Clinics of Oncology

Research Article ISSN: 2640-1037 | Volume 5

Pancreatic Adenocarcinoma with Isolated Venous Involvement: Is Neoadjuvant Treatment Worthy?

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Received: 06 Oct 2021
Accepted: 20 Oct 2021
Published: 25 Oct 2021

Keywords:

Pancreatic adenocarcinoma, Neoadjuvant treatment, Neoadjuvant radio-chemotherapy, Venous involvement, Venous resection, Duodenopancreatectomy

Citation:

Jaffrezic P, Pancreatic Adenocarcinoma with Isolated Venous Involvement: Is Neoadjuvant Treatment Worthy?. Clin Onco. 2021; 5(5): 1-8

1. Abstract

Neoadjuvant Treatment (NAT) is indicated in locally advanced tumors and improves the results of subsequent surgery. In borderline tumors, the place of this preoperative treatment is more controversial, probably because borderline tumors are a heterogeneous group. We focused on the tumors with venous involvement without any arterial involvement and studied the results of neoadjuvant treatment in this particular group.

1.1. Methods: From 2004 to 2016, in Bordeaux University Hospital, Dept. of digestive surgery, 287 patients underwent a Whipple procedure for Pancreatic Adenocarcinoma (PA), 117 had a NAT. We collected all the patients who had on pre-operative screening a tumor with isolated venous involvement and compared patients who had NAT (NA group, n=50) and those who did not (R group, n=34). Pathology results (tumor size, N0 rate, R0 rate), overall and disease-free survival were studied.

1.2. Results: Complete resection was obtained in 43 (86%) patients in NA group vs 25 (74.5%) in R group. There was 46% N+ in NA group vs 73.5% in R group (p=0,01%). Median overall survivals were respectively 35.2m vs 22.3m (p=0.37). Disease-free survival was 20.6m vs 13.6m (p=0.29). Five-year survival was not statistically different.

1.3. Conclusion: This retrospective series is not able to strongly support the indication of neoadjuvant treatment in patient with isolated venous involvement, even if it confirms its safety on surgical out-comes and its efficiency on the tumor down staging. A prospective trial with intention to treat analysis is mandatory to bring a clear response.

2. Introduction

Pancreatic ductal adenocarcinoma has a poor prognosis with overall five-year survival of 6%. It's the seventh deadliest cancer in the world but only the 11th most common cancer [1]. In France, between 1982 and 2012 incidence of pancreatic cancer has increased for men (from 4,8/100000 to 9,6/100000) and women (from 2,3/100000 to 6,8/100000) [2]. In 2014 13346 new patients were treated, 11052 deaths were reported [3]. In US, pancreas cancers are projected to surpass breast, prostate, and colorectal cancers to become the second leading causes of cancer-related death by 2030 [4].

Complete surgical resection is the only curative treatment; however, R0 resection rates are still low (10-22%) [4, 5]. Many studies reported that adjuvant therapy after pancreatic surgery increased patient survival [6-8]. This adjuvant therapy has to be initiated as soon as possible [9], but may be delayed or even cancelled because of surgical complication and delayed recovery [10]. NAT on the contrary is always feasible and moreover, a lot of studies demonstrated that it increases the resection rate [11-15]. In particular, neoadjuvant chemo-radiotherapy can increased resection rate and R0 resection rates with a better median survival [12, 15, 16]. Today, pancreatic cancer 5-year survival rate have risen to a record high, 7.9%, in the UK [17].

Non metastatic pancreatic tumors are often divided in 3 groups: potentially resectable, borderline resectable and locally advanced [18]. NAT is undisputable for locally advanced tumors [19-23], and increased R0 resection rates for borderline tumors [19, 24, 25]. But the question remains open for tu-mors with isolated venous involvement. Indeed, tumors with venous contact are either resectable (if contact <180°) or borderline (if involvement ≥180°) and neoadjuvant treatment is not a paradigm for resectable tumors, especially because venous resection is safe. In fact, surgical mortality is not in-creased with venous resection and is not predictive of disease-free or overall survival [26, 27]. Howev-er, recent study seems to suggest favorable oncologic benefits for this kind of tumors [28].

In this retrospective observational study, we focused on patients with isolated venous involvement or abutment who had Whipple procedure following NAT.

3. Methods

For this observational retrospective study, we included all patients who underwent a Whipple procedure in our center (Bordeaux University Hospital, Department of digestive surgery) for Pancreatic Adenocarcinoma (PA) from January 2004 to December 2016. A total of 287 patients had a Whipple procedure for PA. 169 had surgery first, 112 had a neoadjuvant treatment.

Preoperative contrast-enhanced Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) was performed for all the patients allowing a precise staging.

