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Chemotherapy versus chemoradiotherapy in borderline resectable and locally advanced pancreatic adenocarcinoma

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The role of radiotherapy in borderline resectable (BRPC) and locally advanced pancreatic carcinoma (LAPC) remains controversial. In our study, we retrospectively evaluated 48 patients with BRPC (14; 29.2%) and LAPC (34; 70. 8%) who underwent 6–8 cycles of induction mFOLFIRINOX chemotherapy alone (23; 47.9%) or 4–6 cycles of mFOLFIRINOX followed by hypofractionated radiotherapy (up to the total dose of 39.9 Gy in 15 fractions) (25; 52.1%). Survival parameters were evaluated using the Gehan-Breslow-Wilcoxon Test and compared by using the long-rank test. The addition of radiotherapy was not associated with better survival (16.9 months for chemotherapy only versus 15.9 months for the combined therapy; p=0.486), as well as for both subgroups (13.5 months vs. 18.3 months; p=0.679) and (20.7 months vs. 13.8 months; p=0.425) for BRPC and LAPC, respectively. A higher resection rate was seen in the BRPC group compared to the LAPC group (43% vs. 17.6%, respectively). Our study revealed a significantly higher rate of lung metastases in patients after the combination therapy compared to those treated by chemotherapy only (19% vs. 0%, respectively; p=0.045). Such a borderline result, however, prevents us from drawing clear conclusions about whether this is an artifact caused by the low number of patients or whether radiotherapy leads to a selection of stem cells with a predilection to the generalization to the lungs.

Key words: locally advanced; borderline resectable; pancreatic cancer; radiotherapy; induction chemotherapy

Pancreatic ductal adenocarcinoma (PDAC) has a poor 5-year survival rate not exceeding 15%, with only minor differences depending on the disease stadium and geographical location [1, 2].

Initially, only 10–20% of patients are eligible to undergo a complete resection directly [3–6]. Another 30–40% of patients were initially diagnosed with borderline resectable pancreatic carcinoma (BRPC) or locally advanced pancreatic carcinoma (LAPC) [4–6]. In patients with localized or locoregional PDAC, macroscopically complete surgical resection with adequately timed systemic therapy gives the best potential for longer-term survival [5]. The three main criteria for assessing resectability include the tumor anatomy (abutment or encasement of large vessels) which limits R0 -resectability, tumor biology (CA 19-9), and overall patient status and comorbidities [6].

In the last decade, neoadjuvant therapy (NAT) has been increasingly applied to local and locoregional disease with the aim of the early reduction of systemic tumor cell load in early microscopically generalized disease, as well as downstaging, improved resectability, and improved tolerance and completion of systemic therapy [2, 6–9].

In BRPC, meta-analyses have shown improvement in median overall survival (mOS) in patients with NAT compared to those treated by up-front surgery (22.2 months and 12.8 months, respectively) [10, 11]. Phase II ESPAC-5F trial compared the benefit of NAT between 4 therapy arms, namely up-front surgery and three arms with NAT: i) 4 cycles of FOLFIRINOX, ii) 2 cycles of GEM/capecitabine combination chemotherapy (GemCap), and iii) neoadjuvant chemoradiotherapy (NCRT; total dose of 50.4 Gy with concurrent capecitabine) [12]. The NCRT group demonstrated a higher

R0-resection rate (RR) (37%), compared with 17–18% in both chemotherapy arms. Patients with NAT showed a higher 1 year OS compared to surgery (77% vs. 42%, HR=0.27; p<0.001), with the highest 1 year OS in the FOLFIRINOX arm (84%) followed by GemCap (79%) and CRT (64%). The recently published Alliance A021501 study compared neoadjuvant chemotherapy (8 cycles of modified FOLFIRINOX (mFOLFIRINOX) with combined neoadjuvant chemoradiotherapy (NCRT; 7 cycles of mFOLFIRINOX followed by radiotherapy (either SBRT, to a total dose of 33–40 Gy in 5 fractions, or hypofractionated radiotherapy to a total dose of 25 Gy in 5 fractions). The study did not show any benefit of supplementing mFOLFIRINOX with the studied types of radiotherapy [13].

