Full Length Article

Association of overall survival benefit of radiotherapy with progression-free survival after chemotherapy for diffuse large B-cell lymphoma: A systematic review and meta-analysis

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ARTICLE INFO

ABSTRACT

Objective: To evaluate whether improved progression-free survival (PFS) from radiotherapy (RT) translates into an overall survival (OS) benefit for diffuse large B-cell lymphoma (DLBCL).

Methods: A systematic literature search identified randomized controlled trials (RCTs) and retrospective studies that compared combined-modality therapy (CMT) with chemotherapy (CT) alone. Weighted regression analyses were used to estimate the correlation between OS and PFS benefits. Cohen's kappa statistic assessed the consistency between DLBCL risk-models and PFS patterns. Furthermore, the benefit trend of RT was analyzed by fitting a linear regression model to the pooled hazard ratio (HR) according to the PFS patterns.

Results: For both 7 RCTs and 52 retrospective studies, correlations were found between PFS HR (HR_{PFS}) and OS HR (HR_{OS}) at trial level ($r = 0.639$–0.876), and between PFS and OS rates at treatment-arm level, regardless of CT regimens ($r = 0.882$–0.964). Incorporating RT into CT increased about 18% of PFS, and revealed a different OS benefit profile. Patients were stratified into four CT-generated PFS patterns (>80%, >60–80%, >40–60%, and ≤40%), which was consistent with risk-stratified subgroups (kappa > 0.6). Absolute gain in OS from RT ranged from ≤5% at PFS >80% to about 21% at PFS ≤40%, with pooled HR_{OS} from 0.70 (95% CI, 0.51–0.97) to 0.48 (95% CI, 0.36–0.63) after rituximab-based CT. The OS benefit of RT was predominant in intermediate- and high-risk patients with PFS ≤ 80%.

Conclusion: We demonstrated a varied OS benefit profile of RT to inform treatment decisions and clinical trial design.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is a heterogenous and aggressive disease. Diagnostic and treatment strategies for DLBCL have evolved over the last two decades, mainly with the addition of rituximab into CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone, R-CHOP) and the utilization of modern radiotherapy (RT) techniques and positron emission tomography (PET). Rituximab-based chemotherapy

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(CT) with optional RT is the standard of care.[1–4] The prognosis of newly diagnosed DLBCL has improved, with a 5-year overall survival (OS) rate of 60–95%. However, for patients who failed to achieve progression-free survival (PFS) at 24 months, the subsequent median OS was about 7.2 months after immunochemotherapy.[5] The poor outcomes of patients with recurrent/refractory DLBCL promoted efforts to optimize firstline treatment strategies, such as intensified therapy[6,7] and the addition of a novel agent or RT.[8–11]

CT can cure most patients with newly diagnosed DLBCL, whereas RT is considered a consolidation or adjuvant therapy. Many studies have evaluated the role of RT in DLBCL, with conflicting results.[10–24] Only a few randomized controlled trials (RCTs) have compared combined-modality therapy (CMT) with CT alone.[10–16] These RCTs were mainly conducted in the pre-rituximab era and focused on early-stage or low-risk patients. Large-scale population studies from the United States demonstrated inferior OS for patients not receiving RT, with continuously decreasing use of RT in the rituximab era.[17–19] The inconsistent results between studies may be related to patient selection criteria and the limited sample sizes, but also to variability in treatment aspects and follow-up times.[10–24] Currently, there is a tendency to omit RT in patients with low-risk early-stage DLBCL.[10,20,21] RT may be beneficial in specific high-risk patients with adverse factors, such as extranodal and bulky disease.[22–24] Therefore, RT may not be necessary for the whole DLBCL population. Precisely defining the survival benefit of RT and identifying patient subgroups that may benefit from RT is an important issue.

Recent studies have demonstrated that PFS or event-free survival is a surrogate endpoint for long-term OS after immunochemotherapy for DLBCL.[5,25,26] Furthermore, improved PFS is associated with prolonged OS at trial level and treatment-arm level in RCTs comparing CT regimens.[27] As PFS is an important milestone in stratifying patients and has shown association with long-term outcome, it may also serve as a marker for survival benefit from RT, thereby allowing for precise assessment of RT efficacy. We hypothesize that patients at high risk of disease progression after CT alone may benefit more from RT. Thus, we retrieved all available data from literature reporting RCTs and retrospective comparative studies of CMT vs CT alone. Then, we evaluated the correlations between PFS and OS at trial and treatment-arm levels, stratified patients into different prognostic patterns, and explored whether PFS improvement could be translated into OS advantage of RT.

2. Materials and methods

2.1. Study inclusion and quality control

Eligible studies for inclusion were RCTs and retrospective studies comparing CMT with CT alone in patients with newly diagnosed DLBCL. The detailed literature search strategy, as well as the relevant inclusion and exclusion criteria, were outlined in the Supplementary Methods section. The study was exempted from review by our Institution Review Committee because it used publicly available data and enrolled no human subjects.

Risk of bias in potentially eligible RCTs was assessed using the Cochrane Collaboration tool, as described previously.[27] RCTs with a high risk of bias in any domain were excluded. The quality of retrospective studies was assessed with a maximum 9-star score, using the Newcastle–Ottawa scale (NOS) of selection, comparability, and outcome.[28] Low to moderate bias hazard studies (≥6 stars) were included in the statistical analyses (Supplemental Table 1).[18,22–24,29–76]

The screening procedure for study inclusion is shown in Fig. 1, and a total of 2615 abstracts were reviewed. After excluding 1999 unqualified records, the full texts of 616 records were reviewed. Then, we excluded 550 non-comparative studies, leaving 66 comparative studies of CMT vs CT alone for the quality assessment. Seven studies were excluded because of high risk of bias. Eventually, 7 RCTs (Supplemental Fig. 1)[10–16] and 52 retrospective studies were included with analyses (Supplemen-

tal Table 2).[18,22–24,29–76] These qualified studies included 2635 patients from RCTs and 10,128 patients from retrospective studies, with a median follow-up time of 2–10 years.

