

Current view of neoadjuvant chemotherapy in primarily resectable pancreatic adenocarcinoma

Minireview

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Pancreatic ductal adenocarcinoma (PDAC) is now the 11th most common cancer and in 2018 there were 458,918 new cases worldwide. In the Czech Republic, a total of 2,173 patients were diagnosed in 2015, ranking the second in incidence worldwide. In contrast to other malignancies, recent research has not brought any major breakthrough in the treatment of PDAC and hence the prognosis remains very serious. Radical resection is the only curative approach, but after the initiation of the standard pathological evaluation of the resected tissue, according to the Leeds protocol, 80% of the resections are R1 (resections with microscopically positive margins). The results of studies in patients with borderline resectable or locally advanced PDAC prefer neoadjuvant chemotherapy or chemoradiotherapy. This approach leads to a higher number of radical R0 resections and better survival. For neoadjuvant treatment in patients with primarily resectable PDAC, most results come from retrospective analysis or phase II trials. However, recently, data from three randomized clinical trials with neoadjuvant therapy for resectable PDAC were presented. These results support the use of chemotherapy or chemoradiotherapy prior to surgery. In the trials published to date, there are differences in chemotherapeutic regimens, cytostatic doses, and the definition of resectability. Thus, up-front resection with adjuvant chemotherapy is still the standard of care and a well-designed randomized trial using neoadjuvant therapy is now necessary.

Key words: pancreas, carcinoma, resectable, neoadjuvant, treatment

The most common histological type of pancreatic tumor is pancreatic ductal adenocarcinoma (PDAC) and this accounts for nearly 90% of all pancreatic tumors [1]. Based on the GLOBOCAN 2018 data, PDAC is the 11th most common cancer and in 2018 458,918 new cases and 432,242 deaths were reported worldwide [2]. In the Czech Republic, the incidence rate for pancreatic cancer is alarming and is the second-highest globally; in 2015 it was 20.82 per 100,000. Mortality is still high, 18.58 per 100,000 inhabitants, and almost copies the incidence curve [3]. Parallel with the increasing incidence of risk factors for PDAC, such as obesity, type II diabetes, smoking, and alcohol intake, the incidence of PDAC is increasing [4]. Over the past 30 years,

the 5-year overall survival (OS) rate has increased from 2% to 9% regardless of disease stage [5]. Radical resection is the only potentially curative approach. According to the NCCN resectability criteria, primary resection is indicated in only 10–20% of patients with PDAC, where contact or invasion of the vascular structures has not been identified. However, the relatively high postoperative morbidity rate, which may reach 66.2% within 90 days after resection, must be considered in making the treatment decision [6]. Moreover, in 46–89% of patients, relapse is observed [7]. Most relapses are diagnosed within 2 years after resection, of which approximately 20% are within the first 6 months. Median recurrence-free survival is 11.7 months [8, 9].

Only a minority of patients are detected in the early stage of the disease when the risk of dissemination is lowest. There is no recommended population-based screening program and only patients at high risk of developing PDAC are checked regularly. This group includes patients with genetic risks such as Peutz-Jeghers syndrome, familial melanoma syndrome, Lynch syndrome, or BRCA 1, 2 mutation carriers. However, this covers only 10% of patients [10].

In recent years, there has been some development in the comprehensive treatment of resectable and borderline resectable PDAC. In primarily resectable tumors, resection followed by adjuvant chemotherapy for 6 months is still considered as the standard of care. However, according to NCCN guidelines, neoadjuvant therapy can already be considered in patients with resectable tumors and with risk factors such as large primary tumors, enlarged lymph nodes, high baseline CA 19-9 levels, significant weight loss, or severe pain [11]. Forty-six percent of patients do not receive systemic adjuvant therapy, particularly due to severe postoperative complications, poor clinical status, comorbidities, or early disease recurrence [12, 13]. The average time from diagnosis to the initiation of adjuvant treatment is 2–3 months [14]. Pancreatic cancer is an aggressive disease with a tendency to disseminate in its very early stages. Using mathematical models, Haeno et al. found that tumors with a diameter of 1 cm, 2 cm, and 3 cm had a probability of micrometastatic dissemination of 28%, 73%, and 94% at the time of diagnosis. These models were confirmed by autopsy [15].

