Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: A systematic review and meta-analysis of randomized controlled trials

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Abstract. Liver metastases are a common event in patients with colorectal cancer. Surgical resection, if feasible, produces a survival benefit. We performed a systematic review of randomized clinical trials (RCT) and meta-analysis to address the question if current available studies support the use of systemic chemotherapy as an adjunct to surgery in resected/resectable patients. The search was based on major databases (PubMed, CancerLit, Embase, Medscape and Cochrane) of published literature and selecting abstracts from major cancer meetings. We performed a literature for the January 1982-May 2010 time frame. The hazard ratios (HRs), with confidence intervals, as presented in retrieved studies, referred to the disease- and/or progression-free (DFS and/or PFS) and overall survival (OS) were extracted. The meta-analysis was carried out by the fixed-effect and the random-effects model. Three studies randomizing combined treatment vs. surgery alone for a total of 666 patients (642 evaluable for survival analysis) were selected and included in the final analysis. Evidence for chemotherapy-induced benefit in terms of both DFS (pooled HR, 0.71; CI, 0.582-0.878; P=0.001) and PFS (pooled HR, 0.75; CI, 0.620-0.910; P=0.003) was demonstrated. However, our meta-analysis failed to demonstrate a significant advantage of combined treatment in terms of OS (pooled HR, 0.743; CI, 0.527-1.045; P=0.088). Chemotherapy combined with surgical resection of colorectal liver metastases improves DFS and PFS whereas the benefit in OS is not demonstrated on the basis of the available results of RCTs. New prospective trials in the era of targeted therapy are eagerly awaited on this specific topic.

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Introduction

Colorectal cancer (CRC) is a relevant cause of death in industrialized countries. At present, large bowel tumors are the second cause of male cancer mortality and the third cause of female cancer mortality (1-3).

The treatment of CRC is based on a multidisciplinary approach which includes surgery, radiotherapy and chemotherapy (4-9). Several clinical-pathological factors impact on the prognosis of patients suffering from CRC, but, among them, the stage of the disease at the diagnosis is the variable that mostly influences the final outcome (10). Based on these findings the selections of an appropriate therapeutic approach for hepatic metastases, which affect about half of CRC patients appears imperative (11,12). To date, the surgical resection of hepatic metastases is the only treatment able to ensure long-term disease control (13). One possible explanation of the relevant efficacy of resection approaches is that the hepatic involvement occurs in a relatively early phase of the disease, when tumor cells do not express the end-stage aggressive phenotype (14). At present, it is not clear if all patients with hepatic lesions should undergo surgical evaluation (15). Up to some years ago, patients were selected on the basis of exclusion criteria referring to a higher risk of postsurgical relapse (16-18). Radical surgery now appears to be the most important condition for a long term survival (19-22). New surgical approaches like portal vein embolization, two-stage hepatectomy or their combination with local techniques (radiofrequency ablation, cryotherapy or laser therapy) can allow the resection of liver metastases that were considered not resectable in the past. Moreover, it has to be considered that chemotherapy can reduce the volume and the number of lesions, down-stage the disease and allow radical surgery (23). Guidelines have been developed with novel criteria of resectability based

Table I. Quality assessment of the included studies.

Included studies	Method of randomization	Allocation concealment	Blind	Withdrawal and dropout	Baseline	Quality level
Langer *et al* (52)	Not detailed	Not detailed	No	Not mentioned	Published in abstract form and based on criteria of enrollement including lung metastases	C
Portier *et al* (54)	Central by data center	Not detailed	No	Detailed criteria	Identical to baseline	B
Nordlinger *et al* (55)	Central by data center	Central by data center	No	Detailed criteria	Different timing and schedule of chemotherapy	A

Quality criteria was adapted from the Cochrane reviewers' handbook.

