FULL PAPER

BJC

British Journal of Cancer (2013) 108, 39–48 | doi: 10.1038/bjc.2012.516

Keywords: carcinoma of unknown primary; chemotherapy; meta-analysis; systematic review

Evaluation of survival benefits by platinums and taxanes for an unfavourable subset of carcinoma of unknown primary: a systematic review and meta-analysis

J Lee[1], S Hahn*[,1,2,3], D-W Kim[1,4], J Kim[3], S N Kang[3], S Y Rha[6], K B Lee[7], J-H Kang[8] and B-J Park[1,5]

[1]Medical Research Collaborating Center, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Korea; [2]Department of Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Chongro-Gu, Seoul 110-799, Korea; [3]National Evidence-based Healthcare Collaborating Agency, Changkyung B/D, Wonnam-Dong, Jongno-gu, Seoul 110-799, Korea; [4]Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Korea; [5]Department of Preventive Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Korea; [6]Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul, Korea; [7]Departments of Pathology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu 110-799, Korea and [8]Department of Medical Oncology, Seoul St Mary's Hospital, 222 Banpo-Daero, Seocho-gu, Seoul, Korea

Background: Although chemotherapeutic regimens containing a taxane or platinum agent have been widely recommended for unfavourable carcinoma of unknown primary (CUP), no evidence exists for the superiority of any administered regimens. To date, the efficacy has been mostly assessed in the limited setting of phase II trials, and few attempts have been made to synthesise all available data for survival outcomes.

Methods: Electronic databases were searched from 1980 to 2011. Survival results were combined for each pre-specified category of regimens using a random-effects model, and meta-regression models were used to adjust for heterogeneity in some known prognostic factors.

Results: A total of 32 studies were included for meta-analysis. Tendency towards better survival outcome by platinums or taxanes was indicated. After adjustment for important prognostic factors, however, the difference between the platinum-based and non-platinum regimens became no longer significant. Survival benefits by the taxane-based regimens remained significant, with a prolonged median survival time of 1.52 months ($P = 0.03$) and a higher 1-year survival rate of 6.25% ($P = 0.05$), but the benefit did not sustain for 2 years.

Conclusion: Although no effective therapies have been established, this meta-analysis helps to fill an important gap of evidence. However, caution should still be taken because of the potential unmeasured confounding.

The European Society for Medical Oncology guideline lists recommended chemotherapeutic approaches containing platinums and taxanes as commonly used low-toxicity chemotherapy regimens, but stated that no evidence exists for superior efficacy of any of the administered regimens for unfavourable carcinoma of unknown primary (CUP) patients (Fizazi *et al*, 2011). Although CUP is a relatively common metastatic cancer constituting 3–5% of all human malignancies (McCredie *et al*, 1991; Levi *et al*, 2002), the

*Correspondence: Dr S Hahn; E-mail: hahns@snu.ac.kr

Revised 22 October 2012; accepted 23 October 2012; published online 22 November 2012

prognosis of CUP is very poor, with a median survival of 3–4 months, and its 5-year survival rate is <10% (Abbruzzese *et al*, 1994). Certain CUPs, which are defined as favourable prognostic subsets, show a biology and behaviour similar to known metastatic primary carcinoma (Greco and Pavlidis, 2009). However, patients in the favourable subset constitute only a minority of CUP cases and most patients remain unresponsive to any treatment modalities and have a worse prognosis. As no effective therapies have been established through randomised controlled trials (RCTs) for such patients, empirical systemic treatments considering the performance status of patients are widely accepted.

Some efforts for quantitative integration of survival outcomes of previous clinical studies have been made. A descriptive summary estimated a 9-month median survival time for platinum-based chemotherapy by simply taking the median of the included studies' quoted median survival times (Pentheroudakis *et al*, 2009). A recent multiple treatment comparison meta-analysis based on a small number of RCTs on chemotherapy regimens in unfavourable CUP patients reported great uncertainty about the survival benefit of any particular regimen (Golfinopoulos *et al*, 2009). As the efficacy of chemotherapy for patients with unfavourable CUP has mostly been assessed in the setting of small phase II trials without controls, data from limited numbers of RCTs are insufficient evidence for the superiority of any particular regimen in terms of survival prolongation. Another meta-analysis that combined the response rate from 29 phase II trials showed that the chemotherapeutic regimens were not the sole significant parameters and recommended multivariate analysis to consider the heterogeneity of prognostic factors of previous CUP trials (Adenis *et al*, 2010).

Thus, this study critically evaluated all relevant studies on chemotherapeutic approaches to unfavourable CUPs, which were mostly from single-arm phase II trials, and evaluated whether platinum- or taxane-based regimens could improve survival in patients from the unfavourable subset of CUPs adjusting for some known prognostic factors.

METHODS

Search strategy. Ovid MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched comprehensively without language restrictions, with hand searches for further references. The search period was from 1980, when platinum was introduced into the market, to 2011.

We first searched a combination of keywords: (cancer OR carcinoma OR malignancy OR tumour OR neoplasm) AND (unknown primary OR occult primary OR unknown origin) AND (therapy OR therapeutic OR intervention). A team of reviewers in pairs screened the title and abstract of each article. Any discrepancies in the screening were resolved by re-evaluation and discussion. Each full text of the articles selected by the screening was then reviewed to determine its final inclusion.

Inclusion and exclusion criteria. Studies on chemotherapy for the unfavourable subset of CUP were included. Literature on the favourable subsets, such as papillary adenocarcinoma of the peritoneal cavity in women, poorly differentiated carcinoma with a midline distribution, poorly differentiated neuroendocrine carcinomas, adenocarcinoma involving only the axillary lymph nodes in women, squamous cell carcinoma involving cervical lymph nodes, blastic bone metastases and elevated prostate-specific antigen in men, and a single, small, potentially resectable tumour, were excluded. For the diagnosis of CUP, included studies had to evaluate the origin of metastasis at least by abdominal computerised tomography (CT) with either chest CT or plain chest radiography. Phase II and phase III clinical trials were included and consecutive case series performed with the prospective enrolment of participants following clear inclusion criteria were considered for inclusion. Studies evaluating alternating regimens before disease progression or on second-line chemotherapy were excluded. Duplicate publications were excluded by retaining the one with the longest follow-up or the one that reported the data more comprehensively.

Quality assessment. The Methodological Index for Non-Randomised Studies (MINORS) (Slim *et al*, 2003) was adopted for quality assessment and applied primarily to all the included studies. Assessments for the Risk of Bias were also conducted for the RCTs using the Cochrane guideline (Higgings, 2008).

Data extraction. A pair of reviewers independently extracted relevant data from the studies using a standardised data extraction form. Information on the type of study design, patient follow-up, prognostic factors, chemotherapeutic regimens, and survival outcomes was abstracted. The survival outcomes were extracted using the methods of Tierney *et al* (2007), and confidence intervals were calculated based on the method of Simon (1986).

Statistical analysis. We first explored a combined estimate of survival outcome for each pre-specified regimen group: platinum *vs* no-platinum; taxane *vs* no-taxane; platinum and taxane (P_1T_1) *vs* platinum and no-taxane (P_1T_0) *vs* no-platinum and taxane (P_0T_1) *vs* no-platinum and no-taxane (P_0T_0). The outcomes considered were the median survival time, and the 1- and 2-year survival rates.