Methods

To identify trials for neoadjuvant and adjuvant treatment, a comprehensive search of Clinical trials, Cochrane, Embase, and MEDLINE was performed. Articles were selected based on relevance to our objectives. Search terms included “neoadjuvant,” “adjuvant,” “gemcitabine,” “FOLFIRINOX,” “folinic acid,” “fluorouracil,” “irinotecan,” “oxaliplatin,” “radiotherapy,” “chemoradiotherapy,” “resectable,” “pancreatic cancer,” “drug combination”. Only articles written in English were assessed. A selection was made for prospective and retrospective phase I, II, and III trials, and publication dates from 1998 to 2020.

The current standard of care for resectable PDAC

In 2004, Neoptolemos et al. presented the results of the ESPAC-1 trial with a 2×2 factorial design. This study compared adjuvant 5-fluorouracil (5-FU)-based chemoradiotherapy alone (arm A), adjuvant 5-FU based chemoradiotherapy followed by 5-FU (arm B), adjuvant 5-FU alone (arm C), and observation alone (arm D). Survival was significantly longer in patients who received chemotherapy compared to patients who did not, with a median overall survival (mOS) 20 vs. 16 months (hazard ratio [HR]=0.71; p=0.009). Further-

more, patients with chemoradiotherapy had a mOS 16 vs. 18 months as compared to patients who did not receive chemoradiotherapy ([HR]=1.28; p=0.05) [16]. Thus, in this trial, no benefit of adjuvant chemoradiotherapy was observed.

In 2007, the CONKO-001 trial compared surgical resection with observation vs. resection followed by adjuvant chemotherapy for 6 months with gemcitabine. In the gemcitabine group, disease-free survival (DFS) was 13.4 vs. 6.7 months (p<0.001) [17]. In 2013, a long-term follow-up confirmed the superiority of the adjuvant chemotherapy arm. The mOS was 22.8 vs. 20.2 months ([HR]=0.76), 5-year OS was 20.7% vs. 10.4% (p=0.01) [18].

The ESPAC-4 trial compared two adjuvant regimens, a combination of gemcitabine and capecitabine versus gemcitabine monotherapy for 6 months. A total of 792 patients were divided into both arms at a 1:1 ratio. The mOS was 28.0 vs. 25.5 months in favor of the doublet ([HR]=0.82; p=0.032). Subgroup analysis showed the greatest benefit of this adjuvant doublet in a mOS in patients after radical R0 resection, 39.5 vs. 27.9 months (p=0.0001) [19].

PRODIGE 24 is a randomized phase III multicenter trial that compared a modified mFOLFIRINOX regimen (5-FU, leucovorin, irinotecan, and oxaliplatin) and gemcitabine monotherapy in the adjuvant setting for a duration of 6 months after R0 and R1 resection. A total of 493 patients from 77 centers were enrolled and divided into two arms at a 1:1 ratio (247 patients in the mFOLFIRINOX group and 246 patients in the gemcitabine group). The median disease-free survival (mDFS) was 21.6 vs. 12.8 months ([HR]=0.58; p<0.001). The mOS was also statistically significant, 54.4 vs. 34.8 months ([HR]=0.64; p=0.003), with results in favor of mFOLFIRINOX. Grade 3–4 toxicity was present in 75.9% vs. 52.9% of patients with gemcitabine. The planned treatment was completed in 66% of patients compared to 79% in the gemcitabine arm. In the long-term follow-up of patients, the benefit of this combination regimen was confirmed with 3-year DFS 39.7% vs. 21.4% and 3-years OS 63.4% vs. 48.6%. Thus, this study proved that the mFOLFIRINOX regimen can be safely administered in an adjuvant setting and significantly improves DFS and OS parameters compared to gemcitabine monotherapy. A modified mFOLFIRINOX regimen should be now considered as a new standard of treatment despite increased toxicity [20].

