The prognosis of cancer patients undergoing liposomal doxorubicin-based chemotherapy: a systematic review and meta-analysis

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Abstract

Background It is well known that liposome-based delivery of cytotoxic chemotherapeutics has been proposed as a putative strategy to enhance drug tolerability and efficacy compared to the conventional chemotherapy. However, its potential effects on improving cancer patients prognosis remain largely unknown. The current meta-analysis is to explore the prognosis of cancer patients undergoing liposomal doxorubicin-based chemotherapy. **Methods** A detailed review of English and Chinese literature was conducted from PubMed, Embase, Cochrane Library, China Biology Medicine disc (CBM), China National Knowledge Infrastructure (CNKI) up to March 21st, 2019. We evaluate its possible correlations using hazard ratios (HRs) with 95% confidence intervals (CIs). The pooled data were calculated by STATA software and Review Manager 5.3 software. **Results** Consequently, 26 studies including 7943 patients were satisfied in current analysis. We found that there were no significant differences between liposomal and conventional chemotherapy in OS (HR=0.98, 95%CI: 0.93-1.04, P=0.544) and PFS (HR=1.00, 95%CI: 0.92-1.10, P=0.945). Likewise, subgroup-analysis regarding country, cancer type and sample sizes also showed the similar results of the two paired groups. **Conclusion** Taken together, our findings have demonstrated that there was no association of undergoing liposomal doxorubicin-based chemotherapy with cancer prognosis. However, detailed and further studies are needed to confirm these conclusions.

Background

Generally, patients with malignant diseases often have worse psychological and physical health. An estimation of 2018 cancer statistics revealed about 1,735,350 new cancer cases diagnosed and 609,640 new deaths assigned to cancer in US [1]. Although we have made enormous progress against cancer in the past decade, chemotherapy is of great importance for majority of the patients especially the late-stage patients. However, most patients treated with conventional chemotherapy suffer from serious side effects due to non-selective toxicity of chemotherapeutic drugs to normal cells [2]. There is an urgent need and tremendous value to develop novel chemotherapeutic drug carriers.

Advanced researches indicate that nano-sized carriers have presented a important therapeutic agents in both diagnosis and therapy of cancer because they have longer plasma half-life and may enhance chemotherapeutic drugs delivery while limiting non-tumorous tissue distribution [3]. Consequently, it possesses increase anticancer efficacy and lower toxicity to normal tissue [4]. To date, pegylated liposomal doxorubicin (PLD; Doxil/Caelyx) is unique formulation of doxorubicin, which is confined in liposomes. It is a cytotoxic anthracycline antibiotic extracted from *Streptomyces peucetius* var. *Caesius* [5, 6]. PLD is the first FDA-approved anticancer nano-drug and has demonstrated tremendous benefits compared to conventional chemotherapy. However, the possible mechanism of its anti-tumor has not been explained clearly. It may interfere with the DNA, RNA, and protein synthesis by blocking topoisomerase I and intercalate between adjacent base pairs of the double helix structure of DNA [7, 8]. Despite the well-established role of liposomal doxorubicin-based chemotherapy in prognosis for tumor patients, these conclusions were the focuses of controversy. Meta-analysis is a statistical software that incorporates all available data to derive a pooled and authentic result [9]. Herein, we try to perform a meta-analysis to explore whether cancer patients undergoing liposomal doxorubicin-based chemotherapy is associated with cancer prognosis, which efforts may make a contribution to the clinical therapy.

Methods

Literature search strategy

A detailed review of English and Chinese literature was conducted from PubMed, Embase, Cochrane Library, CBM, CNKI, using the terms ("liposom* and doxorubicin OR DOX-SL OR Lipodox OR Doxil OR Caelyx OR Lipo-Dox OR DaunoXome") and ("cancer OR tumor OR tumour OR neoplasm OR neoplasma OR neoplasia OR carcinoma"). The literature search was last updated on March 21st , 2019. We also searched the reference of the relevant review articles to seek for the potentially included studies. We did not try to contact the corresponding authors if the survival analysis data could not be obtained. The PRISMA statement for reporting systematic reviews and meta-analyses was cited in this meta-analysis [10]. In addition, the ethical approval was not applied in current study because there was no patient's privacy or clinical samples.

