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Primary Tumor Standardized Uptake Value Measured on F18-Fluorodeoxyglucose Positron Emission Tomography Is of Prediction Value for Survival and Local Control in Non–Small-Cell Lung Cancer Receiving Radiotherapy

Meta-Analysis

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Introduction: The 2-[18F]-Fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) has become an imaging tool for clinical assessment of tumor, node, metastasis in non–small-cell lung cancer (NSCLC). Primary tumor maximum standardized uptake value (SUV_{max}) on ^{18}F-FDG PET/CT before and after radiation therapy (RT) has been studied as a potential prognostic factor for NSCLC patients receiving radiotherapy. However, the sample sizes of most studies were small, and the results of the prediction value of SUV_{max} remained undetermined, which lead us to perform a meta-analysis to improve the precision in estimating its effect.

Methods: We performed a meta-analysis of published literature for primary tumor SUV_{max}-based biomarkers of the outcome of NSCLC receiving radiotherapy. The required data for estimation of individual hazard ratios (HRs) to compare patients with a low and a high SUV_{max} were extracted from each publication. A combined HR was calculated by Stata statistical software (Version 11). All of the results were verified by two persons to ensure its accuracy.

Results: Thirteen studies were finally included into this meta-analysis; data are available in 13 studies for pre-RT primary tumor SUV_{max} and in five studies for post-RT. For overall survival, the combined HR estimate was 1.05 (95% confidence interval [CI], 1.02–1.08) and 1.32 (95% CI, 1.15–1.51) for pre-RT SUV_{max} and post-RT SUV_{max}, respectively; 1.26 (95% CI, 1.05–1.52) and 2.01 (95% CI, 1.16–3.46) for local control (LC). In stereotactic body radiotherapy (SBRT) group, HR for LC was 1.11 (95% CI, 1.06–1.18) and 2.19 (95% CI, 1.34–3.60) for pre-SBRT SUV_{max} and post-SBRT SUV_{max}, respectively.

Conclusion: Both pre-RT and post-RT primary tumor SUV_{max} can predict the outcome of patients with NSCLC treated with radiotherapy. Patients with high levels of pre-RT SUV_{max} seemed to have poorer overall survival and LC.

Key Words: Primary tumor maximum standardized uptake value, Prognosis, Non–small-cell lung cancer, Meta-analysis, Radiotherapy.

(*J Thorac Oncol*. 2014;9: 834–842)

Lung cancer is the leading cause of cancer-related death worldwide.[1] Non–small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers. NSCLC is often treated with a combination of multiple types of therapies, including radiation therapy (RT). The dose limitation and therefore therapeutic efficacy of RT have been addressed by recent progresses, including stereotactic body radiotherapy (SBRT) and image-guided and intensity-modulated radiotherapy.[2] For inoperable patients with early stage NSCLC, SBRT presents as a new standard treatment. Despite these improvements, the 5-year survival rate is generally approximately 15%,[3] and somewhat higher at 17% to 47%[4] in patients with early stage NSCLC.

Information about reliable prognostic factors for RT responses (and prognosis in general) is essential in identifying subjects suitable for aggressive RT treatment. The most commonly used factor for predicting RT responses is the tumor-node-metastasis (TNM) stage.[5] Weight loss,[6] performance status,[6] and molecular markers[7,8] were reported to predict the outcome and could be used to stratify patients for the most optimal strategy for RT but require further validation.[9] Morphologic changes as reflected by computed tomography (CT) have also been identified as prognostic factors, but technical issues remain (e.g., it is also difficult to differentiate residual tumor from necrosis or fibrosis).[10,11]

A variety of imaging methods has been developed to examine tumor metabolism.[12–14] For example,

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/14/0906-0834

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is becoming the standard practice for staging and is widely used in post-treatment evaluation of various types of cancer, including breast cancer, lymphoma, head and neck cancer, and NSCLC.[15–18] For NSCLC, ^{18}F-FDG PET/CT has been found useful for diagnosing, restaging at recurrence,[19] delineating radiotherapeutic targets,[20] and evaluating radiotherapeutic or chemotherapeutic effects.[19–21] Maximum standardized uptake value (SUV_{max}) derived from ^{18}F-FDG PET/CT has been reported by some,[22–24] but not all,[25,26] to predict the responses to RT in patients with NSCLC.

In the current study, we systematically reviewed available information of all published studies of primary tumor SUV_{max} of NSCLC. Potential prognostic value of primary tumor SUV_{max} in predicting RT responses was examined using meta-analysis.

MATERIALS AND METHODS

Search Strategy and Eligible Criteria

The PubMed database was searched (updated on April 3, 2013) used the following terms: (non–small cell lung cancer OR NSCLC) AND (PET imaging tomography OR positron emission tomography OR PET OR ^{18}F-FDG OR fluorodeoxyglucose) AND (prognostic OR survival OR prognostic factor OR outcome OR predict) AND ("radiotherapy"[Mesh] OR radiotherapy OR irradiation). References cited by the articles identified in the electronic search were also reviewed. Conference Abstracts were not included in the search because of a lack of meta-analysis. When the same patient population was reported in more than one article, only the most recent or complete report was included in the final analysis.