We pooled the results of each outcome for each category by the inverse variance method to generate a crude overall summary with a 95% confidence interval (95% CI) and descriptively contrasted the point estimates between categories. A multiple meta-regression model was then built up for testing the significance of the differences between platinum and no-platinum; taxane and no-taxane; and each of P_1T_1, P_1T_0, P_0T_1, and P_0T_0 after adjustment for covariates. Being male, a histology of moderate- to well-differentiated adenocarcinoma, poor Eastern Cooperative Oncology Group (ECOG) performance status ($\geqslant 2$), liver metastasis, and multiple metastatic sites were considered potentially important prognostic factors (Pavlidis and Fizazi, 2005). The year of the study could also influence survival outcomes and was considered a potential source of heterogeneity.

A random-effects model was applied to combine the outcomes. The statistical heterogeneity among the studies was evaluated qualitatively with a forest plot as well as quantitatively with the I^2 measure and χ^2 test. The funnel plots asymmetry was assessed for small study effects.

RESULTS

Description of the included studies. A total of 1389 potentially relevant studies, 1385 from the electronic search and four from the hand searches, were identified, and 1281 were excluded by title/abstract screening. Full texts were retrieved for the remaining 108 studies, and 32 of them met all the criteria for inclusion in the analysis (Figure 1).

There were seven RCTs (Shildt *et al*, 1983; Dowell *et al*, 2001; Assersohn *et al*, 2003; Culine *et al*, 2003; Palmeri *et al*, 2006; Huebner *et al*, 2009; Hainsworth *et al*, 2010) and one non-randomised trial (Saghatchian *et al*, 2001) where two treatment arms were evaluated. Six of the included clinical trials primarily explored or estimated the treatment outcome separately; only one phase III trial had a primary objective of directly comparing the two treatment regimens (Hainsworth *et al*, 2010). Another phase III trial identified by electronic search was excluded because only the abstract was accessible and contacting the author yielded no further information (Gross-Goupil *et al*, 2009). Both the phase III

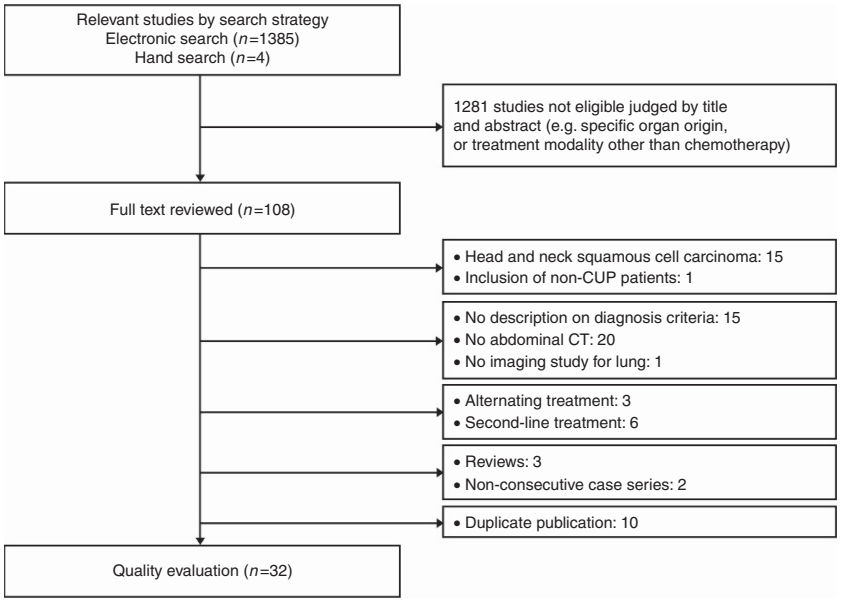

Figure 1. Flow chart of literature selection.

trials were stopped before enrolment of the planned sample size because of slow accrual.

There was one consecutive case series study (Gill *et al*, 1991) and the other 23 studies were single arm clinical trials (Raber *et al*, 1991; Briasoulis *et al*, 1998, 2000, 2008; Parnis *et al*, 2000; Greco *et al*, 2001, 2002; Guardiola *et al*, 2001; Macdonald *et al*, 2002; Balana *et al*, 2003; Mukai *et al*, 2003, 2010; Park *et al*, 2004; Piga *et al*, 2004; Pouessel *et al*, 2004; El-Rayes *et al*, 2005; Pittman *et al*, 2006; Schneider *et al*, 2007; Pentheroudakis *et al*, 2008; Hainsworth *et al*, 2009; Schuette *et al*, 2009; Yonemori *et al*, 2009; Moller *et al*, 2010). Three trials (Briasoulis *et al*, 1998, 2000; Pentheroudakis *et al*, 2008) also involved a small proportion of favourable CUP patients in their studies, and we extracted the data only from the unfavourable subset.

In the quality assessment using MINORS, most studies scored $\geqslant 10$ points; however, three studies conducted before 2000 scored <10 (Shildt *et al*, 1983; Raber *et al*, 1991; Parnis *et al*, 2000). Two independent reviewers evaluated the responses, which were the primary outcome of the study in only two studies (Culine *et al*, 2003; Moller *et al*, 2010). In all, 14 studies reported prospective calculation of the study size (Greco *et al*, 2002; Macdonald *et al*, 2002; Pouessel *et al*, 2004; El-Rayes *et al*, 2005; Palmeri *et al*, 2006; Pittman *et al*, 2006; Schneider *et al*, 2007; Pentheroudakis *et al*, 2008; Hainsworth *et al*, 2009, 2010; Huebner *et al*, 2009; Schuette *et al*, 2009; Yonemori *et al*, 2009; Mukai *et al*, 2010). Among the RCTs, only one study had a clear description of the method of allocation concealment (Assersohn *et al*, 2003). No RCT was blinded; however, we did not consider it a major threat to the validity since the outcomes should not be influenced by blinding.

Among the 42 regimens investigated, 35 were evaluated in studies conducted since 2000. In all, 26 regimens were tested based on a sample of 30 to 60 patients. The proportions of male patients in most of the studies were 50–75%. The efficacy of 14 regimens was tested with patients among whom 50–75% had moderate- to well-differentiated adenocarcinoma, and 13 regimens with patients among whom $<50\%$ had the histological attribute. The proportion of patients with liver metastasis was $<50\%$ in 17 regimens. A total of 24 regimens were assessed with patients among whom $<20\%$ had an ECOG performance status $\geqslant 2$. The proportion of patients with multiple metastases was 50–75% in 21 regimens. Only two regimens out of 42 were monotherapies; 34 regimens contained platinums and 17 included taxanes. Only one regimen had a follow-up duration shorter than 12 months, and 29 regimens were followed for longer than 24 months. The examined regimens and prognostic profiles are summarised in Table 1.

Survival estimation by regimen groups. The combined results by regimen group, 95% CIs, and statistics for heterogeneity are shown in Figure 2. The overall median survival time was 9.0 months (95% CI: 8.1–9.8), 1-year survival rate 35.6% (95% CI: 32.0–39.3), and 2-year survival rate 18.6% (95% CI: 15.4–21.7) across all chemotherapy regimens.

Most regimens (34 out of 42) contained a platinum component, demonstrating that using platinum in CUP treatment has become common. The majority of platinums were cisplatin or carboplatin, and oxaliplatin was used in only 2 out of the 34 regimens. For the meta-analysis, 26 regimens were included in the platinum group and 6 regimens in the non-platinum group. The platinum-based regimens showed a tendency to have better outcomes in the survival: median survival time of 9.4 *vs* 7.2 months; 1-year survival rate of 36.9% *vs* 29.6%; 2-year survival rate of 19.7% *vs* 11.9% for the platinum regimens *vs* non-platinum regimens.

