



Treatment of pancreatic cancer—neoadjuvant treatment in resectable pancreatic cancer (PDAC)

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers. Curative-intended resection and adjuvant chemotherapy represents the current standard of care. Despite substantial improvements in surgical treatment and intensified adjuvant treatment with more powerful regimens over the last years even clearly resectable pancreatic cancer still has an unfavorable prognosis with a high risk of relapse. Neoadjuvant or perioperative multimodal therapies have substantially improved the outcome of other resectable gastrointestinal (GI) cancers such as esophagus and gastric cancer. It is reasonable to assume that efficient chemotherapy and or radiochemotherapy may have a similar impact on the outcome of resectable PDAC. This review is focused on neoadjuvant and perioperative treatment of resectable PDAC (no borderline resectable or locally advanced PDAC), summarizes the pros and cons for neoadjuvant treatment in the context of the current literature, and also provides an overview over the landscape of ongoing clinical trials in this up-and-coming field of PDAC therapy.

Keywords: Pancreatic ductal adenocarcinoma (PDAC); resectable PDAC; neoadjuvant therapy; perioperative therapy

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Pancreatic cancer—even if deemed resectable—has still a dismal prognosis. Surgical treatment of pancreatic ductal adenocarcinoma (PDAC) has substantially improved over the last years and perioperative morbidity and mortality is at an all-time low particularly in high volume centers. It appears therefore unlikely that further improvements in surgical treatment will substantially improve the outcome of patients with PDAC. Multimodal therapies, in particular neoadjuvant chemotherapy and radiochemotherapy, have substantially improved the outcome of other resectable gastrointestinal (GI) cancers such as esophagus and gastric cancer. It is reasonable to assume that efficient chemotherapy and or radiochemotherapy may have a similar impact on the outcome of resectable PDAC. It is important to note that the focus of this paper is on a truly

neoadjuvant approach, i.e., neoadjuvant and perioperative treatment of resectable PDAC. We will not consider downsizing strategies to improve R0 resectability in borderline resectable PDAC or induction treatments to enable resectability of locally advanced PDAC.

Adjuvant treatment—the standard of care

Neoadjuvant treatment of PDAC is at present still experimental. The current standard of care is upfront resection and adjuvant chemotherapy either with Gemcitabine or with a combination chemotherapy. Recently, a modified FOLFIRINOX (mFOLFIRINOX) protocol has demonstrated tremendous efficacy in the adjuvant setting compared to Gemcitabine alone with

a median disease-free survival (mDFS) of 21.6 months compared to 12.8 months and a 3-year DFS rate of 39.7% compared to 21.4% with Gemcitabine alone. The mFOLFIRINOX protocol was superior to Gemcitabine in virtually all subgroups analyzed including patients with T3/4 tumors, N+ tumors, R1 resection and poorly or undifferentiated tumors. The inclusion criteria for the trial were rather strict (ECOG 0-1, no R2 resections, no CA 19-9 >180 U/mL post-surgery, no uncontrolled diarrhea post-surgery and no bowel obstruction). The median age of 63 years in the trial suggests that the majority of patients included were younger than the average population of patients with PDAC (1). It is also important to note that only about 60% of the patients with PDAC receive adjuvant treatment in the real world due to perioperative morbidity even if one extends the start of adjuvant treatment up to 3 months postoperatively (2).

Neoadjuvant treatment—the pros and cons

There are several arguments in favour of neoadjuvant treatment. First of all, efficient downsizing of the tumor could result in a substantial increase in the proportion of R0 resections which we know is prognostic (3,4). There are also data suggesting that neoadjuvant chemotherapy may be more efficient than adjuvant treatment due to a preserved anatomy and vasculature and due to a higher dose intensity in the neoadjuvant setting (5). There is also the systemic effect of neoadjuvant chemotherapy that has to be considered. There are data suggesting that the majority of PDACs is likely to exhibit micrometastases even when only a small primary tumor is detectable by clinical imaging leading to early relapse and death after surgery in the majority of cases (6). Efficient chemotherapy could treat these micrometastases and prevent early relapse post-surgery. From a patient's point of view, it can be considered that neoadjuvant treatment for a defined short period is in general better tolerated than the same treatment after extensive surgery. Neoadjuvant treatment also provides a “window of opportunity” to get to know the biology of a respective tumor. There will be tumors (about 20%) progressing during neoadjuvant treatment and even become unresectable (3,4). However, it is fair to say that it is unlikely that a patient with a tumor progressing rapidly under efficient chemotherapy in a short timeframe of 2–3 months would have been cured by upfront surgery, in particular since in many cases progress is not due to progress of the primary tumor, but due to the occurrence of

distant metastases, e.g., in the liver. Nevertheless, this topic needs to be addressed in randomized trials.

