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REVIEW ARTICLE

Neoadjuvant treatment in pancreatic cancer: Evidence-based medicine? A systematic review and meta-analysis

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Abstract Neoadjuvant treatment in non-metastatic pancreatic cancer (PaC) has the theoretical advantages of downstaging the tumor, sterilizing any present systemic undetectable disease, selecting patients for surgery and administering therapy to each patient. The aim of this systematic review is to analyze the state of the art on neoadjuvant protocols for non-metastatic PaC. A literature search over the last 10 years was conducted, and papers had to be focused on resectable, borderline resectable (BLR) or locally advanced (LA) histo- or cytologically proven PaC; to be prospective studies or prospectively collected databases; to report percentage of protocol achievement and survival data at least in an intention-to-treat (ITT) analysis. Twelve studies were eligible for systematic review. Studies included a total of 624 patients: 248 resectable, 268 BLR, 71 LA and 37 non-specified. All studies were included for meta-analysis. ITT overall survival (OS) was 16.7 months (95% CI 15.16–18.26 months); for resected patients OS was 22.78 months (95% CI 20.42–25.16), and for eventually non-resected patients it was 9.89 months (95% CI 8.84–10.96). Neoadjuvant approaches for resectable, BLR and LA PaC are spreading. Outcomes tend to be better outside an RCT context, but strong evidences are lacking. Actually such treatments should be performed only in a randomized clinical trial setting.

Keywords Pancreatic cancer · Neoadjuvant therapy · Survival · Borderline · Resectable · Surgery

Introduction

Pancreatic cancer (PaC) is one of the most challenging global health burdens that physicians are facing nowadays. Its 5-year survival in non-metastatic stages ranges between 3 and 14% [1], while surgery remains the only chance for long survivors. Currently, the standard of care advocates a surgery-first approach in resectable situations followed by adjuvant treatment, but neoadjuvant approaches are spreading either in resectable and in borderline resectable (BLR) and locally advanced (LA) patients. Whether this attitude provides to the patient a survival advantage is a widespread belief but not a matter of fact. The National Comprehensive National Network states that there is limited evidence to recommend specific neoadjuvants regimens off-study [2]. While the only choice in LA PaC is a loco-regional chemoradiation or systemic chemotherapy and subsequent revaluation, for resectable and BLR we must choose between a surgery-first approach and a neoadjuvant treatment. Over 40% of patients who have clinically a resectable disease are found unresectable at surgery, even though this percentage drops to 20% if a diagnostic laparoscopy is added to the preoperative diagnostic panel [3], and one out of five patients are eventually misdiagnosed as resectable or BLR while having a LA disease. Moreover, 27% of BLR patients will require a vascular resection in order to achieve their pancreatectomy

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[4], but histologic invasion of resected vessel will be confirmed only in 56.7% of specimens [5]. Finally, up to 28% of successfully resected patients will not undergo adjuvant therapies because of surgical morbidity, poor performance status, refusal or early recurrence [5]. A preoperative treatment has the theoretical advantages of delivering systemic therapy to all patients in a healthy tumor bed and identifying tumors with an aggressive biology and thus patients who would not benefit from surgery.

The aim of this systematic review is to analyze the bulk of knowledge on neoadjuvant protocols for non-metastatic pancreatic cancer and derive a meta-analysis of its results.

Materials and methods

Following the criteria of the PRISMA statement, a comprehensive PubMed, Embase and Cochrane library search was conducted looking for studies focusing on neoadjuvant therapies in non-metastatic pancreatic cancer. The keywords used were 'pancreatic cancer or carcinoma' and 'neoadjuvant therapy or treatment.' The research was restricted to the last 10 years (June 2006–June 2016) and to English language articles dealing with human patients. Papers had to be focused on resectable, borderline resectable or locally advanced histo- or cytologically proven pancreatic adenocarcinoma; to be prospective studies or prospectively collected databases; to report the percentage of protocol achievement and survival data at least in an intention-to-treat (ITT) analysis. Exclusion criteria were retrospective studies, RCT papers, periampullary cancers and missing outcomes data. Data extraction was carried out by two independent investigators. Primary outcome was ITT overall survival (OS), and secondary outcomes were protocol achievement, R0 resection rate, specific resectable, resected and unresected OS.

