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ORIGINAL ARTICLE

# Selecting patients for resection after primary chemotherapy for non-metastatic pancreatic adenocarcinoma

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**Background:** Patients with borderline (BL) or locally advanced (LA) pancreatic adenocarcinoma are usually treated with primary chemotherapy (CT), followed by resection when feasible. Scanty data are available about the criteria to candidate patients to resection after CT.

**Patients and methods:** Between 2002 and 2016 overall 223 patients diagnosed with BL or LA pancreatic adenocarcinoma were primarily treated with Gemcitabine combination (4-drugs or nab-paclitaxel-gemcitabine) for 3–6 months followed by surgery and/or chemoradiation. Resection was carried out when radical resection could be predicted by imaging studies and intraoperative findings. The prognostic value of both pre-treatment factors and treatment response was retrospectively evaluated, searching for criteria that could improve the selection of patients for surgery.

**Results:** Median survival (MS) for the whole population was 18.3 months. Surgical resection was carried out in 61 patients; MS in resected patients was significantly longer (30.0 months) as compared with 162 non-resected patients (16.5 months) ($P < 0.00001$). According to response criteria, 48% had a radiological partial response, 47% a stable disease and 5% a disease progression); CA19.9 response (reduction >50%) was obtained in 77.8% of patients. Among resected patients, neither pre-treatment factors, including BL/LA distinction, nor radiological response, were able to prognosticate survival differences. Survival of resected patients having no CA19.9 response was significantly lower as compared with responders (MS 15.0 versus 31.5 months, $P = 0.04$), and was similar to non-responders patients that did not undergo resection (MS 10.9 months, $P = 0.25$). Multivariate analysis carried out on the overall population, showed that Karnofsky performance status, T3–T4 status, resection and CA19.9 response were independent prognostic factors, while radiological response, BL/LA distinction and baseline CA19.9 had not significant influence on survival.

**Conclusions:** CA19.9 response may allow a better selection of patients who will benefit from resection after primary CT for BL or LA pancreatic adenocarcinoma.

**Key words:** pancreatic cancer, primary chemotherapy, surgery, locally advanced disease, borderline resectable disease

## Introduction

Pancreatic ductal adenocarcinoma is one of the most aggressive cancers, yielding the worst prognosis among solid tumors. Only 15%–20% of patients are diagnosed in early stage, while over 50% are metastatic at diagnosis [1].

Between metastatic and resectable disease, locally advanced (LA) and borderline (BL) resectable pancreatic cancer accounts for 30% of patients with various degree of vessels involvement at diagnosis [2]. The definitions of LA and BL resectable tumors have progressively substituted the T factor of the TNM

classification [3] without any validation. In addition, the definitions are heterogeneous, and vary widely over time and among institutions, limiting comparability across series and making the interpretation of results difficult [2, 4]. Furthermore, radiological assessment, on which the judgment of resectability is based, relies on center volume [5], subjective interpretation, and on intrinsic limits of the instrument [6].

Not surprisingly, randomized clinical trials, with few exceptions [7, 8], were unable to complete accrual for patients with LA/BL resectable tumors [9–12] and, accordingly, no universally accepted optimal chemotherapy (CT) regimen has been identified. The role for chemoradiation and the impact of surgery on overall survival (OS) are also unassessed. Surgical resection is considered dogmatically as the only hope of cure in pancreatic adenocarcinoma, and it is also pursued in BL and LA disease after primary treatment. Neoadjuvant therapy can lead to resectability in up to 30%–40% of LA pancreatic cancer patients, yielding an OS similar to primarily resectable cases if radical resection is achieved [13].

The aims of the current analysis are to assess the prognostic value of clinical parameters, including tumor response to treatment, to explore selection criteria for identifying optimal candidates to resective surgery among patients affected by BL or LA pancreatic adenocarcinoma treated with primary CT.