This meta-analysis was limited to the studies on prognostic implications (for either overall survival [OS] or local control [LC]) of primary tumor SUV_{max}, as examined using ^{18}F-FDG PET/CT, in NSCLC patients receiving RT. Case studies and review articles were not included. Studies using prognostic indexes other than OS or LC were also not included.

Data Extraction

Information was independently extracted by two investigators (FFN and CL), and it included authors, publication year, source of patients, sample size, main primary tumor SUV_{max} characteristics, tumor stage, treatment strategy, and survival information (Table 1). OS was defined as the period from the date of enrollment to the date of death. LC was defined as the time between diagnosis and the first local-regional failure.

Study Quality Control

The Newcastle–Ottawa Quality Assessment Scale[27] was used to assess the methodological quality of the meta-analysis; each study was reviewed by two independent reviewers (FFN and CL). A "star system" is used to obtain the score. Briefly, each study was judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest. The number of total stars was used to reflect the quality of the included studies. The evaluation was performed by two investigators independently (FFN and CL).

Statistical Analysis

Stata statistical software Version 11.0 software (Stata Corporation, College Station, TX) was used to perform this meta-analysis. For OS and LC, hazard ratios (HRs) with 95% confidence interval (95% CI) were calculated. The inter-study heterogeneity was evaluated with the Cochrane's Q test ($\alpha = 0.05$) as well as I^2.[28] A fixed effects model (Mantel–Haenszel method) was used to analyze the data as to whether there was no significant heterogeneity; otherwise, a random effects model was used according to the DerSimonian–Laird method.[29] Publishing bias was tested with the Begg's and Egger's bias indicator test.

HR and 95% CI were directly extracted from the studies that used a multivariate survival analysis[22,23,30–35] or univariate analysis.[25,26,36,37] If the HR was not given explicitly,[24] p value and total events were used to calculate the HR based on a method reported by Tierney et al.[38] The final combination of HR was the effect value to show the prognostic significance.

A sensitivity analysis was performed by including only studies of the highest quality (with seven or more stars) or with similar cutoffs.

RESULTS

Study Identification and Quality

The literature search identified 234 relevant studies, among which 170 studies were eliminated from further analysis by the screening based on title/abstract review and supplemental author searches. The full texts of the remaining 64 articles were retrieved. Careful review of the full text eliminated 51 articles because of a lack of sufficient data (Fig. 1). The final analysis included 13 articles, and, according to the sequence of ^{18}F-FDG PET/CT and RT performing, they were divided into two groups: pre-RT primary tumor SUV_{max} and post-RT primary tumor SUV_{max}. Five of the 13 studies had available data for both pre-RT SUV_{max} and post-RT SUV_{max}; the remaining eight studies only had pre-RT SUV_{max} data. The quality of the included studies is shown in Table 1. The quality score ranged from 6 to 8 with a median of 7.38; all 13 studies satisfied most of the items and reported all of the assay method and confounders. Assessment of outcome was the worst described item.

Characteristics of the Included Studies

The basic characteristics of the included studies are summarized in Table 1. Studies are listed twice if they provided survival data for both pre-RT and post-RT. All the studies were published during a period from 2005 to 2013. The sample size ranged from 46 to 132.

All 13 studies reported pre-RT SUV_{max}. In the eight studies (657 patients) that reported OS, three claimed significant positive predict value of OS for RT. In the seven studies (530 patients) that reported LC, three claimed predict effect of LC for RT.

TABLE 1. Characteristic and Results of Eligible Prognostic Studies Evaluating NSCLC Surviving

