



A comparative study of neoadjuvant treatment with gemcitabine plus nab-paclitaxel versus surgery first for pancreatic adenocarcinoma



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ABSTRACT

Introduction: Neoadjuvant treatment has been reported to prolong survival in patients with potentially resectable pancreatic adenocarcinoma (PA). However, there are currently limited clinical results available using nab-paclitaxel and gemcitabine in PA.

This paper compares the oncological results of patients affected by potentially resectable PA who underwent surgery first (SF) versus surgery following neoadjuvant treatment (NAT).

Methods: This is an observational, comparative study whereby data were abstracted from a prospective database of patients affected by PA from 2007 to 2016.

Results: We included a total of 81 patients (36 SF and 45 NAT) which resulted in being preoperatively similar.

Among the NAT patients, treatment was well tolerated and the resection rate was 68.8% (31/45 patients). There was a trend towards a higher R1 resection rate in the SF group compared with the NAT (13.8% vs 3.2%; $p = 0.1$). Median overall survival in the resected NAT group was higher (30.6 vs 22.1 months; $p = 0.04$). In the borderline resectable group, overall survival was found to be four times higher compared with SF (43.6 versus 13.5 months; $p = 0.001$).

Conclusions: These data suggest that neoadjuvant treatment with gemcitabine/nab-paclitaxel is a safe and effective option for potentially resectable PA compared with the SF approach.

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1. Introduction

Pancreatic adenocarcinoma (PA) is still considered a malignancy with an extremely poor prognosis [1]. Only 15–20% of patients at the initial diagnosis are suitable for pancreatectomy as most present with metastases or are locally advanced [2].

When surgery is able to be performed, adjuvant chemotherapy, with or without chemoradiation, has been shown to improve overall survival compared with surgery alone, and thus it is now standard treatment for all patients with resectable PA [3].

However, even after the effort of adjuvant treatment, the rate of overall survival (OS) and disease-free survival (DFS) remains poor [2]. The main reason for this is that there is a high recurrence rate after the resection, even if it has been performed with free margins.

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For this reason, PA is currently considered to be a systemic disease, even in the absence of the radiographic evidence of distant metastases. Indeed, micrometastases are claimed to be the reason for this high recurrence [4]. One of the aims of neoadjuvancy is to control micrometastases, minimizing their recurrence and therefore maximizing survival.

In recent years, different schemes of neoadjuvant treatment have been suggested; for example, gemcitabine/nab-paclitaxel has shown its effectiveness in metastatic unresectable PA [3,4].

However, data are still limited in potentially resectable PA and most of them include differing neoadjuvant regimen [3]. Moreover, to the best of our knowledge, there are currently no studies in the literature which compare surgery first (SF) versus surgery after neoadjuvant treatment (NAT) with gemcitabine/nab-paclitaxel in all potentially resectable PA.

In light of these considerations, the aim of the current study was to investigate retrospectively whether or not neoadjuvant treatment with gemcitabine, in combination with nab-paclitaxel, is superior to immediate surgery for potentially resectable PAC.

2. Material and methods

2.1. Patients

2.1.1. NAT group

From 2011 our oncological department started with the neoadjuvancy study for pancreatic adenocarcinoma. Therefore, we prospectively recruited patients with potentially resectable pancreatic cancer with histological or cytological confirmed PA from August 2011 to March 2016 at Sanchinarro University Hospital, Madrid. Inclusion criteria were as follows: age >18 years old; no prior treatment for pancreatic cancer; Eastern Cooperative Group (ECOG) performance status ≤ 1 ; adequate hematologic, renal and liver function; and potentially resectable PA.

The neoadjuvant protocol used was described in our previous study and consisted of Gemcitabine 1000 mg/m² [2] and Nab-paclitaxel 125 mg/m² [2] administered on days 1, 8 and 15 every 28 days for at least two cycles. Starting in 2013, patients also received radiotherapy (RT), which was an intensity-modulated external beam radiation, delivered five days per week over four weeks. Patients received a maximum total dose of 52 Gy.

Adjuvant treatment consisted of four cycles of standard dose of gemcitabine.

2.1.2. SF group

The source of the information was the Sanchinarro Hospital database where data have been entered prospectively on patients who had undergone a pancreatectomy from the start of 2007 to October 2011, the time at which the preoperative neoadjuvant protocol commenced in our oncological department.

In our study, we included patients with PA confirmed in the final pathological exam with the same inclusion criteria of the NAT group, except for those in need of a preoperative biopsy; that is, for the NAT patients, the biopsy was mandatory, while it was not required for the SF group.

We define localized and resectable PA (R-PA) or borderline resectable (BR-PA) according to the NCCN guidelines [5], and assessed by preoperative study (CT scan, MRI and endoscopic ultrasound).

In order to better compare the two groups, we excluded the locally advanced PA from the comparative analysis, as they were not suitable for surgery if preoperative treatment was not provided.

2.2. Preoperative work up

This included tumoral markers CA 19.9, thoraco-abdominal CT scan, FDG-PET scan measuring the maximum standardized uptake value (SUV), pancreato-biliary MRI and endoscopic ultrasound with fine needle biopsy. In the NAT group, jaundice was treated before neoadjuvancy by metallic fully covered biliary stent. In the SF group, when required, only plastic stents were placed.

