ORIGINAL ARTICLE

Neoadjuvant Chemo-Radiotherapy for Patients with Borderline Resectable Pancreatic Cancer: A Meta-Analytical Evaluation of Prospective Studies

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ABSTRACT

Context For patients with borderline resectable pancreatic cancer, the benefit of neoadjuvant therapy remains to be defined. **Objective** We did a systematic search of the literature on this topic. **Methods** Prospective studies where chemotherapy with or without radiotherapy was given before surgery to patients with borderline resectable cancer, were analyzed by a meta-analytical approach. **Main outcome measures** Primary outcome was surgical exploration and resection rates; tumor response, therapy-induced toxicity, and survival were secondary outcomes. Data were expressed as weighted pooled proportions with 95% confidence intervals (95% CI). **Results** Ten studies with 182 participants were included. Following treatment, 69% of patients (95% CI: 56-80%) were brought to surgery and 80% (95% CI: 66-90%) of surgically-explored patients were resected. Eighty-three percent (95% CI: 74-90%) of resected specimens were deemed R0 resections. The weighted fractions of resected patients alive at 1 and 2 years were 61% (95% CI: 48-100%) and 44% (95% CI: 32-59%), respectively. At restaging following neoadjuvant therapy, weighted frequencies for complete/partial response were 16% (95% CI: 9-28%), 69% (95% CI: 60-76%) for stable disease, and 19% (95% CI: 13-25%) for progressive cancer. Treatment-related grade 3-4 toxicity was 32% (95% CI: 21-45%). **Conclusion** This meta-analysis shows that downstaging of the lesion following neoadjuvant therapies is uncommon for patients with borderline resectable pancreatic cancer. A clear benefit of this regimen could be to spare surgery to patients with progressive disease during the frame-time chemo-radiotherapy is being delivered.

INTRODUCTION

The rationale for delivering preoperative treatment to patients with borderline resectable tumors, as defined originally by Varadhachary *et al.* in 2006, and subsequently endorsed by Americas Hepato-Pancreato-Biliary Association (AHPBA) and National Comprehensive Cancer Network (NCCN) guidelines [1, 2, 3], is based on: a) potential downstaging to maximize R0 resections; b) selecting for surgery patients with stable or responding disease; c) early treatment of micrometastatic disease; and d) giving therapy in a neoadjuvant setting, when it is expected to be better tolerated.

Although this strategy has a sound rationale, its merits have not been demonstrated yet. A number of randomized controlled trials were unable to show a benefit of neoadjuvant chemo-radiotherapy for the subset of patients with locally-advanced pancreatic cancer. However, these studies enrolled heterogeneous groups of patients, as they included either those with a truly unresectable lesions and those with borderline resectable cancers [4, 5].

Objective of the present investigation was to evaluate the effectiveness of chemo-radiotherapy delivered pre-operatively in downstaging the disease in patients with borderline resectable pancreatic cancer, with emphasis on tumor response, resectability, and survival.

METHODS

Trial Selection

We included studies with a prospective design, where the pre-operative administration of chemotherapy, alone or in combination with radiotherapy, was considered in patients with preoperatively staged borderline resectable pancreatic cancer. To refine the selection, we considered only trials carried out according to pre-defined protocols, approved by institutional boards, and those with the following design: neoadjuvant therapy followed by re-staging, and surgical exploration/resection. We excluded retrospective studies, reports of identical patient cohorts, and those available only in abstract form. Further exclusion criteria were: trials including patients with different stages of the disease from which separate results were irretrievable, trials that administered intra-operative radiotherapy, and reports lacking information on pancreatic resection rates.

Search Strategy

Trials were identified by searching MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from 1966 to September 2012. The search strategy included the following: (pancreatic AND (neoplasm OR cancer)) OR "pancreatic neoplasms" [MeSH Terms] AND ((chemotherapy OR irradiation OR neoadjuvant OR

radiotherapy) AND (surgery OR resectable OR unresectable)) AND therapy/broad [FILTER] NOT ((animals [MH] NOT humans[MH]) OR (review [PT] NOT (systematic OR pooling OR pooled OR meta-analysis))). Manual searching included reading through reference lists of relevant papers to capture missing studies that met our inclusion criteria.