## Material and methods

Chemo- and radio-naïve patients with pathologically confirmed pancreatic ductal adenocarcinoma, LA or BL resectable disease treated with primary combination CT at our Institution between January 2002 and February 2016 were considered eligible for the analysis. All patients were offered a combination CT if they had age between 18 and 75 years, Karnofsky performance status > 60%, adequate bone marrow (WBC $\geq$ 3500/mm$^3$, neutrophils $\geq$ 1500/mm$^3$, platelets $\geq$ 100 000/mm$^3$, hemoglobin $\geq$ 10 g/dl), renal (creatinine $\leq$ 1.5 mg/dl), liver (bilirubin $\leq$ 3 mg/dl, ALT and AST $\leq$ 3 ULN) function, and radiologically measurable disease as defined by Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) [14]. All patients signed a written informed consent to receive CT. Patients were assigned to BL resectable or LA group according to the NCCN guidelines [15, 16] and to T3/T4 clinical status according to 2010 TNM classification [17]. Patient assignment to the different categories was blindly made retrospectively in February 2016 by reviewing all baseline CT scans by a high-volume surgeon (GB) and by a radiologist expert in pancreatic diseases (RN). Controversial cases were collegially discussed and reconciled.

Patients were treated with: (i) cisplatin, epirubicin, 5-fluorouracil, gemcitabine (PEFG; $N = 33$; January 2002–May 2005 [18]; (ii) cisplatin, epirubicin, capecitabine, gemcitabine (PEXG; $N = 89$; July 2005–November 2012 [19]; (iii) cisplatin, docetaxel, capecitabine, gemcitabine (PDXG; $N = 22$; July 2005–September 2008 [19]; (iv) cisplatin, nab-paclitaxel, capecitabine, gemcitabine (PAXG; $N = 51$; December 2012–February 2016 [20, 21]; and (v) nab-paclitaxel-gemcitabine ($N = 28$; April 2014–February 2016) [21]. CT was administered for 4–6 months based on tolerance and response.

Pre-treatment evaluation included surgical assessment for resectability, clinical evaluation, KPS assessment, blood tests [including CA19.9 and carcinoembryonic antigen (CEA)] and high resolution thorax and abdomen contrast-enhanced computed tomography (CT) scan. Hematological±chemistry panel was carried out before every CT administration. During treatment, radiological tumor response was assessed every 2 months and the best overall response recorded from the start of treatment until disease progression was registered. After 4 and 6 months of CT, resectability was re-assessed by a multidisciplinary team composed by radiologists, surgeons, oncologists, and radiotherapists. Surgery was considered indicated when a macroscopic radical resection was predictable. Patients who were unsuitable for resection received concomitant chemoradiotherapy consisting of oral capecitabine at 1250 mg/m$^2$/daily and of 40–44.25 Gy by tomotherapy in 15 fractions to primary tumor and involved lymph nodes. Progression-free survival was defined as the time from the first day of CT to the radiological disease progression or death (for any cause), whichever occurred first. OS was defined as the interval between CT start and the date of death and censored at the last follow-up date.

Since this was a retrospective analysis, no formal statistical assumption was carried out. Survival curves were estimated using the Kaplan–Meier method and compared by use of the log-rank test. Multivariate analysis by the Cox's proportional hazard model was done to estimate the independent prognostic role of selected variables. All the probability values were two-sided. Appropriate adjustment for multiple testing and the false positive-report-probability of significant associations were carried out according to Bonferroni correction and Wacholder method [22]. Namely, a $P < 0.005$ was required for statistical significance. All analyses were carried out using Statistica 12.0 statistical package for Windows (Statsoft Inc, 2011, Tulsa, OK).

## Results

Two hundred and twenty-three consecutive patients were considered eligible for this study (Table 1). Median survival (MS) for the whole population was 18.3 months, 2-year OS 31.6% and 5-year OS 6.5%, respectively.

In 72 BL resectable patients and 151 LA patients, MS was 19.2 and 17.7 months; 2-year OS 45.5% and 25.9%; 5-year OS 10.9% and 4.9%, respectively ($P = 0.01$; Figure 1A).

Patients with radiologic T3 disease ($N = 96$; MS: 19.6 months; 2-year OS: 40.2%; 5-year OS: 11.4%) had longer survival as compared with those with T4 disease ($N = 121$; MS: 17.9 months; 2-year OS: 27.4%; 5-year OS: 3.8%; $P = 0.02$; Figure 1B).