2.2. Studies on the establishment and validation of PFS patterns as prognostic stratification subgroups

In order to explore the PFS patterns as prognostic stratification subgroups, we investigated the correlation between DLBCL risk models and the PFS rate through the establishment of studies focused on DLBCL-specific risk models (Supplemental Table 3).[77–82] The DLBCL risk models included the International Prognostic Index (IPI), the revised IPI (R-IPI), the National Comprehensive Cancer Network (NCCN)-IPI, and the International Metabolic Prognostic Index (IMPI). Additionally, we employed RCTs comparing rituximab-based CT regimens as a validation cohort. These RCTs were updated based on our previous study,[27] and 22 of 29 trials (2 trials underwent second randomization) provided available data for paired PFS and OS rates in correlation analysis, with 49 arms and 14,359 patients (Supplemental Table 4).[7–9,83,84]

2.3. Statistical analysis

The correlation analyses of the enrolled studies were performed at trial and treatment-arm levels. At the trial level, the correlation of HR_{OS} with HR_{PFS} was estimated using the Pearson correlation coefficient r in weighted linear regression. At the treatment-arm level, the linear correlation between PFS and OS rates was also evaluated using the correlation coefficient r. The locally weighted regression (LOESS) model was used to estimate the relationship of CT-generated PFS rate with absolute OS benefit or HR_{OS}. Patients were stratified into four CT-generated PFS patterns (>80%, >60–80%, >40–60%, and ≤ 40%) according to OS benefit gains by linear correlation. The consistency between the stratification by PFS patterns and traditional DLBCL risk models was quantified using Cohen's kappa statistic. In meta-analysis, pooled HR was performed using random-effects models when subset heterogeneity was ≥50%, and fixed-effect models when subset heterogeneity was <50%. To assess the benefit of RT in specific patient subgroups in clinical practice, we conducted subgroup meta-analyses that focused on characteristics including bulky disease status, stage, extranodal involvement, and residual disease after CT. R (version 4.0.3) was used for all statistical analyses.

3. Results

3.1. Correlations between treatment effects of PFS on OS in RCTs

We first determined the treatment effects of PFS on OS in seven RCTs of CMT vs CT alone. At the trial level, there was a strong linear correlation between HR_{PFS} and HR_{OS} ($r = 0.876$, Fig. 2A), indicating that treatment gain of RT in PFS can predict OS benefit with an acceptable consistency. At the treatment-arm level, 5-year PFS rate correlated linearly with relative OS rate, regardless of treatments with CMT and CT ($r = 0.945$; Fig. 2B), CMT ($r = 0.962$, Fig. 2C), or CT alone ($r = 0.964$, Fig. 2D). The RCTs demonstrated that the treatment gains for PFS are of pilot benefit for OS at trial and treatment-arm levels.

3.2. Correlations between treatment effects of PFS on OS in retrospective comparative studies

We then determined the treatment effect of PFS on OS in retrospective comparative studies of CMT vs CT alone. At the trial level, a moderate linear correlation was found between HR_{PFS} and HR_{OS} in all studies ($r = 0.639$, Fig. 3A) and rituximab-based CT studies ($r = 0.650$, Fig. 3B). At the treatment-arm level, there was a strong linear correlation between PFS and OS rates across all treatment settings of CMT and CT ($r = 0.908$, Fig. 3C), CMT ($r = 0.891$, Fig. 3E), and CT alone ($r = 0.882$, Fig. 3G). Similar results were observed in the setting of rituximab-based
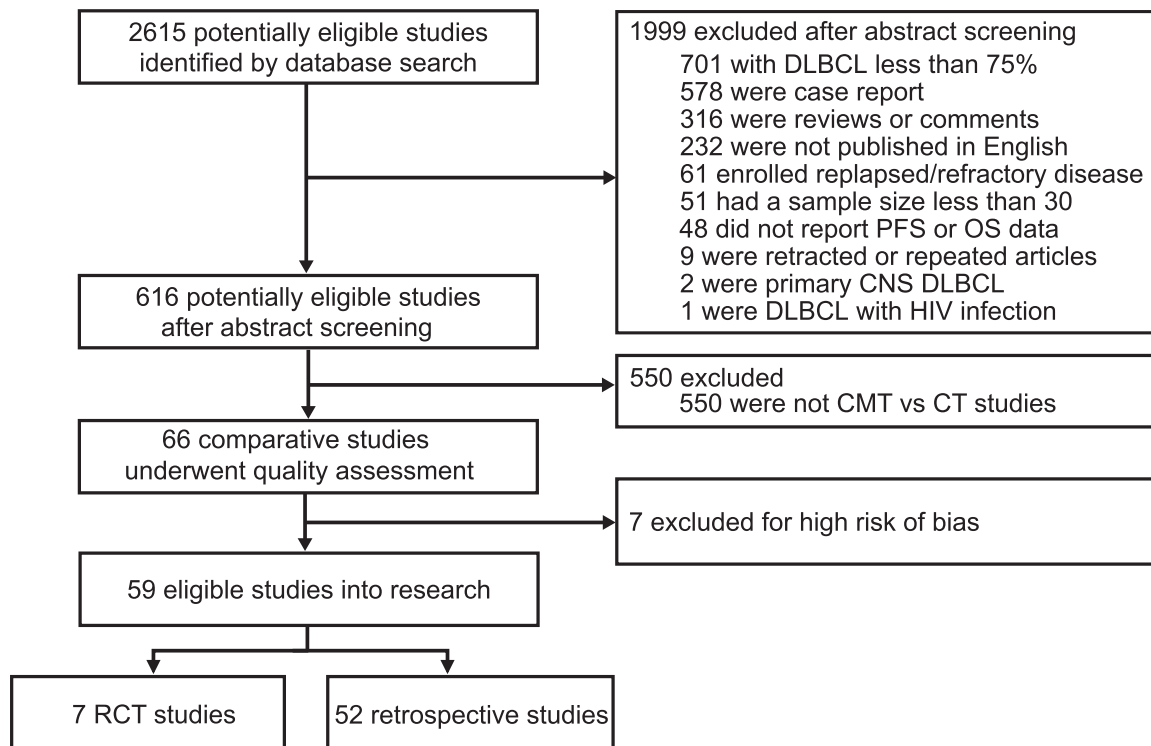
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│    2615 potentially eligible    │        │  1999 excluded after abstract screening        │
│  studies identified by database │        │      701 with DLBCL less than 75%              │
│             search              │        │      578 were case report                      │
└─────────────────────────────────┘        │      316 were reviews or comments              │
                 │                          │      232 were not published in English         │
                 ├────────────────────────▶│      61 enrolled replapsed/refractory disease  │
                 │                          │      51 had a sample size less than 30          │
                 │                          │      48 did not report PFS or OS data           │
                 │                          │      9 were retracted or repeated articles      │
                 │                          │      2 were primary CNS DLBCL                   │
                 │                          │      1 were DLBCL with HIV infection            │
                 ▼                          └──────────────────────────────────────────────┘
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│   616 potentially eligible      │        ┌──────────────────────────────────────────────┐
│  studies after abstract         │        │  550 excluded                                  │
│         screening               │───────▶│      550 were not CMT vs CT studies            │
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│    66 comparative studies       │───────▶│  7 excluded for high risk of bias              │
│  underwent quality assessment   │        └──────────────────────────────────────────────┘
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│  59 eligible studies into       │
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┌──────────────────┐  ┌──────────────────────────┐
│  7 RCT studies   │  │ 52 retrospective studies │
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Fig. 1. PRISMA flowchart showing study inclusion. CMT, combined-modality therapy; CNS, central nervous system; CT, chemotherapy; DLBCL, diffuse large B-cell lymphoma; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial.