Methods of the Review

Three reviewers (A.A., V.F., and G.U.) scanned the abstract of identified studies to determine eligibility. Full articles were then selected for further assessment if the abstract suggested the study was relevant. Papers not meeting inclusion criteria were excluded and reasons for their omission listed. Disagreements were resolved through discussion. Although no randomized phase III trial on this topic has been published so far, general recommendations from the Quality of Reporting of Meta-analyses (QUOROM) [6] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) revision [7] were adopted. Extracted data included publication date, location of study, length of follow up, patient inclusion and exclusion criteria, mean age, male and female proportion, schedule, dose and duration of chemo-radiotherapy, morbidity related to therapy, restaging and surgical exploration/resection, histological status of surgical margins (R0 *vs*. R1/R2), and survival rates. Resectability was determined according to NCCN criteria [3]; if resectability criteria were not clearly stated, tumors were considered according to the stated resectability category. The results of our search and selection of studies are shown in Figure 1.

Methodological Quality Assessment

Quality of each study was evaluated by means of the Evidence Evaluation Process elaborated by the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science, for assessing non randomized trials [8], which uses three quality items with a maximum score of 3 points. The quality terms are defined as "good" if they had all of the relevant quality items (score=3), "fair" if they had some of the items (score=2), and "poor" if they had only a few items but insufficient quality to include for further review (score=0-1).

Assessment of Bias Risk

Due to the risk of overestimating a beneficial intervention, we assessed the influence of the risk bias on our results by using the following domains: trial design (phase II and cohort studies), single or multi-institutional trials, sample size (cut-off: n=30), response criteria (Response Evaluation Criteria in Solid Tumors (RECIST) *vs*. all others) [9], resectability criteria (NCCN *vs*. all others), and
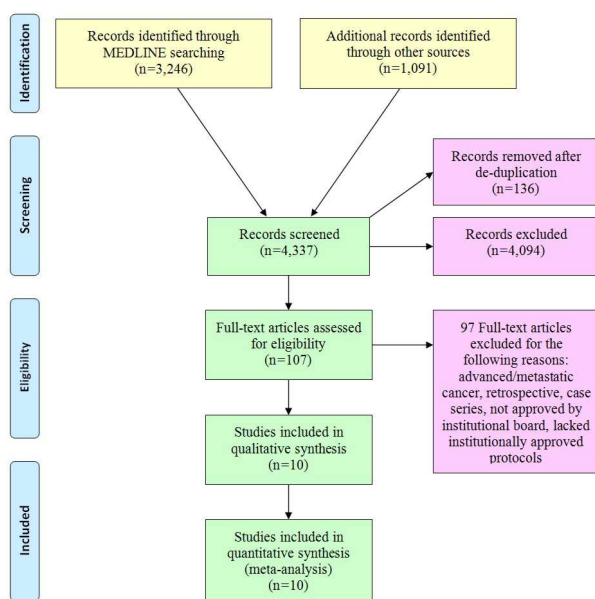

Figure 1. PRISMA 2009 flow diagram of our selection of studies.

Table 1. Selected studies included in the meta-analysis.

Author	Study period	No. of centers	Study design	Chemotherapy	Radiation dose		No. of patients	Median age (years)	Criteria for resectability[a]
					Gy	Gy/ fraction			
Mehta VK, 2001 [16]	1994-2000	2	Cohort	5-fluorouracil	50.4-56	1.8-2	15	54	Others
Magnin V, 2003 [17]	1996-2001	1	Cohort	5-fluorouracil+cisplatin	45	1.8	32	62	Others
Pipas JM, 2005 [18]	2002-2004	1	Phase II	Gemcitabine+docetaxel	50.4	1.8	6	65	RECIST
Massucco P, 2006 [19]	1999-2004	2	Cohort	Gemcitabine	45	1.8	18	62	Others
Le Scodan S, 2009 [20]	1998-2003	3	Phase II	5-fluorouracil+cisplatin	50	1.8	41	59.3	Others
Small W, 2011 [22]	2005-2007	1	Phase II	Gemcitabine+bevacizumab	36	2.4	10	62	RECIST
Sahora K, 2011 [23]	2001-2003	1	Phase II	Gemcitabine+docetaxel	No	No	12	61	RECIST
Sahora K, 2011[24]	2003-2006	1	Phase II	Gemcitabine+oxaliplatin	No	No	15	61	RECIST
Leone F, 2012 [21]	2003-2009	1	Cohort	Gemcitabine+oxaliplatin	50.4	1.8	15	63	RECIST
Lee J, 2012 [25]	2006-2008	1	Cohort	Gemcitabine+capecitabine	No	No	18	61	RECIST

[a] Others: other well defined criteria

therapeutic regimen (gemcitabine *vs.* other regimens as well as chemo/radiotherapy *vs.* chemotherapy alone).