Surgical resection was carried out in 61 (27%) patients [21/151 (13.9%) LA and 40/72 (55.6%) BL resectable]. Surgical outcome is reported in supplementary Table S1 (available at *Annals of Oncology* online). At surgery pT3 was detected in 52 (85%) patients, pT2 in 5; pT1 in 3; pT0 in 1; 27 (44%) were pN0 and 34 pN1; 38 (62.3%) were R0 and 23 R1. G1 was observed in 4 patients; G2 in 34; G3 in 16 and Gx in 7. MS in resected patients was significantly longer (median 30.0 months; 2-year OS 62.7%; 5-year OS 20.8%) as compared with non-resected patients (median 16.5 months; 2-year OS 21.1%; 5-year OS 2.2%; $P < 0.00001$).

**Table 1. Characteristics of the patients at baseline**

| Number of patients | 223 |
|---|---|
| Age (year) | Median 63<br>Range 35–75 |
| Gender—*n* (%) | Female 107 (48)<br>Male 116 (52) |
| Karnofsky performance status score—*n* (%) | 90%–100% 163 (73)<br>70%–80% 60 (27) |
| Pancreatic tumor location—*n* (%) | Head 159 (71)<br>Body/tail 64 (29) |
| Surgical assessment—*n* (%) | Borderline resectable 72 (32)<br>Locally advanced 151 (68) |
| Radiological T stage—*n* (%) | T3 96[a] (44)<br>T4 121[a] (56) |
| Level of carbohydrate 19-9 antigen U/ml—*n* (%) | > ULN 179[b] (80)<br>Median 300<br>Range 41–12 473 |

[a]Data missing for six patients.
[b]One further patient had CEA > ULN at baseline.
ULN, upper limit of normal range.

RECIST response was available in 220 patients: 106 (48%) had a partial response (PR); 103 (47%) a stable disease (SD) and 11 (5%) a disease progression (PD). Survival was significantly longer in patients with PR as compared with those with SD (median 21.6 versus 16.5 months; 2-year OS 41.6% versus 25.2%; 5-year OS 8.9 versus 4.5%; $P = 0.002$).

CA19.9 response was available for 177 of 179 with elevated baseline value (98.9%) patients: CA19.9 reduction at nadir $\geq 50$ was observed in 137 (77.4%) patients who survived longer as compared with those with a reduction $< 50\%$ or an increase ($N = 40$; median 19.2 versus 11.4 months; 2-year OS 35.4% versus 16.3%; 5-year OS 7.0% versus 0%; $P = 0.0003$).

The subset of 61 patients who underwent resection was analyzed, to identify pre-operative factors that could better select patients for surgery. Pre-treatment factors (baseline CA19.9, BL/LA resectability status, baseline T stage, KPS, age, and gender) did not differentiate classes of different survival (Table 2). According to RECIST response criteria, 64% had a radiological PR and 36% a SD. No significant survival difference between PR and SD was observed (Table 2). CA19.9 response was observed in 80.4% of patients and was associated with longer survival as compared with CA19.9 non-responders (Table 2).

Mirroring data were also observed for the subset of unresected patients: a CA19.9 reduction at nadir $\geq 50\%$ ($N = 31$ versus 100) was predictive of longer survival as compared with a reduction of 50% ($P = 0.007$).

In multivariate analysis, when considering the whole population, KPS, baseline T3/4 status, surgery, and CA19.9 response were independently predictive of survival (supplementary Table S2, available at *Annals of Oncology* online). Conversely, resectability status at diagnosis, RECIST response, and baseline CA19.9 had not an independent prognostic relevance (supplementary Table S2, available at *Annals of Oncology* online).

## Discussion

Patients' selection for surgery after neoadjuvant treatment of LA or BL resectable pancreatic adenocarcinoma currently relies on imaging predictivity of a radical resection. The current analysis studied a number of clinical parameters in search of further elements useful for selecting optimal candidates for surgery.

In our analysis, patients who were resected without yielding a CA19.9 reduction or with a reduction at nadir $<50\%$ did not benefit from resection with respect to non-resected patients, and had a shorter survival (15.0 months) when compared with resected patients with a CA19.9 response $\geq 50\%$ (31.5 months). The survival data in this subset of our analysis are numerically similar to those reported elsewhere [23, 24]. CA19.9 can therefore be considered as a surrogate marker of disease-response and may represent a simple marker for deciding referral of patients to surgery.