When 16 taxane regimens and 16 non-taxane regimens were each combined, a slightly longer median survival (9.6 months) was estimated for the taxane regimens overall than the non-taxane regimens (8.3 months). A greater 1-year survival rate (41.3% *vs* 30.8%) was observed for the taxane group, and there was no overlapping of 95% CIs between the taxane group and the non-taxane group. However, the tendency towards better results in the taxane group was no longer definite but was sustained for the 2-year survival rate (21.2% *vs* 16.4%).

Among 14 P_1T_1, 12 P_1T_0, 2 P_0T_1, and 4 P_0T_0 regimens, we found P_1T_1 was the best regimen group and P_0T_0 was the worst for all survival outcomes. While a small number of studies were included, P_0T_1 tended to be better than P_1T_0 for median survival time (9.5 *vs* 8.9 months) and 1-year survival rate (36.6% *vs* 32.1%).

Investigation of heterogeneity. No significant association was found between the study year and outcomes shown by meta-regression analyses (Table 2). In the univariable meta-regression, the median survival was related to the histology and ECOG performance status. The 1- and 2-year survival probabilities were

Table 1. The chemotherapeutic regimens and major prognostic factors of the studies included

			Major prognostic factors, *N* (%)					
Author and year of study	**Regimens**	***N***	**Male sex**	**MWD**	**ECOG ⩾2**	**Liver meta**	**Multiple meta**	**Follow-up (months)**
Shildt *et al* (1983)	5-Fluorouracil	20		—	—	—	—	10.2
Shildt *et al* (1983)	Cyclophosphamide, 5-fluorouracil, doxorubicin	16	—	—	—	—	—	24.5
Raber *et al* (1991)	Cisplatin, 5-fluorouracil, etoposide	46	—	26 (56.5)	2 (4.3)	—	—	—
Gill *et al* (1991)	Cisplatin, etoposide	16	9 (56.3)	6 (37.5)	—	5 (31.3)	10 (62.5)	28.75
Briasoulis *et al* (1998)	Carboplatin, etoposide, epirubicin	45	—	—	—	—	—	40
Parnis *et al* (2000)	Cisplatin, 5-fluorouracil, epirubicin	43	27 (62.8)	—	7 (16.3)	16 (37.2)	31 (72.1)	54
Briasoulis *et al* (2000)	Carboplatin, paclitaxel	33	18 (54.5)	22 (66.7)	—	—	—	47
Dowell *et al* (2001)	Carboplatin, etoposide	17	10 (58.8)	14 (82.4)	6 (35.3)	11 (64.7)	11 (64.7)	17.3
Dowell *et al* (2001)	Paclitaxel, 5-fluorouracil, leucovorin	17	10 (58.8)	11 (64.7)	3 (17.6)	10 (58.8)	10 (58.8)	16
Guardiola *et al* (2001)	Cisplatin, doxorubicin, cyclophosphamide	22	13 (59.1)	8 (36.4)	—	6 (27.3)	12 (54.5)	56.9
Greco *et al* (2001)	Carboplatin, paclitaxel, etoposide	71	35 (49.3)	34 (47.9)	12 (16.9)	—	43 (60.6)	50
Greco *et al* (2001)	Cisplatin, docetaxel	26	13 (50.0)	13 (50.0)	6 (23.1)	—	19 (73.1)	33
Greco *et al* (2001)	Carboplatin, docetaxel	47	25 (53.2)	18 (38.3)	12 (25.5)	—	32 (68.1)	24
Saghatchian *et al* (2001)	Cisplatin, etoposide, ifosfamide, bleomycin	30	15 (50.0)	0 (0)	7 (23.3)	3 (10)	17 (56.7)	32
Saghatchian *et al* (2001)	Cisplatin, 5-fluorouracil, interferon	18	6 ((33.3)	18 (100)	1 (5.6)	6 (33.3)	8 (44.4)	32
Macdonald *et al* (2002)	Cisplatin, 5-fluorouracil, mitomycin	31	18 (58.1)	22 (71.0)	5 (16.1)	7 (22.6)	16 (51.6)	53
Greco *et al* (2002)	Carboplatin, paclitaxel, gemcitabine	120	64 (53.3)	63 (52.5)	16 (13.3)	51 (42.5)	78 (65)	27
Culine *et al* (2003)	Cisplatin, gemcitabine	39	26 (66.7)	26 (66.7)	6 (15.4)	21 (53.8)	29 (74.4)	22
Culine *et al* (2003)	Cisplatin, irinotecan	40	18 (45.0)	24 (60.0)	7 (17.5)	21 (52.5)	30 (75.0)	22
Assersohn *et al* (2003)	5-Fluorouracil	45	28 (62.2)	15 (33.3)	12 (26.7)	30 (66.7)	22 (48.9)	24
Assersohn *et al* (2003)	5-Fluorouracil, mitomycin	43	20 (46.5)	18 (41.9)	15 (34.9)	21 (48.8)	17 (39.5)	24
Balana *et al* (2003)	Cisplatin, gemcitabine, etoposide	40	25 (62.5)	15 (37.5)	4 (10.0)	6 (15.0)	27 (67.5)	29
Mukai *et al* (2003)	Cisplatin, docetaxel	5	1 (20.0)	4 (80.0)	1 (20.0)	—	—	—
Piga *et al* (2004)	Carboplatin, etoposide, doxorubicin	102	54 (52.9)	38 (37.3)	8 (7.8)	27 (26.5)	89 (87.3)	60
Pouessel *et al* (2004)	Docetaxel, gemcitabine	36	23 (63.9)	16 (44.4)	3 (8.3)	15 (41.7)	26 (72.2)	32
Park *et al* (2004)	Cisplatin, paclitaxel	37	20 (54.1)	31 (83.8)	8 (21.6)	12 (32.4)	35 (94.6)	31.5
El-Rayes *et al* (2005)	Carboplatin, paclitaxel	22	13 (59.1)	15 (68.2)	2 (9.1)	17 (77.3)	—	23.2
Palmeri *et al* (2006)	Cisplatin, paclitaxel, gemcitabine	33	25 (75.8)	25 (75.8)	1 (3.0)	8 (24.2)	14 (42.4)	20.5
Palmeri *et al* (2006)	Cisplatin, gemcitabine, vinorelbine	33	27 (81.8)	23 (69.7)	1 (3.0)	10 (30.3)	15 (45.5)	21.5
Pittman *et al* (2006)	Carboplatin, gemcitabine	50	23 (46.0)	—	12 (24.0)	38 (76.0)	—	35
Schneider *et al* (2007)	Carboplatin, gemcitabine, capecitabine	33	19 (57.6)	22 (66.7)	9 (27.3)	20 (60.6)	10 (30.3)	54.1
Pentheroudakis *et al* (2008)	Carboplatin, docetaxel	23	12 (52.2)	—	3 (13.0)	9 (39.1)	13 (56.5)	48
Briasoulis *et al* (2008)	Oxaliplatin, irinotecan	47	33 (70.2)	19 (40.4)	11 (23.4)	27 (57.4)	27 (57.4)	35.5
Huebner *et al* (2009)	Carboplatin, paclitaxel	42	23 (54.8)	—	5 (11.9)	23 (54.8)	36 (85.7)	26
Huebner *et al* (2009)	Gemcitabine, vinorelbine	45	27 (60.0)	—	10 (22.2)	29 (64.4)	37 (82.2)	22
Schuette *et al* (2009)	Oxaliplatin, capecitabine	51	35 (68.6)	7 (13.7)	5 (9.8)	20 (39.2)	—	24
Yonemori *et al* (2009)	Carboplatin, irinotecan	45	23 (51.1)	21 (46.7)	4 (8.9)	8 (17.8)	32 (71.1)	48
Hainsworth *et al* (2009)	Carboplatin, paclitaxel, bevacizumab, erlotinib	60	29 (48.3)	31 (51.7)	0	—	30 (50.0)	25
Mukai *et al* (2010)	Cisplatin, docetaxel	45	23 (51.1)	19 (42.2)	6 (13.3)	—	10 (22.2)	57.1
Moller *et al* (2010)	Cisplatin, paclitaxel, gemcitabine	98	51 (52.0)	—	0	49 (50.0)	53 (54.1)	80
Hainsworth *et al* (2010)	Carboplatin, paclitaxel, etoposide, gefitinib	93	44 (47.3)	49 (52.7)	9 (9.7)	50 (53.8)	75 (80.6)	60
Hainsworth *et al* (2010)	Gemcitabine, irinotecan, gefitinib	105	63 (60.0)	56 (53.3)	8 (7.6)	54 (51.4)	73 (69.5)	60