Outcome Measures

Primary outcome was the proportion of patients explored, resected and of those with R0 margins. Secondary outcomes included survival, toxicity of therapies, and proportions of complete/partial response, stable disease, and progressive disease.

STATISTICS

Data were analyzed using the Comprehensive Meta-Analysis statistical software (version 1.0.25; Biostat, Englewood, NJ, USA) and were presented as proportions along with corresponding 95% confidence intervals (95% CIs), which were calculated by the Wilson score interval [10]. To estimate pooled proportions we used random rather than fixed effects models in order to take into account the heterogeneity of the estimates [11]. Statistical heterogeneity across studies was stated by using the Cochran's test, and quantified by I^2 (percentage of total variation across studies that is attributable to heterogeneity rather than chance)

[12]; values were considered statistically significant when P was less than 0.1. Subgroup analyses were performed to identify possible sources of heterogeneity [13]. Bias of publication was assessed by Egger and Begg tests [14, 15].

RESULTS

We identified 4,337 references: 136 were duplicate records and 4,094 abstracts were excluded as being irrelevant. Of the 107 full articles retrieved for further assessment, 97 were excluded because they were retrospective trials (n=7), lacked institutionally approved protocols (n=3), included metastatic disease (n=82), or because separate data for borderline resectable disease were irretrievable (n=5). In total, 10 studies, published between 2001 and 2012, fulfilled the inclusion criteria [16, 17, 18, 19, 20, 21, 22, 23, 24, 25] (Figure 1).

Characteristics of Selected Studies (Table 1)

The reviewed trials included 182 patients. Seven studies originated from a single centre. Five of the studies selected were phase II trials, and the remaining were cohort studies run under a prospective design and with approved protocols.

Table 2. Scores for quality assessment of included studies.

Author	Were outcomes measured in an objective way?	Were known confounders identified and appropriately controlled for?	Was follow-up of patients sufficiently long and complete?	Total score
Mehta VK, 2001 [16]	Yes	Yes	Yes	3
Magnin V, 2003 [17]	Yes	Yes	Yes	3
Pipas JM, 2005 [18]	Yes	No	Yes	2
Massucco P, 2006 [19]	Yes	Yes	Yes	3
Le Scodan S, 2009 [20]	Yes	Yes	Yes	3
Small W, 2011 [22]	Yes	Yes	Yes	3
Sahora K, 2011 [23]	Yes	Yes	Yes	3
Sahora K, 2011[24]	Yes	Yes	Yes	3
Leone F, 2012 [21]	Yes	Yes	Yes	3
Lee J, 2012 [25]	Yes	Yes	Yes	3

Good quality: 3 factors; Fair quality: 2 factors; Poor or of insufficient quality: 0-1 factor
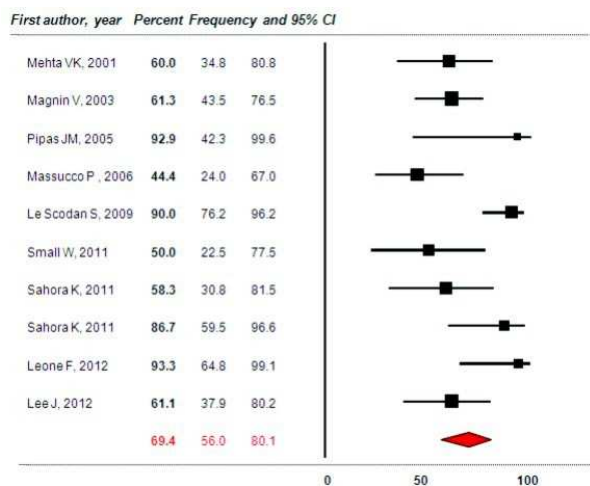
Figure 2. Estimates of surgical exploration proportions in patients following neoadjuvant/pre-operative therapy and re-staging.
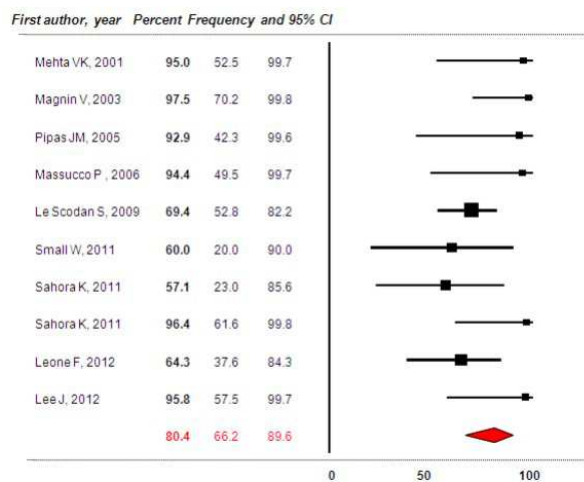
Figure 3. Estimates of resection proportions in patients following neoadjuvant/pre-operative therapy and re-staging.