Noteworthy, among patients who could undergo surgery, lower baseline T stage, baseline BL resectability status, and a better RECIST response were not predictive of longer survival. Lack of correlation between RECIST response and outcome is not surprising because the assessment of treatment response is particularly challenging in pancreatic adenocarcinoma. Radiographic imaging has limitations because in most cases tumor shrinkage is not measurable even in the presence of CT activity, likely due to the dense stromal component that may remain unmodified, and to the development of treatment-related fibrosis after treatment [25, 26]. Recently, a high number of resections following neoadjuvant treatment in BL resectable pancreatic cancer despite no radiological tumor downstaging were reported [27, 28].

Another remarkable and consistent information provided by the present analysis, was the lack of significant survival difference between patients initially classified as BL resectable or LA. About 40 of 72 BL resectable (55.6%) and 21 of 151 (14.0%) LA patients were resected after induction therapy, but this almost fourfold difference in resection rate was insufficient to significantly modify the natural history of the disease. To our knowledge, despite its extensive use, there are no data in the literature endorsing the prognostic role of the resectability status, as defined by NCCN classification. According to our findings, except for a higher possibility to undergo resection after primary CT, BL resectable cancers should not be considered a distinct prognostic subgroup from LA cases. Conversely, TNM classification had a weak prognostic value and may be preferred as a stratification factor in prospective trials until more robust and reliable predictors will be identified. While T3 is a proxy for BL resectable and T4 for LA pancreas cancer, as a matter of fact, the two classifications do not fully overlap and our multivariate analysis suggest an independent prognostic role only for TNM classification, which is also more reproducible and objective.

Albeit retrospective and encumbered by the well know bias and limitations of this kind of study, including different CT regimens and the long time interval that was taken into account, our analysis has a number of strengths in comparison with pooled analyses of reported series: therapeutic and follow-up strategy was homogeneous; patients clustering based on NCCN and TNM classification was blindly reattributed by an expert surgeon and radiologist thus overcoming time-related definition changes; resectability was defined in a single institution; radiological and