2.3. Restaging after neoadjuvant treatment in the NAT group

After completing the neoadjuvant regimen, patients underwent to CA 19.9 serum level, an abdominal CT scan, and an FDG-PET scan. Furthermore, patients were restaged and considered for surgical resection if their disease had not progressed with the emergence of metastatic disease [6].

Surgery was performed between four and six weeks after the last cycle of treatment.

Patients found to be unresectable underwent treatment based on different drugs from gemcitabine and nab-paclitaxel (FOLFIRINOX, Irinotecan).

2.4. Chemotherapy related toxicity for NAT group

Treatment related toxicities were evaluated by the National Cancer Institute Common Terminology Criteria of Adverse Events version [7]. In cases of prolonged toxicity of more than one week, chemotherapy was terminated, and surgery was performed after restaging had excluded distant metastases. Severe adverse events are defined as Grade 3 and Grade 4.

2.5. Surgical team

The pancreatectomies were performed at a high-volume hepato-pancreato-biliary center with a mean of 50 pancreatectomies per year. Pancreatectomies of both groups were performed by the same team of surgeons consisting of two highly experienced surgeons and six consultants.

2.6. OS and DFS

OS and DFS were calculated from the time of the diagnosis with biopsy for NAT and from the time of the radiological diagnosis in the SF group.

2.7. Pathological data

Two pathologists using a standardized technique independently reviewed all pathological data. If they were not in agreement, a third pathologist was asked to revise the specimen.

Tumoral stage was assessed according to the sixth edition of the TNM staging system [8].

For the NAT group specimen, the tumor regression grade (TRG) was determined by adapting the rectal cancer Ryan classification (TRG = 0: complete response; TRG = 1: important response; TRG = 2: partial response; TRG = 3: low or no response) (x). Major pathological regressions are defined as TRG 0-1-2.

R1 resection was considered if there were tumor cells present <1 mm of the resection margin.

2.8. Post-operative complications

Complications were graded according to the Clavien–Dindo scoring system and defined as severe from grade III [9]. Pancreatic fistula was classified according to the International Study Group of Pancreatic Fistula (Degrees A, B and C) [10].

2.9. Surveillance

After the operation, patients were seen in clinic two weeks after hospital discharge and then once monthly during the first year after surgery. Following that, they were then seen every three to four months with a focus on surveillance for possible recurrence with a Ct scan every 6 months.

2.10. Endpoints

The primary outcome measure was the overall survival (OS) and the disease-free survival (DFS) for each group. Secondary outcome measures included the R0 resection rate and histological tumoral response, plus the overall toxicity of the neoadjuvant treatment.

2.11. Ethics

The study was approved by the Institutional Ethical Committee of Sanchinarro University Hospital, Madrid, and all patients included in the NAT group were informed about the treatment and

provided their written informed consent. Only a specific written informed consent for pancreatectomy was provided for the SF patients. All patients who met the criteria were offered entry into the study. The study was conducted in agreement with the Declaration of Helsinki specifications regarding studies with human subjects.

2.12. Statistics

Data was recorded in an SPSS Statistics Version 20.0 database.

OS and DFS were estimated by the Kaplan–Meier method. Patients known to be alive were censored at the time of last contact.

To compare the means of the quantitative variables when the variables followed a normal distribution, a variance analysis and a Student's t-test were used. For the remainder of the variables, both the Mann–Whitney and Kruskal–Wallis tests were performed. Statistical significance was defined as having a P value of <0.05.

3. Results

3.1. Patients' data

A total of 81 patients have been included and evaluated. The main demographic and clinical characteristics for each group are shown in Table 1 and have been found to be similar except for the need of a biliary stent. In 29 cases, a biliary stent was placed in the NAT group (64%) and six in the SF group (16.6%), $p = 0.002$.

According to the NCCN guidelines, the overall R-PA and BR-PA were 36 and 45, respectively, and the distribution of each group is depicted in Table 1.

The mean values of pre-treatment CA19.9, SUV and tumoral size all resulted in being similar between both groups (see Table 1).

A total of 20 patients (44%) underwent concomitant neoadjuvant radiotherapy in the NAT group.

At the time of diagnosis, 18 patients (40%) presented with clinical N+ in the NAT group while 20 patients (55.5%) presented in the SF group ($p > 0.5$). After restaging, only 10 (22%) patients resulted in being radiologically N+ of the NAT group. The mean number of nodes examined were similar in both groups; and were 16.7 in the NAT group and 17.4 in the SF group ($p > 0.5$).

3.2. Toxicity and adverse events

All patients completed neoadjuvancy, and treatment was delayed in only four cases (almost three weeks for both patients) because of a severe adverse event (grade 3), as shown in Table 2.

No patients were required to have their chemotherapy permanently suspended or to leave the protocol for toxicity, and no patients presented severe toxicity (grade 4).

3.3. Resectability

A total of 31 patients (68.8%) out of 45 from the NAT group underwent surgical excision.