In seven studies, the protocols contemplated combination of radiotherapy with gemcitabine, provided as single agent or with other cytotoxic agents. In the remaining studies, 5-fluorouracil either alone or in combination with cisplatin was administered with radiotherapy. Radiotherapy was given at a dose ranging from 36 to 50.4 Gy with most patients receiving 1.8 Gy per fraction. In three studies no radiotherapy was provided.

According to quality evaluation, nine studies reached the score of 3 points (good quality), and one single trial only scored 2 points (fair quality) (Table 2)

Participants

The average age of the 182 patients was 61 years. All patients had a histological diagnosis of pancreatic adenocarcinoma. Three studies [16, 17, 20] enrolled exclusively patients with borderline resectable disease (n=88), whereas data for the remaining patients could be retrieved from the other trials on patients with mixed stages of disease [18, 19, 21, 22, 23, 24, 25]. Only two centers published more than one study, so the potential for an overlapping bias was minimal.

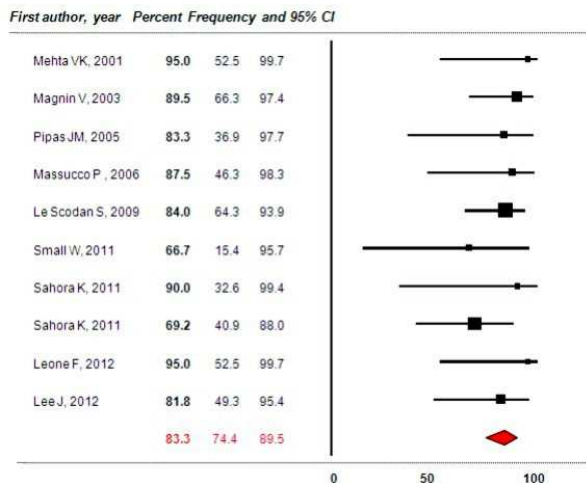**Exploration and Resection**

Of the 180 restaged patients, the weighted frequency of those who underwent surgery was 69% (95% CI: 56-80%) (Figure 2 and Table 3); data were statistically heterogeneous (I^2=59%; P=0.009). Four studies [18, 21, 22, 25] explicitly used the NCCN guidelines of resectability for pancreatic cancer [3]; 5 studies [16, 19, 20, 23, 24] followed

Table 3. Summary estimates and heterogeneity analysis for surgical exploration and pancreatic resection rates following neo-adjuvant therapy in patients with borderline resectable pancreatic cancer.

	No. of studies	No. of patients	Surgically explored/evaluable patients		Surgical resection	
			Frequency (95% CI)	P value[a]	Frequency (95% CI)	P value[a]
Cohort	5	97	61.0% (46.8-73.5%)	0.190	90.7% (68.9-97.7%)	0.115
Phase II	5	83	77.5% (55.1-90.6%)		71.8% (54.1-84.6%)	
Multicentric	3	73	68.6% (34.5-90.0%)	0.996	84.1% (53.1-96.1%)	0.852
Monocentric	7	107	68.5% (54.3-80.0%)		81.6% (61.1-92.6%)	
Sample size ≤30	8	109	65.3% (50.7-77.5%)	0.477	81.3% (63.5-91.6%)	0.767
Sample size >30	2	71	78.4% (39.8-95.2%)		87.0% (31.0-99.0%)	
RECIST	6	76	72.1% (53.7-85.2%)	0.678	76.3% (55.0-89.4%)	0.303
No RECIST	4	104	66.5% (43.8-83.5%)		89.6% (63.2-97.8%)	
NCCC	4	49	73.0% (45.9-89.6%)	0.752	75.8% (50.1-90.7%)	0.446
Others	6	131	68.5% (51.1-81.8%)		85.4% (65.2-94.8%)	
No gemcitabine	3	86	72.9% (47.5-88.9%)	0.687	88.9% (52.6-98.3%)	0.499
Gemcitabine	7	94	67.3% (49.8-81.0%)		79.0% (59.5-90.6%)	
Chemo/radiotherapy	7	135	70.5% (52.0-84.1%)	0.827	78.5% (62.2-89.1%)	0.581
Chemotherapy alone	3	45	67.8% (48.0-82.8%)		87.6% (43.9-98.5%)	
Overall pooled estimates	**10**	**180**	**69.4% (56.0-80.1%)**	**P=0.009[b]** I^2**=59%**	**80.4% (66.2-89.6%)**	**P=0.100[b]** I^2**=39%**