Inclusion and exclusion criteria

Relevant studies should meet the following criteria before being included: (1) the included studies focused on the association of cancer patients undergoing liposomal doxorubicin-based chemotherapy with prognosis; (2) the studies provided survival analysis data of HR and 95%CI or a survival curve from which we could extract the HR, 95%CI; As per the exclusion criteria: (1) no survival analysis data; (2) studies involved cell lines and animals; (3) similar or duplicate study; (4) other type articles including reviews, case reports, letters.

Data extraction and quality assessment

We extracted the relevant data including author, publication year, country, no. of patients, age, cancer type, treatment arms, phase, follow-up time, survival outcomes and HR (95%CI) from included study. The data were independently extracted by 2 authors (Kaiping Zhang and Zhi Sun). Disagreements were resolved by discussion or reviewed by a third author (Min Chao).

Among the relevant data, country came from USA, UK, Greece and others; Sample size was separated into ≥ 100 and < 100 ; Cancer type included soft tissue sarcoma (STS), multiple myeloma (MM), acute myelogenous leukaemia (AML), non-small cell lung cancer (NSCLC), oesophago-gastric (OG) cancer, acute lymphoblastic leukemia (ALL), metastatic breast cancer (MBC), ovarian cancer (OG). Survival outcomes contained overall survival (OS) and progression-free survival (PFS). The quality of included studies was assessed with the Newcastle-Ottawa Scale (NOS), which is composed of three domains: selection, comparability, and exposure. The NOS is a semi-quantitative scale, from which a score of 0-9 was assigned to each study. A total score of ≤ 3 was considered poor quality, 4-6 was considered moderate quality, and 7-9 was deemed high quality.

Statistical analysis

We explored the prognosis of cancer patients undergoing liposomal doxorubicin-based chemotherapy by using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and STATA 12.0 software (Stata Corporation, College Station, TX). HR(95% CI) was obtained for assessing the prognosis of cancer patients after liposomal doxorubicin-based chemotherapy. Meanwhile, the Q statistics and I^2 test were applied to calculate the heterogeneity of eligible study. $P < 0.05$ and/or $I^2 > 50\%$ were considered as statistically heterogeneous, and random effects (DerSimonian and Laird method) model was used to pool the results [11, 12]. Otherwise, fixed effects (Mantel-Haenszel method) model was applied [13].

One-way sensitivity analyses removed each included study were performed to assess the pooled results' stability. Moreover, the publication bias was assessed using Begg's test. $P < 0.05$ indicated that there was a bias of this meta-analysis [14]. Additionally, different subgroups consisted of country, cancer type and sample size were analysed in current meta-analysis.

Results

Study characteristics

Consequently, 26 studies with a total of 7943 participants were selected in our meta-analysis (Fig. 1) [15- 40]. The main study characteristics are provided in Table 1. Among them, Kaye's phase II, open-Label, randomized, multicenter study was performed to explore three different chemotherapy in ovarian cancer [29]. Therefore, we took it as three different studies independently. At length 28 studies were included in this analysis (Table 1).

Among these studies, 27/28 studies came from English database and 1/28 was conducted in the People's Republic of China. The participants of each included studies ranged from 60 to 973. The cancer types contained 9 MBC, 10 OC, 3 NSCLC, 2 MM, 1 ALL, 1 AML, 1 OG cancer and 1 STS. Meanwhile, 26 and 27 out of 28 studies reported OS and PFS, respectively. The detailed information about the involved studies and patients is presented in Table 2. However, the treatment arms differed greatly in these eligible studies .