Pooled survival times and proportions were computed by means of meta-analyses. Each separate meta-analysis conducted was strictly under heterogeneity among studies, by means of a hierarchical Bayesian model. Homogeneity was not assessed due to the limited number of studies, and instead we worked under heterogeneity through hierarchical models [6]. Median survival times and logistic transforms of proportions were assumed to be normally distributed. Each study summary was assumed to arise from a Gaussian centered on a study-specific effect and with variance corresponding to the square of its estimated standard error, inflated by 25% in order to guarantee conservative statements. The study-specific summary was assumed to be Gaussian, centered on an unknown pooled measure, which was the main object of interest. Summaries for proportions were then back-transformed appropriately. As per guidelines with limited number of studies involved, informative priors were used. For the variance of the pooled measures, we assumed an inverse Gamma centered on an estimator obtained with a moment-based approach (inflated by 25% for similar reasons as above). Potential publication bias was estimated using Egger's linear regression tests, which were never significant.

The systematic review's protocol was regularly registered at www.researchregistry.com with the unique identifying number of review registry 102.

Results

Papers selection and systematic review

The extensive literature search led to the identification of 612 English papers over the past 10 years focusing on neoadjuvant treatment for resectable, BLR and LA PaC, of which 12 papers eligible for the systematic review (Fig. 1) [7–18]. Papers were published over a 8-year period, between 2008 and 2015.

Studies characteristics

Studies included between 15 and 246 patients, with a total of 624 patients: 248 resectable, 268 borderline resectable, 71 locally advanced and 37 non-specified (Table 1). Four papers were restricted to resectable patients [9, 12, 17, 18], one to LA patients [8] and one to BLR patients [10]. Treatment plans included: six studies offer a systemic chemotherapy [9, 11, 13, 15, 16, 18], three a loco-regional chemoradiation regimen [8, 12, 17] and three a combination of the two [7, 10, 14]. Gemcitabine has been the most widely used antineoplastic agent (Table 1). All studies reported ITT-OS. One study didn't report OS neither for eventually resected patients nor for post-neoadjuvant unresectable patients [12]. Two studies didn't report OS for post-neoadjuvant unresectable patients [9, 18]. One study didn't report resection margins [8].

Definition of resectability

The definition of resectability varies among studies (Table 2). The most cited classification [10, 14–16] is Callery's one from the expert consensus statement sponsored by the American Hepato-Pancreato-Biliary Association and others [19]. Five studies used their own definitions [9, 11, 12, 17, 18].

Protocol achievement

The ITT population includes 624 patients submitted to neoadjuvant therapy. A total of 395 patients eventually