Abbreviations: MWD = moderate- to well-differentiated adenocarcinoma; ECOG = Eastern Cooperative Oncology Group performance status; meta = metastasis.

www.bjcancer.com | DOI:10.1038/bjc.2012.516

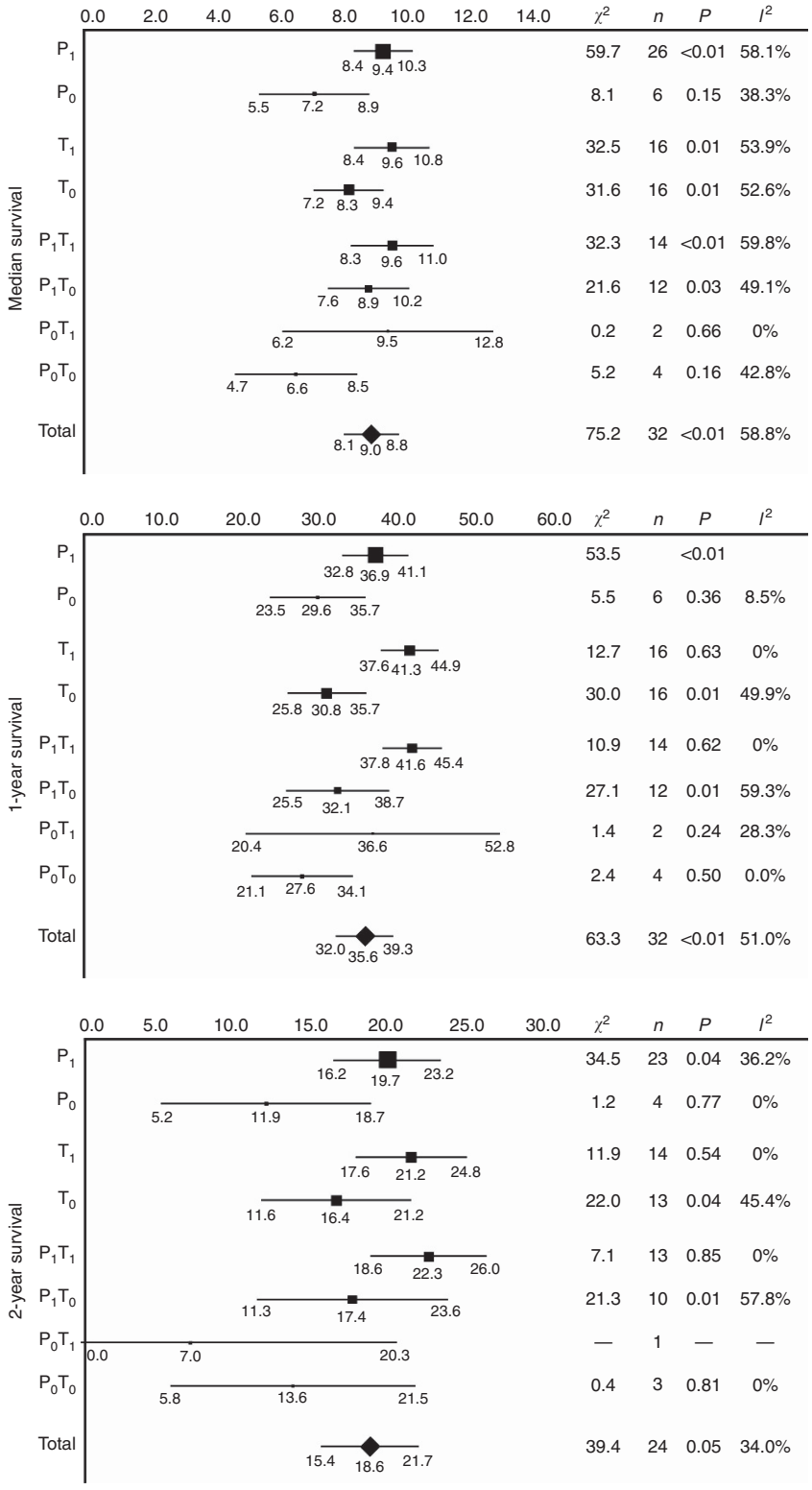

Figure 2. Combined estimates for the survival by treatment strategy. χ^2, chi-squared statistics; *n*, the number of studies that were included to the regimen groups, I^2, I-squared statistics; P_1, platinum; P_0, no platinum; T_1, taxane; T_0, no taxane; P_1T_1, platinum and taxane; P_1T_0, platinum and no taxane; P_0T_1, no platinum and taxane; P_0T_0, no platinum and no taxane; *P*-value is for the χ^2 test.

related to the gender, ECOG performance status, and whether liver metastasis occurred.

Assessment of treatment differences by regimen. The differences we observed in the descriptive comparison of the point estimates of crude overall summaries by platinums became less noticeable and tended to be null after adjustment of the prognostic factors (Table 3). However, the difference in the median survival time by the taxane-containing combination increased to 1.52 months after adjustment for covariates and was statistically significant ($P = 0.03$). The obvious superiority of the 1-year survival rate with taxane-based regimens remained significant ($P = 0.05$), and a

Table 2. Relationship between prognostic factors and survival outcomes

Characteristics	Median survival		1-Year survival		2-Year survival	
	Coefficient[a]	*P*-value	Coefficient[a]	*P*-value	Coefficient[a]	*P*-value
Year of the study	−0.01	0.93	−0.11	0.85	−0.40	0.43
Gender	5.29	0.21	30.23	0.07[b]	31.71	0.02[b]
Histology	5.90	0.07[b]	21.19	0.18	10.24	0.44
ECOG performance	−9.77	0.02[b]	−62.17	<0.01[b]	33.62	0.05[b]
Liver metastasis	−3.78	0.15	−27.1	0.01[b]	−26.61	<0.01[b]
Multiple metastasis	−1.67	0.49	10.98	0.29	−7.34	0.40

Abbreviation: ECOG = Eastern Cooperative Oncology Group performance status.
[a]Coefficient represents a linear relationship between each prognostic factor and the survival outcome by a univariable meta-regression model. The sign of the coefficient indicates the positivity or negativity of the relationship. The *P*-value of each coefficient indicates whether the linear correlation was significant or not.
[b]*P*-value <0.1.