According to the NCCN classification [11], 15 out of 19 patients from the R-PA of the NAT group underwent surgery (78.9%) and 16 out of 26 patients from the BR-PA group underwent pancreatectomy (61.5%).

A total of 12 patients did not undergo resection because of disease progression during neoadjuvant treatment: six hepatic and four pulmonary progressions. Two more patients were found to be unresectable intraoperatively because of peritoneal metastases.

3.4. Surgical outcome

Types of pancreatectomies are shown in Table 3, with no

Table 1
Main patients characteristics.

| | NAT n = 45 | SF n = 36 | p value |
|---|---------------|--------------|--------------|
| Age (years) | | | |
| Mean (range) | 62.3 (42–81) | 63.5 (46–78) | 0.71 |
| Gender | | | 0.80 |
| Male/Female | 26/16 | 21/15 | |
| BMI Kg/m² | | | |
| mean (range) | 24.7 (21–31) | 25.1 (22–32) | 0.83 |
| ECOG | | | |
| 0 | 28 | 25 | 0.72 |
| 1 | 17 | 16 | |
| Tumor location | | | 0.65 |
| Head | 25 | 18 | |
| Uncinate process | 7 | 3 | |
| Body/Tail | 13 | 15 | |
| Biliary stent (n, %) | 29 (64) | 6 (16.6) | 0.002 |
| Tumoral markers | | | 0.76 |
| Ca 19.9 mean U/mL (range) | 1754 | 1621 | |
| SUV mean (range) | 3.8 (1–10.5) | 3.4 (1.5–12) | |
| Tumor size (mean, range) (cm) | 7.5 | 6.8 | 0.81 |
| cT stage^a | | | 0.78 |
| cT1 | 2 | 3 | |
| cT2 | 14 | 11 | |
| cT3 | 29 | 22 | |
| cN stage | | | 0.64 |
| cN0 | 14 | 16 | |
| cN1 | 18 | 20 | |
| AHPBA category | | | 0.82 |
| R-PA | 19 | 17 | |
| BR-PA | 26 | 19 | |
| Borderline resectable criteria^b | | | 0.61 |
| PV-SMV | 17 | 13 | |
| CHA | 6 | 3 | |
| LHA | 2 | 1 | |
| SMA | 1 | 2 | |
| Neoadjuvant treatment | | | |
| Chemotherapy alone | 25 (56%) | None | |
| Chemoradiotherapy | 20 (44%) | | |
| Resectability | | | |
| Resected (n, %) | 31 (68.8) | All resected | |
| Unresected (n, %) | 14 | | |

NAT: neoadjuvant treatment group; SF: surgery first group.

Bold means statistically significant.

^a cT4 (locally advanced) have been excluded from the study.

^b Suspicious affection by ecoendoscopy or CT scan; PV-SMV: portal vein-superior mesenteric vein; SMA: superior mesenteric artery; CHA: common hepatic artery; LHA: left hepatic artery.

Table 2
Adverse events during treatment (n = 45).

| | Toxicity | Grade (Patients) | | | |
|-------------------|----------------------|------------------|----|----------------|----|
| | | G1 | G2 | G3 | G4 |
| Hematological | Neutropenia | 2 | 5 | 4 | 0 |
| | Thrombocytopenia | 1 | 3 | 2 | 0 |
| | Anemia | 7 | 0 | 0 | 0 |
| Non-hematological | Alopecia | 7 | 2 | | |
| | Vomiting | 4 | 1 | 0 | 0 |
| | Rash | 3 | 0 | 0 | 0 |
| | Infection | | 2 | 6 ^a | |
| | Fever | 6 | 0 | 0 | 0 |
| | Sensory neuropathy | 2 | 0 | 0 | 0 |
| | Constipation | 3 | 0 | 0 | 0 |
| | Diarrhea | 4 | 1 | 0 | 0 |
| | Asthenia | 7 | 0 | 0 | 0 |
| | Hypertransaminasemia | 0 | 0 | 1 | 0 |

^a Cholangitis.

difference found between the two groups. A total of 18 pancreatectomies (27%) were performed by minimally invasive approach (laparoscopic and robotic). Of the 67 resected patients, 23 (34%)

Table 3
Operative and pathological characteristics of resected patients.

| | NAT n = 31 | SF n = 36 | p value |
|--|---------------|----------------|-------------|
| Type of resection | | | 0.62 |
| PD | 19 | 26 | |
| DP | 7 | 7 | |
| TP | 5 | 3 | |
| Vascular resection (n; %) | 11 (35.4) | 13 (36.1) | 0.83 |
| PV | 8 | 9 | |
| SMV | 3 | 4 | |
| Clavien-Dindo | | | 0.75 |
| I-II | 7 | 5 | |
| ≥III | 2 | 2 | |
| V | 2 | 2 | |
| Pancreatic fistula (n; %) | 11 (35.4) | 13 (36.1) | 0.71 |
| A | 8 | 10 | |
| B | 2 | 2 | |
| C | 1 | 1 | |
| Mean length of stay days (range) | 16.8 (12–26) | 15.7 (12–34) | 0.82 |
| Mean estimated blood loose ml (range) | 66 (0–850) | 53 (0–900) | 0.67 |
| Marginal status R1 (n; %) | 1 (3.2) | 5 (13.8) | 0.09 |
| TRG | | | |
| 0 | 5 | Not applicable | |
| 1 | 13 | | |
| 2 | 8 | | |
| 3 | 5 | | |
| pTNM | | | 0.85 |
| I | 10 | 4 | |
| II | 19 | 31 | |
| III | 2 | 1 | |
| pN+ (n, %) | 8 (25.8%) | 16 (44%) | 0.02 |

