Original Article

Hazard ratio of progression-free survival is an excellent predictor of overall survival in phase III randomized controlled trials evaluating the first-line chemotherapy for extensive-disease small-cell lung cancer

Hao Chen[1], Nobuyuki Horita[1], Kentaro Ito[2], Yu Hara[1], Nobuaki Kobayashi[1], Takeshi Kaneko[1]

[1]Department of Pulmonology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [2]Respiratory Center, Matsusaka Municipal Hospital, Matsusaka, Japan

Contributions: (I) Conception and design: N Horita, K Ito; (II) Administrative support: Y Hara, N Kobayashi, T Kaneko; (III) Provision of study materials or patients: H Chen, N Horita; (IV) Collection and assembly of data: H Chen, N Horita; (V) Data analysis and interpretation: N Horita, K Ito; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Nobuyuki Horita, MD, PhD. Department of Pulmonology, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, 236-0004, Japan. Email: horitano@yokohama-cu.ac.jp.

Background: Whether hazard ratio (HR) of progression-free survival (HRpfs), odds ratio (OR) of response rate (ORrr), OR of disease control rate (ORdcr), and OR of 1-year overall survival (ORos1y) used for extensive-disease small-cell lung cancer (ED-SCLC) correlate with HR of overall survival (HRos) at a randomized-trial level, especially for a trial that evaluates molecular-targeted therapy (MTT) or immune-checkpoint inhibitor (ICI), is unclear.

Methods: We included an individually randomized controlled trial (RCT) comparing two regimens as the first-line treatment for chemo-naive ED-SCLC, which have been reported in English-language since 2000. A weighted Spearman's rank correlation coefficient (r) was evaluated.

Results: We finally found 42 eligible articles consisted of 11,478 cases. Estimated r with HRos were as followings: HRpfs (29 trial, 8,573 cases, r=0.87), ORrr (39 trials, 11,030 cases, r=0.47), ORdcr (29 trials, 7,799 cases, r=0.48), and ORos1y (40 trials, 11,250 cases, r=0.69). Phase III subgroup (16 trials, 7,079 cases) yielded an excellent r between HRpfs and HRos of 0.96. ORdcr presented the best correlation with HRos for phase II trial subgroup (r=–0.64); however, this result was mainly calculated from MTT trials. HRpfs may overestimate the efficacy of MMT in a phase II trial. ORrr and ORdcr might undervalue the efficacy of ICI even in a phase III trial.

Conclusions: HRpfs can be a good surrogate of HRos, especially in a phase III trial. Depending on a single outcome in a randomized phase II trial may result in unneeded phase III trial or inappropriate abandonment of the regimen.

Keywords: Small-cell lung carcinoma; survival; treatment outcome; molecular targeted therapy

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Introduction

Small-cell lung cancer (SCLC) is a malignant respiratory disease usually preceded by smoking habit (1). Most patients were given the initial diagnosis of extensive-disease (ED)-SCLC because it grows and disseminates before a patient recognizes symptoms such as cough, sputum, and dyspnea. A patient with ED-SCLC is usually treated with systemic chemotherapy as SCLC is a chemotherapy-amenable

malignancy. However, ED-SCLC is not a curable disease. Therefore, the goal of treatment is to prolong survival; thus, overall survival (OS) is the standard outcome to evaluate a chemotherapy regimen.

Although OS is the most widely accepted endpoint for a randomized trial examining the efficacy of chemotherapy for lung cancer and hazard ratio (HR) is the most robust statistic to assess the time to event outcome in a randomized trial (2), some investigators prefer progression-free survival (PFS), response rate (RR), disease control rate (DCR), and milestone 1-year OS (OS1y) instead of HR of OS (HRos) because calculating HRos requires a long-term follow-up (3,4). Whether these surrogate endpoints accurately reflect HRos in an RCT assessing the chemotherapy for ED-SCLC is a serious concern because using an unreliable surrogate endpoint in an RCT critically diminishes the trustworthiness of the result. The validity of these surrogate endpoints was frequently evaluated at an individual level (5-10). However, it has not been sufficiently evaluated at a trial level. In addition, it is still not clear if these surrogate endpoints are useful for a trial that evaluates molecular-targeted therapy (MTT) and immune-checkpoint inhibitor (ICI), which have been featured recently. The goal of the current research is to examine how HR of PFS (HRpfs), odds ratio (OR) of RR (ORrr), OR of DCR (ORdcr), and OR of OS1y (ORos1y) correlate with HRos at a randomized-trial level. The authors present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-377).

Methods

Protocol registration

This protocol of the systematic review has been submitted to the website of International Prospective Register of Systematic Review (ID: 154051) (11). We have composited this protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (12).

Study search

Search formulas for PubMed, Web of Science Core Collection, Cochrane, and EMBASE are presented as Supplementary Text 1. The search was done on October 10th, 2019. An additional manual search was conducted by two investigators (HC and NH) independently.

Candidate articles were first screened and then scrutinized independently by two investigators.

A trial that included both limited disease and ED was included as long as the data for ED cases were separately extractable.

Inclusion criteria, publication type and trial design

We included an individually randomized controlled trial (RCT) comparing two regimens as the first-line treatment for chemo-naive ED-SCLC, which have been reported and published in English-language full papers since 2000. Reports before 2000 were not interest to us because chemotherapy regimens and imaging modalities before 2000 are clearly outdated. English-language conference abstract published after 2015 was also acceptable to collect data for MTT and ICI trials.