CT for CMT and CT ($r = 0.910$, Fig. 3D), CMT ($r = 0.888$, Fig. 3F), and CT alone ($r = 0.892$, Fig. 3H). The retrospective studies further confirmed an association of PFS improvements with higher OS probability.

3.3. Effect of RT on PFS and OS in all RCTs and retrospective comparative studies

We investigated the treatment effect of RT on PFS in all RCTs and retrospective comparative studies of CMT vs CT alone. Frequency distribution of 5-year PFS rates with CT alone followed a normal distribution. There was a shift toward higher PFS rates with CMT, showing a negative-skewed frequency distribution (Fig. 4A and B). The average PFS rate was 79.6% ± 11.7% for CMT compared with 61.6% ± 18.8% for CT alone in all studies (Supplemental Fig. 2A). Similarly, adding RT into rituximab-based CT increased the average PFS rate from 63.6% ± 18.9% for CT alone to 81.5% ± 10.6% for CMT (Supplemental Fig. 2B). RT significantly improved PFS (about 18%), regardless of CT regimens.

To illustrate the relationship between CT-generated PFS rate with absolute OS differences as well as HR_{OS} of CMT vs CT alone for each study, scatter plots was presented and smoothed using the LOESS method (Fig. 4C–F). The squared correlations between the absolute differences in OS and 5-year PFS rates were moderate to good (LOESS $R^2 = 0.508$ in all studies, Fig. 4C; $R^2 = 0.488$ in rituximab-based studies, Fig. 4D). There was a weak squared correlation between HR_{OS} and 5-year PFS rate in all studies ($R^2 = 0.109$, Fig. 4E) and rituximab-based studies ($R^2 = 0.205$, Fig. 4F). The weak correlation observed across the studies indicated a trend toward increased risk of death with decreasing PFS rate. This finding merited further precise risk-benefit evaluation comparing CMT and CT alone.

3.4. Linear association of PFS with OS in risk subgroups by risk model

Previous studies have demonstrated that DLBCL classic risk models were effective to identify the subgroups of patients at high risk of progression or mortality. In this study, at the study-arm level, a strong linear correlation was observed between PFS and OS rates according to the original data from the four risk models (IPI, R-IPI, NCCN-IPI, and IMPI; Supplemental Table 3) ($r = 0.956$, $P < 0.001$; Fig. 5A) and from the IPI model ($r = 0.971$, $P < 0.001$; Fig. 5B).

We further evaluated 5-year PFS after risk stratification. After stratifying by the four classical risk models, the average PFS rates in the low-, low-intermediate-, high-intermediate-, and high-risk subgroups were 87.6% ± 10.1%, 71.0 ± 12.2%, 55.0% ± 7.5%, and 40.0% ± 10.8%, respectively ($r = 0.885$, $P < 0.001$; Fig. 5C). Similarly, after stratifying with the IPI model, the average PFS rates in the corresponding four risk subgroups were 84.3% ± 2.7%, 71.8% ± 6.3%, 58.2% ± 5.9%, and 48.5% ± 7.8%, respectively ($r = 0.925$, $P < 0.001$; Fig. 5D). There was a gradual rise in PFS from high-risk to low-risk subgroups.

3.5. Consistency of risk subgroups with PFS patterns and validation in RCTs of rituximab-based CT regimens

To help relate the effect of RT on PFS to OS, patients were classified into four prognostic patterns according to CT-generated PFS rate: >80%, >60–80%, >40–60%, and ≤40%. Using the Cohen's kappa statistic, substantial consistency was found between the risk subgroups and PFS prognostic patterns (kappa = 0.717, Fig. 5E), and between the IPI-defined risk groups and PFS patterns in the rituximab era (kappa = 0.667, Fig. 5F). These results suggested that survival outcomes could be predicted by both the risk models and CT-generated PFS classification with acceptable agreement.