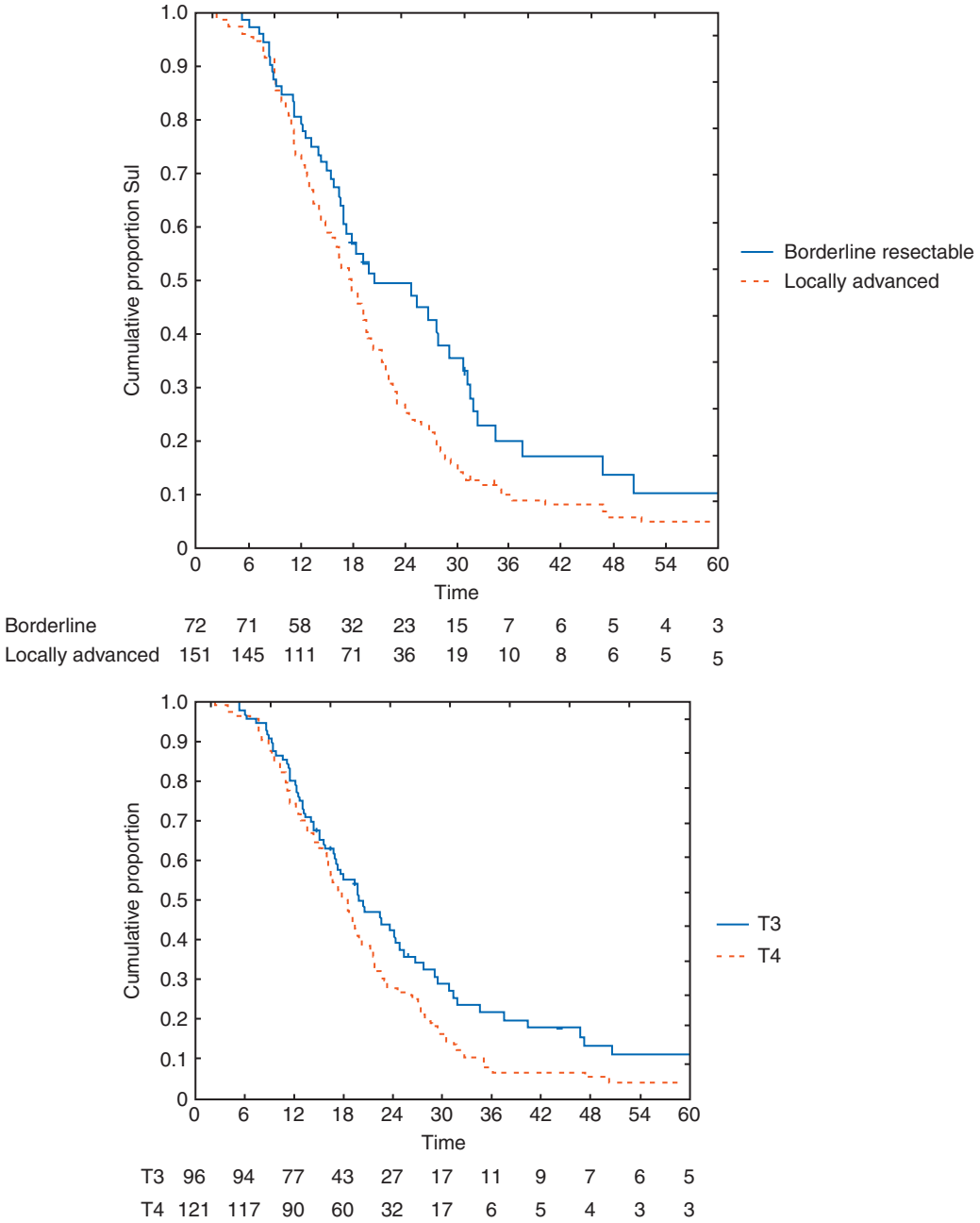


**Figure 1.** Overall survival according to NCCN resectability status (A) and T (B) classification.

CA19.9 assessment was uniform with a constant quality; and the numeric consistency was robust ($N = 223$) and in the range of pooled analyses ($N = 134$–$365$) that merged heterogeneous data from 13 to 20 phase I–II, cohort, retrospective, and observational trials [29–33].

Currently, there is limited evidence on the optimal therapeutic approach for localized pancreatic ductal adenocarcinoma. The limited number of completed prospective trials, the lack of an accepted and widely used definition of resectability and BL resectability and its variability over time, together with the restricted amount of pathologic material, hamper progress in this field. Primary CT is widely considered the wisest therapeutic approach due to the high likelihood that micro-metastatic disease occurs at time of diagnosis. However, albeit FOLFIRINOX is probably today's preferred regimen for disease downstaging, the optimal CT regimen will not be identified until a randomized clinical trial will be carried out. By pooling the data from reports of patients treated with heterogeneous CT combinations using gemcitabine or gemcitabine-based or 5-FU based regimens, with or without chemoradiation, 26.5%–33.2% patients initially staged as having BL/LA disease could undergo resection after primary therapy [29, 30, 34]. Better disease responses can be expected with more recently defined CT regimens [16, 35, 36], all of which were superior to gemcitabine monotherapy in phase III randomized clinical trials. As compared with 'old' combinations, resectability rates were not improved by folic acid, fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX), or gemcitabine plus nab-paclitaxel (GA) (resection rate 20%–28%) [31, 32, 37] or in our series

**Table 2. Overall survival of resected and non-resected patients, according to pre-treatment factors and treatment response**