In order to specify the vascular contacts of the tumor, we used a local classification of vascular involvement. All tumors were classified 0 (no involvement), 1 (abutment or involvement between 0 and 180°) or 2 (involvement >180° or vascular stenosis), for superior mesenteric vein or portal vein (MV), superior Mesenteric Artery (MA), Hepatic Artery (HA) and coeliac artery (C). Every patient was classified MV x, MA x, HA x and C x, depending on diagnostic CT-scan.

We included all patients who had just on CT-scanner or MRI, a venous involvement, i.e., MV 1 or 2, MA 0, HA 0, C 0. All patients who had no pancreatic ductal adenocarcinoma on histologic analysis were excluded from our study.

We divided patients in two groups:

- NA group for patients who had surgery following neoadjuvant treatment
- R group for patients who had surgery without neoadjuvant treatment, i.e. our control group

Every decision of NAT or first-line resection were decided in multidisciplinary meeting, depending on ongoing clinical trials, trials result and medical experience.

Eighty-five patients had a venous abutment or involvement (MV1 or MV2) without any arterial abutment (MA0, HA0, and C0). Pathology exam was not possible for one surgical specimen because of a bad formalin fixation. The patient was excluded from the study. 50 (59.5%) had surgery after NAT (NA group, n= 50), 34 (40.5%) had surgery first (R group, n =34).

NAT consisted in exclusive chemotherapy (CT) for 9 patients, or an association of radiotherapy and chemotherapy (RCT) for 41 patients, protocols of chemotherapy were FOLFIRINOX [25], gemcitabine-based CT [13], Cisplatin LV5 FU2 (4). For patients who had radiotherapy (41/50), radiation doses were applied with daily fractions of 1.8 Gy, 5 days a week, for a total of 45, 50,5 or 59 Gy. Four weeks after completion of first and second rounds of neoadjuvant treatment, CT-scan was con-ducted.

Pancreaticoduodenectomies were conducted with en-bloc resection. During procedure, vascular resection was decided by surgeon, with regards to the adhesion between pancreatic tumor and the vein. Tangential or segmental vein resections were conducted according to the importance of the adherence and the feasibility of reconstruction in-order to achieve R0 resection.

Neoadjuvant treatment, when performed (17 (34%) in NA-group, 24 (70.96%) in R-group), was FOLFOX (or FOLFIRINOX) or gemcitabine-based CT.

Statistical analyses were performed using Prism 6® software program for Mac OS.

Minimal follow-up was 12 months. Overall survival was calculated from the time of surgery to death or the last follow-up day. Disease-free survival was calculated from the time of surgery to recur-rence diagnosis or last follow-up day. Overall survival from diagnosis was calculated from the time of diagnosis to death or last-follow-up day. Disease-free survival was calculated from the time of diag-nostic to recurrence diagnostic or last follow-up day. Survival time was analyzed using Kaplan-Meier method. Differences in survival were compared using log-rank test. Patient's characteristics, periopera-tive outcomes and pathological results among the 2 groups were compared with non-parametrical Mann-Whitney test for continuous variable and Fischer test for categorical variables. Repeated measures data between same pa-

tients were compared with Wilcoxon matched-pairs signed rank test. P-value < 0.05 was considered statistically significant.

Primary endpoint was disease-free survival.

Secondary endpoints were overall survival, complete resection ratio, positive nodes ratio, and tu-mor size.

4. Results

Forty-three patients were male, 41 were female. Median age was 65.7 (59.2-71) years. Thirty-four patients belong to R group, 50 patients to NA group. Patients were older in the R group (68.9 years) than in the NA group (62.2). At diagnosis tumors were bigger in NA group (median = 30 mm) than in R group (median = 25 mm). Tumor characteristics were similar except for uncus tumors, more fre-quents in NA group (18% vs 2.9%). Venous involvement >180° were more important in the NA group (46% vs 17.6%).

Table 1: Demographic and tumor characteristics of 84 patients with venous involvement