Neoadjuvant chemotherapy in resectable PDAC

Next to several retrospective analyzes and phase II trials in which the effect of gemcitabine, platinum derivatives, and 5-fluorouracil in a neoadjuvant setting has been most studied, there are also results from four recently presented clinical trials supporting a neoadjuvant approach in resectable PDAC.

The available data to date cannot be objectively compared because there are differences between the trial designs in terms of the chemotherapy regimens used, cytostatic doses

Table 1. Advantages of the neoadjuvant approach.

- 1) The neoadjuvant approach ensures that systemic treatment is administered to a significantly higher number of patients [12, 13].
- 2) Retrospective data suggest that the neoadjuvant approach is associated with a higher number of patients completing the full period of systemic therapy (83 vs. 58% for adjuvant). These results correlate with a better prognosis [21].
- 3) Early initiation of systemic treatment is associated with a higher chance of eradication of radiographically occult metastatic disease [15].
- 4) The neoadjuvant approach can increase the probability of downstaging and R0 resection rate, which is associated with a better prognosis [22].
- 5) Tumor downstaging after previous treatment reduces the number of subsequent extensive surgical procedures, which are associated with a higher rate of postoperative complications [13, 23].
- 6) Neoadjuvant systemic treatment reduces the risk of the intraoperative iatrogenic dissemination of tumor cells in the abdominal cavity [23].
- 7) During a period of neoadjuvant therapy, time may be gained to improve performance and nutritional status in patients prior to any scheduled resection. Approximately 80% of all patients with pancreatic cancer, regardless of stage, are experiencing weight loss at the time of diagnosis, and approximately 30% of patients lose more than 10% [24, 25].
- 8) In the preoperative period, the distribution of cytostatic agents in the intact vascular supply is increased [26].
- 9) Neoadjuvant chemotherapy can elucidate the biological nature of the tumor and verify its chemosensitivity and aggressiveness. This can help to select patients who are optimal candidates for surgical resection [27, 28].

and unclear definitions of resectability. The advantages and disadvantages of neoadjuvant systemic chemotherapy for resectable PDAC are mentioned in Table 1 [12, 13, 15, 21–28] and Table 2 [29–32].

In a non-randomized, single-arm study by Swiss authors with neoadjuvant chemotherapy with a combination of gemcitabine and cisplatin, from a total of 28 patients with primarily resectable PDAC, resection was performed in 25 (89%) and R0 resection was reported in 20 (80%) cases. DFS was 9.0 months and OS 19.1 months. In addition, prealbumin levels were significantly normalized during the neoadjuvant period ($p=0.008$) [33].

O'Reilly et al. published results from 38 patients who received 4 cycles of gemcitabine and oxaliplatin in a neoadjuvant setting. 27 patients (71%) were subsequently indicated for resection, of which 20 patients (74%) had R0 resection. Thereafter, 5 cycles of gemcitabine were adjuvantly indicated to 26 patients. The mOS for the total population was 27.2 months. For the 27 operated patients, the median recurrence-free survival (mRFS) was 22.0 months [34].

In 2007, Palmer et al. presented results of 50 patients with a primarily resectable pancreatic tumor. They were enrolled in two arms with neoadjuvant treatment, of which 37 (74%) had PDAC. Patients were divided into the gemcitabine monotherapy arm and the gemcitabine and cisplatin arm. The primary focus of the study was the resection rate. Eighteen (70%) patients in the combination arm were resected vs. 9 (38%) patients with monotherapy. The OS at 12 months for the combination and gemcitabine arm was 62% and 42% [35].