In patients with LAPC, NAT may have an additional role as a conversion therapy, which downstages the tumor and may convert a primarily unresectable tumor to the resectable status, thus significantly affecting the patient's survival [2, 4, 10, 14]. The implementation of FOLFIRINOX into the therapy of LAPC significantly improved survival and the possibility of conversion surgery [14]. A large meta-analysis of 11 observational studies with 315 LAPC patients who received induction therapy with FOLFIRINOX reported a conversion rate of 26% (0–43%) [15]. The R0-resection rate was 50–100% and the mOS of 24 months [14, 15]. A more recent meta-analysis of 24 trials of FOLFIRINOX induction chemotherapy in 313 patients reported a higher response rate of 67.8% (95% CI, 60.1–74.6) and R0-rate of 83.9% (95% CI, 76.8–89.1) [10, 14]. In large retrospective trials, some of which combined LA and BRPC, neoadjuvant chemotherapy with FOLFIRINOX led to a 60–78% conversion to resectability, to a higher R0-resection rate (R0–RR) of 40–80%, and to an improvement in mOS to 15.3–37.0 months in resected patients compared to mOS of 8.5–25.0 months in unresected patients [2, 16, 17]. A prospective study from Maggino et al. evaluated the effect of induction chemotherapy in 680 patients with BRPC and LAPC [18]. The overall resection rate (RR) was 15.1% (93 of 614), 24.1% (60 of 249) for BRPC, and 9% (33 of 365) for LAPC; with a resection: exploration ratio of 63.3%. A large SEER analysis of 4,460 patients comparing the effect of adding radiotherapy for LAPC has demonstrated a 1 year OS benefit to patients with radiotherapy compared to those without radiotherapy (43% vs. 29%; p=0.001) [19]. In contrast, other studies and meta-analyses have not reported any benefit of adding radiotherapy to neoadjuvant respective induction chemotherapy [20, 21]. Considering the conflicting results of the available studies, the role of radiotherapy in neoadjuvant therapy of BRPC or LAPC remains questionable.

Patients and methods

We retrospectively evaluated documentation of patients treated for pancreatic carcinoma at the Department of Oncology of the General University Hospital (GUH) in Prague, the 1st Department of Surgery GUH, and the Department of Surgery of the University Military Hospital (UMH) in Prague between September 2014 and May 2021. Inclusion criteria were: patients with histologically or cytologically verified pancreatic carcinoma initially classified as BRPC or LAPC, fit for multimodal neoadjuvant treatment and its completion, performance status ECOG 0–1, no previous oncological treatment, no other active malignant tumor, at least 1 year from the completion of the induction or neoadjuvant therapy, and availability of initial and follow-up images at the time of the analysis for an independent second evaluation.

This pilot analysis aimed to determine the benefit of the combined induction chemoradiotherapy (iCRT) consisting of induction chemotherapy and moderate hypofractionated radiotherapy compared with those of the induction/neoadjuvant chemotherapy (iCT) only (study design, Figure 1) in patients with initially BRPC or LAPC. Induction chemotherapy with mFOLFIRINOX consisted of 4 to 6 cycles in the iCRT arm and 6–8 cycles in the iCT arm; the doses were defined as follows: oxaliplatin (64 mg/m^2, intravenous over 2 h on Day 1), irinotecan (135 mg/m^2, intravenous over 2 h