				The Characteristics of Primary Tumor SUV									
First Author	Year	Treatment	No. of Patients	Technique	Type of SUV	Correction of SUV	SUV Threshold	Stages	OS/LC	HR Estimate	HR	95% CIs	Study Quality/ Stars
Pretreatment													
Clarke[22]	2012	SBRT (50–60 Gy)	82	F18-FDG PET/CT	SUV_{max}	Body weight	5	T1-2N0M0	LC:U+M	HR	1.11	1–1.12	7
Takeda[23]	2011	SBRT (40–50 Gy)	97	F18-FDG PET/CT	SUV_{max}	Body weight	6	T1-4N0M0	LC:U+M	HR	2.688	1.417–5.1	7
Sasaki[24]	2005	CRT (55–66 Gy)	69	F18-FDG PET/CT	SUV_{max}	Body weight	5	Stage I–III	LC:U	events	6.66	2.56–16.66	7
Lopez Guerra[25]	2012	CRT (66 Gy)	49	F18-FDG PET/CT	SUV_{max}	NR	14	Stage III	LC:U	HR	1.01	0.92–1.11	7
									OS:U		1.03	0.97–1.1	
Zhang[26]	2011	SBRT (50 Gy)	68	F18-FDG PET/CT	SUV_{max}	Body weight	5	Stage I	LC:U	HR	6.5	0.5–32.6	7
Zhang[26]	2011	SBRT (50 Gy)	60	F18-FDG PET/CT	SUV_{max}	Body weight	5	NR	LC:U	HR	5.8	0.4–28.9	6
Satoh[30]	2011	SBRT (48–72 Gy)	57	F18-FDG PET/CT	SUV_{max}	Body weight	NR	Stage I	LC:U+M	HR	1.129	0.973–1.311	7
									OS:U+M		1.018	0.838–1.235	
Lee[31]	2013	SBRT (45–60 Gy)	48	F18-FDG PET/CT	SUV_{max}	Body weight	6.8	T1-2AN0M0	LC:U+M	HR	4.48	0.427–42.91	7
Zhang[32]	2010	CRT (60–65 Gy)	46	F18-FDG PET/CT	SUV_{max}	Body weight	9.8	Stage III	OS:U+M	HR	10.56	8.76–12.36	6
Yan[33]	2011	CRT	120	F18-FDG PET/CT	SUV_{max}	Body weight	13	Stage III–IV	OS:U+M	HR	1.041	0.962–1.078	6
Chang[34]	2012	SBRT (50 Gy)	130	F18-FDG PET/CT	SUV_{max}	NR	6.2	Stage I	OS:U+M	HR	2.15	1.06–4.34	7
Borst[35]	2005	CRT (77 Gy)	51	F18-FDG PET/CT	SUV_{max}	Body weight	15	Stage I–III	OS:U+M	HR	1.06	1.02–1.1	7
Vikram Rao[36]	2012	SBRT (60 Gy)	132	F18-FDG PET/CT	SUV_{max}	Body weight	5	Stage I	OS:U+M	HR	4.4	0.5–35	7
Burdick[37]	2010	SBRT (50–60 Gy)	72	F18-FDG PET/CT	SUV_{max}	Body weight	5	T1-2N0M0	OS:U	HR	1.32	0.587–2.99	8
Post-treatment													
Clarke[22]	2012	SBRT(50–60 Gy)	82	F18-FDG PET/CT	SUV_{max}	Body weight	5	T1-2N0M0	LC:U+M	HR	1.68	0.92–3.06	7
Lopez Guerra[25]	2012	CRT (66 Gy)	49	F18-FDG PET/CT	SUV_{max}	NR	14	Stage III	LC:U	HR	1.01	0.92–1.11	7
									OS:U		1.03	0.97–1.1	
Zhang[26]	2011	SBRT (50 Gy)	68	F18-FDG PET/CT	SUV_{max}	Body weight	5	Stage I	LC:U	HR	3.00	1.00–7.9	7
Zhang[26]	2011	SBRT (50 Gy)	60	F18-FDG PET/CT	SUV_{max}	Body weight	5	NR	LC:U	HR	3.30	0.9–10.4	6
Zhang[32]	2010	CRT (60–65 Gy)	46	F18-FDG PET/CT	SUV_{max}	Body weight	9.8	Stage III	OS:U+M	HR	10.56	8.76–12.36	6
Vikram Rao[36]	2012	SBRT (60 Gy)	132	F18-FDG PET/CT	SUV_{max}	Body weight	5	Stage I	OS:U+M	HR	4.4	0.5–35	7
									LC:U+M	HR	7.4	1.4–38.5	7

N, number; SUV_{max}, maximum standardized uptake value; NSCLC, non–small-cell lung cancer; SBRT, stereotactic body radiotherapy; CRT, conventional radiotherapy; OS, overall survival; LC, local control; NR, not reported; HR, hazard ratio; CI, confidence interval; U, univariate analysis; M, multivariate analysis; F18-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