In 2017, Mokdad et al. analyzed data from the National Cancer Database (NCD) in patients treated for early-stage PDAC between 2006 and 2012. Patients with stage I and II pancreatic adenocarcinoma were compared, of which 2005 patients underwent neoadjuvant chemotherapy and 6015 patients were primarily resected. Patients were stratified by age, sex, race, date of diagnosis, economic status, performance status, T and N stage, and type of surgery. Those

Table 2. Disadvantages of the neoadjuvant approach.

- 1) Risk of yield insufficiency in biopsy tissue sampled via endosonography and fine needle aspiration biopsy (FNAB), requiring repetition of the procedure, and possibly delaying the start of chemotherapy. The number of false negative biopsies can be up to 4% [29].
- 2) Complications in endoscopy [30–32]:
 - hemorrhage (0.96%)
 - pancreatitis (0.19%)
 - perforation (0.09%)
 - infection (0.4–1%)
 - hyperamylasemia (4.7%, 3 hours after the procedure)
- 3) Risk of progression during neoadjuvant therapy

patients who underwent neoadjuvant therapy had significantly longer mOS, 26 vs. 21 months ($p<0.01$). However, only 67% of patients completed adjuvant treatment in this analysis. If this subgroup is compared to the neoadjuvant group, preoperative treatment was still associated with longer survival, the mOS was 26 vs. 23 months ($p<0.01$). Furthermore, primarily resected patients had a higher pTNM stage (pT3/4: 86% vs. 73%, $p<0.01$; pN+: 73% vs. 48%, $p<0.01$), as well as a higher rate of R1 resections (24% vs. 17%, $p<0.01$). Higher T stage, N+, and R1 resections are independent prognostic factors. Postoperative complications were similar in both groups [36]. The major limitation of this study is the fact that it is based on retrospective analysis and the fact that patients, who had been reported to have metastatic dissemination after neoadjuvant therapy were excluded from this study. A further limitation is the different chemotherapy regimens used in the neoadjuvant setting.

The data from the previous analysis may be at least partially supported by the results of another retrospective analysis from Tzeng et al. Of 115 patients who underwent neoadjuvant chemotherapy and subsequent resection, 95 (83%) patients completed the planned treatment. In the upfront surgery group, 50 patients were analyzed and treatment was completed in 29 (58%) of them. The most common reason for premature termination of adjuvant therapy was

early disease progression. Completed treatment was associated with a better prognosis, the mOS was 36.0 vs. 11.0 months ($p < 0.001$) [22].

Finally, a phase II–III Preop-02/JSAP-05 trial was conducted in East Asia and included 364 patients with resectable PDAC. They were randomized to either neoadjuvant gemcitabine and S-1 chemotherapy group or an upfront surgery group at a 1:1 ratio. In neoadjuvant group, patients received 2 cycles of combined chemotherapy. S-1 was administered adjuvantly for 6 months after curative resection in both arms. The primary endpoint was OS, secondary endpoints included RFS, resection rate, adverse events, nodal metastases, residual tumor status, and tumor marker kinetics. This study showed survival benefit for the neoadjuvant approach with a mOS 36.7 vs. 26.6 months ([HR]=0.72; $p=0.015$). The OS rate at 2 years was 63.7% vs. 53.5%. All subgroups in this trial had a benefit from the neoadjuvant approach. Moreover, there were no significant differences in terms of surgery-related complications in both arms. However, the resection rate and R0 resection rate were equivalent in the two groups. The most observed grade 3/4 adverse events in the neoadjuvant group were leukopenia and neutropenia (72.8%). This trial was conducted only in Japan and S-1 chemotherapy has not been approved by the Food and Drug Administration (FDA) [37].