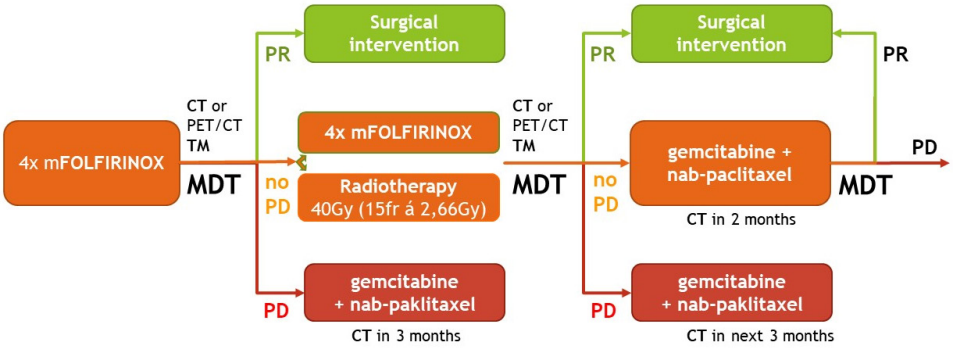

Figure 1. Trial design. Notes: mFOLFIRINOX (oxaliplatin 64 mg/m^2, irinotecan 135 mg/m^2, leucovorin 300 mg/m^2, 5-fluorouracil bolus 300 mg/m^2, 5-fluorouracil 1800 mg/m^2 continual infusion for 46 hours) Abbreviations: CT-computer tomography; PET-CT-positron emission tomography-computer tomography; TM-tumor markers; MDT-multidisciplinary team; PD-progressive disease; no PD-no progressive disease (stable disease or partial remission); PR-potentially resectable disease

on Day 1), leucovorin (300 mg/m^2, intravenous over 2 h on Day 1), 5-fluorouracil (300 mg/m^2, intravenous bolus on Day 1) and 5-fluorouracil (1800 mg/m^2, intravenous continuous infusion over 46 h on Days 1–2). In case of no progression of the disease on the restaging computed tomography (CT) after 4–6 cycles, patients were indicated for continued therapy with induction chemotherapy (September 2014–April 2018) or induction radiotherapy (May 2018–February 2021), with respect to the time period. In the iCRT group was radiotherapy initiated within 2–4 weeks after chemotherapy. Radiotherapy was administered by image-guided radiotherapy (IGRT)-tomotherapy with moderate hypofractionated accelerated fractionation á 2.66 Gy/fraction in 15 fractions, 5 days/week, to a total dose of 39.9 Gy. Planning volume included the macroscopic tumor and, if present, the affected peripancreatic lymph nodes with restriction and consideration of movements using abdominal pressure and ITV concept. Resectability was initially evaluated by a multidisciplinary team based on the multiphase CT. A tumor with arterial involvement <180° (common hepatic artery, superior mesenteric artery, or coeliac trunk) and/or venous involvement >180° (portal vein and/or superior mesenteric vein) without occlusion was considered borderline resectable (BRCP); a tumor with arterial involvement >180° and non-reconstructible venous involvement was considered locally advanced (LAPC). To re-evaluate the resectability after NAT, CT with contrast was performed, supplemented in case of unclear results with 18-FDG PET CT and, where needed, 18-FTL PET CT. Patients with no tumor progression (i.e., partial response (PR) and stabilization of the disease (SD) without tumor enlargement) were always indicated for attempted resection. Patients with disease progression (i.e., SD with tumor enlargement and clear progression of the disease (PD) according to RECIST criteria) continued systemic therapy (mFOLFIRINOX or the 2nd line of systemic therapy was administered depending on the patient's condition). In cases of uncertain resectability, a minimally exploratory laparotomy was performed; depending on the extent of the disease, this exploratory laparotomy was converted to radical surgical resection according to the extent of the disease. R0-resection was considered to be the complete removal of the tumor with a 0 mm margin.

For the purposes of this study, a second independent surgical and radiological evaluation of staging as well as re-staging CT scans after induction chemotherapy and radiotherapy were retrospectively performed. This second reading served as the basis for further analyses.

The primary endpoints of our analysis were the overall survival (OS) and progress-free survival (PFS) and their comparison between patients with and without radiotherapy. OS and PFS were calculated from the day of the therapy course initiation to the event (death and progression of the disease). Secondary outcomes and subgroup analyses compared conversion to resectability and median survival between patient groups (stratified according to the BRPC and LAPC status). We have also evaluated the effect of resection on OS to analyze the meaningfulness of radiotherapy as a part of induction therapy for these patient groups.

Ethics approval. The project was conducted in accordance with the Declaration of Helsinki, and approved by the Multicentric Ethics Committee of the General University Hospital in Prague No.1858/14, informed consent was obtained from all participating subjects.