According to the current guidelines, surgery of PDAC can be performed without prior histological confirmation (7). However, when neoadjuvant treatment is planned a definitive histological or at least cytological diagnosis of PDAC is required before starting chemotherapy. Alas in up to 25% of cases there is not sufficient material obtainable even by repeated EUS-guided FNA to obtain such a diagnosis and surgery gets delayed without neoadjuvant treatment being started (8). Alternative means such as analyzing mutant KRAS [detectable in about 95% of PDACs (tissue based)] in liquid biopsies have so far not shown sufficient sensitivity and specificity in patients with resectable PDAC to substitute tissue analysis. The KRAS mutation rate in plasma/serum was only about 31% compared to 82% in the tumor tissue (9). A way forward may be the use of composite liquid markers. Recently we could show that a combination of circulating free DNA quantification, thrombospondin and CA 19-9 exhibits a c-statistics of 0.9 even for stage I PDAC compared to 0.69 for CA 19-9 alone (10).

Finally, neoadjuvant treatment may improve the outcome, but this has to be weighed against the toxicity of the treatment affecting potentially perioperative morbidity and even mortality. This is particularly important when more aggressive chemotherapy protocols are used.

Neoadjuvant treatment—the data

As stated above neoadjuvant treatment of resectable PDAC is still experimental and there are as yet few data from prospective, randomized, controlled trials. Due to a rather generous use of the term “neoadjuvant treatment” for resectable, but also for borderline resectable and locally advanced tumors in the literature it is sometimes difficult to extract data exclusively for the resectable situation.

Older systematic reviews and meta-analyses found an only marginal efficacy of a neoadjuvant treatment for resectable tumors. Using the chemotherapy protocols available at that time resection rates and survival data of neoadjuvant treatment were comparable with those from upfront surgery plus adjuvant treatment (3,4,11).

However, we know that the efficacy of the neoadjuvant treatment—as determined by pathological tumor response—is paramount for improving survival (12). With the more recent combination chemotherapy protocols such as FOLFIRINOX and Gemcitabine plus nab-Paclitaxel we have more efficient tools in our hands.

A systematic review employed a Markov decision analysis to compare the life expectancy and quality-adjusted life expectancy of neoadjuvant treatment or upfront surgery in resectable PDAC. The authors searched the literature between 2000 and 2015. Twenty-two out of 786 studies fulfilled the criteria. Neoadjuvant treatment resulted in a higher life expectancy (32.2 *vs.* 26.7 months) as well as a higher quality adjusted life expectancy (25.5 *vs.* 20.8 months) (13).

A more recent propensity scores matched analysis included 14,941 patients in the analysis. A 3:1 matching by propensity was performed and finally 6,016 patients with upfront resection and 2005 patients with neoadjuvant treatment plus resection were examined. The authors state that neoadjuvant treatment has a significant beneficial effect on T stage, lymph nodes and resection margins. Neoadjuvant treatment improved overall survival (OS) compared to both, upfront surgery alone (HR =0.73; 95% CI: 0.68–0.76) or surgery plus adjuvant treatment (HR =0.83; 95% CI: 0.78–0.89). Neoadjuvant treatment was an independent predictor of lower mortality in the matched data set with an adjusted HR of 0.74 compared to upfront resection (95% CI: 0.69–0.79) (14).

Apart from these retrospective evaluations the first prospective trials examining neoadjuvant treatment in resectable PDAC are available. A Dutch trial compared upfront surgery plus adjuvant Gemcitabine treatment for 6 cycles with neoadjuvant radiochemotherapy consisting of preoperative Gemcitabine treatment and Gemcitabine-based radiochemotherapy as well as 4 cycles of postoperative Gemcitabine in 246 patients. Primary endpoint of the trial was OS in the ITT group (15). Interestingly, resection rate in the neoadjuvant treatment arm was only 62%. However, the resection rate in the arm receiving upfront surgery was also only 72% suggesting that in a substantial number of patients CT staging missed small metastases that prevented resection. Interestingly, the R0 resection rate was significantly higher ($P<0.001$) in the neoadjuvant (NA) arm with 63% compared to only 31% in the arm with upfront surgery (US). Serious adverse events were comparable in both arms (39% US, 46% NA; $P=0.28$). The trial missed its primary endpoint with a mOS in the UR group of 13.7 months compared to 17.1 months in the NA group (HR =0.74; $P=0.074$). However, when only patients were analyzed that underwent resection there was a significant benefit for the NA arm with a mOS of 29.9 months compared to 16.8 months in the UR group ($P=0.001$). There was also a significant improvement in the DFS in the

NA group. This study shows that neoadjuvant treatment can improve the outcome of patients with resectable PDAC in a prospective setting. However, the protocol used may not be optimal in this setting.