on new technologies and knowledge on the biopathology of CRC (24). The 'OncoSurge' project was developed in order to set up a therapeutic algorithm which takes into account the patient's and the disease's features (25). These criteria are not influenced only by the radiological appearance of metastatic lesions since assessment of resectability must always take into account the functionality of the residual liver. Only 10-15% of hepatic lesions can be surgically resected at diagnosis; (26) this approach can produce survival up to 5 years of the 35% of the patients who, otherwise, would have no hope of long-term survival. Unfortunately, the failure rates are high with more than 75% of the patients experiencing relapse. In order to improve the outcome of patients undergoing resection of liver metastases, combination of chemotherapy with surgery along with rational selection of patients who potentially can obtain benefits from surgical resection has been proposed. Fluorouracil-based chemotherapy, as a primary treatment of CRC, is the mainstay approach to advanced disease with potential benefits in terms of quality of life and long-term survival (27). Benefits have been recently produced by new chemotherapeutic agents (irinotecan, oxaliplatin and oral fluoropyrimidines) and monoclonal antibodies (cetuximab, bevacizumab and panitumumab), which have gradually increased the average survival to about two years vs. six months of the pre-chemotherapy era (28).

It is clear that chemotherapy reduces the risk of relapse and also improves the resectability of primary and/or metastatic lesions (28-33). Upfront systemic chemotherapy has a role in the treatment of hepatic lesions combined to surgery: retrospective or small phase II prospective studies have shown that pre-operative chemotherapy can allow optimal surgery in unresectable disease (conversion chemotherapy). After neoadjuvant chemotherapy, surgical resection would be allowed in up to 30-50% of patients (34-37).

At present, the role of systemic chemotherapy adjunct to surgery in the treatment of resected or resectable hepatic metastases remains still undefined, as compared to conversion (neoadjuvant) chemotherapy whose role is more clearly established and is common practice in specialized institutions.

The aim of this study is to review and to meta-analyze the current evidence derived from prospective randomized trials for a clinical benefit of combinatory approaches based on chemotherapy plus surgery in the management of resected or resectable liver metastases in CRC as compared to surgery alone.

Patients and methods

Literature search. We retrieved the most widely recognized bibliographic sources (PubMed, CancerLit, Embase, Medscape and Cochrane) and selected the abstracts presented at the most important cancer meetings, between 1982, when treatment with 5-FU plus folinic acid was introduced becoming eventually the standard treatment, and May 2010. The published literature is rich in retrospective experiences of single or multi-institutions, but, in order to evaluate the role of systemic therapy, we considered the prospective studies only, in order to reduce or minimize the selection bias (31-37). The search was performed by the following key words: colorectal, tumor, cancer, liver, hepatic, metastases, lesions, chemotherapy, systemic, resectable, resected, prospective study, perioperative, adjuvant and neoadjuvant. The cited words and their combinations used were: colorectal cancer, liver metastases, hepatic lesions, resectable or resected metastases, systemic chemotherapy, perioperative or adjuvant and/or neoadjuvant chemotherapy. The 'related articles' function and the references retrieved from articles were used to perform the search of all related studies, abstracts and citations. For this search the selected language was English.

Selection. In the studies to be included in the present review, patients must have been enrolled according to: inclusion criteria. The studies should report: diagnosis of colorectal adenocarcinoma with resected/resectable liver metastases; age between 18 and 80; performance status according to ECOG scale between 0 and 2; good hepatic, renal function and normal full blood cell count or with toxicity ≤1; no major comorbidities like cardiac or hepatic failure of moderate-serious degree, recent ischemic events, and other tumors (except for no melanoma skin cancers and local cervix tumor); no pregnancy or breast-feeding; informed consent and adhesion to bioethical standards according to the Declaration of Helsinki; adequate staging with at least an abdomen or pelvis CT or MR, thorax X-Ray and electrocardiogram (ECG); and a minimum 24 months of follow-up.