Included patients should be randomized before the chemotherapy initiation. Therefore, randomization after a few cycles of chemotherapy was not allowed.

A trial assessing a specific population defined by age, race, and performance status was permitted.

Inclusion criteria, treatments

A regimen that consisted of cytotoxic agent, MTT, ICI, and combination of these drugs was allowed. However, any regimen that included cytotoxic reagents developed around 1950, so-called the first-generation anticancer drugs, namely Methotrexate, Mitomycin, Vincristine, Cyclophosphamide, Doxorubicin, and Ifosfamide were excluded from our analysis because such regimens are outdated.

A three-arm trial was not included because we should not arbitrarily select two arms form the three arms.

Inclusion criteria, patients

Chemo-naive patients with ED-SCLC who underwent first-line chemotherapy were included.

Quality assessment

The quality of an original study was scored using six domains of the Cochrane Risk of Bias: random sequence generation, allocation concealment, performance, detection, attrition, reporting (13).

Outcomes

How HRpfs, ORrr, ORdcr, and ORos1y correlated with

HROs was evaluated. Then, subgroup analysis based on study phase was conducted.

Trials were further subdivided into three subgroups according to treatment regimens. A "MTT trial", which compared platinum doublet plus MTT versus doublet alone, belonged to "MTT subgroup". "The ICI subgroup" consisted of "ICI trials" focusing on adding an ICI on platinum doublet. No study directly compared two MTT regimens, two ICI regimens, or an MTT regimen versus an ICI regimen. A "cytotoxic-drug trial", which compared two cytotoxic regimens without MTT and ICI, consisted "cytotoxic drug subgroup".

Data extraction

Data for included studies, such as author name, publication year, country of origin, numbers of patients randomized, chemotherapy regimen, and outcomes were extracted by the two investigators (HC and NH) independently. The data extracted by the two investigators were cross-checked and any discrepancies were discussed between them. When necessary, we adopted Parmar's method to extract data from Kaplan-Meier curves (14). Intention-to-treat analysis was preferred over full-analysis-set analysis and per-protocol analysis when two or more of them were available. An updated survival data might be used.

Statistical analyses

RR and DCR were calculate in the standard manner (15). A weighted Spearman's rank correlation coefficient (r) between outcomes was calculated using "cor_spem" command in the "boot" package of R (16) (R foundation, Vienna, Austria). Correlation coefficient, r, which ranges −1 to 1 is usually considered as followings: $|r| < 0.2$, meaningless correlation; $0.2 < |r| < 0.4$, week correlation; $0.4 < |r| < 0.6$, moderate correlation; $0.6 < |r| < 0.8$, strong correlation; $0.8 < |r| < 0.9$, very strong correlation; $0.9 < |r|$, excellent correlation.

A weighted regression line and a determination coefficient, R^2, were calculated with the "lm" command of R software after logarithmization (17).

Results

Study selection and characteristics

We first found 1,431 articles from database searches and 5 articles from hand searches, respectively. Of 1,436 articles that met the preliminary criteria, 569, 669, and 156 were excluded through removal of duplication, title/abstract screening, and whole article scrutinizing, respectively (*Figure 1*). Author group of the CASPIN trial provided detailed unpublished data (18). We finally found 42 eligible articles, of which 29, 39, 29, and 40 provided data for HRpfs, ORrr, ORdcr, ORos1y (*Table 1*, Supplementary Text 2). The total number of ED-SCLC cases across all trial was 11,478.

Trials were reported from USA (N=16), EU (N=13 including 2 reports from UK), Japan (N=6), China (N=4), Korea (N=2), and India (N=1).

HR of PFS

Weighted Spearman's rank correlation, r, yielded from 29 trials with 8,573 ED-SCLC cases was 0.87, which suggests a very strong correlation between HRpfs and HROs (*Figure 2A*). The following regression formula was provided, Log (HROs) = Log (HRpfs) × 0.683 − 0.013 as shown in *Figure 2A*. Coefficient of determination, R^2 was 0.72, suggesting that HRpfs could explain 72% of HROs outcome.

Phase III subgroup (16 trials, 7,079 cases) yielded r of 0.96 and R^2 of 0.90, which meant excellent correlation between HRpfs and HROs (*Figure 2B*). Sixteen phase III RCTs consisted of 11 cytotoxic-drug trials, two MTT trials, and three ICI trials (*Figure 2B*).

Phase II subgroup included three cytotoxic-drug trials, eight MTT trials and no ICI trial (*Figure 2C*). The correlation coefficient yielded from these 11 phase II trials was week (r=0.26) (*Figure 2C*) partly because MTT trials were widely scattered left upper area, wherein HROs is not as good as expected from HRpfs.

Odds ratio of response rate and disease control rate

ORrr (N=39, n=11,030, r=−0.47, *Figure 2D,E,F*) and ORdcr (N=29, n=7,799, r=−0.48, *Figure 2G,H,I*) had moderate correlation with HROs. Phase-based subgroup analyses did not reveal considerable difference between r between phase III and phase II subgroups (*Figure 2E,F,H,I*). ORdcr consistently showed higher |r| than ORrr in all-trial, phase II, and phase III analyses (*Figure 2G,H,I*).