Meta-analysis of OS

As a result, 26 were had analysed the prognosis of cancer patients undergoing liposomal doxorubicin-based chemotherapy. We found that no significant differences was explored between two paired groups in OS (HR=0.98, 95%CI: 0.93-1.04, $P=0.544$) (Fig. 2). Likewise, subgroup analysis demonstrated no significant difference regarding country, cancer type and sample sizes (Table 3).

Meta-analysis of PFS

There were 27 studies involved with PFS. Ultimately, we found that no association of patients after liposomal chemotherapy in tumors was detected with PFS (HR=1.00, 95%CI: 0.92-1.10, $P=0.945$) (Fig. 3). There was no significantly statistical differences in different subgroup analysis rather than subgroup of country and cancer type. The detail were shown in Table 4.

Sensitivity analysis and Publication bias evaluation

Sensitivity analysis by deleting each single study at a time was performed to assess the reliability of the pooled results. It demonstrated that our conclusions were relatively stable between two paired groups in OS (Figure 4) and PFS (Fig. 5). Furthermore, Begg's funnel plot was used to detect the publication bias of the eligible studies, and observed no publication bias in this analysis of OS ($P=0.508$) (Fig. 6A) and PFS ($P=0.983$) (Fig. 6B, respectively).

Discussion

Although cancer is not completely curable by current therapies, it deserves effective treatment. Patients receiving proper chemotherapy would help to relieve the symptom, improve the quality of life (QoL), and prolong survival. However, conventional chemotherapy can not [satisfy people's demands](#). After persistent efforts over the recent years, many anticancer nanoplateforms have been explored and investigated in preclinical and clinical trials. Yet, only the minority has satisfied efficacy criteria for regulatory approval, and many liposomal platforms were applied [41].

Doxorubicin is generally regarded as the most effective anticancer drugs, but its clinical practice has limitation because of a cumulative dose-dependent [cardiotoxicity](#) that could result in some potentially fatal toxicity of non-target normal tissues. PLD is a active and unique formulation of doxorubicin, which has been proven to be a better

therapeutic choice for cancer patients. In this formulation, doxorubicin-encapsulated liposomes are sterically stabilized by grafting polyethylene glycol onto the liposomal surface (Stealth Liposome) [42]. Its liposomal encapsulation reduces plasma free anticancer drug level and drug delivery to normal tissues, possibly decreasing immunosuppression and cardiotoxicity of doxorubicin [43]. It confers different pharmacokinetic characteristics that results in a circulation half-life compared with conventional free doxorubicin, which has a half-life of less than 10 minutes [44]. Then prolonged circulation in cancer tissues permits higher uptake of PLD. The selective accumulation of PLD in cancer tissue led to about 10-fold higher intracellular anticancer drug concentrations than adjacent normal tissues [45]. Consequently, patients who have received PLD reduced risk of nausea or vomiting, myelosuppression, alopecia, and cardiotoxicity [46, 47]. In addition, acquisition of drug resistance of tumor cells in patients is a major challenge in previously treated patients, which could be explained by the barrier of the chemotherapy drug transport across the cell membrane. PLD directly fused with the tumor cell membrane rather than transporting across the cell membrane. [Accordingly](#), PLD was gradually considered the most appropriate chemotherapeutic agents for the cancer patients, especially for resistant tumors [48].

In general, PLD has substantial clinical activity of durable clinical responses in 26% of patients [49]. Recent researches have shown that PLD may prolong both PFS and OS when compared with conventional chemotherapy. Because of these relatively small sample size trials, the results can not be considered definitive. This meta-analysis was performed to explore the prognosis of cancer patients after liposomal doxorubicin-based chemotherapy in various tumors. As results, PLD has not shown significant superiority to other approved conventional chemotherapy drugs in prognosis. No association was detected between liposomal vs. conventional formulations in OS and PFS. Subgroup analysis also showed that there was no statistical difference rather than subgroups of country and cancer type in PFS. However, these results remains to be further evaluated in advanced research. The previously reported studies would suggest that we need to take dose ranges and cycle dependent pharmacokinetic changes into consideration [50]. Maybe larger single doses may be more efficacious than smaller split doses [51]. Thus, detailed studies are required to confirm our conclusions.