Neoadjuvant chemoradiotherapy in resectable PDAC

A combination of radiation and chemotherapy has become a standard treatment option for multiple types of locally advanced cancers. This combined approach can introduce a unique set of DNA aberrations, which differ from those induced by either radiation or chemotherapy alone. Gemcitabine and 5-FU are potent radiosensitizers and are commonly used concomitantly with radiation in the treatment of gastrointestinal malignancies including PDAC. Their activity is thought to be mediated via the redistribution of cells into the S-phase of the cell cycle and the depletion of nucleotide pools. The combination of these agents with radiation leads to the production of complex, slowly repaired radiation-induced DNA damage in S-phase cells, such as the 1-ended double-strand breaks produced as radiation-induced single-strand breaks collide with progressing replication forks [38].

Greer et al. published results from a retrospective review of 102 patients who underwent resection for resectable, borderline resectable, and locally advanced PDAC between 1993 and 2005. Forty-two patients (41%) were treated with neoadjuvant chemoradiotherapy, 41 patients (40%) were treated with adjuvant chemoradiotherapy and 19 patients (19%) had no additional treatment. Patients in the neoadjuvant group were more likely to have locally advanced tumors. Nevertheless, patients receiving neoadjuvant chemoradiotherapy were less likely to have a local recurrence than patients receiving adjuvant chemoradiotherapy, 5% vs. 34% ($p=0.02$). Among patients with resectable PDAC according to initial CT scans,

local recurrences were observed in 31% (10 of 32) of patients in the adjuvant group compared with 7% (1 of 14) in the neoadjuvant group [39].

When chemoradiotherapy was compared to chemotherapy alone in the treatment of patients with locally advanced PDAC, grades 3 and 4 toxicities were similar, at 79% vs. 77% [40]. For resectable tumors, data are still not available.

Chemoradiotherapy has also been studied in multiple prospective clinical trials among patients with resectable PDAC. In a majority of these trials, the number of enrolled patients was not sufficient and trial design was not uniform. However, existing data are encouraging.

In 2015, Golcher et al. conducted the first randomized phase II trial with neoadjuvant concomitant chemoradiotherapy in primarily resectable PDAC. A total of 66 patients were analyzed, of which 33 were enrolled in a neoadjuvant chemoradiotherapy arm based on a combination of gemcitabine and cisplatin concomitantly with radiotherapy. Chemoradiotherapy was initiated in 29 patients. A total of 19 (58%) patients underwent subsequent resection, which was radical in 52% of cases. In the second half of the group, 23 (70%) patients underwent resection first, with R0 resections in 48% of cases. Adjuvant chemotherapy was administered in both groups. Postoperative complications were comparable in both groups. In the intent to treat (ITT) population the mOS was higher in the neoadjuvant group, 17.4 vs. 14.4 months ($p=0.96$). After resection, the mOS was 25.0 vs. 18.9 months ($p=0.79$). The study was terminated prematurely due to slow recruitment and non-significant results [41].

Casadei et al. also investigated the effect of neoadjuvant chemoradiotherapy over primary resection. Only 38 patients were enrolled in this unicentric study, of whom 20 underwent primary resection. Neoadjuvant chemotherapy with gemcitabine alone was administered for 2 cycles followed by concomitant chemoradiotherapy for a total of 6 weeks. Chemoradiotherapy was completed in 14 out of 18 cases. The primary endpoint of the study was the R0 resection rate. However, there was no significant difference between the two groups in this parameter ($p=0.489$) [42].

Mokdad's retrospective analysis also includes data comparing neoadjuvant chemotherapy and chemoradiotherapy. Of 1326 patients, 616 had neoadjuvant chemotherapy and 710 had neoadjuvant chemoradiotherapy. OS differences were not significant between the two arms, the mOS for chemoradiotherapy and chemotherapy was 26.0 and 25.0 months, respectively ($p=0.10$). In addition, chemoradiotherapy was associated with a higher postoperative 90-day mortality rate, 7% vs. 4% ($p=0.03$), and a higher frequency of postoperative hospitalisations, 9% vs. 6% ($p=0.01$). On the other hand, chemoradiotherapy was associated with a lower rate of R1 resection, 14% vs. 21% ($p=0.01$), and node positivity, 35% vs. 59% ($p < 0.01$) [43].

