicity profile and can improve survival outcomes in this frail population. Studies were included if at least 75% of the included patients were treated with SABR as the only treatment modality. Among all patients, median OS ranged from 6.4 to 19.0 months. Three studies that explicitly tracked the survival of patients who received SABR described a median OS of 6.4, 8.6 and 14.0 months. As far as described by the included studies, the acute radiation induced toxicity was grade ≤2 in 74 patients. Late grade ≤2 was reported in 18 patients and late grade ≥3 in 5 patients. Unfortunately, the included studies applied a wide variety of SABR schemes for heterogeneous indications, retaining an appropriate conclusion regarding our research question. However, considering the promising low toxicity rates, and the current advances in the accuracy of imaging modalities as well as the introduction of adaptive planning during the delivery of SABR, proper investigation of its feasibility as a single treatment modality in localized PDAC is warranted.

Following the findings in chapter 7, **Chapter 8** describes the protocol of the ongoing PANCOSAR study, a multicenter randomized trial. The PANCOSAR trial investigates the impact on OS of SABR in patients with localized PDAC that would otherwise be treated with best supportive care, either due to patient's choice, or based on medical reasons. The primary outcome is survival at six months, for which is hypothesized that 50% of patients treated with SABR will be alive at versus 20% of patients treated with best supportive care. Additionally, the PANCOSAR trial will also assess whether SABR can postpone cancer related symptoms and improve (or preserve) quality of life in this frail patient population with a short life expectancy. In total 98 patients will be included and stratified according to their indication to receive best supportive care . SABR will be delivered in five fractions of 8Gy within two weeks and follow up will predominantly consist of consultation by phone. The PANCOSAR study is conducted according to a Trial within Cohorts (TwiCs) design in the PACAP cohort from the Dutch Pancreatic Cancer Group. A TwiCs design has several advantages that is believed to be specifically beneficial for the intended research question and study population of the PANCOSAR trial.

SUMMARY OF RESEARCH QUESTIONS AND MAIN FINDINGS

Chapter	
Chapter 2	*What is the impact of baseline serum CA19-9 levels on the outcome of neoadjuvant chemoradiotherapy in patients with PR-PDAC and BR-PDAC?* Baseline CA19-9 doesn't seem to impact the outcome of neoadjuvant chemoradiotherapy in patients with PR-PDAC and BR-PDAC. Strikingly, patients with baseline CA19-9 below 500 U/ml showed significantly improved survival when treated with neoadjuvant chemoradiation compared to upfront surgery.
Chapter 3	*What are the minimum clinically relevant cut-offs of early CA19-9 response following induction therapy in patients with LAPC?* Following induction chemotherapy, a decrease of ≥40% in CA19-9 is the minimum clinically relevant cut-off associated with improved overall survival in patients with LAPC. A decrease >60% is optimal and was identified as independent predictor for survival.
Chapter 4	*In case of non-elevated baseline CA19-9 in localized PDAC, can serum CEA function as an alternative tumor marker to evaluate disease response after neoadjuvant treatment and predict survival?* CEA has the potential to function as an alternative tumor marker in case of non-elevated CA19-9 at baseline. Both CEA at baseline and at time of response evaluation were associated with worse overall survival, lower resection rates and higher proportions of patients that had radiologically based metastatic disease. Among a small group of patients, normalization of CEA at restaging showed a survival benefit of 14 months compared to no normalization. Elevated CEA at baseline was the only independent predictor for survival.
Chapter 5	*What is the clinical impact of intraoperative ultrasound during pancreatic surgery following neoadjuvant treatment regarding the assessment of vascular involvement and resectability status?* Intraoperative ultrasound can increase the accuracy of determining vascular involvement during a surgical exploration, and change the resectability status in a third of patients during surgical exploration, mainly based on a decrease or disappearance of arterial involvement or a clinically relevant decrease of venous involvement.