Our study has several limitations. First, merely published studies were included for eligible literatures. Then there were inconsistent chemotherapy regimen and dose of eligible studies, and may be influenced our conclusions. Meanwhile, the extreme heterogeneity suggested that potentially possible factors should be taken into consideration. In spite of limitations mentioned above, no association of cancer patients after liposomal doxorubicin-based chemotherapy in prognosis was addressed in our study.

Conclusions

In summary, our study is the relatively detailed analysis to explore the prognosis of cancer patients undergoing liposomal doxorubicin-based chemotherapy. Our meta-analysis revealed that no association was found in overall population as well as the corresponding subgroups. Further clinical studies are required to confirm our conclusion in cancer patients.

Abbreviations

PLD: pegylated liposomal doxorubicin; HR: hazard ratio; CI: confidence interval; OS: overall survival; PFS: progression-free survival; STS: soft tissue sarcoma; MM: multiple myeloma; AML: acute myelogenous leukaemia; NSCLC: non-small cell lung cancer; OG: oesophago-gastric; ALL: acute lymphoblastic leukemia; MBC: metastatic breast cancer; OC: ovarian cancer;

Declarations

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

K.P.Z. and Z.S. conceived the analysis, performed literature search, and wrote the manuscript; Y.Z. contributed to the analysis; C.Z.L., L.Z. and M.C. conceived the analysis, contributed to the analysis. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics of included clinical studies

