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META-ANALYSIS

FDG-PET metrics in advanced non-small cell lung cancer (NSCLC): a review and meta-analysis

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Abstract

Purpose To provide a systematic review and meta-analysis of published literature characterizing the prognostic value of pre-treatment, volume-based FDG-PET metrics in patients with advanced NSCLC.

Methods We conducted a systematic PubMed search to identify studies describing the prognostic value of volume-based PET metrics (total metabolic tumor volume [MTV] and/or total lesion glycolysis [TLG]) obtained prior to initiation of first-line systemic therapy for advanced NSCLC. Clinical endpoints examined were progression-free survival (PFS) and overall survival (OS). Hazard ratios for PFS and OS were taken directly from the original reports when available or extracted from survival curves. Inverse variance meta-analyses were performed to assess associations between PET metrics and clinical outcomes.

Results Thirteen publications including 1,047 patients were included in our analysis. Patients from at least 9 studies received chemotherapy, at least 4 studies utilized targeted therapy, and only 1 study included patients treated with immunotherapy. Random effects models demonstrated that high MTV is significantly associated with inferior PFS (HR 2.97, 95% CI 2.21–4.00, $p < 0.001$) and inferior OS (HR 2.73, 95% CI 2.18–3.41, $p < 0.001$). High TLG is also significantly associated with inferior PFS (HR 2.13, 95% CI 1.56–2.91, $p < 0.001$) and inferior OS (HR 2.06, 95% CI 1.75–2.44, $p < 0.001$).

Conclusion Baseline PET metrics are powerful prognostic factors for advanced NSCLC patients who are treated with chemotherapy or targeted therapy. Further examination of the prognostic value of PET metrics for patients who receive first-line immunotherapy is warranted.

Keywords FDG-PET · Metabolic Tumor Volume (MTV) · Total Lesion Glycolysis (TLG) · Advanced Non-Small Cell Lung Cancer

Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1], despite recent advancements in screening guidelines [2] and treatment options. Non-small cell lung cancer (NSCLC) comprises approximately 80% of all lung cancers, and most patients present with locally advanced to advanced disease. The treatment landscape for patients with advanced disease has changed considerably in recent years, with the incorporation of targeted therapy and immunotherapy into the standard of care [3–8]. Outcomes for patients with advanced disease, however, remain poor overall.

Much effort has been placed on identifying prognostic factors in NSCLC, with disease stage and performance status being among the most well-described [9]. Positron emission tomography with 18-fluorodeoxyglucose (FDG PET) is a key procedure in the workup and staging of NSCLC. Metrics extracted from PET have also emerged as potential prognostic tools. The standardized uptake value (SUV) is defined as the ratio of tissue radioactivity concentration and administered dose of radioactivity. The maximum SUV (SUVmax) is often used to quantify a lesion's metabolic activity, however, it has not been proven to be a valuable prognostic marker. Metabolic tumor volume (MTV) and

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total lesion glycolysis (TLG), on the other hand, are volumetric parameters that have shown promise in predicting clinical outcomes. MTV is the sum of the volume of all voxels with an SUV above a pre-determined threshold value. TLG is calculated by multiplying the MTV and the average SUV, or SUVmean, combining both volumetric and metabolic information.

In 2015, Im et al. published a meta-analysis demonstrating the prognostic value of these parameters across all stages of non-small cell lung cancer [10]. High MTV and high TLG were associated with increased risk of all-cause mortality, with hazard ratios of 2.31 and 2.43, respectively. Our objective was to perform an updated meta-analysis of the published literature characterizing the prognostic value of pre-treatment, volume-based FDG-PET metrics in NSCLC, specifically focusing on patients with advanced disease and considering recent treatment advancements.