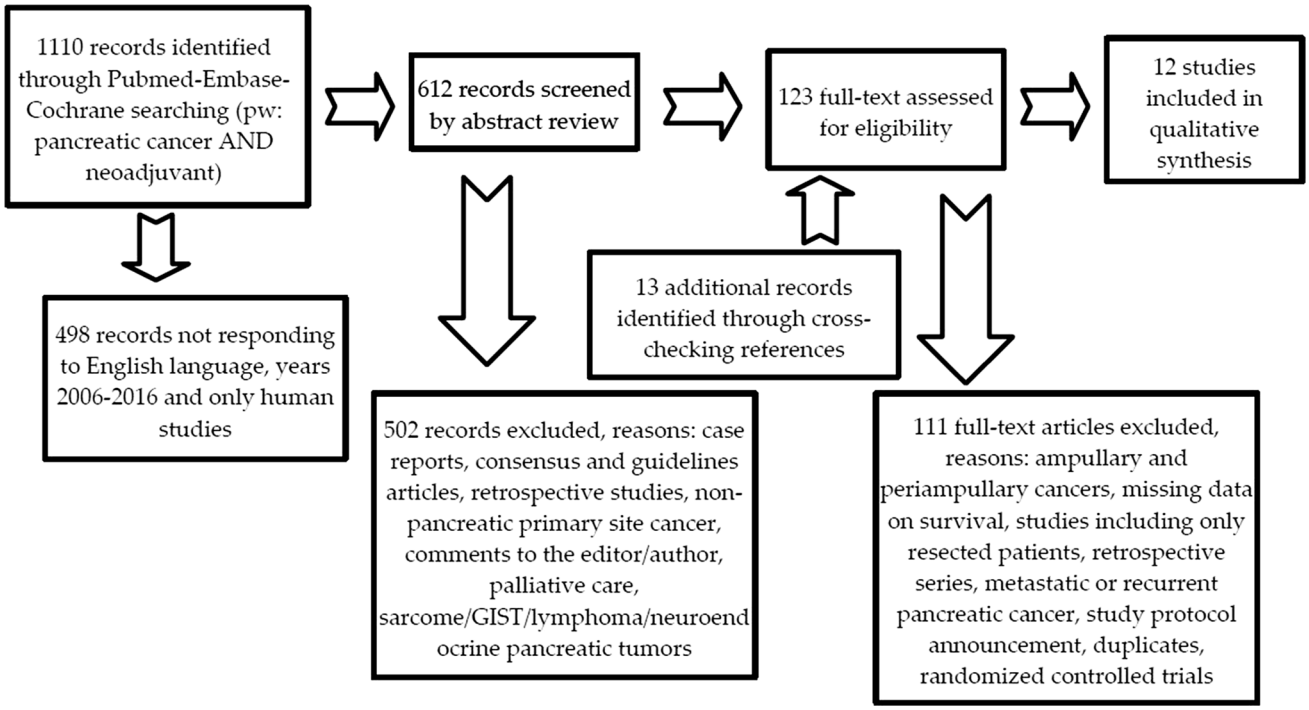

Fig. 1 Studies' selection flow chart

underwent surgical resection with curative intent. Protocol achievement in terms of completion of the proposed neoadjuvant treatment followed by pancreatectomy ranged 26.7–89.28% (Table 1), and at the meta-analysis it was 65% (95% CI 62–67%) with a regression test of $p = 0.366$ (Fig. 2).

Resection margins

One paper failed to report data on resection margins [8]. Of the 395 resected patients, 391 resection margins were specified: 355 R0, 35 R1 and 1 R2. R0 rate ranged 69.2–100% (Table 1), and at the meta-analysis it was 94% (95% CI 93–95%) with a regression test of $p = 0.0913$ (Fig. 3).

Survival

Intention-to-treat overall survival ranged 13.5–27.2 months (Table 1), and at the meta-analysis ITT-OS was 16.7 months (95% CI 15.16–18.26 months) with a regression test of $p = 0.1087$ (Fig. 4).

OS of eventually resected patients ranged 15–36.5 months (Table 1), and at the meta-analysis resected OS was 22.78 months (95% CI 20.42–25.16 months) with a regression test of $p = 0.0582$ (Fig. 5).

Finally OS of post-neoadjuvant treatment unresectable patients ranged 8.6–13.2 months (Table 1), and at the meta-analysis unresectable OS was 9.89 months (95% CI 8.84–10.96 months) with a regression test of $p = 0.379$ (Fig. 6).

We conducted a subgroup analysis of studies dealing with resectable only patients [9, 12, 17, 18], and this analysis takes into account a total of 123 patients: ITT-OS in this setting ranged 15.5–27.2 months (Table 1), and at the meta-analysis resectable ITT-OS was 18.16 months (95% CI 14.08–22.45 months) with a regression test of $p = 0.5293$ (Fig. 7).