First authors	Year	Country	No of patients	Age, Median(range)	Cancer types	Treatment arms	Phase	Follow-up	outcomes
Judson I ¹⁵	2001	USA	50/45	52(19-80)/52(27-77)	STS	PLD 50 mg/m ² every 28 days; Doxorubicin 75 mg/m ² every 21 days	phase II	NA	OS/PFS
Dimopoulos MA ¹⁶	2003	Greece	132/127	65(37-88)/66(37-88)	MM	PLD 40 mg/m ² every 28 days; Doxorubicin 9 mg/m ² every 28 days	phase III	40 months	OS/PFS
O'Brien ME ¹⁷	2004	UK	254/255	59(28-82)/58(25-82)	MBC	PLD 50 mg/m ² every 28 days; Doxorubicin 60 mg/m ² every 21 days	phase III	NA	OS/PFS
Rifkin RM ¹⁸	2006	USA	97/95	60(37-84)/60(44-81)	MM	PLD 40 mg/m ² every 28 days; Doxorubicin 9 mg/m ² every 28 days	phase III	21months	OS/PFS
Hunault-Berger M ¹⁹	2011	France	31/29	68(55-77)/66(60-80)	ALL	PLD 40 mg/m ² days 1-4; Doxorubicin 12 mg/m ² /day days 1-4	phase II	48months	OS/PFS
Batist G ²⁰	2001	Canada	142/155	55(30-80)/54(22-88)	MBC	Liposomal doxorubicin 60 mg/m ² every 21 days; Doxorubicin 60 mg/m ² every 21 days	phase III	20months	OS/PFS
Harris L ²¹	2002	USA	108/116	58(26-85)/58(29-82)	MBC	Liposomal doxorubicin 75 mg/m ² every 21 days; Doxorubicin 75 mg/m ² every 21 days	phase III	4months	OS/PFS
Latagliata R ²²	2008	Rome	148/153	68.2(61-74.8)/68(61-74.8)	AML	Daunoxome 80 mg/m ² days 1-3; Daunorubicin 45 mg/m ² days 1-3	phase III	26.6 months	OS/PFS
Mylonakis N ²³	2010	Greece	47/41	64 (49-83)/66 (52-77)	NSCLC	Liposomal cisplatin 120 mg/m ² every 21 days; Cisplatin 100 mg/m ² every 21 days	phase II	53 months	OS/PFS
Stathopoulos GP ²⁴	2010	Greece	114/115	65(37-80)/66(41-85)	NSCLC	Liposomal cisplatin 200 mg/m ² every 14 days; Cisplatin 75 mg/m ² every 14 days	phase II	15 months	OS/PFS
Yang X ²⁵	2012	China	50/50	55.2(34-76)/53.2(25-73)	NSCLC	Liposomal paclitaxel 150 mg/m ² every 21 days; Paclitaxel 150 mg/m ² every 21 days	NA	20 months	OS/PFS
Roy AC ²⁶	2013	UK	44/44	56(38-81)/62(33-79)	OG cancer	Liposomal irinotecan 120 mg/m ² every 21 days; Irinotecan 300 mg/m ² every 21 days	phase II	NA	OS/PFS
Pignata S ²⁷	2011	Italy	410/410	57(25-77)/57(21-77)	OC	carboplatin and PLD 30 mg/m ² every 3 weeks; carboplatin and paclitaxel 175mg/m ² every 3 weeks	phase III	20 months	OS/PFS
Bafaloukos D ²⁸	2010	Greece	93/96	62(38-89)/63(37-81)	OC	carboplatin and PLD 45 mg/m ² every 3 weeks; carboplatin and paclitaxel 175 mg/m ² every 3 weeks	phase II	43.6 months	PFS