We then validated this finding in 22 RCTs comparing rituximab-based regimens (Supplemental Table 4). A strong linear correlation between PFS and OS rates was observed at the treatment-arm level ($r = 0.891$, $P < 0.001$; Supplemental Fig. 3A). Furthermore, there was a strong correlation between CT-generated PFS patterns and increasing PFS rates ($r = 0.819$, $P < 0.001$; Supplemental Fig. 3B). The average PFS
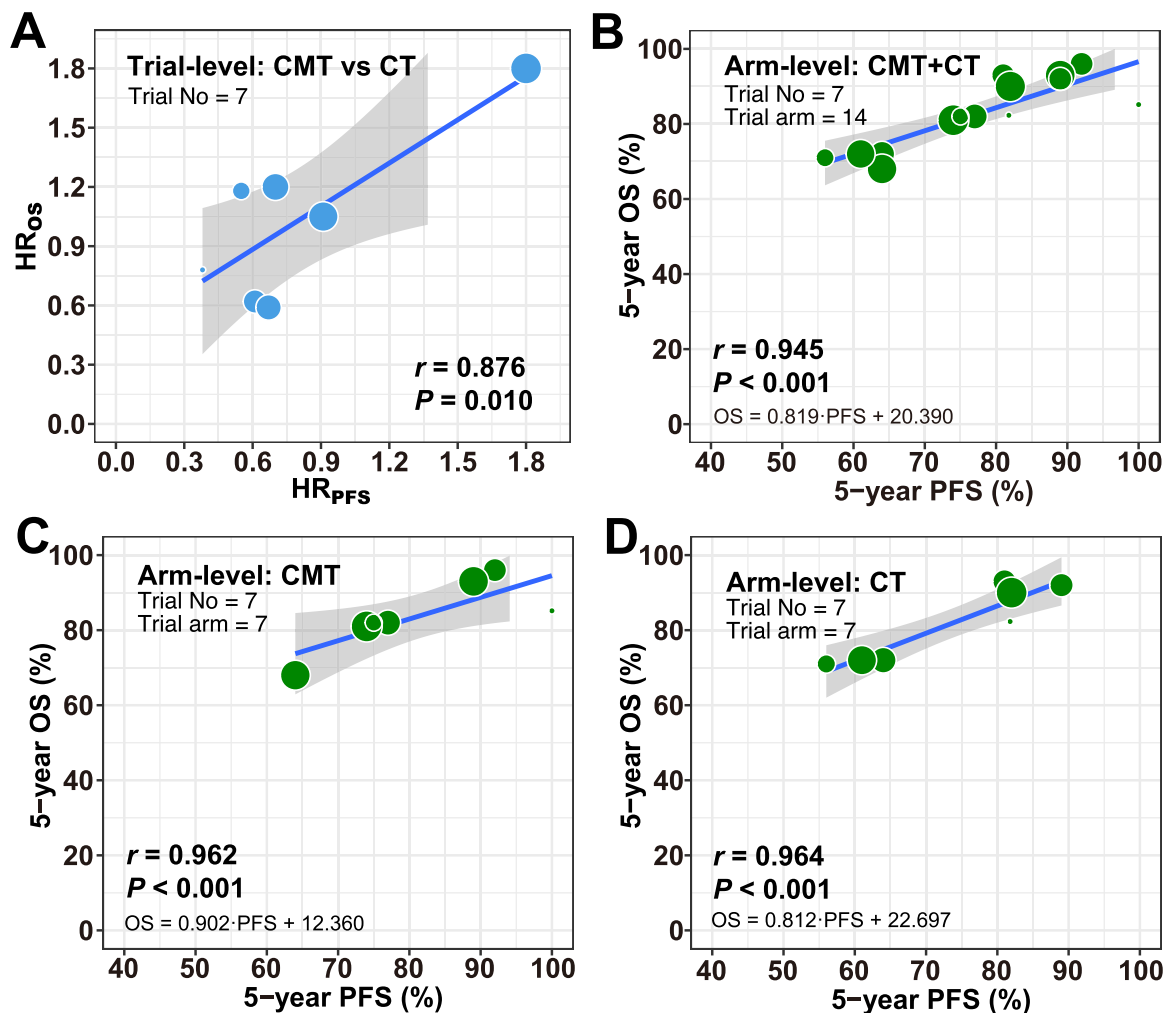
Fig. 2. Correlations between treatment effects on PFS and OS in randomized controlled trials. (A) Trial-level correlations between HR_{PFS} and HR_{OS}. (B–D) Arm-level associations between 5-year PFS and relevant OS rates in the treatment setting of CMT and CT (B), CMT (C), and CT alone (D). Circle size is proportional to the number of patients in each comparison or treatment arm. Blue solid lines represent the fitted weighted linear regression line; shallow dark areas represent their 95% CIs; and r represents the correlation coefficient. CI, confidence interval; CMT, combined-modality therapy; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

rates at PFS >80%, >60–80%, >40–60%, and ≤40% were 86.6% ± 6.3%, 66.7% ± 4.4%, 51.0% ± 3.9%, and 30.0% (one set of data), respectively. These results verified the rationality of PFS prognostic patterns in the modern CT era. In addition, these findings indicated that an association of higher PFS with increased OS probability was not only a feature of comparative studies of CMT vs CT alone, but was also seen in RCTs comparing rituximab-based regimens.

3.6. Effect of RT on OS benefit in a PFS-dependent manner

Finally, we performed an analysis, based on PFS patterns, to identify the subgroups of patients with higher OS benefit from RT. Pooled HR_{OS} for CMT vs CT alone were estimated according to CT-generated PFS patterns (Supplemental Fig. 4 and 5). For all studies (Fig. 6A), the pooled HR_{OS} of CMT vs CT alone in patients with PFS >80%, >60–80%, >40–60%, and ≤40% was 0.79 (95% CI, 0.52–1.20), 0.73 (95% CI, 0.59–0.91), 0.47 (95% CI, 0.32–0.71), and 0.55 (95% CI, 0.41–0.72), respectively. For rituximab-based CT (Fig. 6B), the corresponding pooled HR_{OS} was 0.70 (95% CI, 0.51–0.97), 0.79 (95%CI, 0.67–0.92), 0.37 (95% CI, 0.27–0.50), and 0.48 (95% CI, 0.36–0.63), respectively. Assessments of the risk of bias due to reporting biases revealed no significant asymme-

try, indicating an absence of publication bias during the rituximab era (Supplemental Fig. 6).

The absolute differences in OS between CMT and CT alone increased with decreasing PFS after CT alone, regardless of rituximab. For all studies, the average OS difference between the treatment groups in patients with PFS >80%, >60–80%, >40–60%, and ≤40% was 3.7% ± 5.5%, 8.7% ± 10.7%, 21.0% ± 9.9%, and 21.1% ± 7.6% after rituximab-based CT, respectively (Fig. 6C). For rituximab-based CT, the corresponding OS difference was 5.4% ± 3.5%, 7.6% ± 10.1%, 21.8% ± 9.3%, and 21.7% ± 8.1%, respectively (Fig. 6D). Linear analyses revealed an OS advantage of CMT over CT alone in a PFS-dependent manner (Fig. 6, $r = 0.566$–0.827). OS benefits of RT gradually decreased with increasing PFS rates.