| Variable | Resected patients | | | | Non-resected patients | | | | *P* value[a] |
|---|---|---|---|---|---|---|---|---|---|
| | *N* | mOS | 2-year OS (%) | 5-year OS (%) | *N* | mOS | 2-year OS (%) | 5-year OS (%) | |
| Age | | | | | | | | | |
| ≥70 | 10 | 26.6 | 80.0 | 27.4 | 28 | 17.2 | 13.7 | 0 | 0.00001 |
| <70 | 51 | 31.5 | 59.0 | 20.4 | 134 | 16.0 | 22.4 | 2.6 | 0.0001 |
| *P* value[b] | | 0.92 | | | | 0.74 | | | |
| Gender | | | | | | | | | |
| Male | 27 | 24.8 | 59.3 | 21.0 | 89 | 14.4 | 15.4 | 1.3 | <0.00001 |
| Female | 34 | 31.0 | 64.8 | 19.4 | 73 | 17.9 | 27.9 | 3.3 | 0.00004 |
| *P* value[b] | | 0.71 | | | | 0.03 | | | |
| KPS | | | | | | | | | |
| 90–100 | 48 | 30.0 | 63.2 | 27.7 | 113 | 17.0 | 23.7 | 3.1 | <0.00001 |
| 70–80 | 11 | 20.2 | 63.6 | 0 | 47 | 16.2 | 16.0 | 0 | 0.001 |
| *P* value[b] | | 0.44 | | | | 0.12 | | | |
| Basal CA19.9 | | | | | | | | | |
| ≥300 | 22 | 25.9 | 64.2 | 31.2 | 67 | 17.2 | 27.4 | 1.8 | 0.001 |
| <300 | 22 | 24.8 | 57.8 | 13.2 | 68 | 16.2 | 16.1 | 1.8 | 0.0002 |
| *P* value[b] | | 0.38 | | | | 0.19 | | | |
| Basal T stage | | | | | | | | | |
| T3 | 44 | 27.7 | 59.6 | 25.1 | 52 | 16.7 | 25.0 | 2.5 | 0.0003 |
| T4 | 15 | 25.1 | 80.0 | 13.3 | 106 | 16.5 | 20.2 | 2.1 | <0.00001 |
| *P* value[b] | | 0.82 | | | | 0.52 | | | |
| Resectability | | | | | | | | | |
| Borderline | 40 | 29.1 | 64.4 | 24.8 | 32 | 16.4 | 24.5 | 0 | 0.0004 |
| Locally adv. | 21 | 30.0 | 61.5 | 15.8 | 130 | 16.4 | 20.2 | 2.8 | <0.00001 |
| *P* value[b] | | 0.85 | | | | 0.92 | | | |
| RECIST response | | | | | | | | | |
| Partial | 39 | 31.8 | 67.1 | 21.4 | 67 | 18.9 | 28.2 | 3.1 | 0.00001 |
| Stable | 22 | 25.9 | 55.5 | 18.5 | 81 | 14.8 | 18.4 | 1.7 | 0.004 |
| *P* value[b] | | 0.18 | | | | 0.05 | | | |
| CA19.9 response | | | | | | | | | |
| Decrease ≥50% | 37 | 31.5 | 66.7 | 21.4 | 100 | 17.9 | 25.3 | 2.6 | <0.00001 |
| Decrease <50% | 9 | 15.0 | 29.6 | 0 | 31 | 10.9 | 12.9 | 0 | 0.25 |
| *P* value[b] | | 0.04 | | | | 0.007 | | | |

[a]Resected versus non-resected.
[b]Comparison within resected and non-resected subset based on different variables.

(resection rate 27%). However, the value of this variable as a surrogate end point for survival has never been proved. Actually, despite resection rates were similar, MS was only 11.2–14.0 months in pooled analyses with 'old' regimens [29, 30, 34] as compared with 8.9–25 months with FOLFIRINOX [31, 32, 37] and 18.3 months in the present series. Survival outcome with 'new' regimens appeared better among both unresected (8.4–10.2 months [29, 30, 34] versus 16.5 months in the present series) and resected patients (17.8–22.3 months in pooled analyses; 24.9 months with FOLFIRINOX [33]; 30.0 months in the present series). These figures suggest that resectability is not a reliable surrogate end point and that the final outcome may be influenced by diverse efficacy of CT regimens in addressing micrometastatic disease.

Patients selected for surgery could have a more favorable tumor biology than those who remained unresectable or progressed during induction therapy. Accordingly, better survival figures among resected patients may be the consequence of a selection bias while the risk-benefit ratio of this therapeutic approach has been prospectively neither confirmed nor investigated. Furthermore, and in spite of a potentially 'curative' resection, the vast majority of resected patients experience local recurrence and/or distant metastases and ultimately dies of their disease. Based on these disappointing data and because pancreatic resection is particularly challenging due to high morbidity (23%–39%) and mortality (3%–7%) rates [31, 34], efforts to identify a more selected subset of patients who may benefit from surgery is a relevant medical need.

In brief, our data support to further explore the role of CA19.9 decrease as a selection criterion for referral of patients for surgical resection after induction therapy; advocate to consider TNM classification as a stratification factor for future trials; and

discourage the use of the present NCCN distinction between BL resectable and LA cancer to define different prognostic categories. Altogether, clinical variables are weak and ineffective tools in defining prognosis and in selecting patient who may have more benefit from surgery in patients with non-resectable, non-metastatic pancreatic adenocarcinoma. Future research should explore the role of biological factors and molecular profile in this context.

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## Disclosure

The authors have declared no conflicts of interest.

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