	NA group (n=50)	R group (n=34)	Total (n=84)	p
Age (years) (median)	62.8 (54.2-68.4)	68.9 (57.1-71.3)	65.7 (59.25-71)	0.009
Male	28 (56%)	15 (44.1%)	43 (51.2%)	ns
Tobacco use	16 (32%)	6 (17.6%)	22 (26.2%)	ns
- PA (median)	20 (15-30)	17.5 (11.25-23.75)	20 (10-30)	
ASA (median)	2 (1-2)	2 (2-2)	2 (2-2)	ns
Weight loss (kg) (median)	5 (0-8)	5 (0-7.75)	4.75 (0-8)	ns
BMI (kg/m²) (median)	23.4 (21.1-25.5)	23.2 (21.5-24.6)	23.3 (21.1-25.4)	ns
Tumor size (mm) (median)	30 (25-38)	25 (22-30)	30 (23-34.3)	0,01
Tumor site				
- Head	39 (78%)	32 (94.1%)	71 (84.5%)	
- Uncus	9 (18%)	1 (2.9%)	10 (11.9%)	
- Isthmus	2 (4%)	1 (2.9%)	3 (3.6%)	ns
Dilatation				
- bile duct system	36 (72%)	26 (76.5%)	62 (73.8%)	ns
- pancreatic duct	36 (72%)	26 (76.5%)	59 (70.2%)	ns
Lymph nodes	19 (38%)	11 (32.35%)	30 (35.7%)	ns
MV1	27 (54%)	28 (82.4%)	55 (65.5%)	0.01
MV2	23 (46%)	6 (17.6%)	29 (34.5%)	0.01

Median time from diagnostic to surgery was 1.07 month in R group and 8.38 month in the NA group. Median operating time was longer in NA group (318 min) than in R group (260 min). Venous resection frequency was similar in the two groups. Kind, severity and frequency of complications were similar in the 2 groups, in particular pancreatic fistula (20.6 % in R group vs 19.6 % in NA group). 3 patients had grade C fistula, 1 in NA group, 2 in R group. In postoperative time, 1 patient died in NA group from hemorrhage, no patients in R group.

Table 2: Operative characteristics and post-operative time of the 84 patients

	NA group (n=50)	R group (n=34)	p
Time from diagnostic to surgery (month) (median)	8.47 (7.54-9.56)	1.07 (0.69-2.34)	0.0001001
Operating time (min) (median)	318 (258-403)	260 (227-325)	0.024
Venous resection	25 (50%)	15 (44.1%)	ns
Arterial resection	1 (2%)	0	ns
Pancreatic duct size (mm) (median)	5 (3-7)	5 (3-6)	ns
Anastomosis			
- pancreaticojejunostomy	28 (56%)	17 (50%)	ns
- pancreaticogastrostomy	17 (34%)	16 (47.1%)	ns
- wirsungostomy	2 (4%)	0	ns
- total pancreatectomy	3 (6%)	1 (2.9%)	ns
Length of hospital stay (median)	15 (13-20.5)	17 (13-21)	ns
DINDO			
- I	17 (34%)	10 (29.4%)	ns
- II	25 (50%)	15 (44.1%)	ns
- IIIa	1 (2%)	2 (5.9%)	ns
- IIIb	2 (4%)	1 (2.9%)	ns
- IVa	1 (2%)	1 (2.9%)	ns
- IVb	0	0	ns
- V	1 (2%)	0	ns
Complications			
- Pancreatic fistula	9 (18%)	7 (20.6%)	ns
- Delay gastric emptying	6 (12%)	4 (11.8%)	ns
- Hemorrhage	2 (4%)	1 (2.9%)	ns
- Other	5 (10%)	3 (8.8%)	ns
Rehospitalization	6 (12%)	5 (14.7%)	ns

There were no pT4. There were more pT3 in the R group (91.1%) than in the NA group (68%). Tumor size was not significantly bigger in the R group (p=0.058). Tumoral nodes were more frequent in R group (73.5%) than in the NA group (46%).

For R group, median tumor size was 25 mm (22-30) at diagnostic CT-scan and 28.5 mm (22.25-30.5) at pathological exam (p=0.77). For NA group, median tumor size was 30 mm (25-38) and 23 mm (18-30) at pathological exam (p=0.0009).

Adjuvant treatment was more frequent in R group (n=24, 70.6%) than in NA group (n=17, 32.7%).

Follow-up was at least 12 months. 1 patient was lost of follow-up after 23.7 months because he moved in another country.

Median disease-free survival after surgery was 20.6 months for NA group vs 13.6 months in R group. Median overall survival after surgery was 35.2 months in NA group vs 22.3 in R group. Differences were not significant with log-rank test.

Median disease-free survival from diagnostic was 31 months for NA group vs 16.7 months in R group (p=0.025). Median overall survival from diagnostic was 44.6 months for NA group vs 24.9 month in R group (p=0.11).

Because neoadjuvant treatment was different, we made complementary analysis. Median disease-free survival was 54.4 month for patients from NA group who had FOLFIRINOX or FOLFOX vs 10 months for other patients (p=0.09). Median overall survival was 54.4 months for patients from NA group who had FOLFIRINOX or FOLFOX vs 26.6 months for others patients.