Materials and methods

Data search and study selection

We conducted a systematic PubMed search to identify studies describing the prognostic value of baseline volume-based PET metrics, including total MTV and/or TLG in patients with advanced NSCLC. We searched for English language studies using the search terms "positron emission tomography," "advanced lung cancer," "metastatic lung cancer," "stage IV lung cancer," and "volume." We also searched articles related or similar to those yielded in our initial search. We included publications with advanced NSCLC, baseline FDG-PET obtained prior to initiation of first-line systemic therapy, and measurement of total body tumor burden via MTV and/or TLG. We did not include studies where only the primary tumor was measured. Since we wanted to focus on patients with advanced, or metastatic, disease, for whom the standard of care therapy has recently changed, we chose a cutoff of at least 50%, or a majority of study patients having Stage IV disease, for those studies which included a range of early and late stage NSCLC.

Data extraction and statistical analysis

We recorded study characteristics, including first author, location and year of publication, number of patients, percentage of patients having Stage IV disease, forms of treatment administered, PET techniques, and cutoffs used for high MTV and TLG. The clinical endpoints examined were progression-free survival (PFS) and overall survival (OS). Hazard ratios for PFS and OS were extracted directly from the original reports when available, or estimated indirectly from survival curves, as previously suggested by Parmar et al. [11], using customized scripts in Matlab (The Mathworks, Natick, MA). Briefly, our customized scripts function by digitizing published survival curves and inferring the timing of each patient's clinical event or censoring. Cox proportional hazards models are then fit to the derived patient-level data. Inverse variance meta-analyses using random effects models were performed to assess associations between PET metrics and clinical outcomes. The Q Test was used to identify potential outliers within the data set.

Results

Our electronic search results yielded 416 records. We eliminated 358 entries upon initial screening and identified 58 abstracts to assess further for eligibility. Fourteen full-text articles met our eligibility criteria. We also reviewed articles that were listed as similar to these fourteen entries and upon further investigation, we identified an additional 7 publications to include for analysis. One article was subsequently found to have been retracted and was excluded. Another 7 articles had either duplicate or insufficient data. Thirteen publications were included in our final analysis (Fig. 1), incorporating 1047 patients [12–24].

The percentage of patients with Stage IV disease ranged from 67 to 100%. There were 3 studies we included [21, 23, 24] which did not provide a breakdown of stage, but these articles specifically stated patients with advanced disease were studied. Two of these articles specified that patients with at least Stage IIIB were included [23, 24]. Patients from at least nine studies received chemotherapy and patients from at least 4 studies were treated with targeted therapy. Patients in one study with PD-L1 scores of at least 50% were treated with first-line immunotherapy (Table 1). The majority of the included publications described methods of MTV and TLG delineation, and PET/CT techniques including