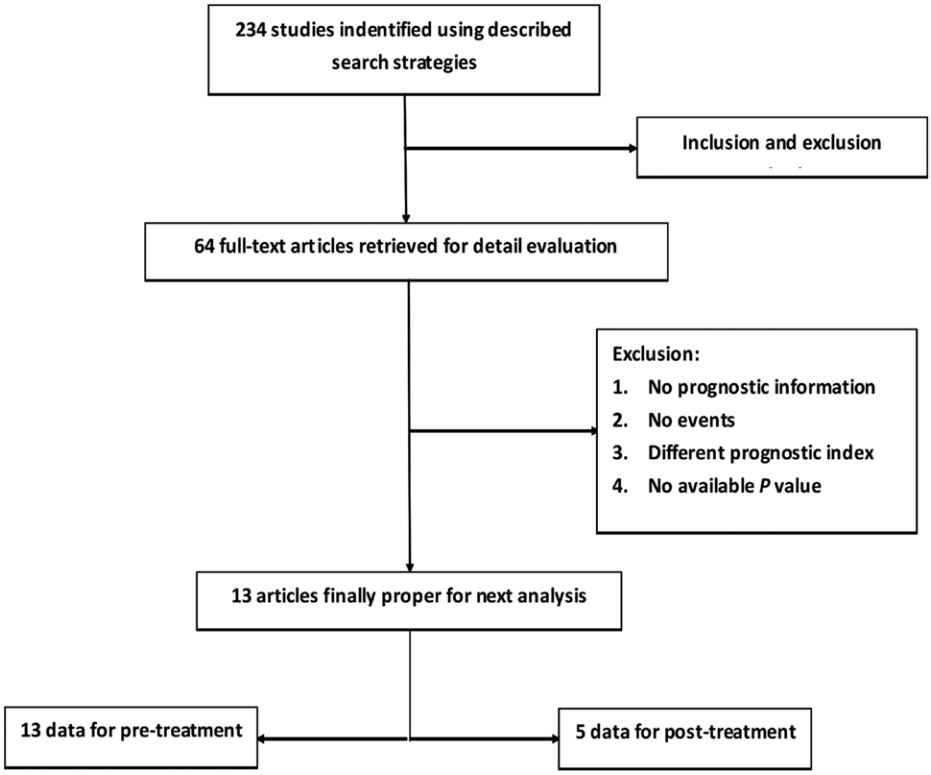

FIGURE 1. Flow diagram of the literature search strategy and assessment of studies identified for meta-analysis.

Post-RT SUV_{max} was described in five studies (all five also described Pre-RT SUV_{max}). In the three studies (227 patients) that reported OS, two claimed that primary tumor SUV_{max} could predict OS for RT. In the four studies (391 patients) that reported LC, three claimed significant positive predict value on LC for RT.

Tumor stage and RT regimen were described in most studies (Table 1). In the analysis of pre-RT SUV_{max}, seven studies (54.5% of the total patients) focused on patients with stage I tumor; all these patients were treated with SBRT, for a total dose of 40 to 70 Gy. In the six remaining studies, the tumor stage was variable: stage I to III (n = 3), stage III (n = 2), stage III to IV (n = 1), and not given (n = 1), and the patients received conventional radiotherapy (CRT) with a total dose of 55 to 77 Gy. In post-RT primary tumor SUV_{max}, two studies included patients with stage III tumor, whereas the remaining three reports focused on stage I tumor and SBRT.

In all 13 studies included in the meta-analysis, all patients had fasted for at least 6 hours before PET/CT scanning and had a measured blood sugar level approximately 130 to 2000 mg/dl at the time of injection. The threshold level was 150 mg/dl[24–26,30,34] in five studies, 200 mg/dl in three,[23,33,36] 130 mg/dl[31] in one, 175 mg/dl[22] in one, and not given in the other three publications.[32,35,37] All the studies obtained emission and transmission scans 60 minutes after the injection of ^{18}F-FDG; however, the dose of ^{18}F-FDG varied across the studies: 5 MBq/kg in three studies,[22,35,36] 10 to 20 mCi in four,[26,33,34,37] 10 to 15 mCi in three,[25,31,32] and 3,[30] 3.5,[23] and 7.4 MBq/kg[32] in the remaining three studies, respectively. Primary tumor SUV_{max} was normalized by body weight in all studies to minimize the partial volume effect.

"High" primary tumor SUV_{max} correlated with the outcome. The cutoff for primary tumor SUV_{max} ranged from 5 to 15 and was chosen with varying methods across the studies: four using the median SUV_{max} of the study sample, four using receiver-operating characteristic curve analysis, one referring to the validation results from another article, and one determined by log-rank test, and not described in the remaining two articles. Optimal timing of ^{18}F-FDG PET/CT after the treatment also varied considerably: 12 weeks (n = 2), 10 weeks (n = 1), 8 to 24 weeks (n = 1), and not described in the remaining one study.[32]

Meta-Analysis

The analysis was performed separately for pre-RT SUV_{max} and post-RT SUV_{max}. The OS and LC data of both groups were analyzed. Eight studies reported pre-RT SUV_{max} and OS[25,30,32,33–37]; seven reported pre-RT SUV_{max} and LC[22,23,25,26,30–32]; three reported post-RT SUV_{max} and OS[25,32,36]; and four studies reported post-RT SUV_{max} and LC.[22,25,26,36] Pooled HRs was then calculated for all groups.

Higher pre-RT SUV_{max} was correlated with shorter OS (pooled HR, 1.69; 95% CI, 1.82–2.42). The heterogeneity was significant (I^2 statistic = 99%, $P_{heterogeneity}$ = 0.000). A forest plot attributed most of the heterogeneity to one study.[32] Reanalyzing the data after exclusion of this article (I^2 statistic = 11.9%, $P_{heterogeneity}$ = 0.339) using a fixed effects model reduced the HR (fixed model) to 1.05 (95% CI, 1.02–1.08) (Fig. 2*A*). Sensitivity analysis (by excluding studies with or below six stars) revealed a combined HR at 1.05 (95% CI, 1.02–1.09) without heterogeneity (I^2 = statistic 25.2%, $P_{heterogeneity}$ = 0.245), indicating that the sensitivity is low and the result is more robust and credible.