Kaye SB-1 ²⁹	2012	UK	33/32	53.0(43-81)/58.5(45-77)	OC	PLD 50 mg/m ² every 28 days; olaparib 200mg every 28 days;	phase II	NA	OS/PFS
Kaye SB-2 ²⁹	2012	UK	33/32	53.0(43-81)/53.5(35-76)	OC	PLD 50 mg/m ² every 28 days; olaparib 400mg every 28 days;	phase II	NA	OS/PFS
Kaye SB-3 ²⁹	2012	UK	33/64	53.0(43-81)/NA	OC	PLD 50 mg/m ² every 28 days; olaparib 400+200mg every 28 days;	phase II	NA	PFS
Alberts DS ³⁰	2008	USA	31/30	66.9(43-	OC	carboplatin and PLD 30 mg/m ²	phase	22.4	OS/PFS

				87)/62.5(31-80)		every 4 weeks; carboplatin every 4 weeks	III	months	
Pujade-Lauraine E ³¹	2010	France	466/507	60.5(24-82)/61(27-82)	OC	carboplatin and PLD 30 mg/m ² every 4 weeks; carboplatin and paclitaxel 175 mg/m ² every 3 weeks	phase III	22 months	OS/PFS
Mutch DG ³²	2007	USA	96/99	62(28-83)/59(38-85)	OC	PLD 50 mg/m ² every 28 days; gemcitabine 1,000 mg/m ² every 21 days	phase III	29.2 months	OS
Gordon AN ³³	2001	USA	239/235	60(27-87)/60(25-85)	OC	PLD 50 mg/m ² every 28 days; topotecan 1.5 mg/m ² every 21 days	phase III	NA	OS/PFS
Colombo N ³⁴	2012	Italy	417/412	59(23-84)/59(25-87)	OC	PLD 50 mg/m ² every 4 weeks; patupilone 10 mg/m ² every 3 weeks	phase III	27 months	OS/PFS
Sparano JA ³⁵	2009	USA	378/373	52.5(26-80)/51.8(30-87)	MBC	PLD 30 mg/m ² and docetaxel 60 mg/m ² every 21 days; docetaxel 75mg/m ² every 21days	phase III	NA	OS/PFS
Chan S ³⁶	2004	UK	80/80	54(19-78)/54(26-82)	MBC	Myocet 75 mg/m ² and cyclophosphamide 600 mg/m ² ; epirubicin 75 mg/m ² and cyclophosphamide 600 mg/m ² every 3 weeks	phase III	21 months	OS/PFS
Keller AM ³⁷	2004	USA	150/151	56(33-87)/56(30-83)	MBC	PLD 50 mg/m ² every 28 days; Vinorelbine or Mitomycin C and Vinblastine every 6 to 8 weeks	phase III	NA	OS/PFS
Baselga J ³⁸	2014	USA	181/182	52(22-79)/53(30-76)	MBC	NPLD 50 mg/m ² every 3 weeks and trastuzumab and paclitaxel; trastuzumab and paclitaxel every 3 weeks	phase III	44 months	OS/PFS
Smorenburg CH ³⁹	2014	Netherlands	40/38	NA	MBC	PLD 45 mg/m ² every 4 weeks; capecitabine 1000 mg/m ² every 3 weeks	phase III	39 months	OS/PFS
Harbeck N ⁴⁰	2017	Germany	105/105	62(36-82)/63(22-85)	MBC	PLD 50 mg/m ² every 28 days; capecitabine 1250 mg/m ² twice daily for 14 days every 21 days.	phase III	NA	OS/PFS