Table 3. Difference between subgroups adjusting prognostic factors as appropriate

Outcomes	Regimens	Coefficient (95% confidence interval)[a]	*P*-value
Median survival (months)[b]	Platinum	0.76 (−1.14 to 2.67)	0.43
	Taxane	1.52 (0.12 to 2.92)	0.03
	No-platinum, no-Taxane	Reference	
	Platinum, no-Taxane	0.78 (−1.16 to 2.72)	0.43
	No-platinum, taxane	2.58 (−1.09 to 6.26)	0.17
	Platinum and taxane	2.02 (−0.05 to 4.09)	0.06
1-Year survival (%)[c]	Platinum	−2.68 (−10.95 to 5.58)	0.52
	Taxane	6.25 (−0.05 to 12.55)	0.05
	No-platinum, no-taxane	Reference	
	Platinum, no-taxane	−2.93 (−11.76 to 5.89)	0.52
	No-platinum, taxane	8.28 (−6.93 to 23.48)	0.29
	Platinum and taxane	3.14 (−6.47 to 12.76)	0.52
2-Year survival (%)[c]	Platinum	2.21 (−5.93 to 10.35)	0.60
	Taxane	0.98 (−5.58 to 7.53)	0.77
	No-platinum, no-taxane	Reference	
	Platinum, no-taxane	−2.30 (−12.04 to 7.43)	0.64
	No-platinum, taxane	−11.63 (−28.04 to 5.63)	0.19
	Platinum and taxane	0.01 (−11.34 to 11.36)	0.99

Abbreviation: ECOG = Eastern Cooperative Oncology Group performance status.
[a]The coefficient from a multiple meta-regression model after adjustment for prognostic factors represents changes of the survival outcome by adding the particular agent(s) to a regimen in comparison to one without them or to the reference.
[b]Adjusted for proportion of moderate- to well-differentiated adenocarcinoma, and proportion of performance status (in ECOG ⩾2).
[c]Adjusted for proportion of male patients, proportion of performance status (in ECOG ⩾2), and liver metastasis.

possible treatment difference of 6.25% remained. No statistically significant survival benefit was observed from the comparison of the regimens containing platinum, taxane, or both to the chemotherapies with agents other than platinums or taxanes, except for the marginal significance of regimens containing both platinums and taxanes for a median survival time of 2.02 months ($P = 0.06$). The results also suggest a decrease in the 2-year survival rate by taxane regimens without a platinum agent, although it was not statistically significant. The only regimens to have positive results, although not reaching statistical significance, at all end points are the regimens containing both platinum and taxane in comparison to regimens containing neither of them.

Comparison of survival rates from randomised controlled clinical trials. None of the five RCTs providing data for calculating a comparative effect measure showed a hazard ratio (HR) significantly different from one for the overall survival rate (Figure 3). Apart from one out of the five studies, all studies involved at least one regimen containing taxane or platinum. Among the four studies comparing regimens containing taxane with others without taxane, two of the studies showed a direction of effect contrasting with the other two studies. The pooled HR was 0.95 (95% CI: 0.65–1.26), suggesting a nonsignificant difference. In examining the regimens for comparison of platinum against non-platinum, there was also heterogeneity in the direction of treatment

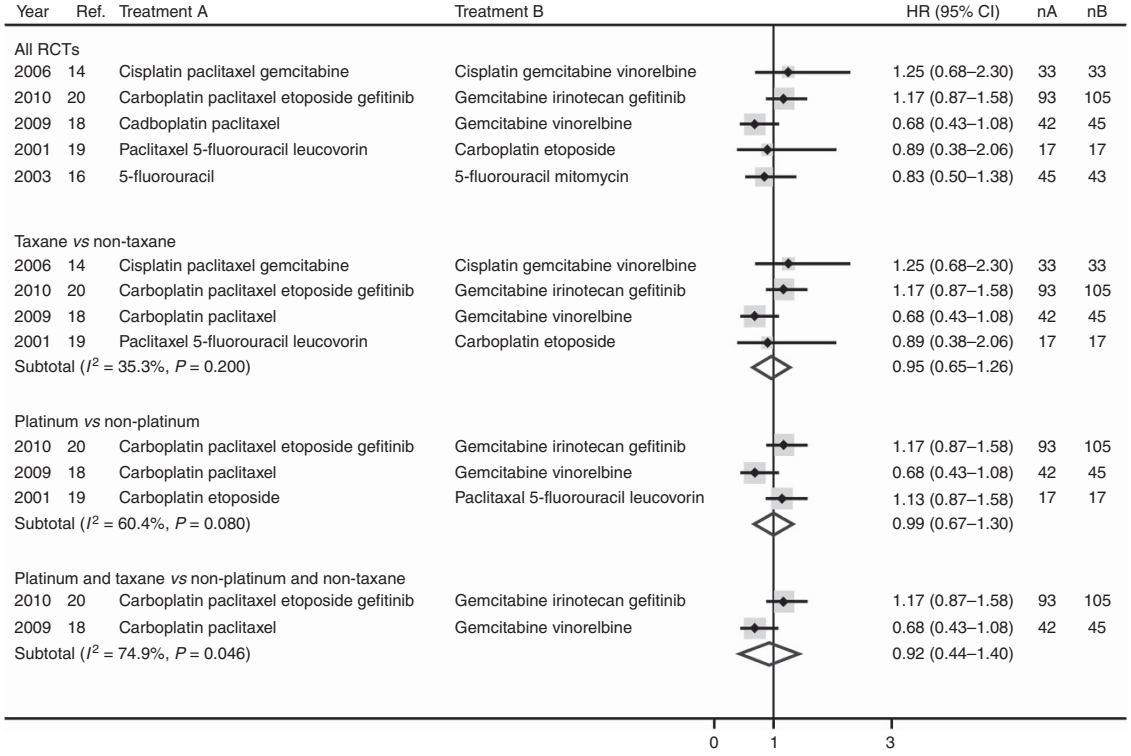

Figure 3. Comparison of survival rates from the randomised controlled clinical trials. The hazard ratio above 1 means that the risk of death by the first regimen is higher than that by the second regimen. nA, number of patients in the treatment A; nB, number of patients in the treatment B.

effect, which produced a pooled HR of 0.99 (95% CI: 0.67–1.30). For the comparison of regimens containing both taxane and platinum against neither of them, there was a significant heterogeneity between the two included results and they produced a pooled HR of 0.92 (95% CI: 0.44–1.40).

Assessment for funnel plot asymmetry. We observed an asymmetric funnel plot in only the median survival time ($P = 0.05$), but no apparent trend in the 1- or 2-year survival rate. The former indicated an association between the treatment results and study size (Figure 4). We performed the Egger test for the median survival time stratified by taxanes and platinums. The small study effect was more salient in the platinum regimens ($P = 0.04$) than non-platinum regimens ($P = 0.33$) and in non-taxane regimens ($P = 0.10$) than taxane regimens ($P = 0.96$).

DISCUSSION

An important target of treating cancer patients should be prolonging survival. However, for the unfavourable subset of CUP patients, there has been no clear understanding of the survival benefits by any chemotherapeutic treatment so far, although platinum- or taxane-based regimens have been commonly and empirically used in current clinical practice. The aim of our study was to estimate the survival efficacy of those regimens by systematically evaluating all relevant data in the literature.

In a recently issued guidance by the National Institute for Health and Clinical Excellence on metastasis with unknown primary, a combination of carboplatin and paclitaxel was suggested to have the highest total expected quality-adjusted life years among the therapeutic approaches, but the probability that the combination was cost-effective was $<50\%$ at a given willingness to pay threshold in current UK clinical practice (Fowell, 2010; MacReady, 2010). The guidance also indicated a lack of information supporting any particular chemotherapy in terms of survival prolongation in patients with CUP not belonging to a specific favourable group in the currently available literature. Our study suggested that the addition of a taxane to the regimen extended the median survival time by 1.52 months (95% CI: 0.12–2.92) and increased the 1-year survival rate by 6.25% (95% CI: 0.05–12.55). Although the survival benefit did not remain for 2 years, the suggested improvement in the median survival time and the 1-year survival probability, accounting for the heterogeneous settings, can provide clinically meaningful evidence of the survival benefit by including taxane in combinatorial chemotherapy.