Table 3: Pathological results for 84 patients

	NA group (n=50)	R group (n=34)	p
Median tumor size (mm)	23 (18-30)	28.5 (22.25-30.5)	0.058
TNM			
- T0	6 (12%)	0 (0%)	0.08
T1	6 (12%)	1 (2.9%)	
T2	4 (8%)	2 (5.9%)	
T3	34 (68%)	31 (91.1%)	0.016
- N+	23 (46%)	25 (73.5%)	0.01
- M+	1 (2%)	1 (2.9%)	ns
Tumoral nodes ratio (median)	0 (0-7.9)	7(0.7-21.7)	0.009
Différenciation			
- well	12 (24%)	8 (23.5%)	ns
- moderate	25 (50%)	20 (58.8%)	ns
- poor	0 (0%)	3 (8.8%)	ns
- other	3 (6%)	1 (2.9%)	ns
Lymphovascular invasion	19 (38%)	19 (55.9%)	ns
Perineural invasion	29 (58 %)	27 (79.4%)	0.059
Complete resection (R0)	43 (86%)	25 (73.5%)	ns

Table 4: Survival and recurrence of 85 patients

	NA group (n=50)	R group (n=34)	p
Adjuvant treatment	17 (34%)	24 (70.6%)	0.0008
One year survival	0.78	0.824	
Two years suvival	0.608	0.385	
Five year survival	0.315	0.292	
Median overall survival (month)	35.2	22.3	ns
Recurrence	28 (56%)	24 (70.6%)	ns
- local	3	4	ns
- nodes	0	0	ns
- lever	6	7	ns
- peritoneal	8	1	0.02
- lung	3	3	ns
- other	0	0	ns
- diffuse	4	6	ns
Median disease-free survival (month)	20.6	13.6	ns

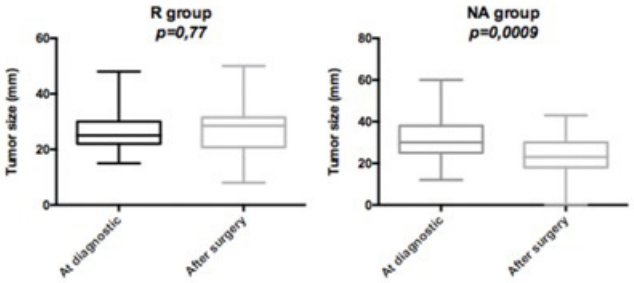

Figure 1: Tumor size at diagnostic (CT-scan) and after surgery (at pathological exam)

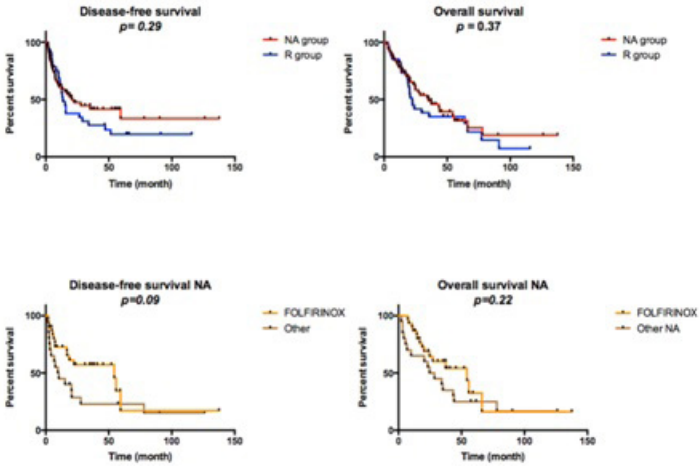

Figure 2: Disease-free and overall survivals

5. Discussion

In pancreatic head adenocarcinoma, vascular and in particular venous abutment or involvement is a key point of resectability and the classifications are partially based on it

- Classifications from NCCN and MDACC in resectable/ borderline/ locally advanced are un-clear. According to NCCN, venous abutment without artery abutment can be either resectable (if <180° without vein contour irregularity), either borderline resectable [29]. According to MDACC (University of Texas D Anderson Cancer Center), venous involvement without oc-clusion is potentially resectable [16, 30].
- From oncological point of view, the question about neoadjuvant treatment has not been solved yet, especially in resectable tumors but also for borderline tumors. Homogenous group of pa-tients are difficult to obtain because of unclear classification (Groups of borderline patients can include patients with just venous involvement but arterial abutment too, venous abutment or involvement can be classified in two kind of group, depending of the classification choice made by medical staff). This question about classification increases the difficulty to interpret studies and metanalyses about neoadjuvant treatment [31, 32].
- From a technical point of view, contrary to arterial resection [33-35], venous resection is con-sidered as safe and useful to achieve complete resection [34, 36, 37]. Lots of questions are still open: is it necessary to do systematic resection [32]? Which kind of resection (lateral, resection, end-to-end anastomosis) is the best [32, 33]?