The PREOPANC trial is a randomized phase III trial with neoadjuvant chemoradiotherapy for resectable or border-

line resectable PDAC. A total of 246 eligible patients were randomized. One hundred and nineteen patients were assigned to preoperative concomitant chemoradiotherapy (arm A) and 127 to immediate surgery (arm B). Adjuvant gemcitabine was administered for 4 cycles in arm A and for 6 cycles in arm B. The primary endpoint was OS by ITT population, which was 16.0 months with preoperative chemoradiotherapy, and 14.3 months with immediate surgery ([HR]=0.78; $p=0.096$). The resection rate was 61% for the neoadjuvant group and 72% for the surgery group ($p=0.058$). The R0 resection rate was 71% (51/72) in patients who received preoperative chemoradiotherapy and 40% (37/92) in patients assigned to immediate surgery ($p<0.001$). Preoperative chemoradiotherapy was associated with a significantly better DFS and a locoregional failure-free interval as well as with significantly lower rates of pathologic lymph nodes, perineural invasion, and venous invasion. Overall survival was improved among patients who underwent preoperative chemoradiotherapy, 35.2 vs. 19.8 months ($p=0.029$), indicating that the results were not statistically significant. Serious adverse events were comparable in both groups, 52% vs. 41% ($p=0.096$) [44].

Thus, the results of the trials presented are inconsistent and we still don't have clear evidence of the survival benefit of neoadjuvant chemoradiotherapy over chemotherapy alone. A summary of neoadjuvant trials is in Table 3 [45, 46].

Ongoing clinical trials

A prospective, multicenter, randomized phase II trial, PANACHE01-PRODIGE48, is evaluating the effect and safety of the two neoadjuvant regimens mFOLFIRINOX and FOLFOX (5-FU, leucovorin, and oxaliplatin) compared to adjuvant administration in resectable PDAC. The primary endpoint of this study is OS and the proportion of patients who fully complete the treatment. The study is expected to be completed in December 2021 [47].

Another ongoing trial with neoadjuvant therapy in primarily resectable PDAC is the randomized, multicenter NEONAX phase II trial comparing perioperative vs. adjuvant gemcitabine and nab-paclitaxel. This study was initiated in 2015 and the first interim results from 48 patients were presented in ASCO 2019. The plan is to include 166 patients. Two cycles of neoadjuvant chemotherapy were applied to

Table 3. Neoadjuvant trials, edited according to Janssen et al. [45] and Piatek et al. [46].