ORrr and ORdcr data regarding ICI were obtainable from three and two studies, respectively, all of which were phase III trials (*Figure 2E,H*). Based on these limited trials, ORrr and ORdcr did not seem to reflect HROs. Of note,

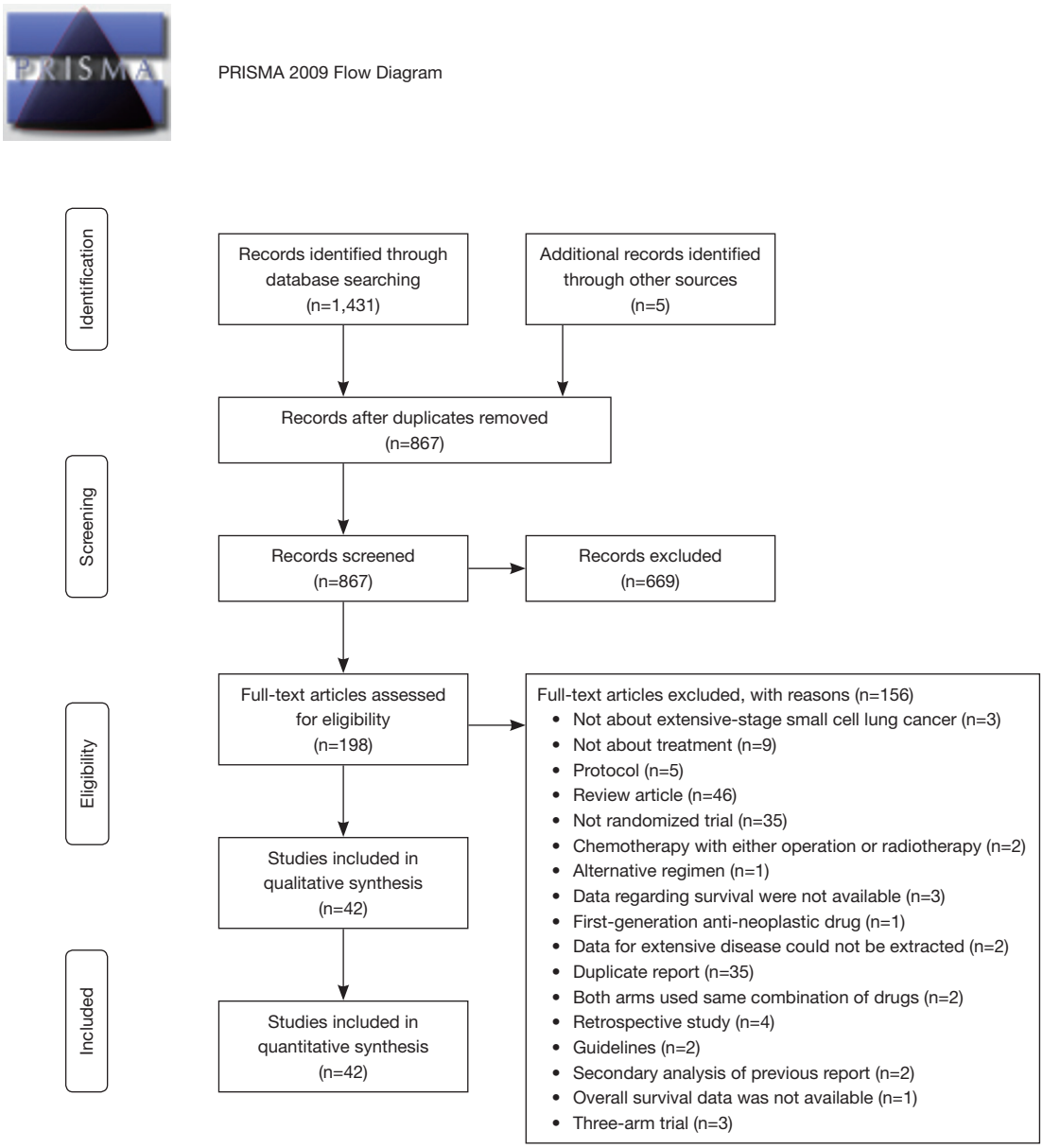

Figure 1 PRISMA flow chart for study selection.

PD-L1 trials were located considerably below the regression line in the ORrr-HRos plot and ORdcr-HRos plot (*Figure 2E,H*). This meant PD-L1 regimens led to longer OS than expected from response or disease-control evaluation. That is, RR and DCR evaluation might underestimate the efficacy of PD-L1 regimen.

Odds ratio of 1-year OS

Forty RCTs with 11,250 cases yielded r of –0.69 between ORos1y and HRos, meaning a strong correlation (*Figure 2J*). The coefficien r were –0.76 in phase III subgroup (*Figure 2K*) and –0.42 in phaseII subgroup (*Figure 2L*).

Discussion

We gathered the outcome data from 42 two-arm randomized trials consisted of 11,478 patients with ED-SCLC and examined how HRpfs, ORrr, ORdcr, and