Among those studies restricted to resectable patients, three reported OS of eventually resected patients [9, 17, 18]: 69 out of 97 clinically resectable patients have been resected. The OS of eventually resected patients in this setting ranged 19.1–32 months, and at the meta-analysis it was 20.87 months (95% CI 17.97–23.82 months) with a regression test of $p = 0.5205$ (Fig. 8).

Discussion

RCTs focusing on neoadjuvant therapies are lacking, and the existing three trials conducted on resectable PaC report a protocol achievement of 18.18–70% and an ITT survival of 9.9–19.4 months [23]: Palmer et al. [24] report a resection rate of 54% after neoadjuvant treatment, of which 75% R0 resections; Golcher reports a non-statistically significant difference of resection rate in the neoadjuvant group (57.57%) versus the upfront surgery group (69.69%), and there is to say that this study has been terminated

Table 1 Studies included in the systematic review

References	Protocol	N. pts	Resectable	BLR	LA	Resected	Protocol achievement (%)	R0	R1	R2	ITT-OS (mo)	Resected OS (mo)	Non-resected OS (mo)	*p*
Miura et al. [7]	Various protocols (CHT, CRT, CHT + CRT)	246	103	143	–	177	72.00	173 (97.7%)	4	–	24.3	36.5	11.7	<0.001
Kapoor e al. [8]	CRT (Capecitabine + 30GY)	15	–	–	15	4	26.70	na	na	na	59.8%[a]	15	8.6	na
O'Reilly et al. [9]	CHT (GEM + Oxaliplatin)	38	38	–	–	27	71.05	20 (74.1%)	7	–	27.2	22[b]	na	0.0006
Rose et al. [10]	CHT (GEM + Docetaxel) ± RT (50.4 GY)	64	–	64	–	31	48.44	27 (87.1%)	4	–	23.6	85.00%[c]	20.00%[c]	na
Motoi et al. [11]	CHT (GEM + S-1)	35	19	16	–	30	85.71	26 (86.7%)	4	–	19.7	34.7[d]	10[d]	0.0017
Shinoto et al. [12]	Carbon-ion RT (30 GY)	26	26	–	–	21	80.77	19 (90.5%)	2	–	18.6	na	na	na
Lee et al. [13]	CHT (Capecitabine + GEM)	43	–	18	25	17	39.50	14 (82.3%)	3	–	16.6	23.1	13.2	0.017
Pipas et al. [14]	CHT (Cetuximab) + CRT (45-54 GY + GEM)	37	na	na	na	25	67.60	23 (92%)	2	–	17.3	24.3	10	na
Sahora et al. [15]	CHT (GEM + Docetaxel)	25	–	12	13	8	32.00	7 (87.5%)	1	–	13.5	16.3	12.2	NS
Sahora et al. [16]	CHT (GEM + Oxaliplatin)	33	–	15	18	13	39.39	9 (69.2%)	3	1	16	22	12	0.046
Turrini et al. [17]	CRT (Docetaxel + 45 GY)	34	34	–	–	17	50.00	17 (100%)	–	–	15.5	32	11	<0.001
Heinrich et al. [18]	CHT (GEM + Cisplatin)	28	28	–	–	25	89.28	20 (80%)	5	–	26.5[e]	19.1	na	na

PI principal investigator, *N* number, *pts* patients, *BLR* borderline resectable, *LA* locally advanced, *R0* no residual tumor, *R1* microscopic residual tumor, *R2* macroscopic residual tumor, *ITT* intention-to-treat population, *OS* overall survival, *mo* months, *p p* value of significance, *CHT* chemotherapy, *CRT* chemoradiotherapy, *GEM* gemcitabine, *RT* radiotherapy, *na* not available, *NS* nonsignificant

[a] 1-year OS

[b] DFS

[c] 2-year OS

[d] OS of resected and M0 patients versus OS of unresected or M1 patients

[e] Comprehensive of one high-grade dysplasia and three cancers of the Ampulla Vateri at final pathology