The majority of platinums in the included regimens were cisplatin or carboplatin, but oxaliplatin was also used in 2 out of the 34 platinum regimens. Oxaliplatin has a particular indication (Cvitkovic, 1998; Graham and Cassidy, 2012) and may better be considered separately from other platinum agents in clinical use, whereas cisplatin and carboplatin can, for the most part, substitute for each other. For this reason, we conducted a reanalysis by removing the two oxaliplatin regimens from the platinum group, which had little impact on the results but a slight shift towards increasing survival: median survival time from 9.4 months (95% CI: 8.4–10.3) to 9.5 months (95% CI: 8.5–10.5); 1-year survival rate from 36.9% (95% CI: 32.8–41.1) to 38.9% (95% CI: 35.9–42.0); and 2-year survival rate from 19.7% (95% CI: 16.2–23.2) to 20.7% (95% CI: 17.9–23.6). Consequently, the differences between subgroups presented in Table 3 were not influenced much by exclusion of oxaliplatin from the platinum group.

Because RCTs provide another level of evidence, we also analysed them separately by categorising them to assess the effects of containing taxane, platinum, or both. Five RCTs were available with data for calculation of HR. The categorised pooled results suggested slightly favourable results toward taxane, platinum, or both in comparison to regimens without any of them, but failed to confirm the effect, mainly due to heterogeneity between the small number of small-sized studies. A previous meta-analysis of RCTs

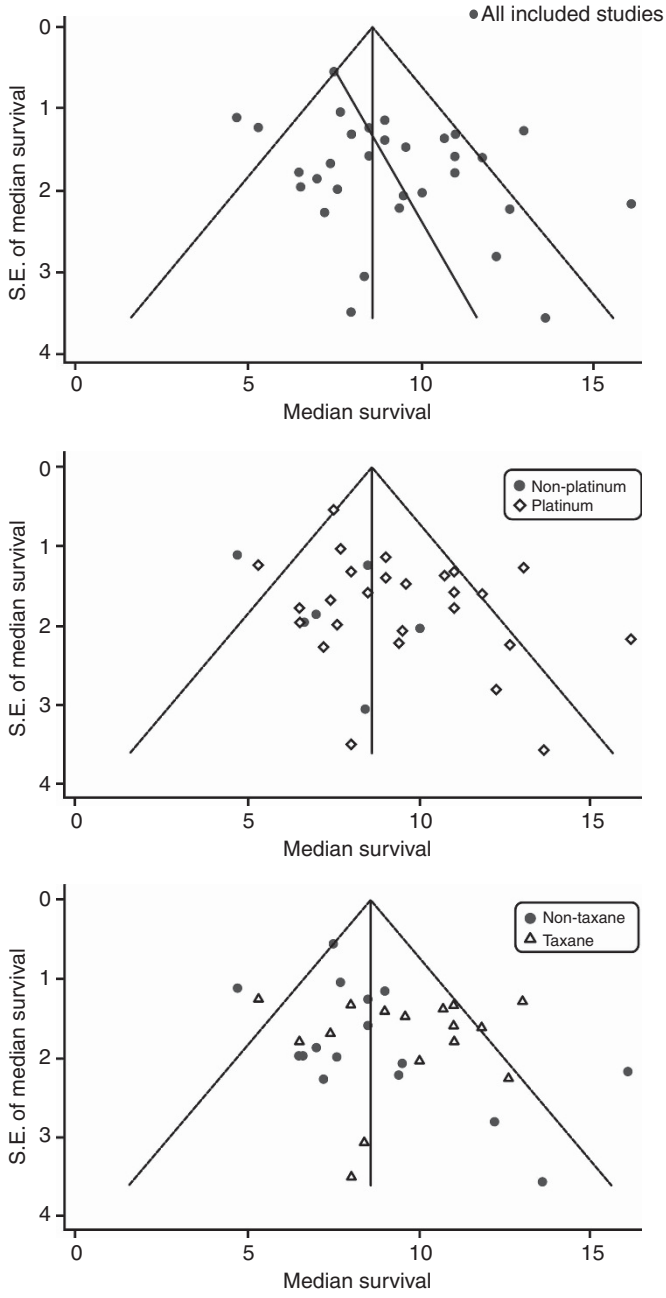

Figure 4. Funnel plot for evaluation of the small trial effect for survival. The fitted line corresponds to the regression test for funnel plot asymmetry proposed by Egger *et al* (1997).

conducted a multiple treatment comparison, a kind of indirect comparison among different treatments using a Bayesian statistical method, which also failed to demonstrate a survival benefit by any chemotherapeutic regimen for CUP (Golfinopoulos *et al*, 2009). The analysis also suggested that the hazard ratios favoured platinum (0.69, 95% CI: 0.39–1.28); taxane (0.66, 95% CI: 0.22–2.08); or both (0.81, 95% CI: 0.34–1.89), in comparison with a monotherapy regimen with an agent other than platinum or taxane. Their analysis included a larger number of RCTs because of less restrictive inclusion criteria applied, in terms of method of diagnosis for CUP, than those used in our study. Their results also suggested a great uncertainty with a wider Bayesian version of CIs. Lack of a large enough number of RCTs, especially for phase III, could be a possible explanation of the failure to demonstrate significance, although the possible efficacy of taxane or platinum was suggested consistently. From the five trials included in our meta-analysis of RCTs, only one trial was a study conducted to evaluate a comparative efficacy in the setting of phase III, but the study also stopped early because of slow accrual of patients. The other trials were randomised studies, but still were phase II studies, which aimed to assess efficacy in each treatment arm rather than for investigating a comparative efficacy. In such a circumstance, this study is of importance by filling the lack of certainty in the current evidence by utilising all available information with a maximum control of incomparability.

The funnel plot of the median survival showed an asymmetry indicating a small study effect. The scatter plot of survival outcome against its standard error is supposed to have a symmetric shape of an inverse funnel, representing a wide variability of estimates from small studies and narrow range of those from large studies. Thus, emptiness in the left base of the funnel suggests that small studies have a tendency to report favourable outcomes, which is referred as the small study effect and is often interpreted as an indication of publication bias. However, it is also a common phenomenon in the early development of a new treatment (Lau *et al*, 2006). The observed small study effect in the current analysis may also be due to such a true heterogeneity (Higgings, 2008), as a short-term benefit from chemotherapy is more likely in patients with high-performance status for tolerating toxicity of the treatment and such patients are more likely to be included in small, early phase clinical trials in the development of new treatment regimens. The stratified funnel plots and Egger test results suggest that the small study effect was more noticeable in the non-taxane or platinum regimens, which may imply that the survival benefits by taxanes were estimated rather conservatively, while those by platinum were still nonsignificant even with possible overestimation.