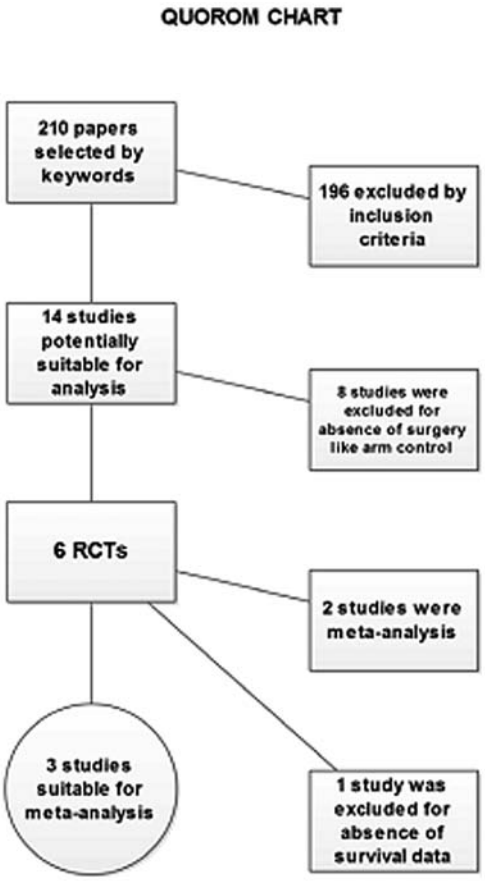

Figure 1. The Quality of Reporting of Meta-analyses (QUOROM) statement flow diagram.

Exclusion criteria. Non-comparative studies; non-prospective studies; other languages; non-comparable endpoints; different modality of administration of chemotherapy agents vs. systemic therapy (eg. intra-arterial infusion); studies including patients with unresectable liver disease were excluded.

Validity assessment. The quality assessment of selected studies was evaluated according to the Cochrane reviewers' handbook for four requirements: method of randomization, allocation concealment, blindness and adequacy of follow-up. One study was scored A (low risk of bias), one was scored B (intermediate risk of bias) and last study was scored C (high risk of bias) (Table I) (38).

Data extraction. The studies were examined independently by two investigators (D.C. and D.F.) in order to select homogeneous studies (39). First author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, number of subjects, length of follow-up, short-term and long-term outcomes were extracted. Any discrepancies were resolved by an arbiter (P.T.). The major endpoint, evaluated in intention to treat analysis, was overall survival (OS). Other outcomes of interest were disease-free survival (DFS) for resected patients only and progression-free survival (PFS) for resectable and resected patients, defined as secondary endpoints. The quality of selected RCTs was evaluated according to the Cochrane reviewers' handbook online version 5.0.2.

Quantitative data synthesis. A meta-analysis was carried out in order to evaluate the overall effects of the combined treatment (chemotherapy-surgery) on the predefined endpoints. Combined therapy was considered the experimental treatment while surgery alone represented the control. The results were extracted as hazard ratios (HRs) of DFS, PFS and OS. The interaction between survival endpoints and chemotherapy plus surgery was obtained through the single studies estimates from the HRs logarithm. The meta-analysis was carried out with the fixed-effects model, on the belief that the studies which have the same effect or meaning were homogeneous. The analysis was also carried out by the random-effect model taking in account the alternative hypothesis of heterogeneity based on the retrieval of three studies only for the final analysis. The combined analysis included the Cochrane's Q-test for the heterogeneity in the studies (40). Pooled data analysis was performed by the Cochran-Mantel-Haenszel test. Data were managed by STATA™ SE v. 10.0. (STATACorp., TX, USA) (41).

Results

Study characteristics. In the time frame covered by the systematic review (1982-2010), fourteen prospective studies were reported as full papers or congress abstracts. They dealt with the chemotherapy combined with surgery in the treatment of resected or resectable liver metastases (Fig. 1).

Eight studies were adjuvant or neoadjuvant phase II-III trials (42-49). These studies did not allow the evaluation of combinatory effects of surgery with chemotherapy, but they were useful to understand the toxicity and long-term effects. As shown in the Table II, neoadjuvant chemotherapy does not preclude the possibility to perform resections R0, even though surgery is delayed. It is clear that after two years of treatment a high percentage of patients (about 50%) is free for relapse. Toxicities reported in studies were of low-moderate degree (42-49). Serious toxicities were typical of chemotherapy (diarrhea, emesis, thrombocytopenia and neutropenia); no toxic deaths were reported.

Two studies were not included in the analysis since they consisted of meta-analysis. The first, presented by Mitry *et al* (50) evaluated the role of the adjuvant chemotherapy after R0 resection, based on the results of two trials, showing no significant improvement of recurrence free-survival (RFS; P=0.058), and a trend in terms of OS benefit for chemotherapy combined with surgery (P=0.125). The second meta-analysis examined the role of the systemic or hepatic arterial chemotherapy after surgery. Carrying out this kind of analysis, Uzzan *et al* (51) circumvented the low statistical power of the studies and showed that the locoregional plus systemic chemotherapy is able to determine a significant advantage, though small, on overall and relapse free survival, [HR OS, 0.81 (95% CI, 0.67-0.99; P=0.04) and HR RFS, 0.77 (95% CI, 0.67-0.89; P=0.001)].