PD: pancreatoduodenectomy; DP: distal pancreatectomy; TP: total pancreatectomy.
TRG: tumor regression grade (Ryan rectal classification).

also underwent venous resection, similarly distributed amongst both groups. The types of vascular resection are shown in Table 3. In the NAT group, surgery was performed after a mean of 20.4 weeks (range: 18–27 weeks) after the biopsy diagnosis. Patients included in the SF group underwent surgery after a mean of 3.2 weeks (range: 2–4 weeks) from diagnosis. The overall mean operative time, estimated blood loss, post-operative complications, and hospital stay results were similar for both groups (Table 3).

There were four perioperative mortalities; two for each group. Two were for massive bleeding secondary to hepatic artery pseudoaneurysm at 18 days after the first surgery in the NAT group. One patient died at 34 days after pancreatectomy. The patients who died in the SF group did so as a result of complications stemming from a pancreatic and biliary anastomotic leak approximately 10 days after surgery.

3.5. Pathological data

The main pathological data of the specimens were found to be similar in both groups, except for the number of affected nodes (pN+). Specifically, there were eight specimens (25.8%) who were pN+ in the NAT group and 16 (44%) of pN+ in the SF group ($p = 0.02$). Furthermore, there were a slightly higher number of R1 resections in the SF group (3.2% versus 13.8%, $p = 0.1$). All patients with R1 resection also underwent post-operative radiotherapy.

Of the 31 resected PA in the NAT group, five had a complete pathological response (TRG 0), 13 had important pathological responses (TRG 1), eight had a partial response (TRG-2), and five did not respond (TRG-3). A major pathological response occurred in 18 cases (58%) (see Table 3).

3.6. Overall survival and disease-free survival

The mean follow-up duration of the study population was 43.5

months in the NAT group (ranging from 8 to 62 months) and 58.6 months (ranging from 31 to 101 months).

The “intention to treat” estimated median OS of the two groups (including patients who did not undergo surgery in the NAT group) had similar results (NAT: 21.65 months versus SF: 22.1 months; $p > 0.05$) (see Fig. 1A).

Among the NAT patients group, the median OS was 30.6 months in the resected group, and 11.4 months in the unresected group ($p = 0.0002$).

The median OS of patients who underwent surgery was higher in the NAT group (30.6 months) compared with those in the SF (22.1 months) ($p = 0.04$) (see Fig. 1B).

The median DFS of the resected NAT group was significantly higher compared with the SF group (NAT: 19 months versus SF: 11 months; $p = 0.031$) (see Fig. 1C).

According to the NCCN classification, the median “intention to treat” OS of R-PA of the NAT group resulted in being similar to that of the R-PA of SF group (22.1 months versus 24.8 months, respectively; $p > 0.05$) (see Fig. 2A).

The median OS of R-PA of the NAT group who underwent surgery only was 23.52 months, similar to that of the SF group ($p > 0.05$) (see Fig. 2B).

Regarding the BR-PA group, the median “intention to treat” OS for all NAT and SF groups was 18.9 months and 13.5 months, respectively ($p = 0.1$) (Fig. 2C). When including the patients who underwent surgery from the NAT group only, the OS of the BR-PA group resulted in being significantly higher (43.6 months) compared with the SF group ($p = 0.001$) (see Fig. 2D).

The median DFS of the resected R-PA of the NAT and SF groups was 21 months and 14 months, respectively ($p > 0.05$) (see Fig. 2E). The median DFS of the resected BR-PA of the NAT and SF groups was 17 months and five months, respectively ($p = 0.002$) (see Fig. 2F).

A total of 38.7% of the patients in the NAT group and 41.6% in the SF group did not undergo adjuvant treatment ($p > 0.05$).