3.7. Subgroup meta-analysis of clinical characteristics

To assess the benefit of RT in specific subgroups of patients in clinical practice, we conducted meta-analyses for each subgroup. These analyses focused on characteristics including bulky disease, stage, extranodal involvement, and residual disease after CT. The detailed results are presented in Supplemental Table 5 and Supplemental Fig. 7–14. Our analyses revealed that adjuvant RT appears to benefit patients with DLBCL
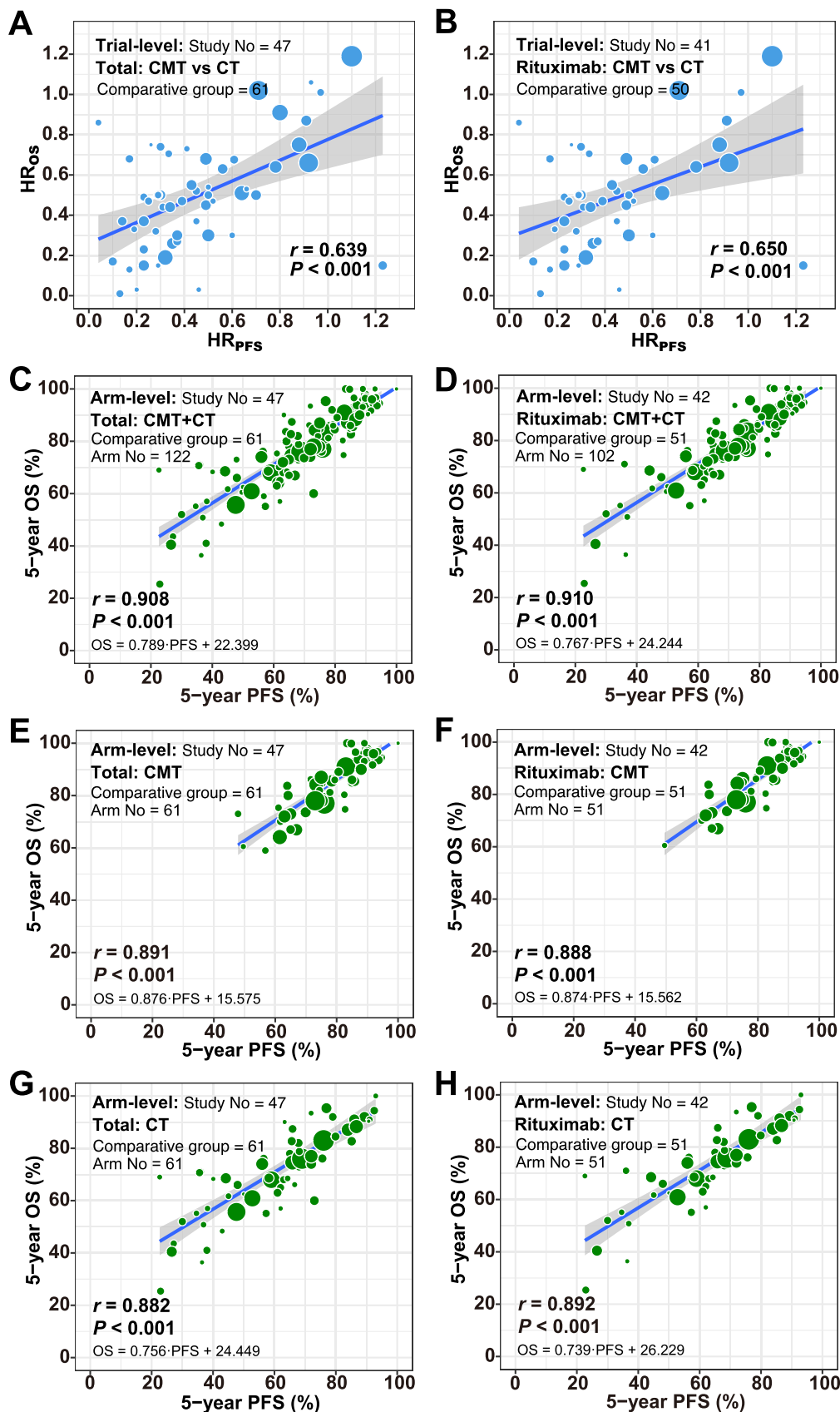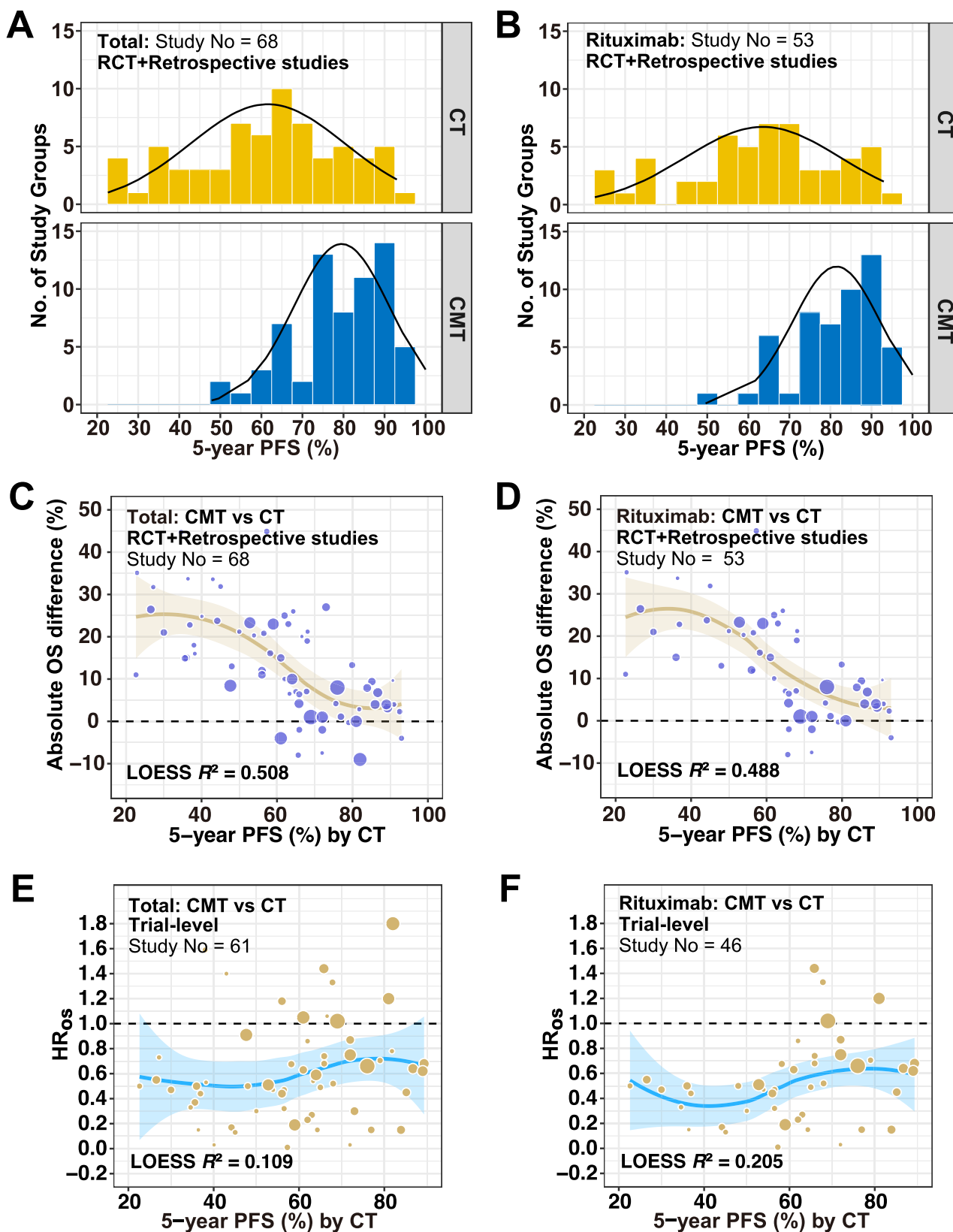
Fig. 3. Correlations of treatment effects on PFS and OS in retrospective comparative studies. (A and B) Trial-level correlations between HR_{PFS} and HR_{OS} in all studies (A), and in rituximab-based CT studies (B). (C–H) Arm-level associations between 5-year PFS and 5-year OS rates the treatment setting of CMT and CT (C), CMT (E), and CT alone (G), for all studies. Arm-level associations between 5-year PFS and 5-year OS rate in the treatment setting of CMT and CT (D), CMT (F), and CT alone (H), for rituximab-based CT studies. Circle size is proportional to the number of patients in each comparison or treatment arm. Blue solid lines represent the fitted weighted linear regression line; shallow dark areas represent their 95% CIs; and r represents the correlation coefficient. CI, confidence interval; CMT, combined-modality therapy; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