Statistical methods. Standard descriptive statistics were used to summarize patients' characteristics. The primary endpoints, i.e. OS and PFS, were estimated via the Gehan-Breslow-Wilcoxon test. The primary analysis included the hazard ratio (HR) estimate and its 95% confidence interval (CI) using the Cox proportional hazards model comparing the two treatment groups. The HR and CI were compared with the non-inferiority margin, which was set to 5%. The statistical analysis was performed in the GraphPad Prism Software (Version 5, El Camino True, CA, USA).

Results

Out of 649 patients diagnosed with PDAC in the participating centers (GUH and UMH) between September 2014 and May 2021, only 48 met the inclusion criteria.

The baseline characteristics of all evaluated patients are summarised in Table 1. There were fewer patients with BRPC (14 patients, i.e., 29.2%) compared to LAPC (34 patients, 70.8%) in our study group.

The primary assessment of the survival and disease progression is summarized in Table 2. No difference was found in the overall response (p=0.724). We recorded partial response (PR) in 13.0% of iCT and 8.0% of iCRT patients, respectively, stabilization of the disease (SD) in 48.0% and 44.0%, and progression of the disease (PD) in 39.0% and 44.0% of patients after iCT and combined iCRT, respectively.

There was no difference in median overall survival (mOS) between patients treated with iCT alone and those after iCRT (16.9 months vs. 15.9 months, p=0.486, HR 0.83, 95% CI=0.44–1.57; Figure 2). One-year and 3-year survival rates were not statistically different either.

Subgroup analysis of patients with initial BRPC was 15.7 months, with an insignificantly higher mOS in the iCRT group (13.5 months in the iCT group vs. 18.3 months in the iCRT group; p=0.679, HR 0.98, 95% CI=0.29–3.30). The median OS of patients with initial LAPC diagnosis was 16.9 months, with insignificantly longer survival in the iCT group (20.7 months in the iCT group and 13.8 months in the iCRT group; p=0.425, HR 0.90, 95% CI=0.42–1.91). 1-year and 3-year survival rates in both subgroups did not differ in either of these subgroups (Table 2).

All potentially resectable patients without evidence of the progression of the disease after the induction therapy whose general condition allowed the possibility of radical resection underwent surgery. The macroscopic complete resection rate (i.e., R0 and R1-resection rate) after induction/neoad-

Table 1. Patient characteristic.

Variables	Total n (%)	iCT only n (%)	iCT and RT n (%)	p-value
Operability status	48	23	25	0.603
BRPC	14 (29.2%)	8 (34.8%)	6 (24%)	
LAPC	34 (70.8%)	15 (65.2%)	19 (76%)	
Age mean (range)	60.3 (35.4-74)	61 (35.4-74)	56 (40.3-71.9)	0.823
≤65 years	31 (64.6%)	14 (60.9%)	17 (68%)	
>65 years	17 (35.4%)	9 (39.1%)	8 (32%)	
Gender				
M	27 (56.6%)	13 (56.5%)	14 (56%)	0.786
F	21 (43.5%)	10 (43.5%)	11 (44%)	0.757
Tumor location				
Head	36 (75%)	16 (69.6%)	20 (80%)	0.346
Body/Tail	12 (25%)	7 (30.4%)	5 (20%)	0.414
cT				
T2	2 (4.2%)	1 (4.3%)	1 (4%)	0.507
T3	11 (22.9%)	3 (13%)	8 (32%)	0.224
T4	34 (70.8%)	19 (82.6%)	15 (60%)	0.160
Tx	1 (2.1%)		1 (4%)	ND
cN				
N0	33 (68.6%)	16 (69.6%)	17 (68%)	0.842
N1	14 (29.2%)	7 (30.4%)	7 (28%)	0.888
Nx	1 (2.8%)		1 (4%)	ND

Abbreviations: n-number of patients; iCT-induction/neoadjuvant chemotherapy only; iCRT-induction/neoadjuvant chemotherapy combined with radiotherapy; BRPC-borderline resectable pancreatic carcinoma; LAPC-locally advanced pancreatic carcinoma; M-male; F-female; cT-clinical tumor staging due to TNM classification 8th edition; cT-clinical regional lymphnodes staging due to TNM classification 8th edition; ND-cannot be evaluated

Table 2. Therapy results after induction therapy.