In our center, every patient's treatment is discussed weekly in multidisciplinary meeting with on-cologists, gastroenterologists, radiologists and specialized digestive surgeons. Tumors and vascular abutment were analyzed for each patient with our simple classification MVx, MAx, HAx and Cx and classified in resectable/ borderline/locally advanced. NAT or not were decided depending on several studies protocols or depending on subjective criteria when no studies protocols were on progress. NAT has been criticized as a loss of chance because some patients progressed in the meantime and did not reach surgery. We believe that one interest of NAT is the selection of patients allowing the exclusion of progressive patients with aggressive tumors which anyway wouldn't be good candidates to surgery.

That's why in our center, the frequency of NAT was high in the group of patients with only ve-nous involment or abutment. As a matter of fact, the decision in our multidisciplinary staff was to per-form the NAT when the tumor seemed aggressive (size, CA19 9). We are aware that the characteristics of the patients from NA group and R group are different: tumors were bigger and median age lower. A case-control study would have been preferable but it was impossible considering the size of the groups.

Moreover, our long-term results need to be examined with precaution because it is not an inten-tion-to-treat study. The period between diagnostic and surgery is significantly longer in NA group be-cause of the pre-operative treatment (8.47m vs 1.07m). We decide to calculate survival after surgery and not after diagnostic to avoid a bias.

Median disease-free survival after pancreaticoduodenectomy was 20.6 month in NA group versus 13.6 months in R group. Log-rank test has found no significant difference between the 2 groups. About overall-survival, we didn't find some significant differences either: median survival was 35.2 months in NA-group and 22.3 months in R-group. It is interesting to note that's the survival in the NAT group, encompassing patients with more advanced tumors, was slightly better than in the front line surgery group, even the statistical difference was not reached, probably because of the small size of the groups.

Recent meta-analysis about resectable and borderline resectable pancreatic adenocarcinoma found lower median survival after resection (26.1m vs 15.0m) [31] probably because of heterogeneity in vascular involvement and neoadjuvant treatment. Some recent study suggests the interest of neoadju-vant treatment for tumors with venous contact only [28]. But considering our primary endpoint we are not able to demonstrate that NAT is beneficial in term

of survival.

Nevertheless, efficiency of NAT on pancreatic adenocarcinoma is confirmed in our study:

- Wilcoxon matched-pairs signed rank test found a significant difference in group NA between tumor size before and after neoadjuvant treatment. This result confirms efficacy of neoadju-vant treatment on downsizing for tumors with only venous involvement.
- Concerning downstaging, 6 patients (12%) in NA group were T0 on pathological analyze. T3 tumors in NA group was less frequent than in R group (68 % vs 91.1%, p=0.016). Positive lymph nodes were more frequent in R group than in NA group (26.5 % vs 54%) with tumoral nodes ratio significantly different. These data are confirmed by other studies [31, 32].

Complete resection was similar in the two groups, 86% in NA group, 73,5% in R group, despite bigger tumors and more venous involment on CT-scan in NA group. This result is in favor of neoadju-vant treatment. In fact, we know than complete resection is a good-prognosis criterion [38-40].

NAT does not influence the postoperative course even if surgery was longer in NA group than in R group. Recent meta-analysis confirms longer procedure after neoadjuvant therapy but it includes local-ly advanced tumors or borderline tumors with arterial involvement [41]. In our series, the prolonged time was mostly due to difficulties in dissection after radiotherapy. Interestingly venous involvement doesn't seem to explain differences for operative length because venous resection was as frequent in R group (44.1%) as in NA group (50%).

Concerning post-operative period, complications were similar in term of frequency, kind or severi-ty. and similar than in other studies [42]. Median length of stay in the hospital is logically not different for the two groups. Unlike some studies, we didn't find less pancreatic fistula in NA group (18%) vs in R group (20.6%) [41]. In NA group, only 34% of patients had adjuvant therapy, but logically 100% of them had systemic treatment before surgery. In R group, 10 patients (29.4%) had no adjuvant therapy after resection because of delayed recovery, less than in other studies [10, 43]. We know that adjuvant therapy must not be delayed to increase survival after resection [6, 9], which can be a challenge be-cause of the morbidity in pancreatocoduodenectomies. That's why neoadjuvant treatment is a better chance for patients to receive a complete treatment (local and systemic). A recent study suggests that the addition of AT after NT is beneficial for patients with low-risk pathology. Today adjuvant treat-ment after NAT should be reconsidered, especially for patient with good response [44].