Study author	Stage	Sample	Regimen	Resection rate [%]	R0 resection rate [%]	Median OS [m]
Clinical trials with neoadjuvant chemoradiotherapy						
Hoffman et al. (1998)	Resectable	62	FU + Mitomycin + 50.4 Gy	45.3	70.8	16
Mornex et al. (2006)	Resectable	41	PF + 50 Gy	63.4	80.7	12
Turrini et al. (2009)	Resectable	102	PF + 45 Gy	60.8	91.8	23
Evans et al. (2008)	Resectable	86	Gem + 30 Gy	64.4	86.4	34
Pisters et al. (2002)	Resectable	37	PXL + 30 Gy (IORT)	54.1	70	19
Golcher et al. (2015)	Resectable	29	PG + 55.8 Gy	65.5	89.5	25
Pisters et al. (1998)	Resectable	35	FU + 30 Gy (IORT)	57	51	37
Sho et al. (2013)	Resectable	61	Gem + 50.4–54 Gy	97	92	NR
Van Buren et al. (2013)	Resectable	59	Gem + Bev + 30 Gy	73	88	17
Van Tienhoven (2020)	Resectable/BRPC	246	Gem – based CHTRT + adjuv. gem (A) vs. surgery + adjuv. gem (B)	61 vs. 72, $p=0.058$	71 vs. 40, $p<0.001$	16 vs. 14.3, $p=0.096$
Clinical trials with neoadjuvant chemotherapy						
Palmer et al. (2007)	Resectable	50	Gem vs. PG	38 vs. 70	75	28
Heinrich et al. (2008)	Resectable	28	PG	89.3	80	27
O'Reilly et al. (2014)	Resectable	38	GemOx	71	74	27
Tajima et al. (2012)	Resectable	34	Gem + S1	100	85	56 % at 24
Motoi et al. (2019)	Resectable	364	Gem + S1 + adjuv. S1 vs. surgery + adjuv. S1	NR	NR	37 vs. 27
Clinical trials with neoadjuvant chemotherapy and chemoradiotherapy						
Varadhachary et al. (2008)	Resectable	90	PG → 30 Gy + Gem	57.8	96.2	31
Talamonti et al. (2006)	Resectable	20	Gem → 36 Gy	85	80	26 (resected)
Faris et al. (2013)	Resectable	22	FOLFIRINOX +/- CHTRT	55	42	NR
Casadei et al. (2015)	Resectable	38	Surgery + adjuv. gem (A) vs. Gem → 54 Gy + Gem → adjuv. gem (B)	75 vs. 61.1, $p=0.489$	25 vs. 38.9, $p=0.489$	19.5 vs. 22.4, $p=0.973$

Abbreviations: Bev–bevacizumab; CHTRT–chemoradiotherapy; FOLFIRINOX–fluorouracil+oxaliplatin+irinotecan+leucovorin; FU–fluorouracil; Gem–gemcitabine; GemOx–gemcitabine+oxaliplatin; Gy–Gray; IORT–intraoperative radiotherapy; NR–not reportable; PF–cisplatin+fluorouracil; PG–cisplatin+gemcitabine; PXL–paclitaxel; S1–tegafur/gimeracil/oteracil; BRPC–borderline resectable pancreatic cancer

22 patients. After a reevaluation on restaging CT, a resection was considered and then 4 cycles of adjuvant chemotherapy were applied. In the second arm, 23 patients were enrolled and up-front surgery was carried out followed by 6 cycles of adjuvant therapy. The primary endpoint is DFS at 18 months after randomization, secondary endpoints include a 3-year OS rate and DFS rate, progression during neoadjuvant therapy, R0/R1 resection rate, and quality of life. The results so far show that patients with perioperative chemotherapy have a higher rate of complications, but they were well managed and had no effect on the increase of peri- and postoperative mortality. Postoperative complications were reported in 45.0% in the neoadjuvant arm and 42.8% in the surgery arm [48].

The SWOG S1505 trial is an ongoing randomized phase II study, which includes patients with resectable PDAC. This trial is designed to determine the most promising perioperative regimen for a larger phase III trial (NCT02562716). This study has completed accrual and randomized 147 patients to 3 cycles of either perioperative mFOLFIRINOX (arm A) or perioperative gemcitabine with nab-paclitaxel (arm B). The primary endpoint of the study is OS at 2 years, and results are anticipated to 2020 [45]. The NorPACT-1 trial is an ongoing multicenter study. Patients with resectable PDAC of the pancreatic head have been randomized in a 3:2 ratio to receive 4 cycles of neoadjuvant FOLFIRINOX and adjuvant 4 cycles of gemcitabine and capecitabine or upfront surgery followed by 6 cycles of adjuvant gemcitabine and capecitabine. The sample size is 90 patients, and the primary endpoint is 1-year OS for those patients who ultimately undergo a resection [49].

It can be assumed that the neoadjuvant approach could lead to a further improvement in OS and DFS in primarily resectable PDAC, and hence this may be preferred in the future. However, it should be noted that results from well-designed prospective randomized trials are currently lacking.