Another phase II/III trial from Japan that has just been presented compared upfront surgery plus adjuvant treatment with S1 with a neoadjuvant treatment with the combination of Gemcitabine plus S1 followed by surgery and adjuvant treatment with S1 (16). There were 180 patients in each arm and the primary endpoint was overall survival for the phase III part and resection rate for the phase II part. In the phase II part of the trial resection rate in the NA arm was 93% compared to 82% in the UR arm. Since the phase II part met its preplanned criteria, the phase III part was initiated. In this part of the trial neoadjuvant treatment showed a significantly better mOS compared to adjuvant treatment: 36.72 *vs.* 26.65 months (HR =0.72; 95% CI: 0.55–0.94; $P=0.015$). Also, the 2-year OS rate was improved by neoadjuvant treatment with 63.7% *vs.* 52.5%. The majority of the subgroups in the Forest Plot analysis benefitted from neoadjuvant treatment. Importantly, neoadjuvant Gemcitabine plus S1 did not affect operation time or operative morbidity (NA: 45.9%; UR: 49.7%). pN1 was also significantly lower in the NA arm compared to the UR arm (59.6% *vs.* 81.5%). Most frequently observed grade 3 or 4 adverse events were leukopenia and neutropenia in 72.8% of cases. However, these side effects did not increase perioperative mortality. Again, these data point to substantial benefit of neoadjuvant chemotherapy in patients with resectable PDAC compared to upfront resection and adjuvant treatment. The limitation of this study is that the trial only recruited Asian patients and there are so far no data on the efficacy of S1 in Caucasian patients with resectable pancreatic cancer.

Neoadjuvant treatment of resectable pancreatic cancer—standard or study?

Given the fact that we have systematic reviews and two prospective trials that show a benefit for neoadjuvant treatment of resectable PDAC one could argue that there is sufficient evidence to implement this strategy in the clinical algorithm.

However, there are still open questions that need to be addressed: What is the best neoadjuvant treatment regimen? FOLFIRINOX, modified FOLFIRINOX, Gemcitabine plus nab-Paclitaxel or other regimens, even radiochemotherapy? How much neoadjuvant treatment shall be given? 2, 3,

Table 1 Neoadjuvant/perioperative trials in progress (>phase I) for resectable pancreatic adenocarcinoma (www.clinicaltrials.gov)

No	Trial	rPDAC	brPDAC	n	Phase	NCT number
Neoadjuvant/perioperative chemotherapy						
1	<i>CISPD-1</i> : sequential use of Gem/nab-P and mFOLFIRINOX as neoadjuvant CTX	+	-	416	II	NCT03750669
2	<i>NEONAX</i> : neoadjuvant plus adjuvant or only adjuvant Gem/nab-P (17)	+	-	166	II	NCT02047513
3	Pre-operative Gem/nab-P + hydroxychloroquine +/- avelumab	+	-	120	II	NCT03344172
4	<i>SWOG 1505</i> : perioperative mFOLFIRINOX vs. Gem/nab-P	+	-	112	II	NCT02562716
5	Neoadjuvant/adjuvant GVAX pancreas vaccine (with CY) +/- nivolumab and urelumab	+	-	75	I/II	NCT02451982
6	<i>nITRo</i> : nal-IRI/5-FU/LV and oxaliplatin	+	-	67	II	NCT03528785
7	Perioperative Gem/nab-P	+	+	50	II	NCT02723331
Neoadjuvant/perioperative concepts including radiation therapy						
1	<i>PRO33061</i> : stereotactic body RT vs. conventionally fractionated CRT preoperatively	+	+	102	II	NCT03704662
2	<i>ESR-16-12315</i> : neoadjuvant CRT (gemcitabine/durvalumab) + adjuvant gemcitabine/durvalumab	+	+	71	II	NCT03572400
3	Preoperative CRT with gemcitabine	+	-	64	II	NCT01333124
4	<i>UVA-PC-PD101</i> : neoadjuvant pembrolizumab (+ radiation)	+	+	56	I/II	NCT02305186
5	Neoadjuvant Gem/nab-P followed by RT	+	-	44	II	NCT02427841
6	<i>PIOPPO</i> : neoadjuvant carbon ions RT	+	+	30	II	NCT03822936

PDAC, pancreatic ductal adenocarcinoma; rPDAC, resectable PDAC; brPDAC, resectable PDAC; Gem/nab-P, gemcitabine/nab-paclitaxel; CTX, chemotherapy; RT, radiation therapy; CRT, chemoradiotherapy.

4 cycles? What is the role of the postoperative treatment after neoadjuvant chemotherapy? A substantial number of trials are currently underway that address these topics and will present data in due course (*Table 1*).

Pancreatic cancer is a highly heterogeneous disease. In a time of personalized tumor treatment, one could argue that a neoadjuvant treatment should be tailored to the individual tumor, e.g., by establishing chemotherapy specific response signatures in PDACs that could be used to predict the response of an individual tumor. There are already examples in the literature suggesting that this may be a realistic approach at least for a substantial proportion of tumors. This approach could ensure that an individual patient with a resectable PDAC receives a neoadjuvant treatment with a high chance of efficacy thereby providing the best ratio between risk by adverse effects and benefit by improving overall survival.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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