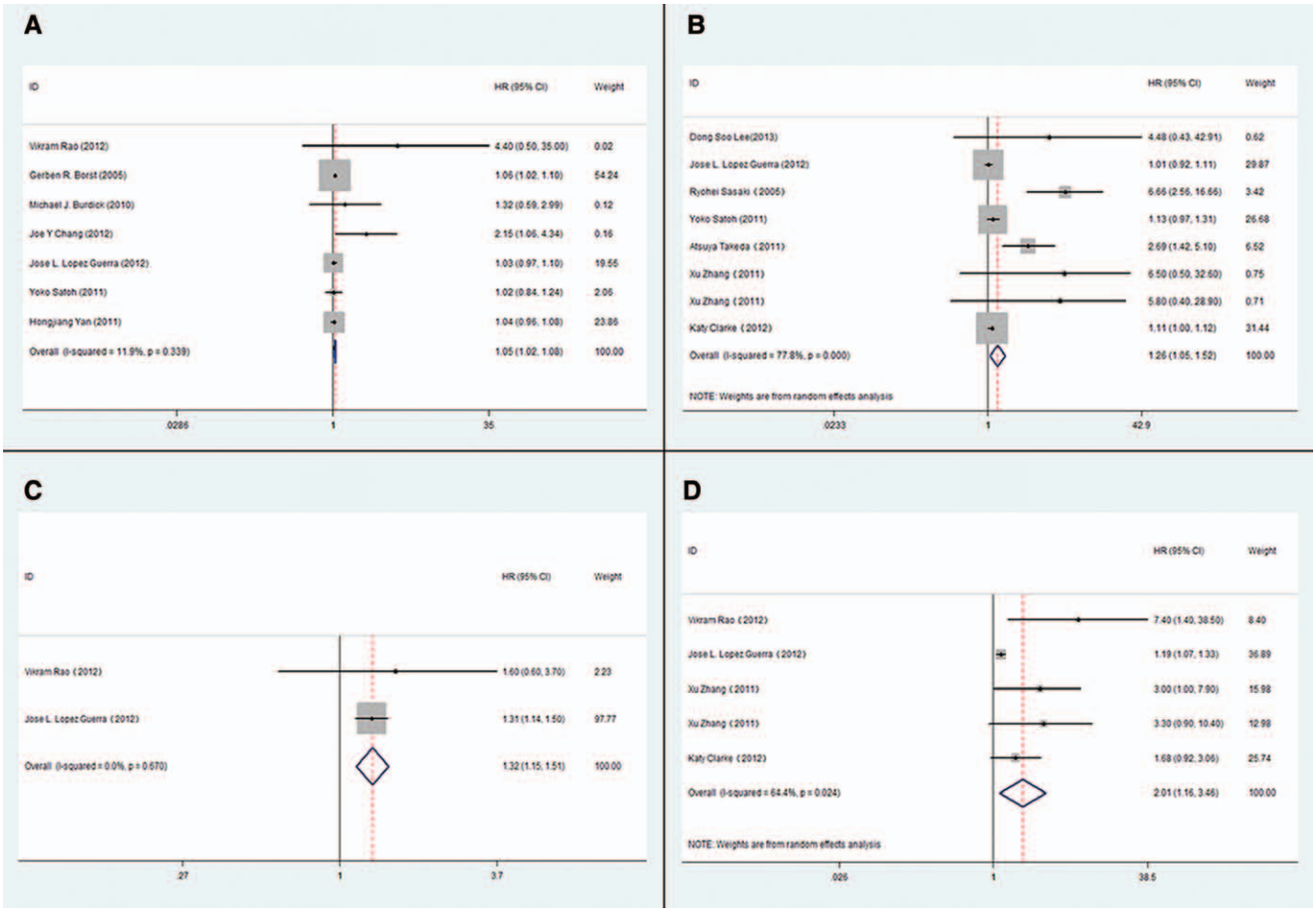

FIGURE 2. The association between primary tumor SUV_{max} and OS and LC of NSCLC treated by radiotherapy. A, The pooled HR estimate for OS of pre-RT primary tumor SUV_{max}; B, The pooled HR estimate for LC of pre-RT primary tumor SUV_{max}; C, The pooled HR estimate for OS of post-RT primary tumor SUV_{max}; D, The pooled HR estimate for LC of post-RT primary tumor SUV_{max}. (OS, overall survival; LC, local control; HR, hazard ratio; CI, confidence interval.)

The pooled HR estimate for LC of the six studies using a random-effects model (I^2 statistic = 77.8%, $P_{heterogeneity}$ = 0.000) was 1.26 (95% CI, 1.05–1.52) (Fig. 2*B*). The combined HR was 1.24 (95% CI, 1.04–1.49) n a sensitivity analysis (I^2 = statistic 79.5%, $P_{heterogeneity}$ = 0.0255).