Variables	Total n (%)	iCT only n (%)	iCRT n (%)	p-value
Clinical response				0.724
PR	5 (10.4%)	3 (13%)	2 (8%)	0.568
SD	22 (45.8%)	11 (47.8%)	11 (44%)	0.790
PD	20 (41.7%)	9 (39.2%)	11 (44%)	0.733
X	1 (2.1%)		1 (4%)	ND
mOS all (month)	15.9	16.9	15.9	0.486
1y OS (n, %)	30 (62.5%)	15 (65.2%)	15 (60%)	0.709
2y OS (n, %)	11 (22.9%)	5 (21.7%)	6 (24%)	0.852
3y OS (n, %)	3 (6.3%)	2 (8.7%)	1 (4%)	0.502
mOS-BRPC (month)	15.7	13.5	18.3	0.679
1y OS (n, %)	8 (57.1%)	4 (50%)	4 (66.7%)	0.897
2y OS (n, %)	1 (7.1%)	1 (12.5%)	0	ND
3y OS (n, %)	1 (7.1%)	1 (12.5%)	0	ND
mOS-LAPC (month)	16.9	20.7	13.8	0.425
1y OS (n, %)	22 (64.7%)	11 (73.3%)	11 (57.9%)	0.790
2y OS (n, %)	10 (29.4%)	4 (26.7%)	6 (31.6%)	0.573
3y OS (n, %)	2 (5.9%)	1 (6.7%)	1 (5.2%)	0.952
PFS all (month)	7.5	9.2	6.6	0.303

Abbreviations: n-number of patients; iCT-induction/neoadjuvant chemotherapy only; iCRT-induction/neoadjuvant chemotherapy combined with radiotherapy; BRPC-borderline resectable pancreatic carcinoma; LAPC-locally advanced pancreatic carcinoma; PR-partial response; SD-stable disease; PD-progressive disease; X-invaluable response; mOS-median overall survival; 1 y OS-overall survival in one year; 2y OS-overall survival in the second year; 3y OS-overall survival in the third year, mPFS-median progress-free survival; ND-cannot be evaluated

juvant therapy was 25%, without any statistically significant difference between iCT alone versus iCRT (21.7% vs. 28.0%; p=0.863; Table 3). As expected, a higher resection rate was observed in patients with BRPC than LAPC, although this difference was insignificant (42.9% vs. 17.6%; p=0.143). Of patients who underwent surgery, the rate of R0-resection was similar between the BRPC and LAPC groups (82% vs. 67%; p=0.887). The same proportion of pathological complete remissions (pCR) was observed in both groups. 1-year and 3-year survival did not differ between the iCT and iCRT subgroups (Table 3). Patients who underwent resection had significantly better overall survival than those unable to undergo resection (25.3 months vs. 13.8 months; p=0.004, HR 0.38, 95% CI=0.19–0.73; Figure 3).

The difference between OS in patients who underwent resection after iCT and iCRT was not statistically significant (27.3 months in iCT vs. 23.6 months in iCRT group; p=0.422, HR 0.64, 95% CI=0.14–2.98; Figure 4).