Table 2 Definitions of resectable, borderline resectable and locally advanced pancreatic cancer among studies

References	Resectable	Borderline resectable	Locally advanced	Reference classification
Miura et al. [7]	No CA/SMA/HA abutment; SMV, PV or SMV-PV confluence narrowing <50%	SMA or CA abutment <180°; abutment or short encasement of HA; SMV, PV or SMV-PV confluence narrowing >50% or short segment occlusion (allowing for reconstruction); suspicion (not diagnosis) of metastatic disease	SMA/CA encasement >180°; occlusion of SMV, PV or SMV-PV confluence not allowing for reconstruction	Appel et al. [20]
Kapoor et al. [8]	–	–	Encasement/involvement of SMA/CA	Tempero et al. [21]
O'Reilly et al. [9]	Clear fat plane around CA and SMA, patent SMV/PV, no SMV encasement or PV involvement, no HA or SMA encasement, no extra-regional nodal disease	–	–	–
Rose et al. [10]	No evidence of SMV or PV abutment, distortion, tumor thrombus or venous encasement and clear fat planes around CA, HA and SMA[a]	Involvement of SMV/PV allowing for reconstruction, GDA or HA involvement/encasement w/o extension to CA or abutment of SMA < 180°[a]	Major venous thrombosis of PV/SMV, encasement of SMA, CA or proximal HA[a]	Callery et al. [19][a]
Motoi et al. [11]	–	Encasement of PV/SMV and/or abutment of HA or SMA within 180°	–	–
Shinoto et al. [12]	No involvement of HA, CA or SMA	–	–	–
Lee et al. [13]	Clear tissue plane around SMA, CA, HA and SMV/PV	SMA or CA abutment or GDA encasement up to origin of HA or SMV short segment occlusion	SMA or CA or HA encasement or SMV/PV occlusion	NCCN Pancreatic Adenocarcinoma Guidelines version 1.2008 [22]
Pipas et al. [14]	No evidence of SMV or PV abutment, distortion, tumor thrombus or venous encasement and clear fat planes around CA, HA and SMA	Involvement of SMV/PV allowing for reconstruction, GDA or HA involvement/encasement w/o extension to CA or abutment of SMA < 180°	Major venous thrombosis of PV/SMV, encasement of SMA, CA or proximal HA	Callery et al. [19]
Sahora et al. [15]	No evidence of SMV or PV abutment, distortion, tumor thrombus or venous encasement and clear fat planes around CA, HA and SMA	Involvement of SMV/PV allowing for reconstruction, GDA or HA involvement/encasement w/o extension to CA or abutment of SMA < 180°	Major venous thrombosis of PV/SMV, encasement of SMA, CA or proximal HA	Callery et al. [19]
Sahora et al. [16]	No evidence of SMV or PV abutment, distortion, tumor thrombus or venous encasement and clear fat planes around CA, HA and SMA	Involvement of SMV/PV allowing for reconstruction, GDA or HA involvement/encasement w/o extension to CA or abutment of SMA < 180°	Major venous thrombosis of PV/SMV, encasement of SMA, CA or proximal HA	Callery et al. [19]
Turrini et al. [17]	Involvement of SMV/PV < 180°, no occlusion of SMV or PV confluence, no extension to SMA or CA, no extrahepatic disease	–	–	–
Heinrich et al. [18]	cT1, cT2, cT3s. AJCC classification 7th ed.	–	–	–

PI principal investigator, *SMV* superior mesenteric vein, *PV* portal vein, *HA* hepatic artery, *CA* celiac axis, *SMA* superior mesenteric artery, *GDA* gastroduodenal artery, *w/o* without, *AJCC* American Joint Committee on Cancer