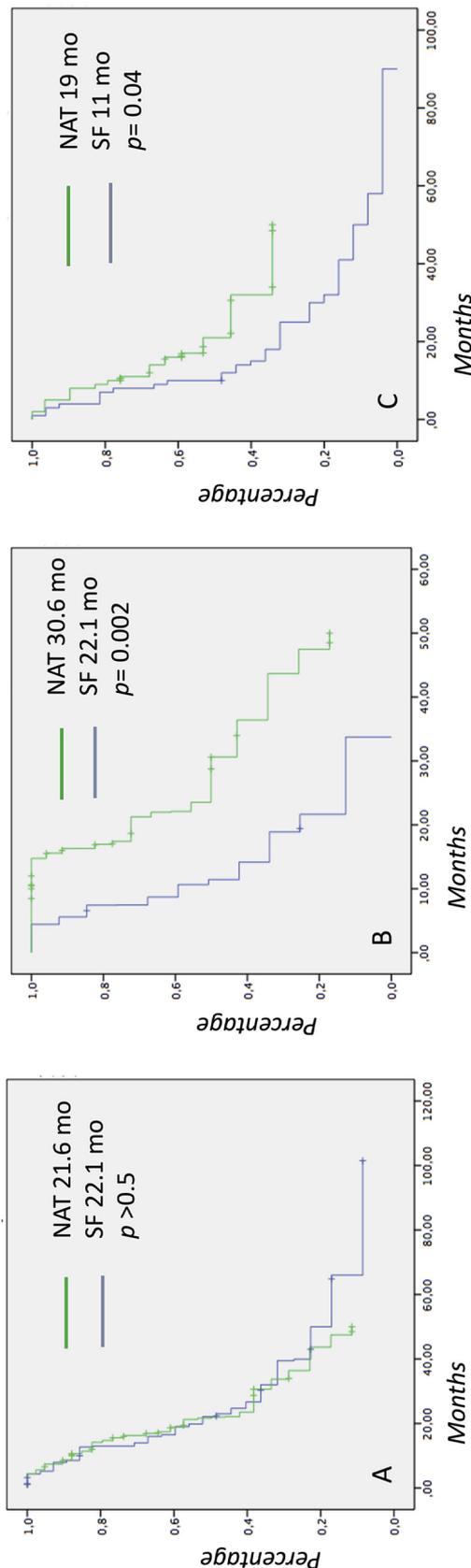


Fig. 1. A: "intention to treat" median OS of NAT and SF groups; B: median OS of resected patients only; C: median DFS of the resected groups.

OS and DFS resulted in being similar for patients who underwent adjuvant treatment, as showed in Fig. 3A and C. On the other hand, OS and DFS resulted in being significantly higher in the NAT group for those patients who did not receive adjuvancy after resection, as showed in Fig. 3B and D. The five patients of the NAT group who had complete pathological response survived a mean of 48.1 months.

4. Discussion

Pancreatic adenocarcinoma is still one of the malignancies with the poorest prognoses. Surgery followed by adjuvant chemotherapy is the only treatment option currently available with the chance of long-term survival at 20–25%.

The main claimed benefit of neoadjuvant therapy is to improve the OS by increasing the R0 resections, delivering chemotherapy to all patients, and making an adequate selection of patients who are likely to benefit from a pancreatectomy [4]. However, despite these claimed potentialities, to date, most studies have failed to show a clear change of survival in favour of the NAT group compared with the SF group, and this poor prognosis remains almost unchanged over the last two decades [12,13].

Nevertheless, more recently, a better understanding of the molecular biology of PA has allowed the development of novel chemotherapeutic agents and combinations, such as FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) or nab-paclitaxel (an albumin-coated formulation of paclitaxel) [14,15]. Both of these regimens have shown promising results in advanced, metastatic, unresectable PA in the MPACT and PRODIGE 4/ACCORD 11 trials, respectively, by increasing survival time from seven to 11 months [16,17].

Given these good results, this regimen can start to be used in potentially resectable PA: first, as adjuvant treatment (the results of which are still under investigation in the AFACT study) [18]; and later, as neoadjuvant treatment. In fact, as our center participated to the MPACT study [16], we decided to use this regimen as neoadjuvant treatment.

To the best of our knowledge, in the current literature there are only a few studies using gemcitabine/nab-paclitaxel in borderline resectable PA, mainly associated with other regimens, and none at all in potentially resectable PA [4,17].

The aim of this report is to present, for the first time, data in the use of gemcitabine, nab-paclitaxel, with or without radiotherapy, for potentially resectable PA, and to compare this data with those who underwent SF.

In combination with gemcitabine, nab-paclitaxel drugs, in a previously published study from our center, have been found to disrupt the PA stroma which surrounds the cancer when comparing it with specimens without any preoperative treatment [19]. It allows an increase in the intratumor concentration of gemcitabine by approximately three-fold in xenograft models inducing a tumor response. In fact, in our study, histopathologic examination has found that 18 out of 31 patients (58%) had major pathological responses (TRG 0-1) which have been shown to be directly correlated to survival.

Moreover, our study demonstrates that patients undergoing systemic therapy prior to surgery are more likely to have node negative resection compared with upfront surgery (25.8% versus 44%, $p = 0.02$). This conclusion has been confirmed in a recent systematic review demonstrating the clear effect of preoperative treatment on the histo-patho-morphological features of PA in upfront, resected cases [20].