Abbreviations: STS, Soft tissue sarcoma; MM, Multiple myeloma; AML, Acute myelogenous leukaemia; NSCLC, Non-small cell lung cancer; OG, Oesophago-gastric; ALL, Acute lymphoblastic leukemia; MBC, Metastatic breast cancer; OC, Ovarian cancer; NA, Not available; OS, overall survival; PFS, Progression-free survival; PLD, pegylated liposomal doxorubicin; NPLD, nonpegylated liposomal doxorubicin.

Table 2 The survival data of the selected studies

First authors	Year	Country	No of patients	Cancer types	outcome	HR(95%CI)
Judson I	2001	USA	50/45	STS	OS	0.64(0.38-1.10)
Judson I	2001	USA	50/45	STS	PFS	1.09(0.75-1.58)
Dimopoulos MA	2003	Greece	132/127	MM	OS	1.36(0.85-2.17)
Dimopoulos MA	2003	Greece	132/127	MM	PFS	1.15(0.80-1.64)
O'Brien ME	2004	UK	254/255	MBC	OS	0.94(0.74-1.19)
O'Brien ME	2004	UK	254/255	MBC	PFS	1.00(0.82-1.22)
Rifkin RM	2006	USA	97/95	MM	OS	0.69(0.31-1.52)
Rifkin RM	2006	USA	97/95	MM	PFS	1.15(0.67-1.98)
Hunault-Berger M	2011	France	31/29	ALL	OS	0.97(0.54-1.77)
Hunault-Berger M	2011	France	31/29	ALL	PFS	1.16(0.67-2.03)
Batist G	2001	Canada	142/155	MBC	OS	1.04(0.77-1.41)
Batist G	2001	Canada	142/155	MBC	PFS	1.03(0.80-1.33)
Harris L	2002	USA	108/116	MBC	OS	0.76(0.56-1.04)
Harris L	2002	USA	108/116	MBC	PFS	0.92(0.66-1.26)
Latagliata R	2008	Rome	148/153	AML	OS	0.95(0.72-1.26)
Latagliata R	2008	Rome	148/153	AML	PFS	1.10(0.80-1.50)
Mylonakis N	2010	Greece	47/41	NSCLC	OS	0.92(0.54-1.56)
Mylonakis N	2010	Greece	47/41	NSCLC	PFS	0.91(0.59-1.42)
Stathopoulos GP	2010	Greece	114/115	NSCLC	OS	1.21(0.87-1.68)
Stathopoulos GP	2010	Greece	114/115	NSCLC	PFS	0.86(0.64-1.16)
Yang X	2012	China	50/50	NSCLC	OS	1.27(0.81-1.97)
Yang X	2012	China	50/50	NSCLC	PFS	0.76(0.53-1.09)
Roy AC	2013	UK	44/44	OG cancer	OS	1.32(0.79-2.21)
Roy AC	2013	UK	44/44	OG cancer	PFS	1.06(0.71-1.57)
Pignata S	2011	Italy	410/410	OC	OS	0.82(0.72-1.12)
Pignata S	2011	Italy	410/410	OC	PFS	0.95(0.81-1.13)
Bafaloukos D	2010	Greece	93/96	OC	PFS	1.15(0.78-1.66)
Kaye SB-1	2012	UK	33/32	OC	OS	0.66(0.27-1.55)
Kaye SB-1	2012	UK	33/32	OC	PFS	0.91(0.48-1.74)
Kaye SB-2	2012	UK	33/32	OC	OS	1.01(0.44-2.27)
Kaye SB-2	2012	UK	33/32	OC	PFS	0.86(0.45-1.62)
Kaye SB-3	2012	UK	33/64	OC	PFS	0.88(0.51-1.56)
Alberts DS	2008	USA	31/30	OC	OS	0.46(0.22-0.95)
Alberts DS	2008	USA	31/30	OC	PFS	0.54(0.32-0.93)
Pujade-Lauraine E	2010	France	466/507	OC	OS	0.99(0.85-1.16)
Pujade-Lauraine E	2010	France	466/507	OC	PFS	0.82(0.72-0.94)
Mutch DG	2007	USA	96/99	OC	OS	1.02(0.71-1.42)
Gordon AN	2001	USA	239/235	OC	OS	0.82(0.68-1.00)
Gordon AN	2001	USA	239/235	OC	PFS	0.79(0.67-0.94)
Colombo N	2012	Italy	417/412	OC	OS	1.07(0.91-1.26)
Colombo N	2012	Italy	417/412	OC	PFS	0.95(0.8-1.12)
Sparano JA	2009	USA	378/373	MBC	OS	0.98(0.82-1.17)
Sparano JA	2009	USA	378/373	MBC	PFS	1.52(1.29-1.79)
Chan S	2004	UK	80/80	MBC	OS	1.15(0.77-1.72)
Chan S	2004	UK	80/80	MBC	PFS	1.52(1.06-2.19)
Keller AM	2004	USA	150/151	MBC	OS	1.05(0.82-1.33)
Keller AM	2004	USA	150/151	MBC	PFS	1.26(0.98-1.62)
Baselga J	2014	USA	181/182	MBC	OS	1.27(0.98-1.65)
Baselga J	2014	USA	181/182	MBC	PFS	1.19(0.92-1.53)
Smorenburg CH	2014	Netherlands	40/38	MBC	OS	0.87(0.53-1.43)
Smorenburg CH	2014	Netherlands	40/38	MBC	PFS	0.68(0.42-1.09)
Harbeck N	2017	Germany	105/105	MBC	OS	1.12(0.79-1.58)
Harbeck N	2017	Germany	105/105	MBC	PFS	1.08(0.76-1.54)

Abbreviations: STS, Soft tissue sarcoma; MM, Multiple myeloma; AML, Acute myelogenous leukaemia; NSCLC, Non-small cell lung cancer; OG, Oesophago-gastric; ALL, Acute lymphoblastic leukemia; MBC, Metastatic breast cancer; OC, Ovarian cancer; NA, Not available; OS, Overall survival; PFS, Progression-free survival; HR, hazard ratio; CI, confidence interval;

Table 3 Stratified analysis of liposomal doxorubicin-based chemotherapy

and overall survival.