[a] P values test the frequencies between strata

[b] Heterogeneity test: P values test homogeneity between studies for overall pooled estimates and I^2 values show the percentage of total variation across studies that is attributable to heterogeneity rather than chance. Heterogeneity was considered statistically significant when P value was less than 0.10
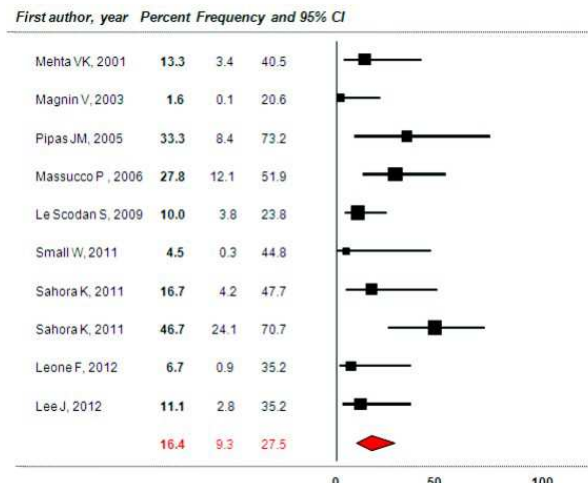
Figure 4. Estimates of R0 resection proportions in patients following neoadjuvant/pre-operative therapy and re-staging.

Figure 5. Estimates of complete/partial response proportions in patients following neoadjuvant/pre-operative therapy and re-staging.

different, but clearly defined, criteria and in a single study [17] criteria were ill-defined. For the 128 surgically explored patients, the estimated fraction of resected patients was 80% (95% CI: 66-90%) (Figure 3 and Table 3). Data across trials were homogeneous (I^2=39%). Finally, for the 107 resected patients, the weighted proportion of R0 resection amounted to 83% (95% CI: 74-90%) (Figure 4). Data were homogeneous across the trials (I^2=0%).

Tumor Response

Tumor response following neoadjuvant therapy was evaluated according the RECIST criteria [9] in 6 studies, whereas different, but clearly stated, criteria were used in the remaining studies. The

weighted fraction of patients with complete/partial response at restaging (Figure 5 and Table 4) was 16% (95% CI: 9-28%); 69% (95% CI: 60-76%) of patients were documented to have stable lesions, and 19% (95% CI: 13-25%) a progressive disease. When previous figures were subjected to the analysis of heterogeneity, the respective I^2 values equaled 48%, 15% and 0%, suggesting consistent homogeneity of data across the trials (Table 4).

Toxicity

Grade 3-4 toxicity was estimated at 32% (95% CI: 21-45%) for all patients, with a corresponding I^2 value of 58% (P=0.010) (Table 4). In the three studies where radiotherapy was not given, the gemcitabine plus docetaxel combination was

Table 4. Summary estimates and heterogeneity analysis for restaging and toxicity rates following neo-adjuvant therapy in patients with borderline resectable pancreatic cancer.