In our study, resectability was 68.8%, slightly lower compared with the literature reports which widely range from 50 to 100%. However, the resectability rate should not be considered as a

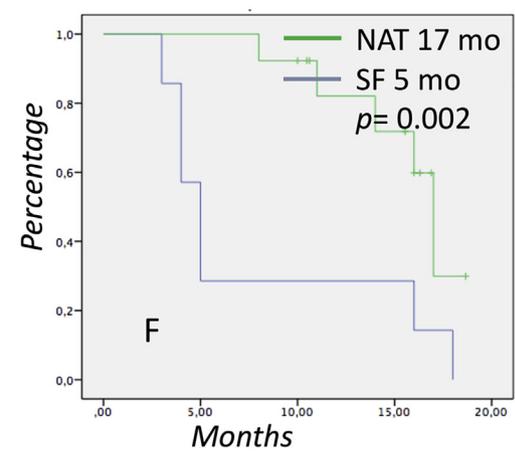
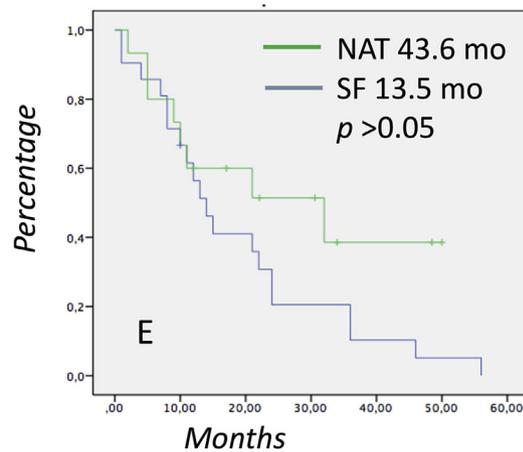
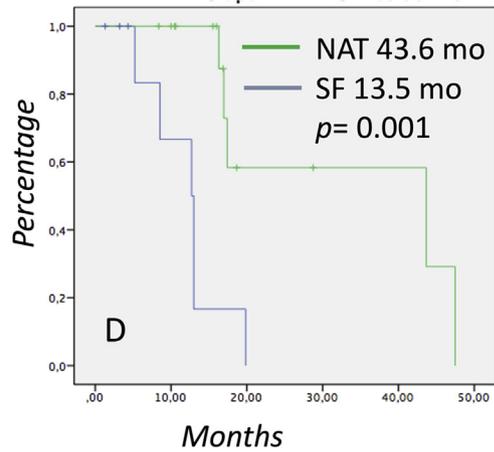
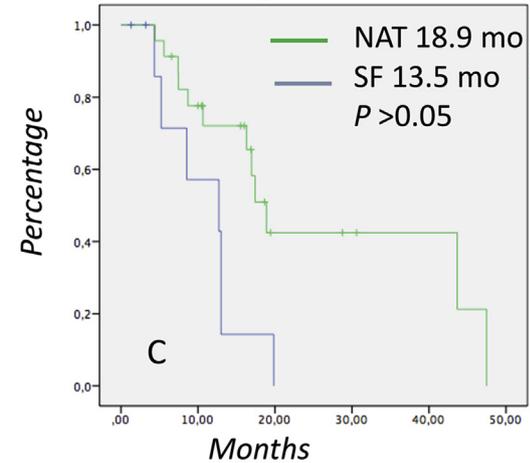
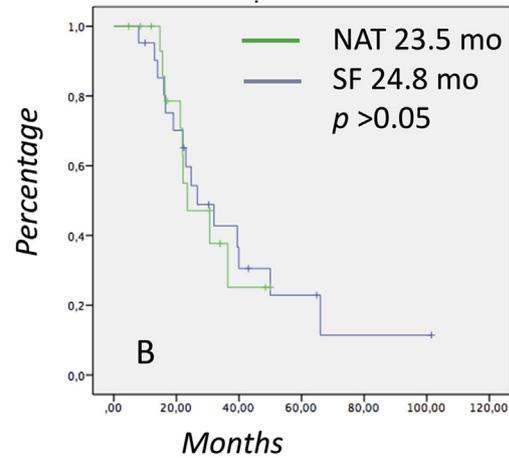
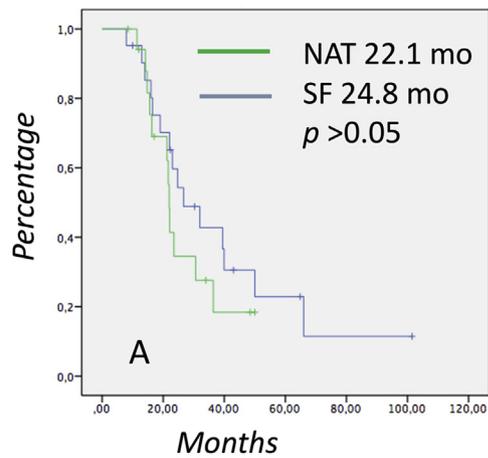


Fig. 2. A: "intention to treat" median OS of R-PA of NAT and SF groups; B: median OS of R-PA resected patients only; C: "intention to treat" median OS of BR-PA; D: median OS of BR-PA resected patients only; E: median DFS of R-PA resected patients; F: median DFS of BR-PA resected patients.