Table 1 Characteristics of included studies

Study	Country	Phase, n	Primary endpoint	Treatment 1	Treatment 2	ROBH/U/L
Cheng_2019	China	P3, 234	PFS	Lobaplatin 30 mg/m^2 d1+ ETP 100 mg/m^2 d1–3, q3w	CDDP 80 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	2/0/4
Kim_2019	Korea	P3, 362	OS	CDDP 70 mg/m^2 d1 + CPT11 65 mg/m^2 d1, 8, q3w	CDDP 70 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	2/2/2
Owonikoko_2019, ECOG-ACRIN2511	USA	P2, 128	PFS	Treatment 2 + Veliparib 100 mg d1–7, q3w	CDDP 75 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	0/2/4
Paz-Ares_2019, CASPIAN	Spain	P3, 557	OS	Treatment 2 + Durvalumab 1,500 mg, q3w	(CDDP 75–80 mg/m^2 d1 or CBDCA ACU5-6) + ETP 80–100 mg/m^2 d1–3, q3w	2/2/2
Reck_2019	Germany	P2, 140	PFS	Treatment 2 + Roniciclib 3d/w, q3w	(CDDP 75 mg/m^2 d1 or CBDCA ACU5) + ETP 100 mg/m^2 d1–3, q3w	0/2/4
Weiss_2019	USA	P2, 77	–	Treatment 2 + Trilaciclib 240 mg/m^2 d1–3, q3w	CBDCA AUC5 d1 + ETP 100 mg/m^2 d1–3, q3w	1/0/5
Horn_2018, IMpower133	USA	P3, 403	OS, PFS	Treatment 2 + Atezolizumab 1,200 mg d1, q3w	CBDCA AUC5 d1 + ETP 100 mg/m^2 d1–3, q3w	0/0/6
Jalal_2017, MATISSE	USA	P3, 188	OS	Treatment 2 + Palifosfamide 130 mg/m^2 d1–3, q3w	CBDCA AUC4 d1 + ETP 100 mg/m^2 d1–3, q3w	2/0/4
Morikawa_2017, NJLCG0901	Japan	P2, 71	RR	CBDCA AUC4 d1 + AMR 35 mg/m^2 d1–3, q3w	CBDCA AUC5 d1 + CPT11 70 mg/m^2 d1, 8, q3w	1/2/3
Salgia_2017	USA	P2, 94	PFS	Treatment 2 + LY2510924 20 mg d1–7	CBDCA AUC5 d1 + ETP 100 mg/m^2 d1–3, q3w	2/2/2
Sanborn_2017, LUN06-113	Portland	P2, 67	–	Treatment 2 + Vandetanib 100 mg/d	(CDDP 60 mg/m^2 d1 or CBDCA ACU5) + ETP 120 mg/m^2 d1–3, q3w	1/2/3
Seckl_2017, LUNGSTAR	UK	P3, 482	OS	Treatment 2 + Pravastatin 40 mg/d for 2 years	(CDDP 60 mg/m^2 d1 or CBDCA ACU5-6) + ETP 120 mg/m^2 d1, 100–120 mg/m^2 d2, 3, q3w	0/0/6
Tiseo_2017, GOIRC-AIFA FARM6PMFJM	Italy	P3, 205	OS	Treatment 2 + Bevacizumab 7.5 mg/kg d1	CDDP 25 mg/m2 d1–3 + ETP 100 mg/m^2 d1–3, q3w	2/0/4
Oh_2016	Korea	P3, 157	RR	CDDP 60 mg/m^2 d1 + Belotecan 0.5 mg/m^2 d1–4, q3w	CDDP 60 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	1/2/3
Reck_2016	Germany	P3, 1,132	OS	Treatment 2 + Ipilimumab 10 mg/kg	(CDDP 75 mg/m^2 d1 or CBDCA ACU5) + ETP 100 mg/m^2 d1–3, q3w	0/0/6
Sun_2016	China	P3, 300	OS	CDDP 80 mg/m^2 d1 + AMR 40 mg d1–3, q3w	CDDP 80 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	2/0/4
Beniwal_2015	India	–, 120	–	CDDP 60 mg/m^2 d1 + CPT11 65 mg/m^2 d1, 8, q3w	CDDP 40 mg/m^2 d1-2 + ETP 120 mg/m^2 d1–3, q3w	3/3/0

Table 1 (*continued*)