About neoadjuvant and adjuvant treatment, protocols evolved with time. Before FOLFIRINOX, other treatments (5-FU, Gemcitabine) were the reference. With FOLFIRINOX, disease-free survival seemed to be better in our study but we need more follow-up time to confirm it. This chemotherapy is relatively new in neoadjuvant treatment. It already proves its interest for locally advanced pancreatic cancer [19, 20, 24, 45] and for metastatic pancreatic cancer [46] despite lower quality of life [47]. Some new results in neoadjuvant treatment for borderline tumors are interesting [48, 49] but we still need more studies. Moreover, in the similar study of Lee et al., neoadjuvant treatment was based on Gemcitabine [28]. Literature reports better results for FOLFIRINOX compared to gemcitabine or cape-citabine in neoadjuvant treatment for locally advanced tumors [50]. Today it should be interesting to consider FOLFIRINOX in neoadjuvant for tumors with venous involment alone. Gemcitabine/Nab-Paclitaxel may be a good option for neoadjuvant therapy too [51, 52].

In conclusion, pancreaticoduodenectomy after neoadjuvant for adenocarcinoma with venous involvement only is as safe as up-front surgery. It provides good results in term of downsizing (smaller tumors) and down staging (more T0, T1 and T2, less N+)., Despite bigger tumors with worse venous involvement, frequency of complete resection is the same after neoadjuvant treatment than without. De-spite longer surgery, frequency of post-operative complications is the same. Despite worst prognosis tumors, long-term survival and disease-free survival are comparable. Despite post-operative complications or longer recovery, every patient operated after neoadjuvant treatment had complete treatment.

This study confirms that neoadjuvant treatment can be an option for selected patients with only venous involvement. But insufficient number of patient, retrospective character and differences in neoadjuvant protocols are major disadvantages that we share with other studies. That's why multicenter series and meta-analyses would be interesting to study the benefit of NAT in this particular group. In order to eliminate the biais, a randomized trial, even difficult to construct, would be indeed the best option.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. Févr. 2015; 65(1): 5-29.
2. Bouvier A-M, Uhry Z, Jooste V, Drouillard A, Remontet L, Launoy G, et al. Focus on an unu-sual rise in pancreatic cancer incidence in France. Int J Epidemiol. 2017; 46(6): 1764-72.
3. Maire F, Cibot J-O, Compagne C, Hentic O, Hammel P, Muller N, et al. Epidemiology of pan-creatic cancer in France: descriptive study from the French national hospital database. Eur J Gastroen-terol Hepatol. 2017; 29(8): 904-8.
4. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014; 74(11): 2913-21.

5. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, et al. Resected adenocar-cinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2000; 4(6): 567-79.
6. Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, et al. Adjuvant chemora-diotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet Lond Engl. 2001; 358(9293): 1576-85.
7. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007; 297(3): 267-77.
8. Garofalo MC, Regine WF, Tan MT. On statistical reanalysis, the EORTC trial is a positive trial for adjuvant chemoradiation in pancreatic cancer. Ann Surg. 2006; 244(2): 332-3.
9. Murakami Y, Uemura K, Sudo T, Hashimoto Y, Kondo N, Nakagawa N, et al. Early initiation of adjuvant chemotherapy improves survival of patients with pancreatic carcinoma after surgical re-section. Cancer Chemother Pharmacol. 2013; 71(2): 419-29.
10. Wu W, He J, Cameron JL, Makary M, Soares K, Ahuja N, et al. The impact of postop-erative complications on the administration of adjuvant therapy following pancreaticoduodenectomy for adenocarcinoma. Ann Surg Oncol. 2014; 21(9): 2873-81.
11. Spitz FR, Abbruzzese JL, Lee JE, Pisters PW, Lowy AM, Fenoglio CJ, et al. Preopera-tive and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol Off J Am Soc Clin Oncol. 1997; 15(3): 928-37.
12. Varadhachary GR, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PWT, et al. Preopera-tive gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocar-cinoma of the pancreatic head. J Clin Oncol Off J Am Soc Clin Oncol. 2008; 26(21): 3487-95.
13. Landry J, Catalano PJ, Staley C, Harris W, Hoffman J, Talamonti M, et al. Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin fol-lowed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. J Surg Oncol. 2010; 101(7): 587-92.
14. Pisters PW, Abbruzzese JL, Janjan NA, Cleary KR, Charnsangavej C, Goswitz MS, et al. Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radia-tion therapy for resectable pancreatic adenocarcinoma. J Clin Oncol Off J Am Soc Clin Oncol. 1998; 16(12): 3843-50.
15. Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PWT, et al. Preopera-tive Gemcitabine-Based Chemoradiation for Patients With Resectable Adenocarcinoma of the Pancre-atic Head. J Clin Oncol. 2008; 26(21): 3496-502.
16. Katz MHG, Pisters PWT, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline re-sectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008; 206(5): 833-46.
17. Action PC. Pancreatic cancer survival rates now almost 8% · Pancreatic Cancer Action [Internet]. Pancreatic Cancer Action. 2020.
18. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, et al. Bor-derline resectable pancreatic cancer: A consensus statement by the International Study Group of Pan-creatic Surgery (ISGPS). Surgery. 2014; 155(6): 977-88.
19. Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, et al. Neoadjuvant Modified (m) FOLFIRINOX for Locally Advanced Unresectable (LAPC) and Borderline Resectable (BRPC) Adenocarcinoma of the Pancreas. Ann Surg Oncol. 2015; 22(4): 1153-9.
20. Faris JE, Blaszkowsky LS, McDermott S, Guimaraes AR, Szymonifka J, Huynh MA, et al. FOLFIRINOX in Locally Advanced Pancreatic Cancer: The Massachusetts General Hospital Cancer Center Experience. The Oncologist. 2013; 18(5): 543-8.
21. Turrini O, Viret F, Moureau-Zabotto L, Guiramand J, Moutardier V, Lelong B, et al. Neoadjuvant chemoradiation and pancreaticoduodenectomy for initially locally advanced head pan-creatic adenocarcinoma. Eur J Surg Oncol EJSO. 2009; 35(12): 1306-11.
22. Zhu C-P, Shi J, Chen Y-X, Xie W-F, Lin Y. Gemcitabine in the chemoradiotherapy for locally advanced pancreatic cancer: a meta-analysis. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2011; 99(2): 108-13.
23. Gillen S, Schuster T, Meyer zum Büschenfelde C, Friess H, Kleeff J. Preopera-tive/Neoadjuvant Therapy in Pancreatic Cancer: A Systematic Review and Meta-analysis of Response and Resection Percentages. PLoS Med [Internet]. 2010; 7(4): e1000267.
24. Christians KK, Tsai S, Mahmoud A, Ritch P, Thomas JP, Wiebe L, et al. Neoadjuvant FOLFIRINOX for Borderline Resectable Pancreas Cancer: A New Treatment Paradigm? The Oncolo-gist. 2014; 19(3): 266-74.
25. Tang K, Lu W, Qin W, Wu Y. Neoadjuvant therapy for patients with borderline resec-table pancreatic cancer: A systematic review and meta-analysis of response and resection percentages. Pancreatology. 2016; 16(1): 28-37.
26. Kelly KJ, Winslow E, Kooby D, Lad NL, Parikh AA, Scoggins CR, et al. Vein In-volvement During Pancreaticoduodenectomy: Is There a Need for Redefinition of "Borderline Resec-table Disease"? J Gastrointest Surg. 2013; 17(7): 1209-17.
27. Murakami Y, Satoi S, Motoi F, Sho M, Kawai M, Matsumoto I, et al. Portal or superior mesenteric vein resection in pancreatoduodenectomy for pancreatic head carcinoma. BJS. 2015; 102(7): 837-46.
28. Lee JH, Kang CM, Bang SM, Choi JY, Seong JS, Hwang HK, et al. The Role of Neoad-juvant Chemoradiation Therapy in Patients With Borderline Resectable Pancreatic Cancer With Isolat-ed Venous Vascular Involvement. Medicine (Baltimore) [Internet]. 2015; 94(31): e1233.
29. Tempero MA, Malafa MP, Behrman SW, Benson AB, Casper ES, Chiorean EG, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines. J Natl Compr Cancer Netw JNCCN. 2014; 12(8): 1083-93.

30. Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol. 2006; 13(8): 1035-46.

31. Versteijne E, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or border-line resectable pancreatic cancer. Br J Surg. 2018; 105(8): 946-58.

32. Pan L, Fang J, Tong C, Chen M, Zhang B, Juengpanich S, et al. Survival benefits of ne-oadjuvant chemo(radio)therapy versus surgery first in patients with resectable or borderline resectable pancreatic cancer: a systematic review and meta-analysis. World J Surg Oncol [Internet]. 2019; 18: 1.

33. Amano H, Miura F, Toyota N, Wada K, Katoh K, Hayano K, et al. Is pancreatectomy with arterial reconstruction a safe and useful procedure for locally advanced pancreatic cancer? J Hepatobiliary Pancreat Surg. 2009; 16(6): 850-7.

34. Zettervall SL, Ju T, Holzmacher JL, Huysman B, Werba G, Sidawy A, et al. Arterial, but Not Venous, Reconstruction Increases 30-Day Morbidity and Mortality in Pancreaticoduodenec-tomy. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2019; 24(3): 578-84.