	Complete/partial response		Progressive disease		Toxicity	
	Frequency (95% CI)	P value[a]	Frequency (95% CI)	P value[a]	Frequency (95% CI)	P value[a]
Cohort	12.8% (5.8-26.1%)	0.405	17.0% (10.1-27.2%)	0.690	22.6% (13.6-35.1%)	0.011
Phase II	20.7% (8.5-42.0%)		19.5% (12.0-29.9%)		46.1% (33.1-59.6%)	
Multicentric	16.2% (8.0-30.2%)	0.916	17.0% (7.7-33.6%)	0.956	30.2% (8.2-67.8%)	0.976
Monocentric	15.3% (6.2-32.9%)		17.4% (11.1-26.4%)		29.7% (21.3-39.8%)	
Sample size ≤30	20.7% (12.0-33.4%)	0.136	11.8% (6.8-19.8%)	0.025	31.8% (23.3-41.7%)	0.965
Sample size >30	6.2% (1.2-26.3%)		25.4% (16.6-36.7%)		32.9% (4.8-82.6%)	
RECIST	19.3% (8.6-37.7%)	0.498	12.6% (6.7-22.6%)	0.161	34.4% (24.5-45.9%)	0.503
No RECIST	13.1% (5.4-28.2%)		21.4% (13.7-31.9%)		23.9% (7.1-56.5%)	
NCCC	13.1% (5.5-28.0%)	0.565	11.0% (4.6-24.0%)	0.164	30.7% (19.4-44.8%)	0.978
Others	18.0% (8.4-34.4%)		20.6% (14.3-28.8%)		31.0% (15.5-52.4%)	
No gemcitabine	9.4% (4.4-19.0%)	0.078	23.7% (15.8-33.9%)	0.042	20.5% (3.0-67.8%)	0.549
Gemcitabine	21.7% (11.8-36.4%)		11.6% (6.3-20.3%)		33.2% (24.3-43.4%)	
Chemo/radiotherapy	13.5% (7.0-24.6%)	0.361	17.9% (11.2-27.4%)	0.742	28.8% (15.2-47.7%)	0.531
Chemotherapy alone	23.6% (8.0-52.3%)		15.6% (7.6-29.3%)		35.9% (23.1-51.1%)	
Overall pooled estimates	**16.4% (9.3-27.5%)**	**P=0.044[b]** I^2**=48%**	**18.5% (13.2-25.3%)**	**P=0.590[b]** I^2**=0%**	**32.0% (21.2-45.1%)**	**P=0.010[b]** I^2**=58%**

[a] P values test the frequencies between strata

[b] Heterogeneity test: P values test homogeneity between studies for overall pooled estimates and I^2 values show the percentage of total variation across studies that is attributable to heterogeneity rather than chance. Heterogeneity was considered statistically significant when P value was less than 0.10

associated with 46% rate of toxicity, and the gemcitabine plus oxaliplatin and gemcitabine plus capecitabine regimens with a rate of 30%.

Publication Bias

For all previous analyses, publication bias assessments, evaluated by the Egger's regression intercept, were not significant.

Survival Analysis

Among studies reporting median survival rates [16, 17, 19, 20, 23, 24, 25], only a few included values for confidence intervals, P values, or analysis of variance were reported. Therefore, we were unable to run a meta-analysis of median survival times, and we simply calculated the mean of median survival times weighing by the number of patients at risk in each study. The weighted mean of median survival amounted to 12.4 months (range: 9 to 16 months) for the overall cohort of patients, 22.0 months (range: 12-32 months) for those who were resected, and 9.7 months (range: 8-41 months) for unresected patients. The weighted fractions of resected patients alive at 1 and 2 years were 61% (95% CI: 48-100%) and 44% (95% CI: 32-59%), respectively.

Analysis of Heterogeneity (Tables 3 and 4)

Although only a few meta-analytical results yielded data of moderate heterogeneity ($I^2>50\%$), multivariable meta-regression analyses for different variables were run to explore the likely sources of heterogeneity across the studies. For the complete/partial response at restaging, the only characteristic that could explain the heterogeneity was the sample size of the studies: small (≤30 patients) studies reported a downstaging rate higher than the rate reported in larger studies: 21% (95% CI: 12-33%) *vs.* 6% (95% CI: 1-26%). As compared to gemcitabine monotherapy, the administration of gemcitabine with other cytotoxic drugs tended to be associated with either higher downstaging rate and a lower progression rate: 22% (95% CI: 12-36%) *vs.* 9% (95% CI: 4-19%), and 12% (95% CI: 6-20%) *vs.* 24% (95% CI: 16-34%).

The heterogeneity for the toxicity data could only be related to the different design of the included studies, with phase II studies reporting more severe toxicity than cohort studies: 46% (95% CI: 33-60) *vs.* 22% (95% CI: 14-35%) (P=0.011). In small-size studies patients were less likely to undergo surgical exploration than those evaluated in larger-size studies: 57% (95% CI: 44-69%) *vs.* 78% (95% CI: 65-87%) (P=0.024). Of relevance, higher rates of pancreatic resection were reported in cohort studies in comparison to the rates given in phase II studies: 91% (95% CI: 69-98%) *vs.* 72% (95% CI: 54-85%) (P=0.115).