Fig. 4. Effect of RT on PFS and OS in all RCTs and retrospective comparative studies. (A and B) Frequency distribution of PFS in CMT and CT in all studies (A), and in rituximab-based CT studies (B). (C and D) The LOESS model showed a good inverse S-curve between absolute OS differences (CMT vs CT) and CT-generated PFS rate in all studies ($R^2 = 0.508$; C), and in rituximab-based CT studies ($R^2 = 0.488$; D). (E and F) The LOESS model showed weak squared correlations between HR_{OS} (CMT vs CT) and CT-generated PFS rate in all studies ($R^2 = 0.109$; E), and in the rituximab-based CT studies ($R^2 = 0.205$; F). Solid central curves were smoothed based on the LOESS regression with 95% CI in the shaded regions. Circle size is proportional to the number of patients in each comparison or treatment arm. R^2 represents the determination coefficient of LOESS regression. CI, confidence interval; CMT, combined-modality therapy; CT, chemotherapy; HR, hazard ratio; LOESS, locally weighted regression; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RT, radiotherapy.
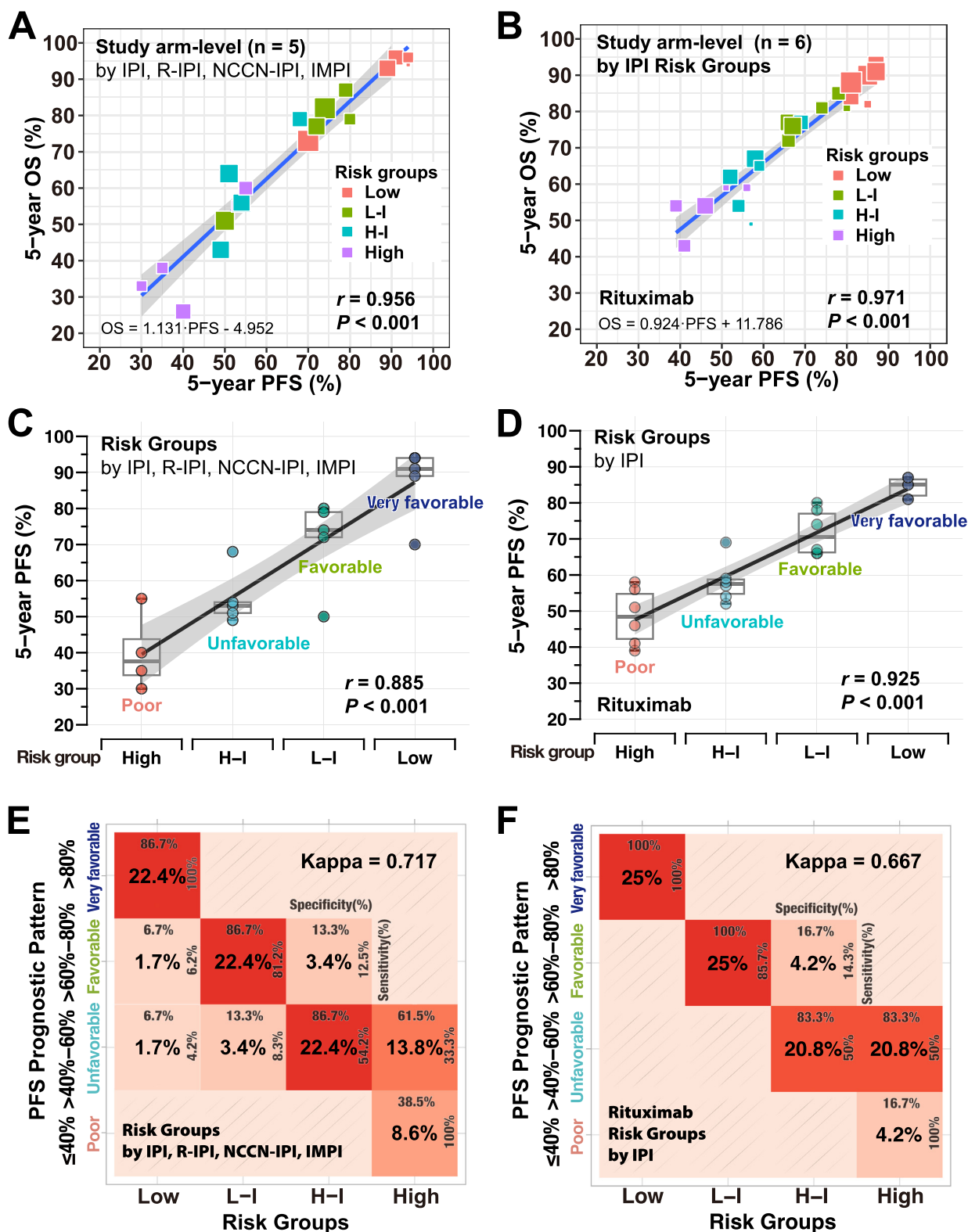
Fig. 5. Linear association of PFS with OS in risk-stratified subgroups and consistency of risk-stratified subgroups with PFS prognostic patterns. (A and B) At study-arm level, linear regression revealed strong correlations between PFS and OS rates according to the IPI, R-IPI, NCCN-IPI, and IMPI (A), and the IPI in the setting of rituximab-based CT (B). (C and D) There were strong linear correlations between PFS rates and four risk-stratified subgroups according to the