Our study results should be interpreted with caution because of several limitations. In this setting, a selection of studies with similar populations is particularly difficult, because of the heterogeneous nature of the CUP population, the availability of mostly single institute-based small studies, and the long interval from which the studies were selected. Although we tried to adjust for the differences in known prognostic factors among studies using a meta-regression in the evaluation of the treatment effect, the limitation of this study is that comparisons between those studies can barely substitute for RCTs even after correction for some characteristics across trials. This meta-analysis could still be susceptible to some bias from unmeasured confounders potentially influencing the overall survival, for example, palliative care offered or second-line treatment. Since the included studies have been conducted over a couple of decades, the identification of treatable subsets has changed during the time, which may also cause such heterogeneity as an unmeasurable confounder. Many of the trials, particularly in the first decade, contained some patients who would currently be identified and treated with regimens other than empiric therapy. On the other hand, a significant improvement in the supportive care and the health-care system can also influence the outcomes of the treatments. Most of the included studies were, in fact, found to be carried out within the past decade, and such an evolution effect might therefore have been minimised. We indeed observed lack of a relationship between the survival outcomes and the year of the study (Table 2).

The potential limitations notwithstanding, our study showed that combinations containing a taxane agent demonstrated a prolongation of the median survival time and higher 1-year survival rate in the first-line treatment of unfavourable CUP compared with those without taxanes. However, such a benefit did not seem to be sustained for 2 years. Summaries of available RCTs suggested addition of platinum, taxane, or platinum and taxane to a regimen tends to extend survival of CUP patients; however, those findings based on RCTs were said to be very uncertain owing to a

so small number of RCTs. This systematic review and meta-analysis utilising all available clinical trials fills an important gap of certainty in the current evidence by demonstrating a beneficial effect in the use of taxane for unfavourable CUP patients.

REFERENCES

Abbruzzese JL, Abbruzzese MC, Hess KR, Raber MN, Lenzi R, Frost P (1994) Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients. *J Clin Oncol* **12**(6): 1272–1280.

Adenis A, Ferte C, Penel N (2010) Phase II trials in patients with carcinoma of unknown primary: a pooled data analysis. *Invest New Drugs* **28**(2): 178–184.

Assersohn L, Norman AR, Cunningham D, Iveson T, Seymour M, Hickish T, Massey A, Prior Y, Hill ME (2003) A randomised study of protracted venous infusion of 5-fluorouracil (5-FU) with or without bolus mitomycin C (MMC) in patients with carcinoma of unknown primary. *Eur J Cancer* **39**(8): 1121–1128.

Balana C, Manzano JL, Moreno I, Cirauqui B, Abad A, Font A, Mate JL, Rosell R (2003) A phase II study of cisplatin, etoposide and gemcitabine in an unfavourable group of patients with carcinoma of unknown primary site. *Ann Oncol* **14**(9): 1425–1429.

Briasoulis E, Fountzilas G, Bamias A, Dimopoulos MA, Xiros N, Aravantinos G, Samantas E, Kalofonos H, Makatsoris T, Mylonakis N, Papakostas P, Skarlos D, Varthalitis I, Pavlidis N (2008) Multicenter phase-II trial of irinotecan plus oxaliplatin [IROX regimen] in patients with poor-prognosis cancer of unknown primary: a hellenic cooperative oncology group study. *Cancer Chemother Pharmacol* **62**(2): 277–284.

Briasoulis E, Kalofonos H, Bafaloukos D, Samantas E, Fountzilas G, Xiros N, Skarlos D, Christodoulou C, Kosmidis P, Pavlidis N (2000) Carboplatin plus paclitaxel in unknown primary carcinoma: a phase II Hellenic Cooperative Oncology Group Study. *J Clin Oncol* **18**(17): 3101–3107.

Briasoulis E, Tsavaris N, Fountzilas G, Athanasiadis A, Kosmidis P, Bafaloukos D, Skarlos D, Samantas E, Pavlidis N (1998) Combination regimen with carboplatin, epirubicin and etoposide in metastatic carcinomas of unknown primary site: a Hellenic Co-Operative Oncology Group Phase II Study. *Oncology* **55**(5): 426–430.

Culine S, Lortholary A, Voigt JJ, Bugat R, Theodore C, Priou F, Kaminsky MC, Lesimple T, Pivot X, Coudert B, Douillard JY, Merrouche Y, Allouache J, Goupil A, Negrier S, Viala J, Petrow P, Bouzy J, Laplanche A, Fizazi K (2003) Cisplatin in combination with either gemcitabine or irinotecan in carcinomas of unknown primary site: results of a randomized phase II study-trial for the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01). *J Clin Oncol* **21**(18): 3479–3482.

Cvitkovic E (1998) Ongoing and unsaid on oxaliplatin: the hope. *Br J Cancer* **77**(Suppl 4): 8–11.

Dowell JE, Garrett AM, Shyr Y, Johnson DH, Hande KR (2001) A randomized phase II trial in patients with carcinoma of an unknown primary site. *Cancer* **91**(3): 592–597.

Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**(7109): 629–634.

El-Rayes BF, Shields AF, Zalupski M, Heilbrun LK, Jain V, Terry D, Ferris AM, Philip PA (2005) A phase II study of carboplatin and paclitaxel in adenocarcinoma of unknown primary. *Am J Clin Oncol* **28**(2): 152–156.

Fizazi K, Greco FA, Pavlidis N, Pentheroudakis G (2011) Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* **22**(Suppl 6): vi64–vi68.

Fowell A (2010) *Metastatic Malignancy of Unknown Primary: Full Guidance*. National Collaborating Centre for Cancer: Wales.

Gill I, Guaglianone P, Grunberg SM, Scholz M, Muggia FM (1991) High dose intensity of cisplatin and etoposide in adenocarcinoma of unknown primary. *Anticancer Res* **11**(3): 1231–1235.

Golfinopoulos V, Pentheroudakis G, Salanti G, Nearchou AD, Ioannidis JP, Pavlidis N (2009) Comparative survival with diverse chemotherapy regimens for cancer of unknown primary site: multiple-treatments meta-analysis. *Cancer Treat Rev* **35**(7): 570–573.

Graham JS, Cassidy J (2012) Adjuvant therapy in colon cancer. *Expert Rev Anticancer Ther* **12**(1): 99–109.

Greco FA, Burris 3rd HA, Litchy S, Barton JH, Bradof JE, Richards P, Scullin Jr. DC, Erland JB, Morrissey LH, Hainsworth JD (2002) Gemcitabine, carboplatin, and paclitaxel for patients with carcinoma of unknown primary site: a Minnie Pearl Cancer Research Network study. *J Clin Oncol* **20**(6): 1651–1656.

Greco FA, Gray J, Burris III HA, Erland JB, Morrissey LH, Hainsworth JD (2001) Taxane-based chemotherapy for patients with carcinoma of unknown primary site. *Cancer J* **7**(3): 203–212.

Greco FA, Pavlidis N (2009) Treatment for patients with unknown primary carcinoma and unfavorable prognostic factors. *Semin Oncol* **36**(1): 65–74.

Gross-Goupil M, Fourcade A, Blot E, Penel N, Negrier S, Culine S, Merrouche Y, Bouzy J, Laplanche A, Fizazi K (2009) A randomized trial of cisplatin with or without gemcitabine in patients (pts) with carcinoma of an unknown primary (CUP) and without poor prognostic factors: results of the GEFCAPI 02 trial. [Abstract No. 798P] In *Annals of Oncology*. p 248.

Guardiola E, Pivot X, Tchicknavorian X, Magne N, Otto J, Thyss A, Schneider M (2001) Combination of cisplatin–doxorubicin–cyclophosphamide in adenocarcinoma of unknown primary site: a phase II trial. *Am J Clin Oncol* **24**(4): 372–375.

Hainsworth JD, Spigel DR, Clark BL, Shipley D, Thompson DS, Farley C, West-Osterfield K, Lane CM, Cescon T, Bury MJ, Greco FA (2010) Paclitaxel/carboplatin/etoposide *versus* gemcitabine/irinotecan in the first-line treatment of patients with carcinoma of unknown primary site: a randomized, phase III Sarah Cannon Oncology Research Consortium Trial. In *CancerJ (Sudbury, MA)* 70–75.