Chapter 6 *Which clinical parameters can optimize patient selection for SABR following chemotherapy in patients with unresectable localized PDAC?*

A significant favorable profile for stereotactic ablative radiation therapy exists in case of a combination of at least two of the following parameters: A performance score ≥ 90, age <70 and absence of pain prior to SABR.

Chapter 7 *What current knowledge is available regarding toxicity and survival benefit when stereotactic ablative radiation therapy is administered as single therapy in localized PDAC?*

SABR as a single therapy in patients with localized PDAC has been scarcely investigated, predominantly using less advanced radiation modalities and delivery of lower treatment doses compared to current practice. The promising survival outcomes and local control rates, in combination with an acceptable toxicity profile warrant further investigation regarding this research question using pragmatic randomized trials

Chapter 8 *How to study whether SABR is of clinical benefit in patients with localized PDAC who are unfit for chemotherapy and surgery?*

A trial-within-cohorts approach can be used to assess the impact of SABR in patients with localized PDAC who are unfit for chemotherapy and surgery. Considering the frail study population, improvement or preservation of quality of life are considered as important as survival outcomes. The study is embedded in a nationwide cohort that validly objectifies outcomes on quality of life.

DISCUSSION AND FUTURE PERSPECTIVES

Localized pancreatic ductal adenocarcinoma (PDAC) is diagnosed in a heterogeneous population in a relatively low incidence, i.e. 1500 patients per year in the Netherlands, and presents itself in different stages: primary resectable, borderline resectable, and locally advanced PDAC (respectively PR-PDAC, BR-PAC and LAPC).1 As a result, there are substantial differences between these stages of localized PDAC that warrant different treatment strategies. Currently, both systemic and local treatment, or a combination of both, are included in the management of localized PDAC. However, selecting appropriate candidates per treatment regime represents an ongoing challenge. This thesis aims to contribute to the optimization of patient selection for both systemic or local treatment strategies in different stages of localized PDAC by improving the interpretation and convenience of different clinical parameters and implementation of new treatment techniques. This chapter addresses the interpretation and clinical implications of our findings, as well as the orientation for future research.

New insights in the treatment of localized pancreatic cancer

To date, CA19-9 is the best validated tumor marker for the surveillance in all stages of pancreatic ductal adenocarcinoma (PDAC)[2], and is associated with survival in PR- and BR-PDAC.[3,4] Hence, in PR-PDAC neoadjuvant treatment is recommended in case of elevated CA19-9, despite international guidelines not recommending neoadjuvant therapy in PR-PDAC.[2,5] Contrary, in BR-PDAC neoadjuvant therapy is recommended regardless the level of serum CA 19-9.

Two randomized controlled trials (RCTs), the multicenter PREOPANC trial from the Netherlands and a Korean trial, demonstrated a significant improved overall survival following neoadjuvant chemoradiation therapy (CRT) compared to upfront resection in patients with PR- and BR-PDAC .[6,7] Strikingly, **Chapter 2** demonstrated that specifically patients with a CA19-9 level below 500 U/ml had a better OS following neoadjuvant CRT compared to upfront surgery, whereas in patients with CA19-9 above 500 U/ml this difference was not significant. These findings suggest that selection for neoadjuvant CRT in PR- and BR-PDAC should not be based on the level of baseline CA19-9, contrary to the recommendation of international guidelines.

Possibly, patients with PR-PDAC will also benefit from a neoadjuvant approach rather than an adjuvant approach, especially considering that adjuvant administration of chemotherapy is often (30-50%) hampered due to post-operative complications as a result of which these patients receive no effective dose of systemic therapy.[8] Furthermore, despite a lower resection rate in the neoadjuvant CRT group in patients with CA19-9 above 500 U/ml, OS was better in this group. Similarly, the ESPAC5 trial describes a significantly better 1-year overall, and disease-free

survival after administration of a short course of neoadjuvant therapy, despite higher resection rates in the upfront surgery group.[9] Also, long term outcomes following the PREOPANC-1 trial demonstrate a consistent survival benefit in the CRT group compared to upfront surgery despite resectability status or clinical subgroup.[10] Potentially, neoadjuvant CRT can avoid futile surgery and increase the proportion of R0-resection. However it remains unknown if the delay to surgery following neoadjuvant treatment, withholds patients from the opportunity to undergo a radical surgical resection. Hence selection of patients prior to treatment is key as well as optimization of the required neoadjuvant regime for an individual.