35. Loveday BPT, Zilbert N, Serrano PE, Tomiyama K, Tremblay A, Fox AM, et al. Neoad-juvant therapy and major arterial resection for potentially reconstructable arterial involvement by stage 3 adenocarcinoma of the pancreas. HPB. 2019; 21(6): 643-52.

36. Ravikumar R, Sabin C, Hilal MA, Al-Hilli A, Aroori S, Bond-Smith G, et al. Impact of portal vein infiltration and type of venous reconstruction in surgery for borderline resectable pancreat-ic cancer. BJS. 2017; 104(11): 1539-48.

37. Alemi F, Rocha FG, Helton WS, Biehl T, Alseidi A. Classification and techniques of en bloc venous reconstruction for pancreaticoduodenectomy. HPB. 2016; 18(10): 827-34.

38. de Geus SWL, Kasumova GG, Sachs TE, Ng SC, Kent TS, Moser AJ, et al. Neoadju-vant therapy affects margins and margins affect all: perioperative and survival outcomes in resected pancreatic adenocarcinoma. HPB. 2018; 20(6): 573-81.

39. Delpero JR, Bachellier P, Regenet N, Le Treut YP, Paye F, Carrere N, et al. Pancreati-coduodenectomy for pancreatic ductal adenocarcinoma: a French multicentre prospective evaluation of resection margins in 150 evaluable specimens. HPB. 2014; 16(1): 20-33.

40. Campbell F, Smith RA, Whelan P, Sutton R, Raraty M, Neoptolemos JP, et al. Classifi-cation of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. Histopathology. 2009; 55(3): 277-83.

41. Cools KS, Sanoff HK, Kim HJ, Yeh JJ, Stitzenberg KB. Impact of neoadjuvant therapy on postoperative outcomes after pancreaticoduodenectomy. J Surg Oncol. 2018; 118(3): 455-62.

42. Bassi C, Marchegiani G, Giuliani T, Di Gioia A, Andrianello S, Zingaretti CC, et al. Pancreatoduodenectomy at the Verona Pancreas Institute: the Evolution of Indications, Surgical Tech-niques and Outcomes: A Retrospective Analysis of 3000 Consecutive Cases. Ann Surg. 2021.

43. Aloia TA, Aloia TE, Lee JE, Vauthey J-N, Abdalla EK, Wolff RA, et al. Delayed re-covery after pancreaticoduodenectomy: a major factor impairing the delivery of adjuvant therapy? J Am Coll Surg. 2007; 204(3): 347-55.

44. Olecki EJ, Stahl KA, Torres MB, Peng JS, Dixon M, Shen C, et al. Adjuvant Chemo-therapy After Neoadjuvant Chemotherapy for Pancreatic Cancer is Associated with Improved Survival for Patients with Low-Risk Pathology. Ann Surg Oncol. 2021; 28(6): 3111-22.

45. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. A patient-level meta-analysis of FOLFIRINOX for locally advanced pancreatic cancer. Lancet Oncol. 2016; 17(6): 801-10.

46. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFI-RINOX versus Gemcitabine for Metastatic Pancreatic Cancer. N Engl J Med. 2011; 364(19): 1817-25.

47. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guim-baud R, et al. Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial. J Clin Oncol. 2013; 31(1): 23-9.

48. Murphy JE, Wo JY, Ryan DP, Jiang W, Yeap BY, Drapek LC, et al. Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resec-table Pancreatic Adenocarcinoma. JAMA Oncol. 2018; 4(7): 963-9.

49. Katz MHG, Shi Q, Ahmad SA, Herman JM, Marsh R de W, Collisson E, et al. Preopera-tive Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Border-line Resectable Pancreatic Cancer. JAMA Surg. 2016; 151(8): e161137.

50. Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, et al. Locally Advanced Pancreatic Cancer: Neoadjuvant Therapy With Folfirinox Results in Resectability in 60% of the Patients. Ann Surg. 2016; 264(3): 457-63.

51. Dhir M, Zenati MS, Hamad A, Singhi AD, Bahary N, Hogg ME, et al. FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel for Neoadjuvant Treatment of Resectable and Borderline Resec-table Pancreatic Head Adenocarcinoma. Ann Surg Oncol. 2018; 25(7): 1896-903.

52. Vreeland TJ, McAllister F, Javadi S, Prakash LR, Fogelman DR, Ho L, et al. Benefit of Gemcitabine/Nab-Paclitaxel Rescue of Patients with Borderline Resectable or Locally Advanced Pan-creatic Adenocarcinoma After Early Failure of FOLFIRINOX. Pancreas. 2019; 48(6): 837-43.