Evaluation of radicality

As already mentioned, one of the arguments favoring the neoadjuvant approach is the possibility of increasing the chance of R0 resection. According to several studies mentioned in Table 3, neoadjuvant therapy leads to a high probability of radical resection. R1 resection is associated with poor prognosis [50, 51]. The cause of R1 may be the false negativity of perioperative cryobiopsy or the impossibility of radical surgery due to the proximity of major vessels. Evaluation of the radicality of resection is still problematic. The definition of microscopic resection margins involvement is not uniform. Prior to the introduction of a standardized pathological evaluation of the resected tissue according to the Leeds protocol, the frequency of R1 resections was 17–30% [52–54]. In the US centers, an R1 resection was defined as surface infiltration, i.e. 0 mm [55]. In most

European centers, the definition of an R1 resection is the presence of tumor cells <1mm from the edge [56]. The low frequency of R1 resections in a center is used, among other things, as an indicator of the quality of surgery.

Thus, the results of studies comparing long-term survival after R0 and R1 resections published before 2006 may be distorted by the different histopathological methodologies used at the centers. Currently, when the resected tissue is evaluated by a pathologist according to the Leeds protocol, the frequency of R1 resections is 80% [57]. Standardized evaluation best correlates with radical surgery, the frequency of local recurrences, and overall survival.

Summary

The current recommended procedure in primarily resectable PDAC is resection followed by adjuvant chemotherapy for 6 months. The PRODIGE 24 trial demonstrated the efficacy of mFOLFIRINOX that provides the longest mDFS (21.6 months) and mOS (54.4 months) of all the regimens studied in an adjuvant setting. To be noted, in this trial the population was very select. In general, 46% of patients with resected PDAC are not eligible for adjuvant therapy due to postoperative complications or very early progression. When adjuvant therapy is initiated, attention must be taken especially among patients with comorbidities. PDAC is most commonly diagnosed between the ages of 65 and 75. Grade 3 and 4 adverse events reach up to 75.5% with an mFOLFIRINOX regimen. Therefore, an adjuvant regimen of mFOLFIRINOX is reserved for only a highly select proportion of patients with very good performance status and a minimum of comorbidities. The combination of gemcitabine and capecitabine is also associated with relatively numerous adverse reactions, especially myelotoxicity and diarrhea. Risk factors such as a large primary tumor, enlarged lymph nodes, high baseline CA 19-9 levels, significant weight loss, or severe pain can be considered indications for neoadjuvant therapy in primarily resectable patients.

Early evidence showing the efficacy of neoadjuvant therapy in patients with resectable PDAC is already available. The main goal of this approach is to increase the number of patients treated with systemic therapy, as well as to reach downstaging, and to increase the likelihood of R0 resections. Moreover, early initiation of systemic treatment can eradicate the micrometastatic disease. The use of chemoradiotherapy in a neoadjuvant setting is associated with a higher R0 resection rate, but not with significant improvement in overall survival.

In conclusion, the treatment of resectable PDAC should be multidisciplinary and concentrated in high-volume centers. It is necessary to evaluate the approach to treatment individually based on the tumor stage, the patient's performance status, and comorbidities. Radical resection is the only curative-intent treatment, but post-operative morbidity and mortality is still relatively high. The current

standard of care in this setting is up-front surgery with adjuvant chemotherapy. Despite selection bias affecting survival outcomes in neoadjuvant compared to adjuvant trials, patients enrolled in the neoadjuvant trials seem to benefit from this approach. Neoadjuvant treatment can improve patient selection and identify those who can benefit from resection. Moreover, systemic treatment prior to surgery can help apply cytostatics to a much larger population and eliminate radiographically occult metastatic lesions. Ongoing clinical trials are investigating the effect of the multi-agent regimen FOLFIRINOX in a neoadjuvant setting.

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