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Study	Country	Phase, n	Primary endpoint	Treatment 1	Treatment 2	ROBH/U/L
Lu_2015	China	P2, 140	PFS	Treatment 2 + Endostatin 7.5 mg/m^2 d1–14	CBDCA AUC5 d1 + ETP 60 mg/m^2 d1–5, q3w	1/2/3
Shi_2015	China	P2, 62	PFS	CDDP 75 mg/m^2 d1 + CPT11 65 mg/m^2 d1, 8, q3w	CDDP 75 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	2/2/2
Langer_2014	USA	P2, 155	RR	Treatment 2 + Obatoclax 30 mg d1–3	CBDCA AUC5 d1 + ETP 100 mg/m^2 d1–3, q3w	2/2/2
Satouchi_2014, JCOG0509	Japan	P3, 284	OS	CDDP 60 mg/m^2 d1 + AMR 40 mg d1–3, q3w	CDDP 60 mg/m^2 d1 + CPT11 60 mg/m^2 d1, 8, 15, q3w	1/2/3
Sekine_2014	Japan	P3, 62	OS	AMR 40–45 mg/m^2 d1–3, q3w	CBDCA AUC5 d1 + ETP 80 mg/m^2 d1–3, q3w	2/2/2
Fink_2012	Germany	P3, 680	OS	CDDP 75 mg/m^2 d5 + TOP 1 mg/m^2 d1–5, q3w	CDDP 75 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	2/0/4
Schmittel_2011	Germany	P3, 226	PFS	CBDCA AUC5 d1 + ETP 140 mg/m^2 d1–3, q3w	CBDCA AUC5 d1 + CPT11 50 mg/m^2 d1, 8,15, q3w	2/2/2
Spigel_2011, SALUTE	USA	P2, 102	PFS	Treatment 2 + Bevacizumab 15 mg/kg d1	(CDDP 75 mg/m^2 d1 or CBDCA ACU5) + ETP 100 mg/m^2 d1–3, q3w	0/2/4
Zatloukal_2010	Germany	P3, 405	OS	CDDP 80 mg/m^2 d1 + CPT11 65 mg/m^2 d1, 8, q3w	CDDP 80 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	2/2/2
Lara_2009, SWOG0124	USA	P3, 671	OS	CDDP 60 mg/m^2 d1 + CPT11 60 mg/m^2 d1, 8,15, q3w	CDDP 80 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	2/0/4
Lee_2009	UK	–, 240	OS	CBDCA AUC5 d1 + GEM 1,200 mg/m^2 d1, 8	CDDP 60 mg/m^2 d1 + ETP 120 mg/m^2 d1, 100 mg d2–3, q3w	2/0/4
Socinski_2009	USA	P3, 908	OS	CBDCA AUC5 d1 + PEM 500 mg/m^2 d1, q3w	CBDCA AUC5 d1 + ETP 100 mg/m^2 d1–3, q3w	2/2/2
Dimitroulis_2008	Greece	P3, 108	OS, TTP	CDDP 80 mg/m^2 d1 + PTX 175 mg/m^2 d1–3, q3w	CDDP 80 mg/m^2 d1 + ETP 120 mg/m^2 d1–3, q3w	1/1/4
Hermes_2008	Germany	P3, 140	OS	CBDCA AUC5 d1 + ETP 120 mg/m^2 d1–5, q3w	CBDCA AUC5 d1 + CPT11 175 mg/m^2 d1, q3w	2/0/4
Rudin_2008, CALGB30103	USA	P2, 56	OS	Treatment 2 + Oblimersen 7 mg/kg d1–8	CBDCA AUC5 d6 + ETP 80 mg/m^2 d6–8, q3w	2/0/4
Sekine_2008	Japan	P2, 109	–	Treatment 2 + ETP 50 mg/m^2 d1–3	CDDP 60 mg/m^2 d1 + CPT11 60 mg/m^2 d1, 8, q3w	3/0/3
Okamoto_2007, JCOG9702	Japan	P3, 220	OS	CBDCA AUC5 d1 + ETP 80 mg/m^2 d1–3, q3w	CDDP 25 mg/m^2 d1–3 + ETP 80 mg/m^2 d1–3, q3w	2/2/2
Eckardt_2006	USA	P3, 784	OS	CDDP 60 mg/m^2 d5 + TOP 1.7 mg/m^2 d1–5, q3w	CDDP 80 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	2/2/2
Hanna_2006	USA	P3, 331	OS	CDDP 30 mg/m^2 d1, 8 + CPT11 65 mg/m^2 d1, 8 q3w	CDDP 60 mg/m^2 d1 + ETP 120 mg/m^2 d1–3, q3w	2/2/2
Socinski_2006	USA	P2, 78	RR	CDDP 75 mg/m^2 d1 + PEM 500 mg/m^2 d1, q3w	CBDCA AUC5 d1 + PEM 500 mg/m^2 d1, q3w	2/2/2

Table 1 (*continued*)

Table 1 (*continued*)

Study	Country	Phase, n	Primary endpoint	Treatment 1	Treatment 2	ROBH/U/L
Greco_2005	USA	P2, 120	RR, TTP	CBDCA AUC6 d1 + ETP 50–100 mg/m^2 d1–10 + PTX 200 mg/m^2 d1, q3w	TOP 1.5 mg/m^2 d1–3 + PTX 175 mg/m^2, q3w	2/2/2
Niell_2005, CALGB9732	USA	P3, 587	OS, TTP	Treatment 2 + PTX 175 mg/m^2 d1	CDDP 80 mg/m^2 d1 + ETP 80 mg/m^2 d1–3, q3w	1/2/3
Quoix_2005	France	P2, 82	–	CDDP 50 mg/m^2 d5 + TOP 1.25 mg/m^2 d1–5, q3w	ETP 60 mg/m^2 d1–5 + TOP 0.75 mg/m^2 d1–5, q3w	2/2/2
Lyss_2002, CALGB9430	USA	P2, 57	–	TOP 1 mg/m^2 d1–5 + PTX 175–230 mg/m^2, q3w	CDDP 75 mg/m^2 d1 + TOP 1 mg/m^2 d1–5, q3w	3/2/1
Noda_2002, JCOG9511	Japan	P3, 154	OS	CDDP 60 mg/m^2 d1 + CPT11 60 mg/m^2 d1, 8, 15, q3w	CDDP 80 mg/m^2 d1 + ETP 100 mg/m^2 d1–3, q3w	2/0/4

P2, phase II trial; P3, phase III trial; n, number of patients randomized to concerned arms; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression; d, day; q3w, every 3 weeks; /m^2, per body surface area square meter; brackets were used to interpret "or." CDDP, cisplatin; CBDCA, carboplatin; AUC, area under curve by Calvart formula; ETP, etoposide; CPT11, irinotecan; GEM, gemcitabine; PEM, pemetrexed; PTX, paclitaxel; TOP, topotecan. Treatment 1 and Treatment 2 may be switched from the original publication to place the reference arm to Treatment 2. ROB H/U/L: risk of bias high/unclear/low. Six domains of Cochrane risk of bias were assessed. 6/0/0, meaning 6 domains with high risk of bias, is the poorest score. 0/0/6, meaning 6 domains with low risk of bias, is the best score.