We selected four trials that appeared suitable for a meta-analytic evaluation on the predefined endpoints. The first study by Langer *et al* (52) has only been presented as an abstract at the ASCO Meeting in 2002. The primary endpoint was the efficacy of chemotherapy with 5-fluorouracil (5-FU) plus folinic acid after resection of liver metastases, vs. surgery only. One hundred and twenty-nine patients were randomized,

Table II. Phase II-III trials evaluated for systemic chemotherapy in resectable liver disease in CRC patients.

Studies (Ref)	Study design	Treatment	n	Resected (%)	DFS rate (%)
Lorenz *et al* (44)	Neoadjuvant	FOLFOX	42	81	ND
Wein *et al* (43)	Neoadjuvant	OX+HD 5-FU	20	80	52 (2 years)
2010 update (46)					25 (5 years)
Bathe *et al* (42)	Neoadjuvant	FOLFIRI	ND	ND	ND
2009 update (47)			35	85	ND
Taieb *et al* (45)	Perioperative	FOLFOX-7 followed by FOLFIRI	47	100	47 (2 years)
Lubezky *et al* (48)	Adjuvant vs. perioperative	FOLFOX or FOLFIRI	105	53	ND
Ychou *et al* (49)	Adjuvant	FUFA vs. FOLFIRI	306	100	ND

DFS, disease-free survival; ND, no data; OX+HD, oxaliplatin + high dose; CRC, colorectal cancer.

Table III. Selected four trials suitable for a meta-analytic evaluation on the predefined endpoints.

Langer *et al* (52)

	Treatment	Study arm	Median DFS (months)	4-year DFS % mean (range)	Median OS (months)	4-year OS % mean (range)
	Adjuvant FUFA	Arm 1 (n=52) (CHT+S)	39	45 (29-61)	53	57 (41-73)
		Arm 2 (n=55) (S)	20	35 (21-50)	43	47 (31-63)
				HR (S vs. CHT+S), CI 95%		HR (S vs. CHT+S), CI 95%
				1.28 (0.76-2.14) P=0.35		1.30 (0.71-2.36) P=0.39

Portier *et al* (54)

	Treatment	Study arm	Median DFS (months)	5-year DFS (%)	Median OS (months)	5-year OS (%)
	Adjuvant FUFA	Arm 1 (n=86) (CHT+S)	24.4	33.5 (SE=5.4)	62.1	51.1 (SE=5.7)
		Arm 2 (n=85) (S)	17.6	26.7 (SE=5.1)	46.4	41.9 (SE=5.7)
				HR (CHT+S vs. S) (CI 95%)		HR (CHT+S vs. S) (CI 95%)
				0.66 (0.46-0.96) P=0.028		0.73 (0.48-1.10) P=0.13

Nordlinger *et al* (55)

	Treatment	Arm 1 patients (CHT+S), n	Arm 2 patients (S), n	% Absolute difference in 3-year PFS	Hazard ratio (CI 95%)	P-value
	Perioperative FOLFOX-4					
All patients		182	182	+ 7.2 (28.1-35.4)	0.79 (0.62-1.02)	0.058
All eligible patients		171	171	+ 8.1 (28.1-36.2)	0.77 (0.60-1.00)	0.041
All resected patents		151	152	+ 9.2 (33.2-42.4)	0.73 (0.55-0.97)	0.025

Lopez-Ladron *et al* (53) ND

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; SE, standard error; CHT, chemotherapy; S, surgery; PFS, progression-free survival; ND, no data.