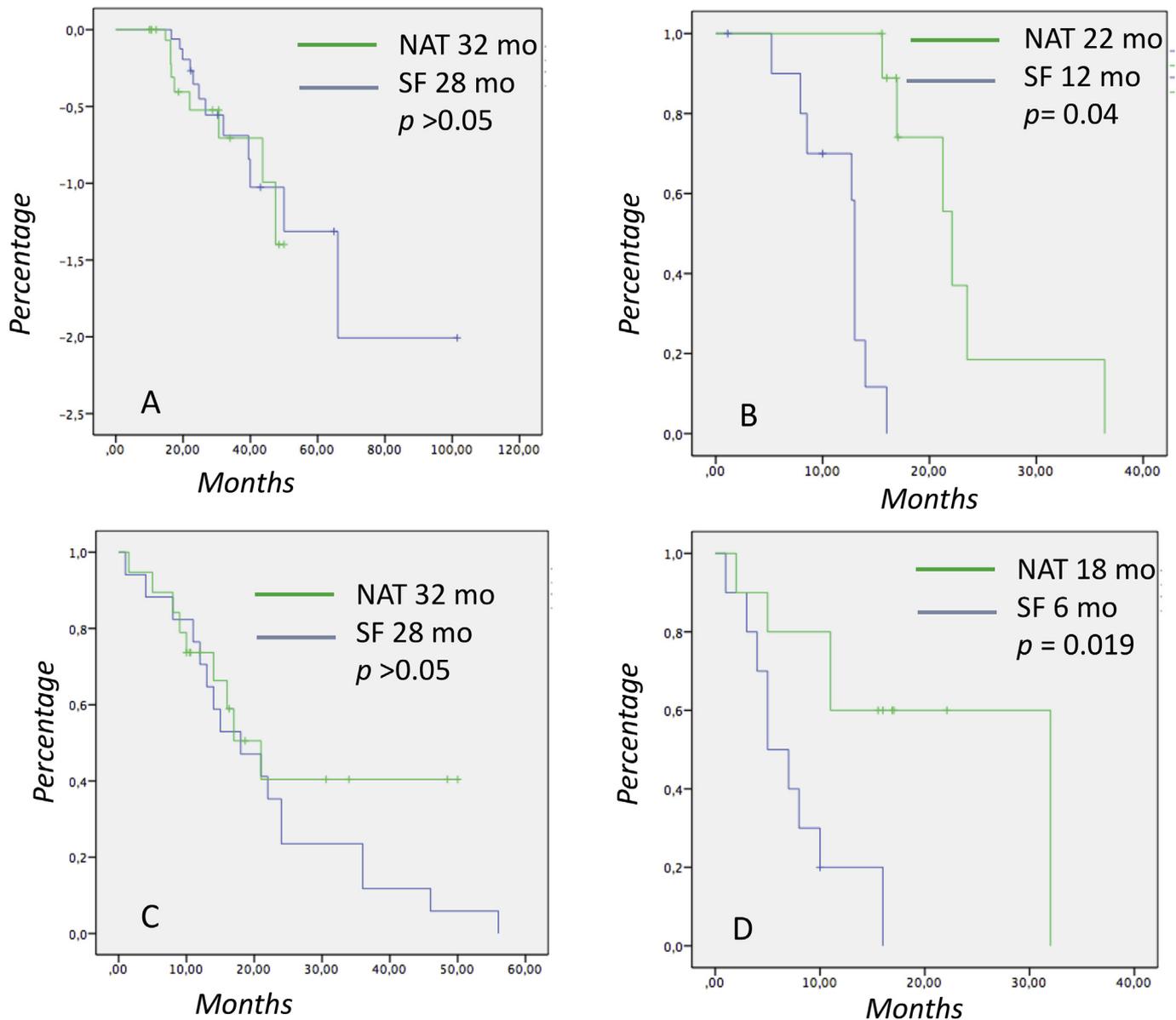


Fig. 3. A: median OS of patients who underwent adjuvancy; B: median OS of patients who did not undergo adjuvancy; C: median DFS of patients who underwent adjuvancy; D: median DFS of patients who did not undergo adjuvancy.

primary end-point of neoadjuvancy effectiveness, but as a filter by which to detect the patients who may develop early metastatic disease prior to surgery.

The primary end-point of these studies must be OS. In an “intention to treat” our analysis, this study did not find any significant difference in OS and DFS between the NAT and SF groups. However, when considering only the resected patients in the NAT group, there exists a higher OS in this group of patients compared with the SF group (30.6 versus 22.1 months, $p = 0.04$). This higher OS is a result of a higher DFS in the NAT group, as shown in Fig. 1B.

Neoadjuvant therapy is currently recommended for the treatment of BR-PA, where the “selection” of patients who are going to benefit from pancreatectomy is clearly evident [21]. However, this strategy is not universally practiced.

In our study, the OS and DFS of the BR-PA was almost four times higher when compared with the same subgroup of SF (Fig. 2D).

The neoadjuvant benefit for resectable patients remains a highly controversial issue and few studies address it. According to our

results, in the localized R-PA subgroup, even if they had been resected, the OS and DFS did not change significantly (see Fig. 2B–E). In this latter situation, it appears that neoadjuvant treatment did not increase survival rates, but, on the other hand, in 21% of the resectable patients, surgery was able to be avoided along with its potential morbidities. Therefore, selection may be an important factor for R-PA and merit to be investigated in larger randomized studies.