A recent meta-analysis in 1279 patients with PR- and BR-PCDAC found that multi-agent chemotherapy with (m)FOLFIRINOX (i.e. a combination of [modified] 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) or abraxane/gemcitabine based chemotherapy, show superior survival outcomes compared to other chemotherapeutic regimens in PR- and BR-PDAC .[11] Unfortunately, in **Chapter 2**, neoadjuvant CRT was gemcitabine-based whereas administration of (m)FOLFIRINOX may have been a more adequate treatment in some cases.[12] The findings of the PREOPANC-2 trial will soon give more insight whether there is a survival difference between (m)FOLFIRINOX or gemcitabine based CRT, when administered in patients with PR- and BR-PDAC with a good performance score.[13] Nonetheless the latter studies give more insight on the appropriate systemic neoadjuvant regimens, appropriate patient selection remains unknown. To further investigate the assumption that selection of patients for neoadjuvant treatment should not be based on (markedly elevated) CA19-9 at baseline, future extensive research is required, also including patients that received (m)FOLFIRINOX. Perhaps, future research may also highlight alternative factors such as differentiation of subtype-specific biology prior to treatment[14] or advances in artificial intelligence (AI) identifying patterns on pre-treatment imaging or pathological specimen slice, or certain biomarkers in the blood for optimization of patient selection and prediction of treatment response.

In patients with LAPC, international guidelines recommend to start with induction chemotherapy.[2,5] Rather than treatment selection prior to treatment, guidelines remain indifferent about adequate response evaluation and subsequent treatment selection for patients with LAPC. Guidelines state that a significant decrease in CA19-9 following induction therapy is an important parameter to consider to proceed to surgery. However, specification on optimal CA19-9 response in patients with LAPC treated with induction therapy remains unkown.[15,16] **Chapter 3** demonstrated that among patients with LAPC and elevated CA19-9 at baseline (i.e. above 37 U/ml), a decrease of more than 60% was the most impactful cut-off with regard to OS and a decrease of more than 40% was the minimal clinically relevant cut-off. Furthermore, normalization was associated with prolonged OS, and an increase of CA19-9

was associated with worse OS compared to any decrease. Similar to our findings, other series also describe the impact of 50% decrease and the importance of normalization of CA19-9 in localized PDAC, however these outcomes were among patients with PR-PDAC and BR-PDAC and also in patients after a surgical resection.[17-20]

Additionally, we found higher resection rates among patients with any decrease in CA19-9 compared to patients with any increase in CA19-9 at time of response evaluation, although no interaction between resection and relative decrease in CA19-9 was identified. Given that a surgical resection remains a very important predictor for survival, and normalization of CA19-9 is not always not often observed or obtainable, our findings may contribute to clinical decision making as well as for clinical consultation with respect to prognostic expectations. Yet, more has to be investigated regarding the best treatment option following the response to induction therapy in LAPC, i.e. local ablative treatment options, surgical approaches, continuation or switch in chemotherapeutic regimes or best supportive care. Despite the findings in **Chapter 3**, it remains important to consider the response of CA19-9 together with other clinical parameters for adequate clinical decision making.[21] Likewise, **Chapter 6** found that clinical parameters like performance score, age, and absence of pain were independently associated with better OS, especially when combined, in patients with LAPC treatment with both chemotherapy and stereotactic ablative body radiation therapy (SABR). Unfortunately, in **Chapter 6** we were not able to analyze the impact of CA19-9 due to a high proportion of invalid CA19-9 values. It would be interesting to investigate whether incorporation of the identified parameters in **Chapters 3** and **6** could be incorporated in the selection of patients with LAPC for local treatments following induction therapy.