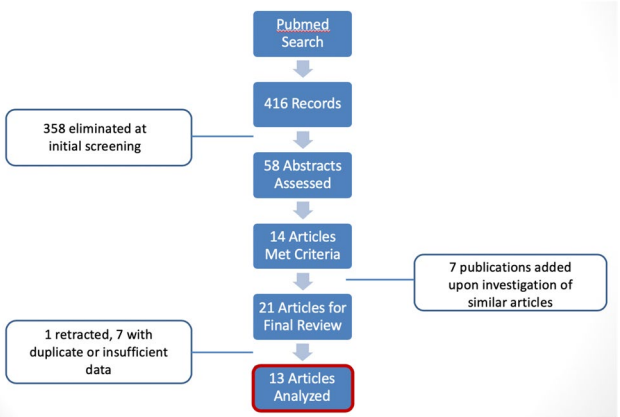

Fig. 1 Search strategy and study inclusion

Table 1 Study characteristics

First author	Year of publication	Country	Number of patients	Study design	Single or multi-center	% Patients with stage IV disease	Form of therapy	Endpoints studied	PET metrics	MTV cutoff value (cm^3)	TLG cutoff value (cm^3)	Determination of cut-off value
Liao	2012	USA	92	Retrospective	Single	100	CHT, TT	OS	MTV, TLG	248	968	Median
Yoo	2012	Korea	57	Retrospective	ND	100	CHT, TT	PFS	MTV, TLG	656.2	442.2	ROC
Zaizen	2012	Japan	81	Retrospective	Single	75	CHT	PFS, OS	TLG	_	33	Maximizing the profile partial likelihood
Chung	2014	Korea	106	Retrospective	Single	70	CHT, TT	PFS, OS	MTV, TLG	90	600	ROC
Nygaard	2014	Denmark	53	Prospective	Single	68	CHT	PFS, OS	MTV, TLG	95	444	Median
Han	2015	Korea	33	Retrospective	Single	70	CHT	OS	MTV	55.4	_	Maxstat (maximal X2 method)
Ho	2015	China	25	Retrospective	Single	≥ 72	TT	OS	TLG	_	412	ROC
Ooi	2016	Taiwan	157	Retrospective	Single	ND	CHT	PFS, OS	MTV, TLG	30.8	383.3	Maximizing the profile partial likelihood
Wang	2016	China	176	Retrospective	Single	ND	ND	PFS, OS	TLG	_	259.9	ROC
Sharma	2018	India	60	Prospective	Single	73	CHT	OS	MTV, TLG	160	1350	ROC
Hyun	2019	Korea	101	Prospective	Multi	89	ND	PFS, OS	MTV, TLG	100	500	X-tile software
Pellegrino	2019	Italy	43	Retrospective	Single	67	CHT	PFS, OS	MTV	81.6, 100.2[a]	_	ROC
Seban	2020	France	63	Retrospective	Multi	ND	IO	PFS, OS	MTV, TLG	84	597.2	Median

CHT Chemotherapy, *TT* Targeted Therapy, *IO* Immunotherapy, *ND* Not Described

[a]Different MTV cutoff used for PFS and OS

patient fasting time prior to imaging, injected activity, uptake time, scan time, and reconstruction and attenuation correction details (Table 2).

The median cutoff used to define high MTV across studies was 93 cm^3. Random effects models demonstrated that high MTV is significantly associated with inferior PFS (Fig. 2), with a hazard ratio (HR) of 2.97 (95% CI 2.21–4.00, $p < 0.001$), as well as inferior OS (Fig. 3), with a HR of 2.73 (95% CI 2.18–3.41, $p < 0.001$). Similar findings were seen with regards to TLG. The median cutoff used to define high TLG across studies was 444 cm^3. Random effects models demonstrated that high TLG is significantly associated with inferior PFS (Fig. 4), with a HR of 2.13 (95% CI 1.56–2.91, $p < 0.001$) as well as inferior OS (Fig. 5), with a HR of 2.06 (95% CI 1.75–2.44, $p < 0.001$).

Discussion

In our analysis, high MTV and high TLG were significantly associated with worse PFS and OS outcomes in patients with advanced NSCLC. Several studies have been published in recent years examining the prognostic value of pre-treatment PET/CT in advanced NSCLC across multiple lines of therapy [25–29]. This meta-analysis establishes its value prior to first line therapy, thus providing a useful tool to help guide expectations at the time of initial diagnosis.

Our findings largely corroborate a previous meta-analysis published by Im, et al. Unlike the previous study, we focused on patients with advanced NSCLC, mitigating