[a] Criteria specified at restaging

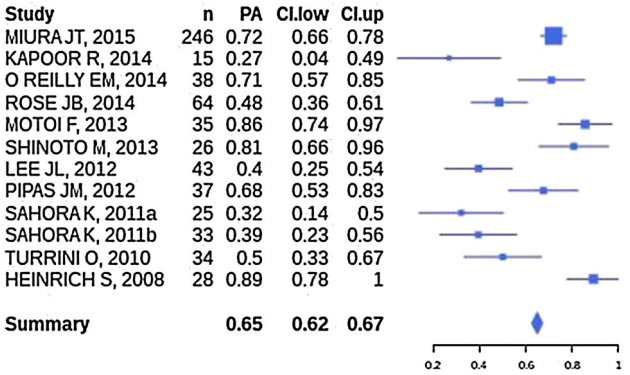

Fig. 2 Forest plot protocol achievement

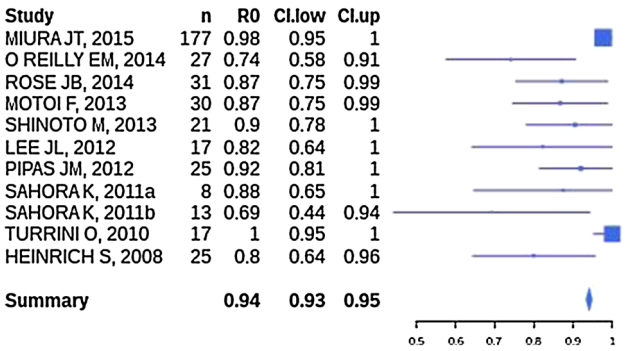

Fig. 3 Forest plot R0

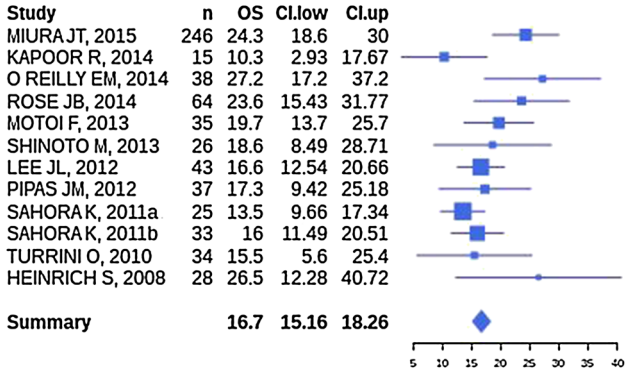

Fig. 4 Forest plot ITT-OS

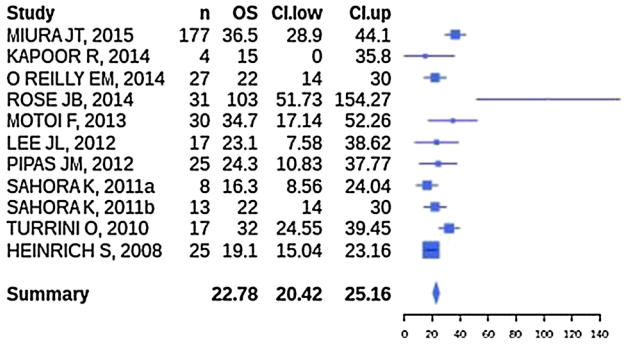

Fig. 5 Forest plot resected OS

because of the poor recruitment rate and did not reach the necessary sample size [25]; Landry reported a resection rate of 23.8% after neoadjuvant treatment of locally advanced potentially resectable PaC, of which 40% R0 resections [26].

Selected retrospective single-institution experiences over resectable BLR and LA PaC report OS up to 43.4 months in resected patients following chemotherapy or chemoradiation [27]. According to Mellon and colleagues, patients with BLR or LA PaC and sufficient response to neoadjuvant multi-agent chemotherapy and stereotactic body radiation therapy have similar or improved perioperative and long-term survival outcomes compared to upfront resection patients [28]. In this paper neoadjuvant therapy in BLR–LA patients was compared to upfront resected patients. In the ITT analysis the neoadjuvant group had a worse survival (17.0 vs 22.1 months, $p = 0.029$); such comparison has little significance because in the first group 61.6% of patients was eventually unresectable while in the upfront surgery group accounted only resected patients. Moreover, patients of the upfront surgery group who failed to receive adjuvant treatment (20.3%) were excluded from analysis. Indeed, there was no significant difference in survival between the two groups among only resected patients (33.5 vs 23.1 months, $p = 0.057$) [28].