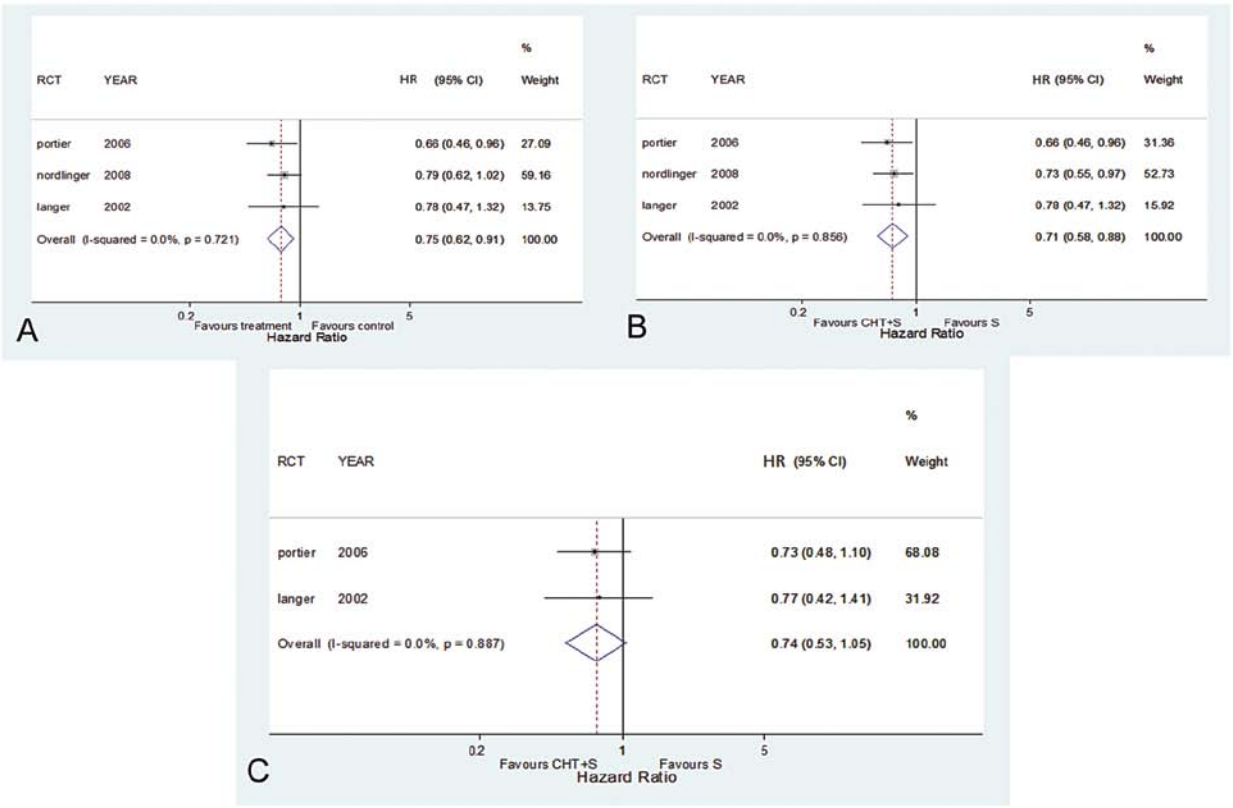

Figure 2. (A) Meta-analysis of HRs in terms of PFS in valuable patients (TEST HR, 1; Z, 2.93; P=0.003). (B) Meta-analysis of HRs in terms of DFS in resected patients (TEST HR, 1; Z, 3.19; P=0.001). (C) Meta-analysis of HRs in terms of OS in valuable patients (TEST HR, 1; Z, 1.71; P=0.088).

among them 107 were evaluable for the survival analysis. The Lopez-Ladron *et al* (53) study, presented as an abstract at the ASCO meeting in 2003, was excluded from the analysis, since, though it had a design similar to other studies, there was no adequate follow-up (only 15 months) and the authors did not present any survival analysis, but they simply reported the average survival in the two groups (30 months in the chemotherapy-surgery group and 15 months in the surgery group). The second trial by Portier *et al* (54) selected for the analysis was a multicenter randomized study with the same design and treatment of the previous one, but with a greater number of patients. One hundred and seventy-three patients were randomized, 171 valuable for intention-to-treat analysis with an 87-month follow-up. In this study the patients were stratified for gender, age and lesion number. After adjustment for the most influential prognostic factors, the 5-years-DFS rate was 33.5% in the chemotherapy arm and 26.7% in the control. The 5-years-OS rate was 51.1% in the chemotherapy arm and 41.1% in the surgery group.