Categories	Subgroups	No	Case/Control	HR(95%CI)	P-value	I ²	Ph
All		26	3843/3911	0.98(0.93-1.04)	0.544	15.6%	0.239
Country	USA	9	1330/1326	0.91(0.79-1.06)	0.217	51.0%	0.038
	UK	5	331/363	1.01(0.84-1.21)	0.918	0.0%	0.609
	Greece	3	293/283	1.18(0.93-1.50)	0.178	0.0%	0.543
	Others	9	1889/1939	1.00(0.92-1.08)	0.915	0.0%	0.670
Cancer types	MBC	9	1438/1455	1.01(0.92-1.11)	0.799	0.0%	0.443
	OC	8	1692/1757	0.94(0.86-1.02)	0.132	35.1%	0.148
	NSCLC	3	211/206	1.16(0.92-1.47)	0.215	0.0%	0.620
	Others	6	502/493	0.98(0.82-1.18)	0.867	22.2%	0.267
Sample sizes	≥100	18	3567/3620	0.99(0.94-1.05)	0.819	17.0%	0.250
	<100	8	276/291	0.86(0.69-1.06)	0.152	5.2%	0.390

Abbreviations: UK, The United Kingdom; NSCLC, Non-small cell lung cancer; MBC, Metastatic breast cancer;OC, Ovarian cancer; HR,Hazard ratio; CI, Confidence interval; P^h, P-value of heterogeneity test;

Table 4 Stratified analysis of liposomal doxorubicin-based chemotherapy

and progression-free survival.

Categories	Subgroups	No	Case/Control	HR(95%CI)	P-value	I ²	Ph
All		27	3840/3908	1.00(0.92-1.10)	0.945	60.7%	0.000
Country	USA	8	1234/1227	1.04(0.83-1.31)	0.720	82.1%	0.000
	UK	6	411/443	1.06(0.91-1.22)	0.468	3.3%	0.396
	Greece	4	386/379	1.00(0.83-1.19)	0.964	0.0%	0.518
	Others	9	1809/1859	0.91(0.85-0.98)	0.017	12.9%	0.327
Cancer types	MBC	9	1438/1455	1.14(0.98-1.32)	0.101	64.8%	0.004
	OC	9	1689/1754	0.87(0.81-0.94)	0.000	14.1%	0.316
	NSCLC	3	211/206	0.84(0.68-1.03)	0.086	0.0%	0.800
	Others	6	502/493	1.11(0.94-1.31)	0.204	0.0%	1.000
Sample sizes	≥100	18	3564/3617	1.03(0.93-1.15)	0.526	70.3%	0.000
	<100	9	276/291	0.90(0.77-1.06)	0.217	0.0%	0.499

Abbreviations: UK, The United Kingdom; NSCLC, Non-small cell lung cancer; MBC, Metastatic breast cancer;OC, Ovarian cancer; HR,Hazard ratio; CI, Confidence interval; P^h, P-value of heterogeneity test;

Figures

Figure 1

Flow diagram of the study selection process in the meta-analysis.

Figure 2

Forest plot of the association between liposomal doxorubicin-based chemotherapy in various tumors and OS. Notes: The squares and horizontal lines correspond to the study-specific HR and 95% CI. The area of the squares reflects the weight. The diamond represents the summary HR and 95% CI. Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Figure 3

Forest plot of the association between liposomal doxorubicin-based chemotherapy in various tumors and OS. Notes: The squares and horizontal lines correspond to the study-specific HR and 95% CI. The area of the squares reflects the weight. The diamond represents the summary HR and 95% CI. Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, Progression-free survival.

Figure 5

One-way sensitivity analysis of liposomal doxorubicin-based chemotherapy in various tumors with PFS. Note: Individually removed the studies and suggested that the results of this meta-analysis were stable. Abbreviations: PFS, Progression-free survival.

Figure 6

Begg's funnel plot for publication bias test. (A) OS of liposomal doxorubicin-based chemotherapy in various tumors; (B) PFS of liposomal doxorubicin-based chemotherapy in various tumors. Notes: The x-axis is log (HR), and the y-axis is natural logarithm of HR. The horizontal line in the figure represents the overall estimated log (HR). The two diagonal lines indicate the pseudo 95% confidence limits of the effect estimate. Abbreviations: HR, hazard ratio; OS, overall survival; PFS, Progression-free survival.