ORos1y reflected HRos. RR and DCR are easily available in two months of patient entry. However, they had only moderate correlation with HRos. Milestone OS1y is often featured in non-small cell lung cancer trials as a surrogacy of long-term survival, especially ICI-treated patients (3,4). However, late-phase OS plateau has not been observed in a cohort of ICI-treated ED-SCLC cases (18,19), thus OS1y does not presumed a long survival of ED-SCLC cases. Besides, OS1y is not a robust statistic because OS1y represents OS data at a single time point though OS1y is a biomarker that is directly derived from OS survival curve. One year after the entry of the last patient, OS and PFS curves may be sufficiently mature. Thus, we need not use milestone OS1y for the first-line ED-SCLC trial. In contrast, HRpfs, which had very strong correlation with HRos (r=0.89), is a reasonable surrogacy of HRos.

In the phase III setting, r between HRpfs and HRos was as high as 0.96 and R^2 between them was 0.90. In other words, PFS alone almost determined OS in a phase III trial for the 1st-line ED-SCLC. This is comparable with the fact that sensitivity to the first-line chemotherapy predict the response to later-line chemotherapy and post-progression survival (20). This excellent r was also supported large number of randomized patients in a phase III trial. As OS of an ED-SCLC case has recently been becoming longer thanks to ICI, evaluating HRos demands extended follow-up (18,19). HRpfs can be a desirable surrogate outcome in a future phase III trial.

In a randomized phase II trial, PFS and RR were often selected as the primary outcome. Nonetheless, HRpfs did not correlate well with HRos in phase II trials (*Figure 2C*). Furthermore, we do not have sufficient data to clarify how HRpfs is useful for phase II ICI trial and cytotoxic-drug trial because most of randomized phase-II trials were MTT trials (*Figure 2C*). ORdcr showed higher |r| of 0.64 with HRos in the phase II setting compared to that of ORrr (|r|=0.41). Lara *et al.* showed that DCR is a better patient-level surrogate of OS compared to RR in the ED-SCLC in the second-line setting (5). They also analyzed SCLC cases who underwent the first-line platinum doublet and found that DCR better predicts OS than RR does because patients who had DCR had similar OS with those who had a response. RR is usually a more preferred outcome than DCR (*Table 1*); however, DCR may be another reasonable option. In any case, none of RR, DCR, and PFS cannot warrant OS outcome in the phase II setting. Relying on a single outcome in the randomized phase II trials to start or to dismiss phase III trial might be risky.