The last study selected for analysis was that of Nordlinger *et al* (55). Unlike previous studies, the aim of this trial was the comparison between a perioperative chemotherapy and surgery alone. The treatment schedule was FOLFOX-4, administered for six cycles before and after surgery. In the study 364 patients were randomized, fairly divided in the two treatment groups (182:182); one hundred and seventy-one patients were found to be eligible in each group. The study design was aimed to demonstrate a 10% increase of PFS vs. surgery only. The survival analysis was performed on an intention-to-treat population (Table III).

Quantitative data synthesis. We analyzed the hazard ratios (HRs), with HR confidence intervals (CIs), as presented in the studies, referred to the DFS and OS. We selected this analysis in order to compare the survival in different studies, since it takes into account the change of the risk in the patients during that time. The influence of single studies was evaluated by the HRs logarithm (CIs 95%). Evidence in favor of chemotherapy plus surgery vs. surgery alone was derived from the HR analysis both in terms of PFS (pooled HR, 0.75; CI 95%, 0.620-0.910; P=0.003, Figs. 2A and 3A) in the study where chemotherapy was performed in the perioperative setting and of DFS (pooled HR, 0.71; CI 95%, 0.582-0.878; P=0.001, Fig. 2B and 3B) in studies where chemotherapy was performed in the post-surgical setting and which achieved successful resection on the basis of study design. We failed to demonstrate an overall survival benefit but only a trend advantage for the combined treatment compared to surgery alone (pooled HR, 0.743; CI 95%, 0.527-1.045; P=0.088, Fig. 2C and 3C). We did not include in the last analysis the study of Nordlinger *et al* where survival data have not been presented due to inadequate follow-up at the time of analysis for publication.

Discussion

We performed a systematic review in order to conduct a meta-analysis of studies evaluating if perioperative (neoadjuvant and/or adjuvant) chemotherapy has an impact on the survival and general outcome of CRC patients with resectable liver disease. In our search we excluded other approaches including