A detailed overview of all relapses (80.4%) in patients of both groups is provided in Table 4. Until the date of the final evaluation on 18th August 2022, four patients (27%) survived without evidence of distant generalization and/or local progression in the iCT-only group, compared to four patients (16%) in the iCRT group (p=0.791). Relapse or progression involving the original location was seen in 17% of patients, namely in 26.3% of patients in the iCT group and 9.5% of those in the iCRT group (p=0.163). As expected, liver and peritoneal metastases were the most frequent sites of generalization; the liver was the first site of distant metastases in 46.3% of metastases, followed by the peritoneum (36.5%). Sub-analysis found no statistically significant difference in the liver metastasis rate between the iCT-only and the iCRT groups (52.5% vs. 43.0%; p=0.537). The rate of peritoneal metastases was insignificantly higher in the iCT-only group than in the iCRT group (52.6% vs. 33.0%, p=0.218). The rate of pulmonary metastases, however, significantly differed between the studied groups – while no pulmonary generalization was found in the iCT-only group, pulmonary metastases were detected in four patients in the iCRT group (0% vs. 19%; p=0.045). The nodal generalization frequency did not differ between the iCT and iCRT groups (19.0% vs. 10.5%; p=0.45). Time to distant metastasis (dMFS) did not significantly differ between both groups (9.2 months for iCT only vs. 6.6 months for iCRT; p=0.182).

Discussion

Despite all the advances in systemic therapy and improvements in the efficacy and accuracy of radiotherapy techniques, radical resection remains the only modality significantly improving the survival in patients with PAC. Micrometastatic dissemination at an early stage is one of the likely reasons for the poor prognosis. While preoperative systemic therapy has established a stable position in the treatment of localized primarily unresectable, or borderline

resectable PAC, the role of radiotherapy in this treatment remains, due to conflicting results, unclear. Current guidelines allow the consideration of consolidation radiotherapy (normofractionated CRT or SBRT) after systemic therapy in BLRP and LAPC with potential resectability [22–24].

The demographic distribution of patients in our analysis corresponded to the demographics of the large analysis by Trinh et al. [25]. The ratio of BRPC to LAPC patients (approx. 30:70) is roughly in line with ratios for these two subgroups reported in other studies [4, 6, 8, 15, 26]. Stable disease after the neoadjuvant/induction therapy was achieved in 47.8% of patients with iCT and 44.0% of patients with iCR, which was consistent with the results of previously published papers [8, 27, 28]. Progression was observed in 42% of patients. Early progression was mainly caused by distant metastases, which correlates with published data [27].

Rates of resection and R0-resection in patients with BRPC in the meta-analysis by Janssen et al. were 33–69% and 79–89%, respectively [29]. The RR in Maggiano's prospective study in the BRPC group was 24.1% (60 of 249) [18]. However, Dhir et al. reported in their meta-analysis the resection rate after neoadjuvant therapy was 60–70% for BRPC [28]. During the revision process, another article from Bott et al. was published where the resection rate for BRPC was 39% with an R0 resection rate of 69%, and from the LAPC group, the resection rate was 10% with an R0 resection rate of 100% (2/19 patients) [30]. The overall resection rate in our BRCP patient group was 42.9%, with a resection rate in patients on combined iCRT (50%; 3 pts) compared with iCT-only (37.5%; 3 pts). This resection rate is consistent with the resection rates reported in the aforementioned studies, or slightly lower than the RR in other studies [28–30]. This could be explained by the predominantly small sample size, as well as the selection of patients for surgery, where only patients without any disease progression on the restaging CT scan after NAT were indicated for resection within our multidisciplinary team.

In patients with initial LAPC diagnosis, an insignificant improvement in OS was observed in patients with combination therapy (mOS: 20.7 months in the iCT vs. 13.8 months in the iCRT group, p=0.425). This corresponds with the mOS of 13.6 months (10.6–32 months) reported elsewhere [15, 28, 30]. In the meta-analyses and prospective studies, resection rates ranged widely from 9% to 68% [15, 18, 28, 29]. In our LAPC group, resectability was achieved in 17.6% of patients, with an R0-resection rate of 67%, which approximately corresponds with the results of the other studies [15, 18, 28–30] Moreover, the rate of pathologic complete remission (pCR) in our patients who underwent resection was 4.2%, which was consistent with the overall pCR (3–11%) reported in other published papers [6, 8, 27, 31].

The mOS of 13 patients who underwent resection in our study was 25.3 months (6.6–109.7), with no significant difference between patients with iCT and iCRT (25.3 months and 23.6 months, respectively; p=0.422). Survival of patients after resection, detailed in Table 3, correlates with the results of the ESPAC-5F study and the meta-analysis by Gillens [8, 12].