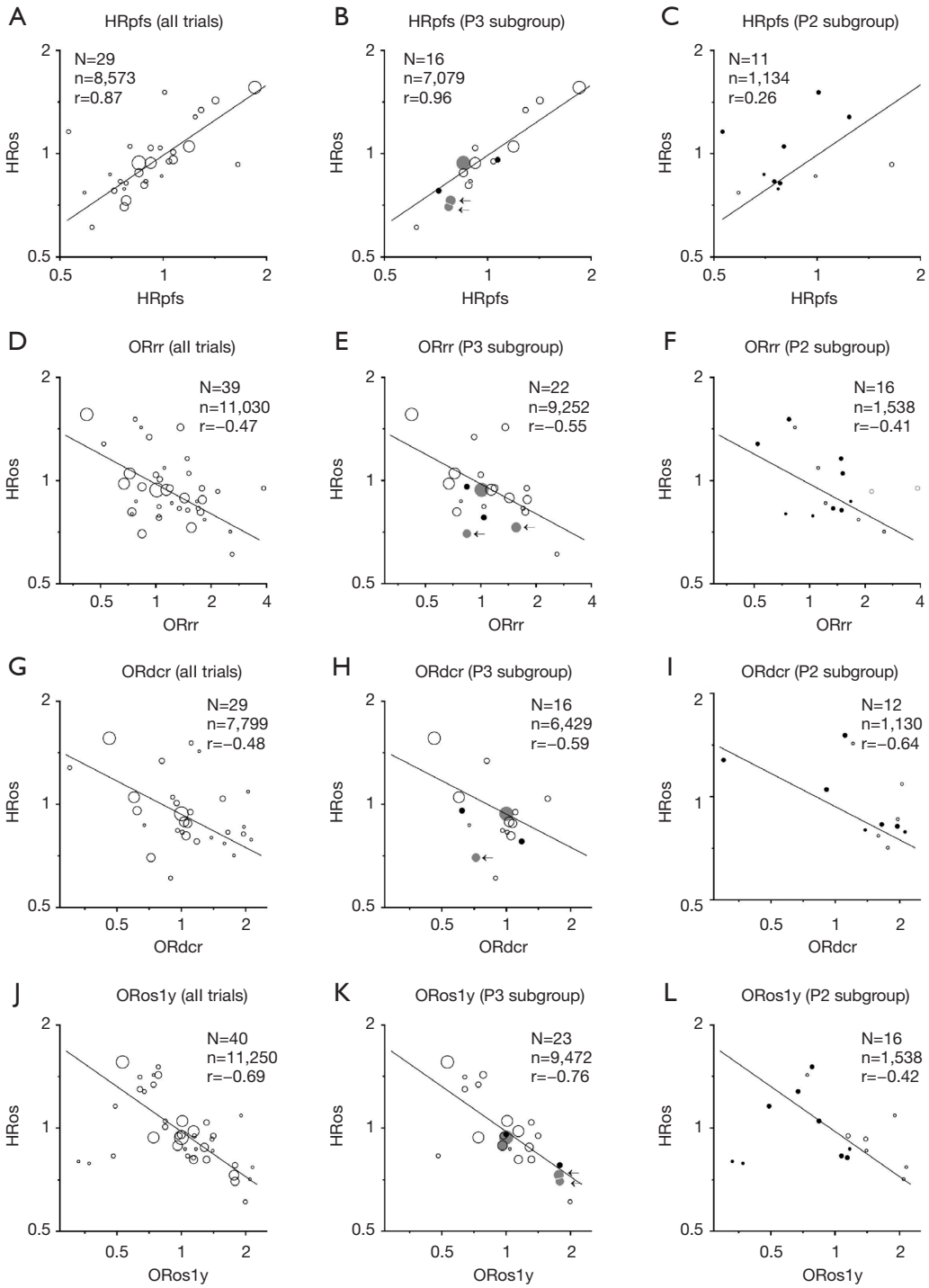

Figure 2 Correlation between surrogate outcomes and hazard ratio of overall survival. Each circle represents a randomized trial and a size of the circle represents a sample size. A line in the scatter plot is a regression line after logarithmization based on the all trials as shown in the left panel (A,D,G,J). The same regression line is drawn for the other panel. In a scatter plot of P3 and P2 subgroups (middle and right panels), an open circle indicates a cytotoxic-drug trial, a filled circle indicates molecular-targeted therapy, and a grey circle indicates an immune checkpoint inhibitor trial, and left pointing arrow indicates PD-L1 trial. N, number of trials; n, number of patients in a trial; r, Weighted Spearman's rank correlation coefficient; HRos, hazard ratio of overall survival; HRfps, hazard ratio of progression-free survival; ORrr, odds ratio of response rate; ORdcr, odds ratio of disease control ratio; P3, phase III; P2, phase II.

Although not conclusive because of a limited number of ICI trials, neither ORrr nor ORdcr could not predict HRos in ICI trials. Of note, ORrr and ORdcr in PD-L1 trials underestimated HRos of PD-L1 trials (*Figure 2F,I*). Surprisingly, patients treated by atezolizumab regimen in IMpower133 trial had longer survival with HRos of 0.70 and HRpfs of 0.77 though RR and DCR in atezolizumab arm was lower than those in the standard arm (19). In the era of ICI, RR and DCR might fall into desuetude.

We need to discuss agreement and disagreement between our data and published data. In 2009, Hotta *et al.* revealed that RR difference was modestly associated with the mean survival time difference (R^2=0.3314) at trial-level using data from 48 phase III trials (7). R^2=0.3314 is roughly equivalent to correlation coefficient of 0.58, which does not conflict with r=–0.47 between ORrr and HRos in our analysis (*Figure 2D*).

A report by Foster *et al.* in 2011 showed that progression-free at 4 and 6 months was associated with OS at the individual level. This supports that HRpfs reflect OS as shown in our analysis (*Figure 2A*) (8). They also divided data of three trials into 32 unit-level components and described that HRpfs and HRos had r of 0.73, which does not conflict with r of 0.87 between HRpfs and HRos in our analysis. In 2015, Foster *et al.* also reported that weighted least square R^2 was 0.83 between HRpfs and HRos using the data of 7 trials (10), which was compatible with R^2=0.72 between HRpfs and HRos in our analysis(*Figure 2A*). Because our data were largely enriched by a larger number of trials including MTT trials and ICI trials, our analysis provides useful information for future trial designing.

Imai *et al.* reported that PFS was moderately correlated with OS of 0.58 at the patient level (9). Some may think that these coefficients may seem poorer than our data (r=0.87, *Figure 2A*). However, patient level OS and PFS are clearly less robust and strong correlation is rarely achieved. Thus, the discrepancy between Imai and us is explainable.

In 2014, Nickolich analyzed 66 trials that were published until 2010 and did not find significant correlation between PFS and OS of ED-SCLC cases at trial level (unweighted Pearson's correlation coefficient =0.369) (6). The coefficient estimated by Nickolich may seem much lower than that in our analysis (r=0.87, *Figure 2A*). This large discrepancy may be introduced by methodology difference. We believe that the weighted Spearman's rank correlation coefficient, which we applied, is a reasonable and robust statistic to evaluate the correlation using data of trials with a variety of sample sizes.

One limitation of our study is that surrogacy of outcomes in a ICI trial could not be sufficiently evaluated because of the limited number of trials. Another is that the result concerning phase II RCT was largely driven by MTT trials.

In conclusion, when all trials were analyzed collectively, HRpfs very strongly correlate with HRos (r=0.87, R^2=0.72, *Figure 2A*) at the randomized trial level. In a phase III subgroup, the correlation was excellent (r=0.96, R^2=0.90, *Figure 2B*). HRpfs is an excellent surrogate outcome of HRos, especially in a phase III trial. ORdcr presented the best correlation with HRos for randomized phase II trials (*Figure 2I*, r=–0.64). However, this correlation did not reach the level of very strong correlation. Besides, this result was mainly calculated from MTT trials (*Figure 2I*). Depending on a single outcome in a randomized phase II trial may result in unneeded phase III trial or inappropriate abandonment of the regimen. For a phase III ICI trial, PFS seems a reasonable surrogate of OS (*Figure 2B*), but RR (*Figure 2E*) and DCR (*Figure 2H*) undervalue OS. PFS often overestimate the efficacy of MTT in a randomized phase II trial (*Figure 2C*).