Although CA19-9 is currently the only recommended biomarker included for clinical decision making in PDAC, it has several limitations hampering its interpretation and applicability. First, Ca19-9 may be falsely elevated due to cholestasis, and second, CA19-9 is not secreted at all by 5-10% of the population due to a negative phenotype (non-secretors).[22,23] Together with non-secretors, approximately one-third of patients with PDAC do not have elevated CA19-9 values (i.e., below 37 U/ml) at time of diagnosis, making response evaluation using CA19-9 unreliable or even impossible.[24] Among patients with non-elevated CA19-9 at baseline, the value of serum carcinoembryonic antigen (CEA) at baseline as well as at time of restaging, as well as its dynamics following treatment with (m)FOLFIRINOX could potentially function as an alternative marker (**Chapter 4**). We found that patients with elevated CEA levels (i.e., >5 ng/ml) had higher rates of radiologically based distant metastasis, lower resection rates and had a shorter median OS compared to patients with non-elevated CEA levels (i.e., below 5 ng/ml). Elevated baseline CEA remained independently associated with worse overall survival, like in earlier series with

other therapeutic regimens.[25] Intriguingly, normalization of CEA at restaging showed a beneficial difference in median OS of 14 months compared to the absence of normalization at restaging, which did not reach statistical significance due to small sample sizes. Either normalization of serum CEA will always appear in a small proportion of patients and is therefore not a competent parameter, or by increasing the power in larger series with consequent assessment of CEA, this parameter has the potential to be clinically relevant.

The findings in aforementioned chapters enhance the interpretation and applicability of common tumor markers in the management of localized PDAC, where guidelines remain ambiguous. However, they also indicate the urge for future larger prospective studies to validate these findings as well as the need for additional new (combinations of) parameters to decide for neoadjuvant treatment and evaluate response evaluation. Metabolic response to neoadjuvant therapy on FDG PET-CT (fluoro-2-deoxy-D-glucose positron emission tomography-CT) , is described as a strong predictor for pathologic response as well as for survival.[26,27] Also, AI will increasingly become an asset to improve determination of treatment response i.e. more accurate and quicker analysis of response evaluation on cross-sectional imaging. Future steps are required for it to be safely integrated, i.e. development of high-quality data sets and external validation.[28,29] Both AI and metabolic response may be incorporated in future response evaluation following induction therapy, though emphasize the importance of a multidisciplinary and multi-institutional approach to adequately optimize future response evaluation. The ongoing nationwide non-randomized PREOPANC-4 trial (NCT05524090) aims to implement best clinical practice for patients with LAPC by, among other things, incorporating decision making within international multidisciplinary expert panels at the point of restaging following induction therapy.[30] Apart from surgical and survival outcomes, the PREOPANC-4 also aims to elucidate quality of life and healthcare satisfaction of patients with LAPC. These outcomes will be most interestingly for future clinical (shared) decision making in the management of LAPC.

Overall, by increasing the accuracy of response evaluation, the question arises whether patients should be withheld from invasive/aggressive treatment when unfavorable predictors or prognostic factors occur. Possibly no treatment or a less aggressive approach may be more adequate in some individuals to preserve quality of life and should be addressed in future research. Obviously, this concerns a challenging research question, though novel trial designs like a Trial within Cohorts (TwiCs) design or a patient-preference design may be helpful to fulfill these questions.[31,32] Accordingly, **Chapter 8** describes the applicability of a TwiC design to compare SABR with best supportive care in patients localized PDAC.