Nevertheless, there are some issues concerning the preoperative classifications between R-PA and BR-PA which are based mainly on vascular involvement [8]. In fact, as shown by Katz et al., in almost 30% of cases, the vascular resection was unexpectedly performed in the resectable group also, while it was not performed in the borderline group [22]. For this reason, in our opinion, pre-operative treatment should be provided to all patients with PA.

The main reason for the poor survival after pancreatectomy for PA is clearly related to the short DFS time after surgery, and some authors believe it could be related to the presence of

micrometastases [23]. Micrometastases are low volume metastases which are occult in most of the pre-operative radiological studies and which may grow rapidly after surgery [22]. This hypothesis may be supported by the high percentage of early recurrences after pancreatectomy (30% of distant recurrences during the first post-operative year after surgery in the SF group versus 13% in the NAT group). In this setting, neoadjuvant therapy may not only provide early treatment directly to the tumor, but also early treatment of these micrometastases.

This difference in the DFS is directly related to the OS, which is significantly higher in the NAT group in the Kaplan-Meier estimation (see Fig. 1A and B).

These data have been confirmed by a recent meta-analysis by Schorn et al. which summarizes that neoadjuvant therapy in PA leads to overall and local tumor recurrence control [24].

According to our results, main intra- and peri-operative data results in being similar in both groups, as depicted in Table 3, supporting our premise that preoperative treatment does not increase surgical complications.

With the intention to being able to further downstage tumors, from 2013, our oncological center commenced the use of modular radiotherapy in the preoperative treatment of PA.

One of the main benefits claimed by preoperative treatment with radiotherapy is to increase the R0 resection rate. Even if our study has not find any significant difference between the two groups, there is a slightly higher R1 resection rate in the SF compared with the NAT group (3.2% versus 13.8%, $p = 0.1$). To date, only a few studies have shown a clear higher R0 resection rate in patients who have undergone preoperative treatment.

Some authors support the contention that radiotherapy may increase pancreatic fibrosis that minimizes the risk of post-operative fistula [24].

In our attempt to consider the effects of radiation therapy on outcomes, we have found that radiation therapy does not provide any additional survival advantage in patients treated with neoadjuvant treatment. Given the low number of patients, our ability to evaluate the role of radiation is, however, limited.

It has been speculated that for neoadjuvant treatment a pre-treatment tissue diagnosis is mandatory, which may be associated with potential complications [25]. However, currently, ultrasound-guided fine needle aspiration has the highest overall diagnostic accuracy of any modality and has a complication rate of only 2% [21]. In our series, we have not recorded any complication related to the biopsy. Our current practice to increase diagnostic accuracy is to perform an elastography ultrasound guided biopsy. With this technique, the hardest tumoral area tissue is selected for biopsy.

In most of cases, neoadjuvant therapy implies the need for a preoperative biliary stent. In fact, as expected, there is a two-series difference in the number of stents needed (64% versus 16.6%, $p = 0.02$). This has been claimed to be one of the disadvantages of this strategy because of the morbidity and obstruction related to the stents [26]. However, the new fully covered, self-expanding metal stents, also used in our series, are showing a low rate of complication and are more durable. In the NAT series, only six patients (13%) suffered from low-grade cholangitis/pancreatitis, which was conservatively managed. Pre-operative stenting may also be the cause of severe complications that can compromise the patient operability. However, in our experience we did not detected any major post-operative complications related to stenting. In fact, according to our results, post-operative complications resulted to be similar in both group, despite the higher number of stenting in the NAT group (Table 3).

As shown in previously published data, almost 40% of patients completed the standard treatment: upfront surgery followed by

adjuvancy [13]. This is because pancreatectomy is still related to a high morbidity that incapacitates the marginal performance status patient in receiving post-operative treatment, (usually delivered up to three months after pancreatectomy).

Bliss LA et al. have shown that an incomplete treatment is directly correlated with lower survival rates [27]. Given this data, it would make more sense to deliver the treatment to all patients preoperatively, and this hypothesis is supported by our results. Concomitant with other series, almost 40% of patients from both groups were not able to receive adjuvant treatment. If they did have the opportunity to receive treatment before surgery, survival rates would have clearly been higher when compared with the SF group (see Fig. 3A–B).

This study has some limitations which include the relatively small sample size and lack of randomization due to the retrospective nature of this report. However, to the best of our knowledge, most similar studies have included less than 50 patients, and there are only 2 randomized prospective study where the conclusions were affected by problems with the standardization of staging and surgery [28,29]. Furthermore, most studies analyze results after including different types of regimens and chemotherapies, therefore, decreasing the value of the results [20–24]. The results of this study highlight the need for further prospective randomized trials comparing neoadjuvant to surgical first approach.

5. Conclusions

Our study confirms a survival advantage of neoadjuvant treatment compared with resection alone in BR-PA.

Our results also suggest that receiving systemic therapy before resection affords the potential for a significantly higher survival advantage over patients who do not receive adjuvant treatment.

Disclosure statement

The authors declare no conflict of interest.

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