Hainsworth JD, Spigel DR, Thompson DS, Murphy PB, Lane CM, Waterhouse DM, Naot Y, Greco FA (2009) Paclitaxel/carboplatin plus bevacizumab/erlotinib in the first-line treatment of patients with carcinoma of unknown primary site. *Oncologist* **14**(12): 1189–1197.

Higgings JGS (2008) *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley-Blackwell: West Sussex.

Huebner G, Link H, Kohne CH, Stahl M, Kretzschmar A, Steinbach S, Folprecht G, Bernhard H, Al-Batran SE, Schoffski P, Burkart C, Kullmann F, Otremba B, Menges M, Hoffmann M, Kaiser U, Aldaoud A, Jahn A (2009) Paclitaxel and carboplatin vs gemcitabine and vinorelbine in patients with adeno- or undifferentiated carcinoma of unknown primary: a randomised prospective phase II trial. *Br J Cancer* **100**(1): 44–49.

Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I (2006) The case of the misleading funnel plot. *BMJ* **333**(7568): 597–600.

Levi F, Te VC, Erler G, Randimbison L, La Vecchia C (2002) Epidemiology of unknown primary tumours. *Eur J Cancer* **38**(13): 1810–1812.

Macdonald AG, Nicolson MC, Samuel LM, Hutcheon AW, Ahmed FY (2002) A phase II study of mitomycin C, cisplatin and continuous infusion 5-fluorouracil (MCF) in the treatment of patients with carcinoma of unknown primary site. *Br J Cancer* **86**(8): 1238–1242.

MacReady N (2010) NICE issues guidance on cancer of unknown primary. *Lancet Oncol* **11**(9): 824.

McCredie M, Coates M, Churches T, Taylor R (1991) Cancer incidence in New South Wales, Australia. *Eur J Cancer* **27**(7): 928–931.

Moller AKH, Pedersen KD, Gothelf A, Daugaard G (2010) Paclitaxel, cisplatin and gemcitabine in treatment of carcinomas of unknown primary site, a phase II study. *Acta Oncol* **49**(4): 423–430.

Mukai H, Katsumata N, Ando M, Watanabe T (2010) Safety and efficacy of a combination of docetaxel and cisplatin in patients with unknown primary cancer. *Am J Clin Oncol* **33**(1): 32–35.

Mukai H, Watanabe T, Ando M, Katsumata N (2003) Unknown primary carcinoma: a feasibility assessment of combination chemotherapy with cisplatin and docetaxel. *Int J Clin Oncol* **8**(1): 23–25.

Palmeri S, Lorusso V, Palmeri L, Vaglica M, Porta C, Nortilli R, Ferrau F, Comella G, Massidda B, Danova M (2006) Cisplatin and gemcitabine with either vinorelbine or paclitaxel in the treatment of carcinomas of unknown primary site: results of an Italian multicenter, randomized, phase II study. *Cancer* **107**(12): 2898–2905.

Park YH, Ryoo BY, Choi SJ, Yang SH, Kim HT (2004) A phase II study of paclitaxel plus cisplatin chemotherapy in an unfavourable group of patients with cancer of unknown primary site. *Jpn J Clin Oncol* **34**(11): 681–685.

Parnis FX, Olver IN, Kotasek D, Norman J, Taylor A, Russell J, Patterson K, Keefe D, Marafioti T (2000) Phase II study of epirubicin, cisplatin and continuous infusion 5-fluorouracil (ECF) for carcinoma of unknown primary site. *Ann Oncol* **11**(7): 883–884.

Pavlidis N, Fizazi K (2005) Cancer of unknown primary (CUP). *Crit Rev Oncol Hematol* **54**(3): 243–250.

Pentheroudakis G, Briasoulis E, Kalofonos HP, Fountzilas G, Economopoulos T, Samelis G, Koutras A, Karina M, Xiros N, Samantas E, Bamias A, Pavlidis N (2008) Docetaxel and carboplatin combination chemotherapy

as outpatient palliative therapy in carcinoma of unknown primary: a multicentre Hellenic Cooperative Oncology Group phase II study. *Acta Oncol* **47**(6): 1148–1155.

Pentheroudakis G, Greco FA, Pavlidis N (2009) Molecular assignment of tissue of origin in cancer of unknown primary may not predict response to therapy or outcome: a systematic literature review. *Cancer Treat Rev* **35**(3): 221–227.

Piga A, Nortilli R, Cetto GL, Cardarelli N, Fedeli SL, Fiorentini G, D'Aprile M, Giorgi F, Parziale AP, Contu A, Montironi R, Gesuita R, Carle F, Cellerino R (2004) Carboplatin, doxorubicin and etoposide in the treatment of tumours of unknown primary site. *Br J Cancer* **90**(10): 1898–1904.

Pittman KB, Olver IN, Koczwara B, Kotasek D, Patterson WK, Keefe DM, Karapetis CS, Parnis FX, Moldovan S, Yeend SJ, Price TJ (2006) Gemcitabine and carboplatin in carcinoma of unknown primary site: a phase 2 Adelaide Cancer Trials and Education Collaborative study. *Br J Cancer* **95**(10): 1309–1313.

Pouessel D, Culine S, Becht C, Ychou M, Romieu G, Fabbro M, Cupissol D, Pinguet F (2004) Gemcitabine and docetaxel as front-line chemotherapy in patients with carcinoma of an unknown primary site. *Cancer* **100**(6): 1257–1261.

Raber MN, Faintuch J, Abbruzzese JL, Sumrall C, Frost P (1991) Continuous infusion 5-fluorouracil, etoposide and *cis*-diamminedichloroplatinum in patients with metastatic carcinoma of unknown primary origin. *Ann Oncol* **2**(7): 519–520.

Saghatchian M, Fizazi K, Borel C, Ducreux M, Ruffie P, Le Chevalier T, Theodore C (2001) Carcinoma of an unknown primary site: a chemotherapy strategy based on histological differentiation − results of a prospective study. *Ann Oncol* **12**(4): 535–540.

Schneider BJ, El-Rayes B, Muler JH, Philip PA, Kalemkerian GP, Griffith KA, Zalupski MM (2007) Phase II trial of carboplatin, gemcitabine, and capecitabine in patients with carcinoma of unknown primary site. *Cancer* **110**(4): 770–775.

Schuette K, Folprecht G, Kretzschmar A, Link H, Koehne CH, Gruenwald V, Stahl M, Huebner G (2009) Phase II trial of capecitabine and oxaliplatin in patients with adeno- and undifferentiated carcinoma of unknown primary. *Onkologie* **32**(4): 162–166.

Shildt RA, Kennedy PS, Chen TT, Athens JW, O'Bryan RM, Balcerzak SP (1983) Management of patients with metastatic adenocarcinoma of unknown origin: a Southwest Oncology Group study. *Cancer Treat Rep* **67**(1): 77–79.

Simon R (1986) Confidence intervals for reporting results of clinical trials. *Ann Intern Med* **105**(3): 429–435.

Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* **73**(9): 712–716.

Tierney JFSL, Ghersi D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. *BioMed Central Trials* **8**: 16.

Yonemori K, Ando M, Yunokawa M, Hirata T, Kouno T, Shimizu C, Tamura K, Katsumata N, Hirakawa A, Matsumoto K, Yamanaka Y, Arioka H, Fujiwara Y (2009) Irinotecan plus carboplatin for patients with carcinoma of unknown primary site. *Br J Cancer* **100**(1): 50–55.