New treatment approaches in localized PDAC

Anatomical treatment response after induction therapy is currently based on CT and MRI modalities, which have limited ability to distinguish vital tumor tissue from inflammatory and fibrotic tissue (caused by the induction therapy).[33,34] Considering these limitations, some evidence is arising on the accuracy and effectiveness of intraoperative ultrasound (IOUS), however large prospective series were lacking.[35-38] The findings of the ULTRAPANC study described in **Chapter 5**, provide additional evidence that IOUS may be a helpful modality during surgical exploration with regard to the examination of local vascular involvement, i.e. in addition to the detection of distant metastases in earlier studies. In this study, the resectability status was downstaged in one-third of patients based on IOUS images. In patients with preoperatively involvement of the superior mesenteric artery (SMA), two-third had no involvement of the SMA upon examination with IOUS. Among these patients, 75% underwent a resection and all had negative resection margins upon pathologic examination. Given that resectability is predominantly based on arterial involvement, IOUS may guide the surgical team to determine resectability during surgical exploration. Regarding venous contact, IOUS showed a decrease in involvement of the superior mesenteric vein (SMV) in half of patients with more than 180 degrees involvement on preoperative imaging. This could potentially be helpful to select for the required/appropriate venous resection during a surgical exploration.

The increasing incidence of PDAC and new insights regarding induction therapy, have increased the number surgical explorations (and resections).[39] IOUS is a convenient, non-invasive tool that may speed up and improve the current surgical exploration. These findings are one step towards its implementation, however, validation with respect to its pathological one-to-one correlation and objectification of its ability to change surgical strategies is yet to be investigated by the subsequent ULTRAPANC-II study.

SABR is a promising and emerging local non-invasive treatment modality within in the management of localized PDAC but needs further investigation in all stages of localized PDAC. Considering the increasing implementation and advances of magnetic resonance guided SABR (hereafter MRgRT), it is possible with the use of daily adaptive planning to escalate the total dose in the tumor, while sparing the surrounding radiosensitive organs. As a result, MRgRT has minimal radiation induced toxicity allowing it to be feasible in more patients with localized PDAC in order to increase local control and hopefully overall survival. In patients with LAPC that remain locally unresectable after induction therapy, a dose of 40Gy within 5 fractions can be considered safe, has the ability to is decrease cancer related symptoms and has satisfactorily local control rates an OS outcomes as described in **Chapter 6** and previous studies [40-43]. Quick resumption of chemotherapy following SABR is convenient, future research is challenged to

investigate further dose escalation and optimal combination with systemic treatment regimen and its timing, perhaps depending on patients' preference or expected chemotherapy induced toxicity.

The significant survival differences between groups with favorable and unfavorable clinical parameters prior to SABR described in **Chapter 6** warrant further investigation regarding treatment doses as well as patient selection for SABR. As mentioned before, by increasing the accuracy of prognostic or predictive profiles, the question derives if some patients should be treated differently/less aggressive in case of an unfavorable clinical profile. However, the past and continuous advances in MRgRT resulted in acceptable toxicity rates and may even allow safe delivery of high radiation doses in frail patients with localized PDAC for whom chemotherapy or surgery is not possible.[44,45] Though this specific application of SABR has only been investigated in small retrospective studies(**Chapter 7**), hence this thesis describes the protocol of the pending PANCOSAR trial (**Chapter 8**) to gain randomized evidence to apply SABR monotherapy in frail patients with localized PDAC. Similarly, the ARCADE trial is investigating whether SABR is beneficial in the treatment of non-metastasized recurrent pancreatic cancer with or without concurrent/subsequent systemic chemotherapy.[46]

Proceeding towards personalized treatment strategies

Despite extensive clinical research to improve patient selection and treatment strategies in PDAC, great advances to enhance patient selection and predict treatment response may lie within other undiscovered disciplines than the scope of today's known parameters i.e. genome sequencing and machine learning/AI. Until then, improving our understanding and validation of known and new parameters is warranted to create patient profiles to predict treatment and survival outcomes in individuals. Moreover, only by increasing the availability of reliable evidence, adequate shared decision making is possible.[47] As our understanding of PDAC improves, there is growing recognition that a one-size-fits-all approach to treatment is not optimal. Instead, individualized treatment strategies that take into account a patient's specific (tumor) characteristics, genetic profile, overall health status and patient's preference may be more effective. In the future, hopefully personalized medicine may lead to better outcomes and improved quality of life for patients suffering from this unfortunate, devastating disease.

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