DISCUSSION

The benefit of preoperative therapy for patients with pancreatic carcinoma is still unclear. Three recent meta-analyses [4, 5, 26] failed to support a benefit of neoadjuvant therapies. Gillen *et al.* [4] demonstrated that in resectable patients, neoadjuvant treatment did not impact on resectability, resection margins status or patients' outcome, compared to upfront resection. On the contrary, in locally advanced patients, about 1/3 of the tumors became resectable at restaging. Our previous meta-analysis [5] did not support the benefit of preoperative therapy for patients with resectable lesions, and indicated a potential advantage only for a minority of those with unresectable cancers. On the same line, the meta-analysis by Assifi *et al.* [26] documented a benefit only for patients with locally advanced disease.

Current investigation considered only trials on patients with borderline resectable pancreatic adenocarcinoma who received neoadjuvant therapy, later restaged, and eventually resected. Relying on the results of the three previous meta-analyses [4, 5, 26], we were expecting neoadjuvant therapy to impact positively on the anatomic extent and overall outcome of patients. Contrary to our expectation, downstaging the lesion was accomplished in only 16% (95% CI: 9-28%) of the whole study cohort (Figure 5). Of more concern were data from large (>30 patients) size trials, where the weighted estimate of downstaging dropped to 6% (95% CI: 1-26%). The vast majority of patients with borderline resectable cancer had the lesion stable (69%; 95% CI: 60-76%) or progressive (19%; 95% CI: 13-25%) at restaging following neoadjuvant therapies. Thus, 2/3 of patients did not change his status, and 1/5 progressed despite therapy. On the basis of anatomic definitions of disease stage, this meta-analysis shows that radiographic downstaging is an uncommon event following neoadjuvant treatment, even among patients with borderline resectable disease, who had to experience significant (grade 3/4) toxicity in a considerable number of cases (32%; 95% CI: 21-45%). These data are in line with a recent study by Katz *et al.* [27] where a borderline resectable cancer was converted by preoperative therapy to a resectable lesion in only 1 of 129 evaluated patients.

Only a minority of patients with borderline resectable cancer were downstaged by therapy: whether this represents an actual benefit of preoperative chemoradiation or an over/under estimate of unresectability by cross-imaging at pre-surgical staging remains unclear. It is well known that current imaging modalities understage pancreatic cancers [28], as some patients undergo laparotomy but they have not resection because of

local disease spread. The extent of over-staging of pancreatic cancers by preoperative computed tomography or magnetic resonance remains unknown and would be difficult to quantify, given that patients staged as locally advanced are denied surgery and consequently do not undergo objective verification of the preoperative staging.

A distinct advantage of this treatment approach is to allow selection for surgery of patients without disease progression. Presently, these two distinct groups of patients, i.e. those with progressive and those with non-progressive disease, cannot be differentiated at the time of diagnosis by current staging modalities. Efforts to separate these two categories by evaluating some biological characteristics of either the tumor or the patients seem most rewarding.

One major strength of the present study was the homogeneity of the meta-analytical data. In the most recent years, sub-categories of patients with borderline cancers in respect to the degree and type of vessel involvement have been delineated and emerged as a new issue to be taken into consideration when discussing therapies for patients with borderline resectable. Despite the definition of subcategories of borderline pancreatic cancers might have varied from one to the other study, our data resulted homogeneous at the statistical evaluation, indirectly suggesting a homogeneous definition of the borderline cancer stage, adopted in the selected studies. Notwithstanding that, two factors which could partly explain some differences appearing across the studies were identified: small size trials tended to either over-report the benefit of the preoperative treatment and to surgically explore less frequently patients; composite chemotherapeutic regimens seem to double the rate of complete/partial response without a significant increase in severe toxicity profile.

In summary, present investigation lends support to the results of previous meta-analyses showing that the promises of neoadjuvant therapies are partially fulfilled for either patients with resectable pancreatic cancers, for those initially deemed marginal for operative intervention, and for patients with truly locally-advanced disease. We acknowledge that marginally better results emerged from studies that administered combined chemo-radiotherapy over gemcitabine mono-therapy, suggesting that the value of neoadjuvant therapies should be worth exploring in future trials with new chemotherapeutic drugs.

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