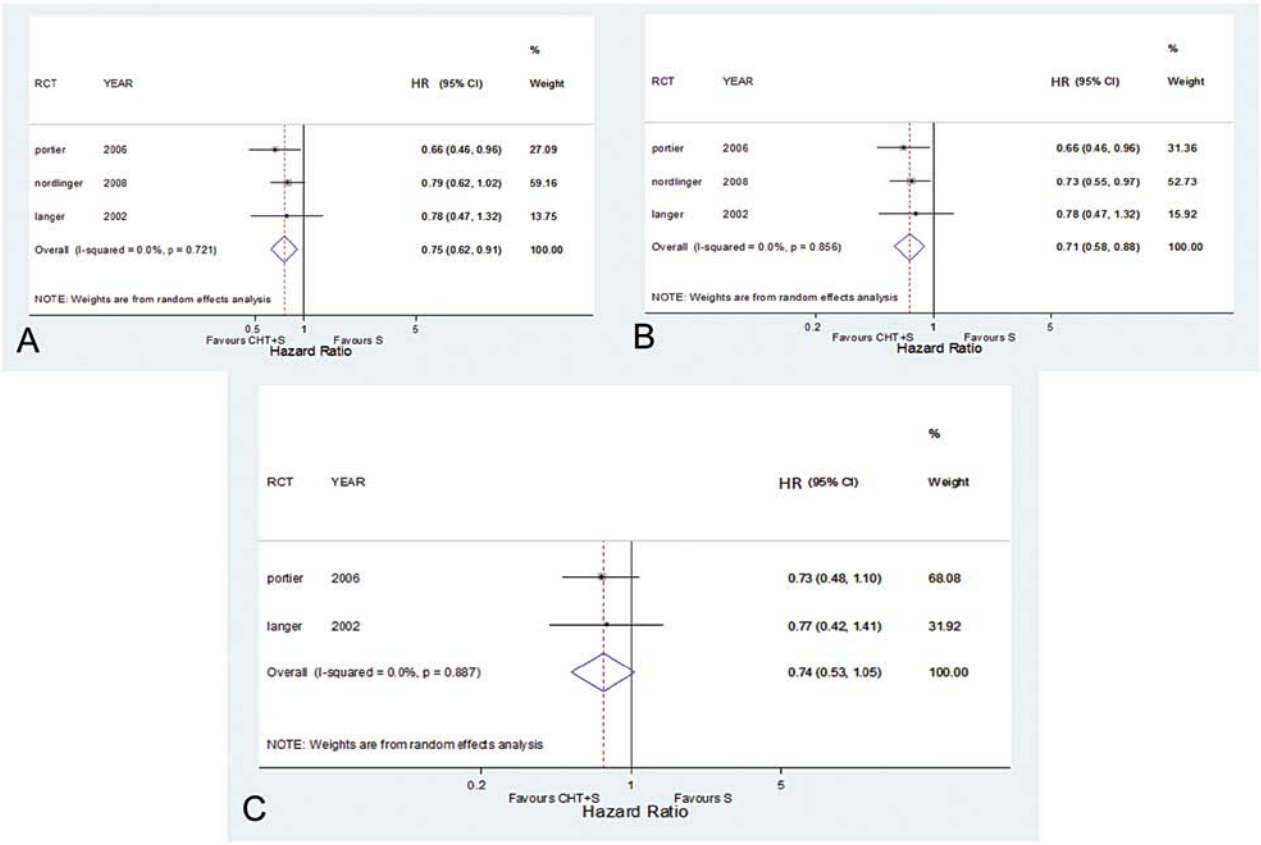

Figure 3. (A) Meta-analysis of HRs in terms of PFS in valuable patients (TEST HR, 1; Z, 2.93; P=0.003). (B) Meta-analysis of HRs in terms of DFS in resected patients (TEST HR, 1; Z, 3.19; P=0.001). (C) Meta-analysis of HRs in terms of OS in valuable patients (TEST HR, 1; Z, 1.71; P=0.088). All analysis were performed with a random effect model.

intraarterial or other locoregional infusional techniques because their use is limited to highly experienced single institutions. We demonstrated that the combined treatment was effective in terms of DFS and PFS but not in terms of OS.

The lack of evidence in our meta-analysis of an OS benefit does not necessarily indicate a lack of effect of the combined treatment if we consider that in CRC, DFS and PFS are considered surrogate of OS benefit as demonstrated by different literature-based analyses (56-59). It can be hypothesized therefore that a long-term follow-up could have led to the formal evidence of such a benefit.

A limit of our meta-analysis is that it does not allow to solve the problem if the perioperative treatment should be given with a predefined number of courses or may be individualized based on the patient response. Prospective studies may be designed with this aim. An additional point, at present, is that the choice among the different drugs and schedules is not unambiguous, but it depends on different factors. In the case of a resectable disease an aggressive (i.e. FOLFOX-IRI) four-drug combination in the preoperative chemotherapy could allow surgery with the possibility to spare hepatic parenchyma in order to preserve liver function (60). In 2005 Folprecht *et al* pointed out that the possibility to undergo an R0 surgery was directly correlated to the response to the neoadjuvant chemotherapy (61). Radical surgery is the main endpoint of neoadjuvant chemotherapy; even if the results obtained by a medical treatment are excellent in terms of short-term control of the disease, they will eventually fail in a long-term period (62). This risk was underlined by a retrospective study by Benoist *et al* in 2006 (63), where the authors analyzed the outcome of patients that had had a complete clinical response to systemic chemotherapy. All patients underwent surgery of the liver areas where some lesions had been identified before chemotherapy (63). The results of this study pointed out that, even in the presence of a complete radiological response, one third of patients had a macroscopic residual disease at surgery and the 80% of resected areas, even in the absence of an evident illness, included neoplastic cells. Adjuvant therapy could also be used in order to fill the current gap of imaging techniques, which are unable to identify the residual microscopic disease and to identify 'cured' patients (64).

The growing interest for biological agents like cetuximab or bevacizumab in the perioperative setting indicate the need of prospectively designed studies. At present, proof-of-principle of benefit for these biological agents comes from retrospective studies in the neoadjuvant setting but no data are available on the perioperative setting in patients with resectable disease or in the post-resection setting (65).

In conclusion, the purpose of a meta-analysis is not to modify the clinical practice, but to raise questions in order to challenge the current beliefs and/or to design prospective studies. We think that our results provide support to the general view that patients with resectable liver lesions should be evaluated not only for surgery but also for systemic treatment, since such approach provides benefit in terms of PFS and DFS and is overally well-tolerated. This meta-analysis, however, does

not demonstrate statistical significant benefit in OS of the peri-operative systemic treatment and this point needs to be addressed in prospective trials including last generation drugs and biologicals.

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