Post-RT SUV_{max} also correlated with OS and LC. For OS, the pooled HR was 2.47 (95% CI, 0.58–13.03; I^2 statistic = 99.3%, $P_{heterogeneity}$ = 0.000). Excluding the same study excluded in the post-RT/OS association,[32] the HR was reduced to 1.32 (95% CI, 1.15–1.51) with well homogeneity (I^2 statistic = 0.0%, $P_{heterogeneity}$ = 0.670) (Fig. 2*C*). The pooled HR estimate using a random effects model for LC was 2.01 (95% CI, 1.16–3.46) (Fig. 2*D*). Again, there was considerable heterogeneity (I^2 statistic = 70.6%, $P_{heterogeneity}$ = 0.017). A sensitivity analysis was assessed after excluding studies with six stars[33] and excessive cutoff value (cutoff = 14).[25] The combined HR (HR, 2.19; 95% CI, 1.34–3.60 and HR, 2.32; 95% CI, 1.47–3.68) indicates that the sensitivity is low and the result is robust and credible.

The studies were stratified into two groups: SBRT and CRT. In pre-SBRT primary tumor SUV_{max} group, the subjects were stage I patients, and high pre-SBRT SUV_{max} was not significantly associated with poor OS (HR, 1.10; 95% CI, 0.91–1.31) with modest homogeneity across the four included studies (I^2 statistic = 49.3%, $P_{heterogeneity}$ = 0.245) (Fig. 3*A*). High pre-SBRT SUV_{max} also correlated to unfavorable LC (HR, 1.28; 95% CI, 1.02–1.60). Eliminating heterogeneity (I^2 statistic = 63.4%, $P_{heterogeneity}$ = 0.018) by excluding a study that included T1-4N0M0 tumors[23] reduced the HR estimate for LC to 1.11 (95% CI, 1.06–1.18; I^2 statistic = 28.3%, $P_{heterogeneity}$ = 0.242) (Fig. 3*B*). The post-SBRT SUV_{max} correlated to LC (HR, 2.19; 95% CI, 1.34–3.60; I^2 statistic = 37.1%, $P_{heterogeneity}$ = 0.204) (Fig. 3*C*), with limited data that prevented analysis of OS. For CRT, both high pre-CRT and post-CRT SUV_{max} correlated to poor OS (Table 2).

Publication Bias

Publication bias was assessed by Begg's and Egger's test. Begg's test did not find overt publication bias. Formal evaluation using Egger's test also failed to identify significant publication bias in the analysis of pre-RT SUV_{max} versus OS (p = 0.317), and post-RT SUV_{max} versus LC (p = 0.916).