IPI, R-IPI, NCCN-IPI, and IMPI (C), and the IPI in the setting of rituximab-based CT (D). (E and F) There was substantial consistency between CT-generated PFS prognostic pattern (>80%, >60–80%, >40–60%, and ≤40%) and risk-stratified subgroups (low, L-I, H-I, high) according to the IPI, R-IPI, NCCN-IPI, and IMPI (kappa = 0.717; E), and the IPI in the setting of rituximab-based CT (kappa = 0.667; F). The central number in each cell (E and F) indicated the consistency percentage between risk-stratified subgroups and PFS prognostic patterns; the numbers located at the edges of each cell represent the relevant specificity and sensitivity. CMT, combined-modality therapy; CT, chemotherapy; H-I, high-intermediate risk subgroup; IMPI, International Metabolic Prognostic Index; IPI, International Prognostic Index; L-I, low-intermediate risk subgroup; NCCN-IPI, National Comprehensive Cancer Network IPI; OS, overall survival; PFS, progression-free survival; R-IPI, Revised International Prognostic Index.
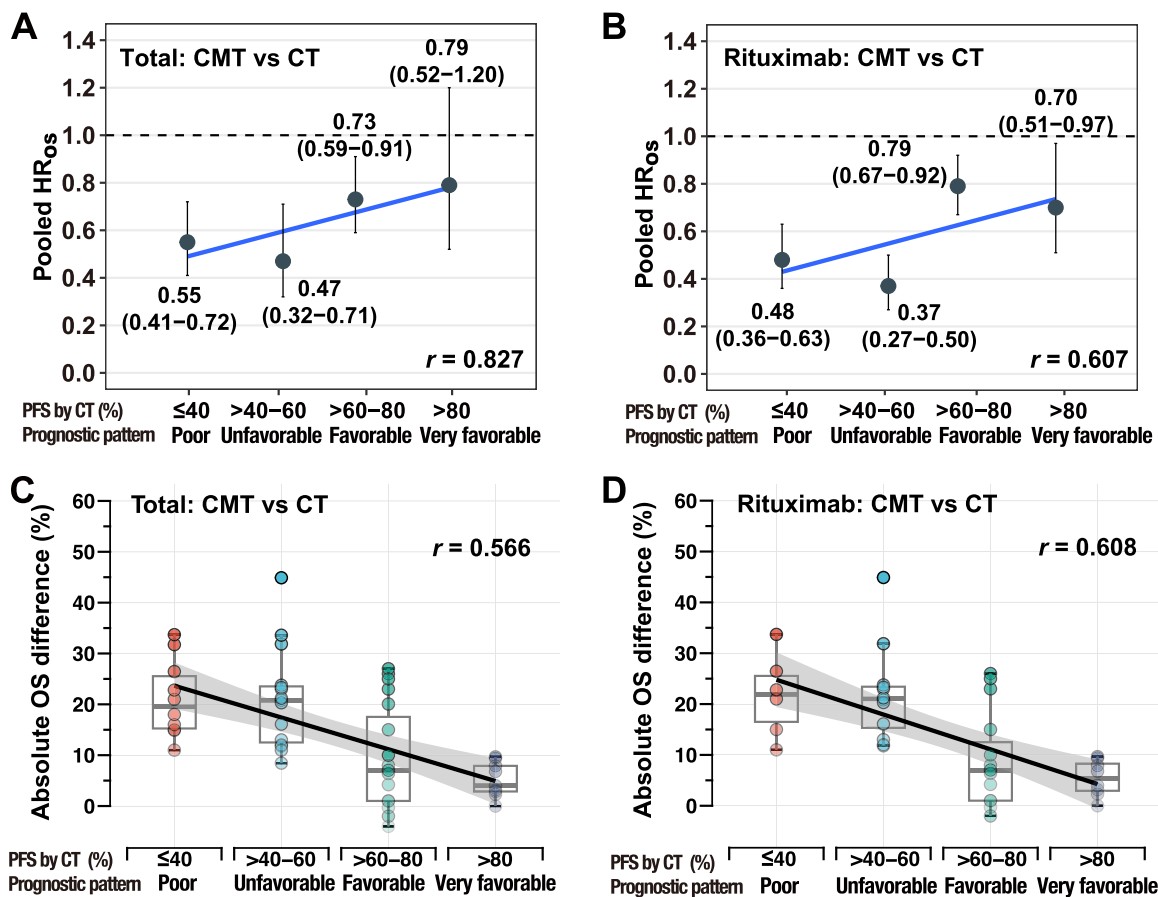
Fig. 6. Treatment effect of RT on OS according to CT-generated PFS prognostic pattern. (A and B) The pooled HR_{OS} of CMT vs CT alone according to CT-generated PFS prognostic pattern in all studies (A), and in the setting of rituximab-based CT (B). (C and D) The association of absolute OS differences between CMT and CT alone according to CT-generated PFS prognostic pattern in all studies (C), and in the setting of rituximab-based CT (D). CMT, combined-modality therapy; CT, chemotherapy; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