The representation of the sites of generalization in our cohort was similar to the results of analyses by other authors,

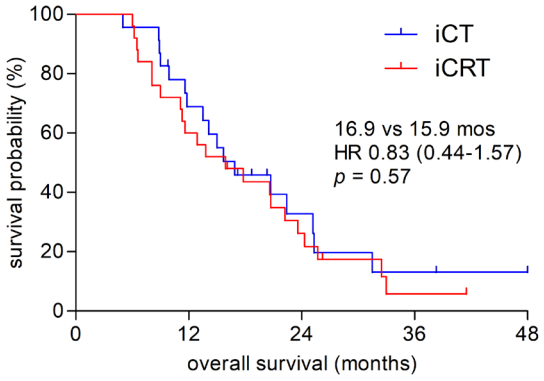

Figure 2. Overall survival of all patients. Abbreviations: iCT-induction/neoadjuvant chemotherapy only (mFOLFIRINOX); iCT+RT-induction/neoadjuvant chemotherapy and consolidation radiotherapy

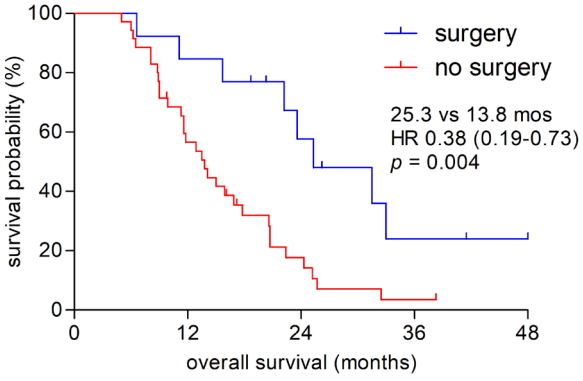

Figure 3. Overall survival of resected versus non-resected patients.

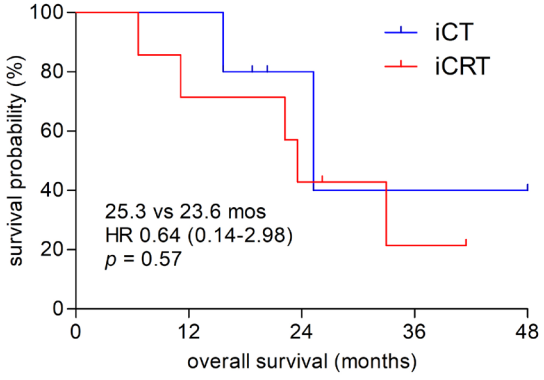

Figure 4. Overall survival of resected patients. Abbreviations: iCT-induction/neoadjuvant chemotherapy only (mFOLFIRINOX); iCT+RT-induction/neoadjuvant chemotherapy and consolidation radiotherapy

Table 3. Resectability and therapy results in resected patients.

Variables	Total n (%)	iCT only n (%)	iCRT n (%)	p-value
resectability:	12 (25%)	5 (21.7%)	7 (28%)	0.863
BRPC	6 (42.9%)	3 (37.5%)	3 (50%)	0.920
LAPC	6 (17.6%)	2 (13.3%)	4 (21%)	0.887
pCR	2 (4.2%)	1 (4.3%)	1 (4%)	0.952
mOS resected (month)	25.3	27.3	23.6	0.422
1y OS (n, %)	10 (83.3%)	5 (100%)	5 (71.4%)	0.882
2y OS (n, %)	6 (46.1%)	3 (60%)	3 (42.9%)	0.913
3y OS (n, %)	2 (16.7%)	1 (20%)	1 (14.3%)	0.952

Abbreviations: n-number of patients; iCT-induction/neoadjuvant chemotherapy only; iCRT-induction/neoadjuvant chemotherapy combined with radiotherapy; BRPC-borderline resectable pancreatic carcinoma; LAPC-locally advanced pancreatic carcinoma; pCR-pathological complete remission; mOS-median overall survival; 1y OS-overall survival in one year; 2 y OS-overall survival in the second year; 3y OS-overall survival in the third year

Table 4. Disease relapse/progression.