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Footnote:

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tlcr-20-377

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-20-377). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary Text 1: Search formulas

PubMed

(Small cell lung cancer [title] OR small cell lung carcinoma [title] OR SCLC[title]) AND (ED OR extended OR extensive) AND (randomized OR randomised OR RCT OR phase 3 OR phase III OR randomly OR blinded OR blind OR placebo) and (Doxorubicin or Adriamycin or Epirubicine or Ifosfamide or Topotecan or Irinotecan or Etoposide or Cisplatin or Gemcitabin or Carboplatin or Teniposide or Epirubicin or Paclitaxel or apatinib or amrubicin or LY2510924 or Bevacizumab or Vismodegib or Cixutumumab or teniposide or Adriamycin or vindesine or nivolumab or ipilimumab or Atezolizumab OR Pembrolizumab OR Avelumab OR Durvalumab) not (NSCLC[title] or non-small[title])

Restricted by "publication since 2000" and "English language".

Web of Science

#1 TI=(Small cell lung cancer OR small cell lung carcinoma OR SCLC) AND TS=(ED OR extended OR extensive) AND TS=(randomized OR randomised OR RCT OR phase 3 OR phase III OR randomly OR blinded OR blind OR placebo) and TS=(Doxorubicin or Adriamycin or Epirubicine or Ifosfamide or Topotecan or Irinotecan or Etoposide or Cisplatin or Gemcitabin or Carboplatin or Teniposide or Epirubicin or Paclitaxel or apatinib or amrubicin or LY2510924 or Bevacizumab or Vismodegib or Cixutumumab or teniposide or Adriamycin or vindesine or nivolumab or ipilimumab or Atezolizumab OR Pembrolizumab OR Avelumab OR Durvalumab) NOT TI=(NSCLC or non-small)

Restricted by "English", "Article" and "2000-2019".

#2 TI=(Small cell lung cancer OR small cell lung carcinoma OR SCLC) AND TS=(ED OR extended OR extensive) AND TS=(randomized OR randomised OR RCT OR phase 3 OR phase III OR randomly OR blinded OR blind OR placebo) and TS=(Doxorubicin or Adriamycin or Epirubicine or Ifosfamide or Topotecan or Irinotecan or Etoposide or Cisplatin or Gemcitabin or Carboplatin or Teniposide or Epirubicin or Paclitaxel or apatinib or amrubicin or LY2510924 or Bevacizumab or Vismodegib or Cixutumumab or teniposide or Adriamycin or vindesine or nivolumab or ipilimumab or Atezolizumab OR Pembrolizumab OR Avelumab OR Durvalumab) NOT TI=(NSCLC or non-small)

Restricted by "English", "Letter/Meeting abstract" and "2015-2019."

#3 #1 or #2

Cochrane Search Manager

#1 Small cell lung cancer:ti OR small cell lung carcinoma:ti OR SCLC:ti

#2 ED OR extended OR extensive

#3 randomized OR randomised OR RCT OR phase 3 OR phase III OR randomly OR blinded OR blind OR placebo

#4 Doxorubicin or adoriamicyn or Epirubicine or Ifosfamide or Topotecan or Irinotecan or Etoposide or Cisplatin or Gemcitabin or Carboplatin or Teniposide or Epirubicin or Paclitaxel or apatinib or amrubicin or LY2510924 or Bevacizumab or Vismodegib or Cixutumumab or teniposide or Adriamycin or vindesine or nivolumab or ipilimumab or Atezolizumab OR Pembrolizumab OR Avelumab OR Durvalumab

#5 NSCLC:ti or non-small:ti

#6 #1 AND #2 AND #3 AND #4 NOT #5

Restricted by "Trial" and "2000-"

EMBASE

('small cell lung cancer':ti OR 'small cell lung carcinoma':ti OR sclc:ti) AND (ed OR extended OR extensive) AND (randomized OR randomised OR rct OR 'phase3' OR 'phase iii' OR randomly OR blinded OR 'blind'/exp OR blind OR 'placebo'/exp OR placebo) AND ('doxorubicin'/exp OR doxorubicin OR adriamycin OR 'epirubicine'/exp OR epirubicine OR 'ifosfamide'/exp OR ifosfamide OR 'topotecan'/exp OR topotecan OR 'irinotecan'/exp OR irinotecan OR 'etoposide'/exp OR etoposide OR 'cisplatin'/exp OR cisplatin OR 'gemcitabin'/exp OR gemcitabin OR 'carboplatin'/exp OR carboplatin OR 'epirubicin'/exp OR epirubicin OR 'paclitaxel'/exp OR paclitaxel OR 'apatinib'/exp OR apatinib OR 'amrubicin'/exp OR amrubicin OR ly2510924 OR 'bevacizumab'/exp OR bevacizumab OR 'vismodegib'/exp OR vismodegib OR 'cixutumumab'/exp OR cixutumumab OR 'teniposide'/exp OR teniposide OR 'adriamycin'/exp OR adriamycin OR 'vindesine'/exp OR vindesine OR 'nivolumab'/exp OR nivolumab OR 'ipilimumab'/exp OR ipilimumab OR 'atezolizumab'/exp OR atezolizumab OR 'pembrolizumab'/exp OR pembrolizumab OR 'avelumab'/exp OR avelumab OR 'durvalumab'/exp OR durvalumab) NOT (nsclc:ti OR

'non small':ti) AND [english]/lim AND ((([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [letter]/lim) AND [2015-2019]/py) OR ([article]/lim AND [2000-2019]/py))

Supplementary Text 2: Reference list of analyzed trials

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