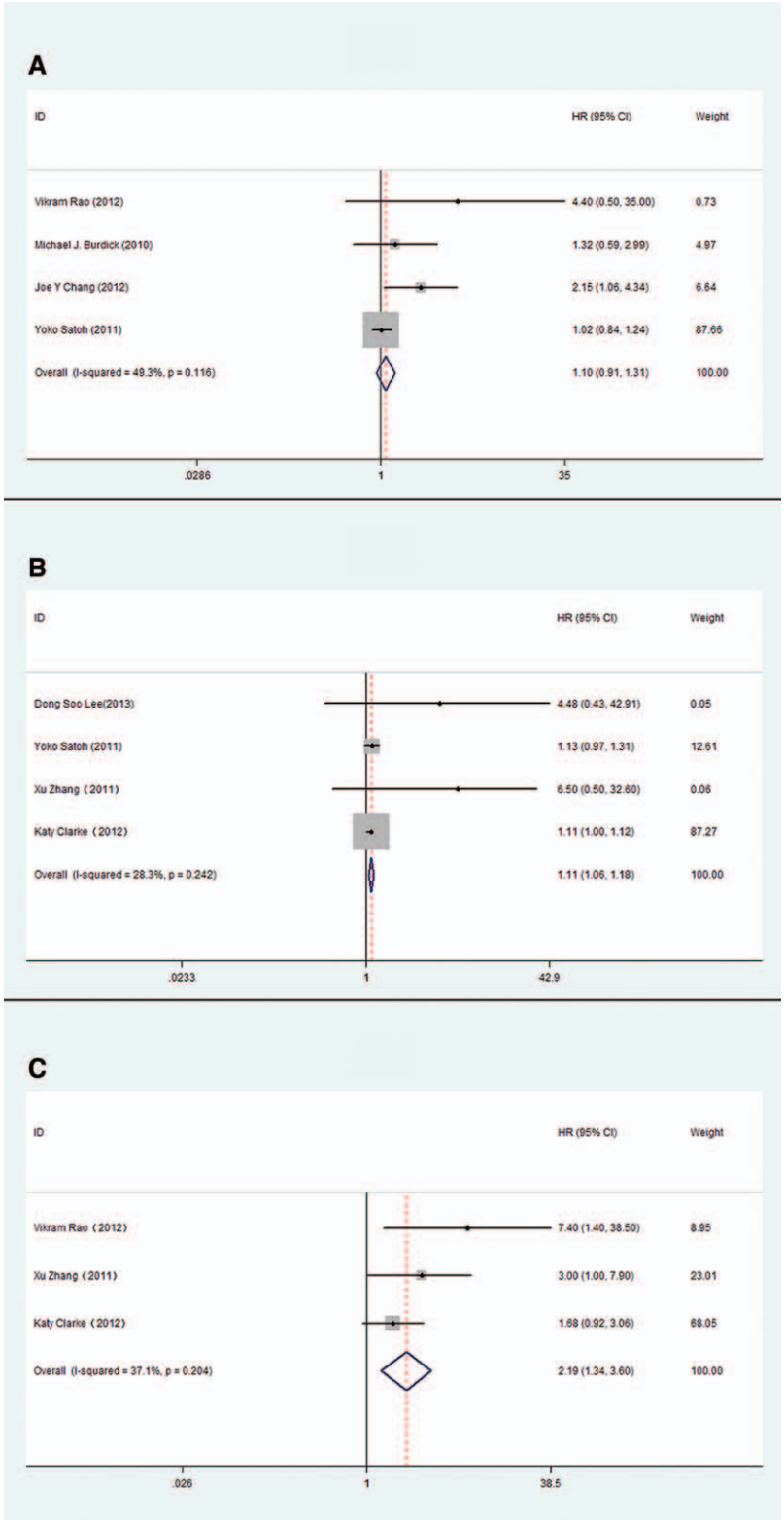

FIGURE 3. The association between primary tumor SUV_{max} and OS and LC of NSCLC treated by SBRT. A, The pooled HR estimate for OS of pre-SBRT primary tumor SUV_{max}; B, The pooled HR estimate for LC of pre-SBRT primary tumor SUV_{max}; C, The pooled HR estimate for LC of post-SBRT primary tumor SUV_{max}.

Similarly, there was no evidence for significant publication bias in pre-SBRT SUV_{max} versus OS ($p = 0.107$) and in pre-CRT SUV_{max} versus OS ($p = 0.139$). The results with heterogeneity adjusted are listed in Table 2.

DISCUSSION

During the past decade, the role of ^{18}F-FDG PET/CT has become increasingly important to the patients staging and the radiation treatment planning process in NSCLCs. It has

TABLE 2. Meta-Analysis after Correcting Heterogeneity

Group	Studies (N)	Q test *p* Value	Model Selected	HR (95% CI)	*p* Value	Egger's Test *p* Value
ALL						
OS						
Pre-RT	7	0.339	Fixed	1.05 (1.02–1.08)	0.001	0.117
Post-RT	2	0.670	Fixed	1.32 (1.15–1.51)	0.000	—
LC						
Pre-RT	8	0.000	Random	1.26 (1.05–1.52)	0.012	0.017
Post-RT	5	0.024	Random	2.01 (1.16–3.46)	0.012	0.002
SBRT						
OS						
Pre-SBRT	4	0.116	Fixed	1.10 (0.91–1.31)	0.326	0.107
LC						
Pre-SBRT	4	0.242	Fixed	1.11 (1.06–1.18)	0.000	0.057
Post-SBRT	3	0.204	Fixed	2.19 (1.34–3.60)	0.002	0.015
CRT						
OS						
Pre-CRT	3	0.709	Fixed	1.05 (1.02–1.08)	0.001	0.777
Post-CRT	2	0.670	Fixed	1.32 (1.15–1.51)	0.000	—
LC						
Pre-CRT	2	0.000	Random	2.44 (0.39–15.45)	0.343	—
Post-CRT	1	—	Random	1.19 (1.07–1.33)	0.002	—

HR, hazard ratio; CI, confidence interval; OS, overall survival; RT, radiation therapy; LC, local control; SBRT, stereotactic body radiotherapy; CRT, conventional radiotherapy.

been widely reported that SUV_{max} of the primary tumor in the ^{18}F-FDG PET/CT analysis has potential prognostic use among differently staged and treated populations.[22,37,39] For patients with resectable NSCLC, a meta-analysis of 13 studies showed that primary tumor SUV_{max} has significant prognostic value on patient survival.[39] Some previous studies suggested an association of high SUV_{max} before RT with poor LC[22] and OS,[34] but such findings were not replicated by others.[30]

The results of the correct study confirmed a significant correlation of high level of both pre-RT and post-RT SUV_{max} with the increased risk of death and local recurrence. Stratified analysis (SBRT versus conventional radiation) also confirmed the prognostic value of primary tumor SUV_{max} regardless of the type of the treatment. These results are generally consistent with a previous study,[24] and particularly so for stage I NSCLC patients treated with SBRT. Whether SUV_{max} is a prognostic factor of the outcome in NSCLC patients receiving RT regardless of stage and performance status requires further evaluation.