Variables	Total n (%)	iCT only n (%)	iCRT n (%)	p-value
dMFS (month)	8.5	9.2	6.6	0.182
Relapse	40 (80.4%)	19 (73%)	21 (84%)	0.791
Local-LR/LP	7 (17.1%)	5 (26.3%)	2 (9.5%)	0.163
Liver	19 (46.3%)	10 (52.6%)	9 (43%)	0.537
only	14 (34.1%)	7 (36.8%)	7 (33%)	0.816
combined	5 (12.2%)	3 (15.8%)	2 (9.5%)	0.550
Peritoneal	15 (36.6%)	10 (52.6%)	7 (33.3%)	0.218
only	7 (17.1%)	5 (26.3%)	3 (14.3%)	0.342
combined	4 (9.7%)	5 (26.3%)	4 (19%)	0.583
Pulmonal	4 (9.7%)	0	4 (19%)	0.045
only	2 (4.9%)	0	2 (9.5%)	ND
combined	2 (4.9%)	0	2 (9.5%)	ND
Lymphonodal	6 (14.6%)	2 (10.5%)	4 (19%)	0.451
only	1 (2.4%)	0	1 (4.8%)	ND
combined	5 (12.2%)	2 (10.5%)	3 (14.3%)	0.720
Other	1 (2.4%)	0	1 (4.8%)	ND

Abbreviations: n-number of patients; iCT-induction/neoadjuvant chemotherapy only; iCRT-induction/neoadjuvant chemotherapy combined with radiotherapy; BRPC-borderline resectable pancreatic carcinoma; LAPC-locally advanced pancreatic carcinoma; dMFS-distant metastasis-free survival; LR-local relapse; LP-local progression; ND-cannot be evaluated

with the highest proportion of hepatic metastases (46.3%) followed by peritoneal (36.5%) and other metastases (e.g., pulmonary, lymph nodal, approx. 10–15%) [32, 33]. The significantly higher incidence of lung metastases in the chemoradiotherapy group compared to the chemotherapy group (19% of patients in the iCRT vs 0% in the ICT group; p=0.045) observed in our study has not been described so far. Nine percent of patients in the iCRT group had solely lung metastases, which corresponds to the incidence of metachronous metastases only in the lungs of 5.3–6.4% described elsewhere [34, 35]. This borderline significant difference could be caused either by chance (arising as an artifact caused by small numbers) but, considering that no difference between groups was detected in the other metastases, the possibility of selection of organotropic lung-specific clones on the basis of applied radiotherapy could not be excluded [32, 35–37]. Recently published works have confirmed organotropism, suggesting that the site of relapse can be predicted by genetic profiling of the original tumor. In those studies, approx. 20 genes were proposed, the differential expression of which has been identified as a causative factor for specific organotropism and better prognosis for patients with lung metastases only (CD63, LAMP1) [37, 38].

The major limitations of our study are its retrospective design and the rather small cohort of patients. Although the two participating departments are among the largest in the Czech Republic treating this disease, covering approx. over 2 mil. population, we were unable to collect a larger eligible patient group. Despite the small cohort size, our results on the efficacy of induction combined therapy versus chemotherapy alone were more or less consistent with other published work, both in terms of patient distribution, as well as resectability and survival parameters [10, 12, 30, 39].

The results of our study are in line with other studies describing the ambiguous role of radiotherapy as a part of systemic therapy in borderline resectable and locally advanced upfront unresectable pancreatic cancer. However, adding radiotherapy to the induction/neoadjuvant mFOLFIRINOX chemotherapy had no proven significant impact on the survival of patients. Our results confirmed that in these patients, the ability to undergo radical resection after the neoadjuvant treatment (based on a reasonable evaluation of expected morbidity/mortality) remains the only prognostic factor for prolonged survival. It is worth highlighting the significantly higher rate of lung metastases in the group of patients treated with combination therapy compared to chemotherapy alone. Whether this is due to bias because of the small sample size or due to the possibility of clonal selection with primary lung organography, could only be shown by further research.

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