across most subgroups, except non-bulky disease and nodal involvement subgroup in the rituximab-era.

4. Discussion

Prediction and refinement of RT efficacy and benefit are challenging in the management of DLBCL. This large-scale study combined qualified comparative studies of CMT vs CT alone to assess the survival benefit of RT. Improved PFS and prolonged OS were correlated at trial level and treatment-arm level, regardless of CT regimens. The linear correlation between PFS and OS rates was also verified using independent data from the prognostic models and RCTs comparing rituximab-based CT regimens. Patients can be readily classified into four CT-generated PFS patterns: >80%, >60–80%, >40–60%, and ≤40% for prognosis. OS benefit of RT was predominant in patients at intermediate and high risk of progression (PFS ≤ 80%), but very limited in those at low risk of progression (PFS > 80%). Given an acceptable consistency between risk stratification models and PFS patterns, traditional DLBCL models such as IPI can continue to be employed for guiding the selection of RT for newly diagnosed patients in the absence of other clear risk factors. Our results provide useful information for evaluating the risks and benefits of RT as part of a treatment strategy, as well as indications for further investigation.

Owing to a lack of high-level evidence, the use of RT in DLBCL treatment varied between institutions. The commonly adopted parameters for RT prescription in clinical practice are disease related or CT-response related. To our knowledge, this is the first hypothesis-driven study to assess the risk-benefit profile of RT in the modern era. We confirmed

markedly variable survival outcomes in DLBCL. The OS benefit of adjuvant RT varied, mainly depending on PFS rates after CT alone. Absolute gains in OS from RT ranged from around 5% at PFS >80% to around 21% at PFS ≤40%, with HR_{OS} ranging from 0.70 (95% CI, 0.51–0.97) to 0.48 (95% CI, 0.36–0.63). The efficacy of RT was mainly influenced by PFS prognostic pattern or risk stratification. Adding RT into CT did not significantly affect the outcome of low-risk patients with very favorable prognoses (PFS > 80%) following CT alone as much as expected. However, the results emphasized the importance of RT to intermediate- and high-risk patients with unfavorable prognoses (PFS ≤ 80%). Patients in each prognostic pattern may require different treatment strategies to optimize outcome. Moreover, we included the seven high-risk studies previously excluded (Supplemental Table 6) in a sensitivity analysis. Our findings indicate that the inclusion of these studies did not impact the overall results or conclusions.

We demonstrated that low-risk patients with PFS >80% have very favorable prognoses, with 5-year OS exceeding 90%. These patients at low-risk of progression who achieved adequate response to rituximab-based CT are candidates for RT omission. Currently, 4–6 cycles (even 4 cycles) of R-CHOP with or without RT resulted in similarly excellent outcomes in RCTs[10,11,20] and single-arm prospective studies.[21,85] All these trials were restricted to low-risk or intermediate-low-risk patients with stage- or age-adjusted IPI 0–1.[10,11,20,21,85] However, low-risk patients had very limited room for further improvement in OS from the addition of RT. Given the few events with immunochemotherapy, a larger sample size of low-risk patients is required to achieve the statistical power to see an explicit benefit from RT.[10,11] Considering that continued risk of relapse can occur in early-stage patients,[12] further study is needed

to evaluate the long-term outcomes of a de-escalated treatment strategy for low-risk patients. The addition of RT in low-risk patients should be discussed with the patients, taking into consideration their unique clinical characteristics and any associated risk factors.

The results of this study contribute to the ongoing development of an evidence-based approach for identifying intermediate- and high-risk patients with DLBCL. The OS benefit of RT was more apparent in patients with PFS ≤80% after CT alone. The difference in the survival benefits of RT between studies can be attributed to the presence of adverse clinical features that constitute the IPI model, but also to other factors.[17,22,23,29,35,36,73] Although not integrated into the IPI model, bulky and extranodal disease were identified as adverse factors, indicating a potential benefit of RT.[22–24] Recent studies demonstrated that interim or post-CT FDG-PET scan can discriminate patient prognoses, guiding the use of RT.[24,47,86] Freeman et al provide valuable benchmark data for PET-negative DLBCL patients, yet at least 25% of these patients still progress despite achieving a complete metabolic response (CMR) on end-of-treatment PET.[47] This underscores the relevance of considering adjuvant RT for these patients, given the poor prognosis of relapsed DLBCL after R-CHOP. The study's population-based, non-randomized approach and the heterogeneity among PET-negative patients suggest the need for a tailored strategy.[47] In fact, the role of adjuvant RT in DLBCL patients who achieve CMR after CT remains controversial. The survival benefit of RT for intermediate- and high-risk patients who have a complete response or a CMR has been confirmed in some studies,[14,29,35,45,68] but not in others.[24,47,64,66,71,87–90] Particularly for primary mediastinal B-cell lymphoma (PMBCL), recent studies suggest that RT may not be necessary for patients who achieve CMR.[87–90] Importantly, it is often observed that the PFS rates for these PMBCL patients exceed 90%. Based on these findings, an RT benefit in patients with unfavorable prognoses (PFS ≤ 80%) requires urgent confirmation in RCTs.

The strengths of this study include its quality controlled design, large sample size, and attention to risk-benefit analysis. First, the data were obtained from RCTs and retrospective studies comparing CMT vs CT alone that enrolled large-scale cohorts (12,763 patients). The positive relationships between the HR_{PFS} and HR_{OS}, as well as the PFS and OS rates, were demonstrated using patient data across different countries, CT regimens, and follow-up times. The diversity of inclusion eligibility and RT use between studies reflected general practice and allowed for a broad risk-benefit assessment of RT. Moreover, as CMT vs CT alone was investigated in heterogeneous studies, we were able to re-examine for variability in treatment outcomes, improving the generalizability of our study. Second, the generation of PFS patterns for describing the OS benefit profile of RT is unique. This design reinforces the role of risk-adapted RT for patients with different PFS rates after immunochemotherapy.

There are limitations to this study. First, CT regimens were not uniform in the RCTs of CMT vs CT alone, and treatments in retrospective studies were selected by physicians based on clinical features and other unknown but potentially confounding considerations. Primary refractory DLBCL patients typically do not receive RT according to the physician's discretion. This selection bias of retrospective studies can lead to an overestimation of the benefits of RT. Second, the current management of DLBCL has undergone a paradigm shift with the approval of novel agents in the upfront and salvage setting.[9] This might impact the possible PFS benefit translating into OS with utilizing RT in the contemporary era. As observed in the POLARIX trial, successful novel salvage treatments such as bispecifics and CAR-T cells may decrease the strong association between HR for PFS and OS.[9] Thirdly, this is a literature-based data analysis without individual patient data; therefore, risk-benefit assessment of RT at individual patient level was absent. In addition, as the studies analyzed span across decades, PET imaging and Lugano response criteria were not routinely used. This could have potentially impacted the results with respect to implementation of RT in the modern era. Finally, as with every hypothesis-driven study, we must be careful not to overinterpret the data and to rather use it for hypothesis generation to be tested in future RCTs. Further study is needed to search for a specific risk-adapted RT model with the integration of clinical factors and biomarkers, to identify which patients will benefit from RT.

In conclusion, this study confirms an increasing OS benefit of RT over declining PFS after CT in the treatment of DLBCL, and provides valuable data for predicting and optimizing outcomes with therapeutic implications. The use of RT needs careful tailoring in both clinical practice and in RCTs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets used and/or analyzed during the current study are available in the supplemental materials.

Author contributions

S.Q. and Y.L. designed the research. Y.L., S.Q., X.L., C.H., J.W. and Y.W. collected and analyzed data. J.W., X.L., Y.W., S.Q., and Y.L. wrote the paper. All authors discussed the results, given comments, and approved the paper.

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2024.04.002.

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