In the analysis of pre-RT versus OS, most of the heterogeneity could be attributed to one study performed in 46 Chinese patients with stage III NSCLC.[32] This heterogeneity may be explained by the different methods used to estimate the results and the different threshold used. For example, the method used by the excluded study[32] to estimate the results was logistic regression model. The analysis of post-RT with OS also had significant heterogeneity (because of the same study). Excluding the prediction value of primary tumor SUV_{max} for OS turned into significant (HR, 1.32; 95% CI, 1.15–1.51) from insignificant (HR, 2.47; 95% CI, 0.58–13.03) and demonstrated a poorer OS with high SUV_{max}. It is noteworthy, however, that only two studies with 181 patients were included in meta-analysis with acceptable heterogeneity. The results, therefore, must be validated by additional studies. Varying cutoff levels, different scanning equipment, and fractionated dose schemes also contributed to the heterogeneity.

Patients in all studies, including the SBRT subgroup analysis, had stage I NSCLC. As a result, the association of high pre-SBRT SUV_{max} with unfavorable OS and LC is not clear in patients with more advanced NSCLC. Also, the prognostic value of post-SBRT SUV_{max} on OS could not be confirmed in this meta-analysis because of the insufficient available data. A similar situation seems to be true of CRT as well: analysis of all five CRT studies using a random-effects model failed to confirm an association between the pre-CRT or post-CRT SUV_{max} and OS/LC; but reducing heterogeneity by excluding the study from China[32] revealed significant association.

In addition to the absolute value of pre-RT or post-RT SUV_{max}, the change of duel time primary tumor SUV_{max} also correlated with patient outcome after RT. A study by Clarke et al.[22] found significantly higher rate of distant failure in patients with a post-SBRT SUV_{max} of 2 or more and a reduction of less than 2.55. Another study[25] also reported the greater decrease in primary tumor SUV_{max} that had the highest SUV_{max} at diagnosis, the longer OS and disease-free survival for RT. The Satoh study[30] also suggested that, in comparison with pre-SBRT SUV_{max}, high retention index and reduced ratio of SUV_{max} had better prognostic value (HR, 47.546; $p = 0.026$). The value of the change in dual time points FDG-PET/CT as a prognostic factor for outcome in NSCLC patients receiving RT needs to be further studied, with attention to the method of calculating this change and the cutoff value.

TABLE 3. Newcastle–Ottawa Quality Assessment Scale[a]

Selection

(1) Representativeness of the exposed cohort
- (a) Truly representative of the average "NSCLC patient receiving radiotherapy" in the community (one star)
- (b) Somewhat representative of the average "NSCLC patient receiving radiotherapy" in the community (one star)
- (c) Selected group of users (e.g., nurses, volunteers)
- (d) No description of the derivation of the cohort

(2) Selection of the nonexposed cohort
- (a) Drawn from the same community as the exposed cohort (one star)
- (b) Drawn from a different source
- (c) No description of the derivation of the nonexposed cohort

(3) Ascertainment of exposure (*proof of NSCLC and primary tumor SUVmax measurement*)
- (a) Secure record (e.g., surgical records) (one star)
- (b) Structured interview (one star)
- (c) Written self-report
- (d) No description

(4) Demonstration that outcome of interest was not present at start of study
- (a) Yes (one star)
- (b) No

Comparability

(1) Comparability of cohorts on the basis of the design or analysis
- (a) Study controls for "the level of primary tumor SUV_{max}" (one star)
- (b) Study controls for any additional factor (one star) (*age, stage, grade, etc.*)

Outcome

(1) Assessment of outcome (*death or local recurrence*)
- (a) Independent blind assessment (one star)
- (b) Record linkage (one star)
- (c) Self-report
- (d) No description

(2) Was follow-up long enough for outcomes to occur? (*death or local recurrence*)
- (a) Yes ("2 years") (one star)
- (b) No

(3) Adequacy of follow-up of cohorts
- (a) Complete follow-up—all subjects accounted for (one star)
- (b) Subjects lost to follow-up unlikely to introduce bias—small number lost "(25%)" or description provided of those lost (one star)
- (c) Follow-up rate "<75%" and no description of those lost
- (d) No statement

[a]A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. Underlined and quoted phrases are provided in the scale to allow for adjustment to particular studies. Italicized phrases indicate our interpretation of the question relevant to this study.

NSCLC, non–small-cell lung cancer; SUV_{max}, maximum standardized uptake value.

The number of the studies, as well as the number of the patients, included in this meta-analysis is relatively small. Also, the data in some of the included studies were analyzed using univariate analysis. As a result, the nature of the observed association is obscure. Another fact is that most of the data were derived from patients with stage I NSCLC. As a result, whether the observed association could be extrapolated to patients with more advanced NSCLC is not certain. Therefore, more high-quality studies with sufficient information needs to be performed, and it should lead to a more significant meta-analysis.

In summary, the current meta-analysis confirmed an association of high pre-RT and post-RT SUV_{max} of primary tumor with poor outcome in NSCLC patients receiving RT. Such an association seems to be particularly strong for patients with stage I NSCLC receiving SBRT. And it supports further and high-quality investigations of SUV_{max} on ^{18}F-FDG PET/CT for predicting poor outcome in NSCLC patients receiving RT.

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