In this meta-analysis including resectable, BLR and LA PaC, we observe a protocol achievement of 65% with an R0 rate of 94% and an ITT survival of 16.7 months. The subgroup analysis restricted to resectable patients shows an ITT survival of 18.16 months, and among them eventually resected patients have OS of 20.87 months. Overall, two patients out of three have been treated as intended/planned.

Surprisingly, survival of patients eventually resected among resectable ones wasn't better than overall survival of resected patients (20.87 vs 22.78 months). This may be explained by the fact that preoperative staging is far from being accurate. As already said, to the best of clinical practice, one out of five patients is wrongly taken to the OR with a curative intent while having a LA PaC.

In Miura' study, while in the ITT analysis clinically BLR disease was an independent poor prognostic indicator, among resected patients OS did not differ between preoperatively classified resectable and BLR patients [7]. This confirms that once resected, preoperative staging doesn't influence patients' outcomes.

Histologic confirmation of the disease is mandatory before administering neoadjuvant treatment even though up to 16% of preoperatively cyto/histologically diagnosed pancreatic cancers eventually receive a final pathological diagnosis other than PaC [18], thus receiving a useless

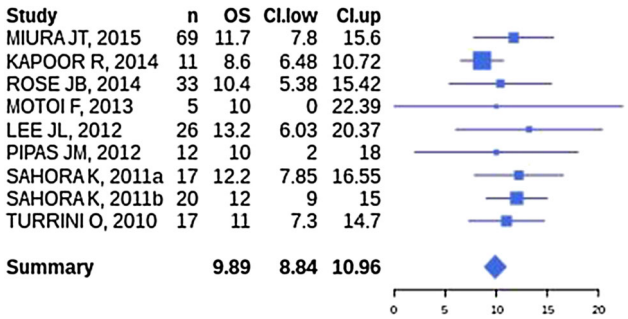

Fig. 6 Forest plot unresectable OS

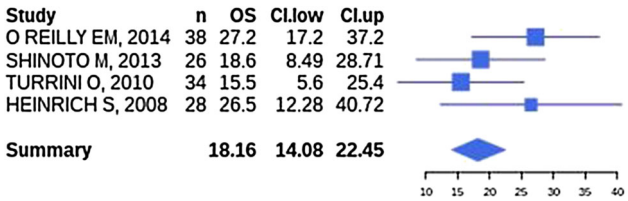

Fig. 7 Forest plot resectable ITT-OS

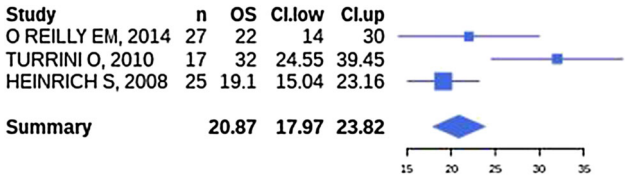

Fig. 8 Forest plot resected among resectable OS

neoadjuvant treatment. In Golcher' study pathological diagnosis of PaC at biopsy has been rejected in 4.5% of resected patients (because of the finding of a distal choledochal adenocarcinoma and a duodenal adenocarcinoma) [25].

The use of different classifications over time makes extremely difficult the interpretation of the literature. NCCN guidelines endorse the consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association [29] to define resectable, borderline resectable and locally advanced pancreatic cancer. The unanimous use of this classification might clarify the impact of neoadjuvant treatments on the survival of those patients.

Outcomes tend to be better outside an RCT context; the literature is influencing our conduct, but strong evidences come only from well-designed randomized trials. More effort should be addressed toward the comprehension of the potential benefit that patients could gain from neoadjuvant approach.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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