Table 2 PET Parameters

First author	Injected activity (MBq)	Mean time from administration to acquisition (min)	Type of PET	PET 2D or 3D	CT parameters	Contrast used	Reconstructed PET matrix size	Reconstructed PET voxel size (mm)	Tumor Volume delineation method (Threshold)
Liao	370–555	60	Reveal HD	3D	130 kV, 70–80 mA	No	128 × 128	5	MIM/PET Edge
Yoo	7.4/kg	60	GE Discovery ST	2D	120 kV, 10–130 mA	ND	ND	ND	SUV (2.5)
Zaizen	158.7–362.6	60	Philips ALLEGRO	3D	ND	ND	ND	ND	SUV (2.5)
Chung	4.8/kg	60	Philips GEMINI	3D	120 kV, 50 mA	No	ND	ND	SUVmax (40%)
Nygaard	271–405	60	Philips GEMINI	ND	120 kV, 50 mA	ND	ND	ND	SUV (2.5)
Han	370–555	60	Siemens Biograph Duo	ND	130 kV, 80 mA	No	ND	6.5	Mean Liver SUV + 2 SDs
Ho	370–444	50	GE Discovery ST 16; Siemens Biograph	3D	ND	ND	ND	ND	SUV (2.5)
Ooi	ND	ND	GE HS or LS	ND	ND	Yes	ND	ND	SUVmax (50%)
Wang	5.55–7.4/kg	60	GE Discovery ST	2D	140 kV, 150 mA	No	128 × 128	ND	SUVmax (40%)
Sharma	5.18–7.77/kg	60	Siemens Biograph	3D	120 kV, 120 mA	Yes	200 × 200	2	SUV (2.5)
Hyun	5–6/kg	60	Philips GEMINI	ND	ND	No	ND	ND	SUV (2.5)
Pellegrino	370	60	GE Discovery LS	2D	140 kV, 80 mA	Yes	ND	8	SUV (2.5)
Seban	ND	ND	GE Discovery-690, 710, MI; Philips Vereos	ND	ND	ND	256 × 256 and 288 × 288	2–6.4	SUVmax (42%)

ND Not Described, *SD* Standard Deviation

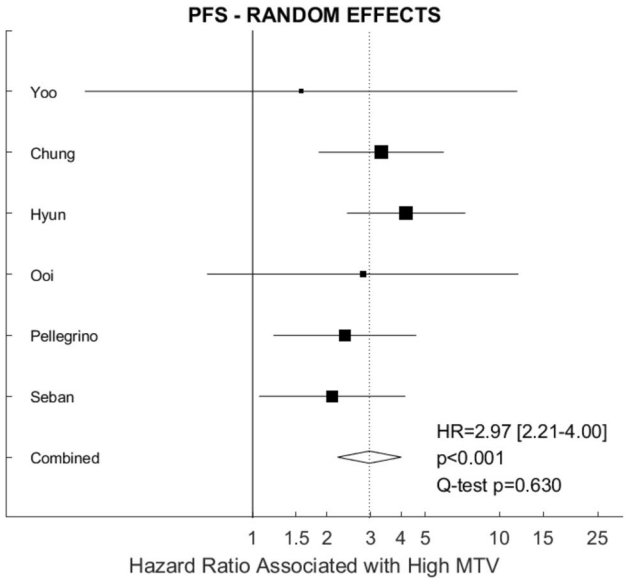

Fig. 2 Association between MTV &PFS

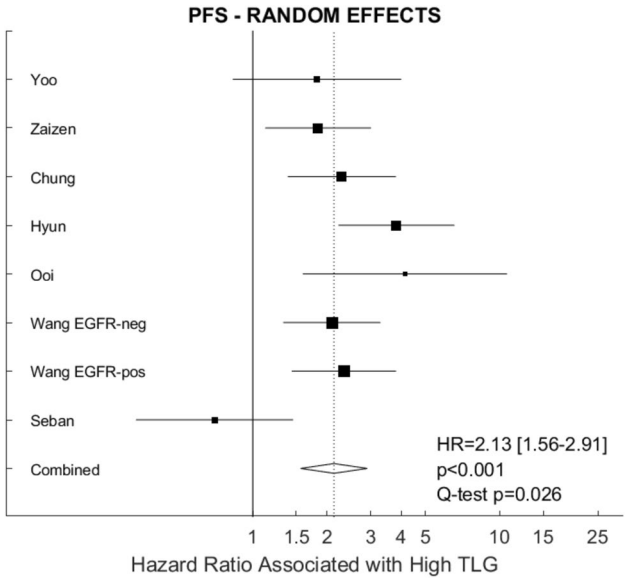

Fig. 4 Association between TLG & PFS

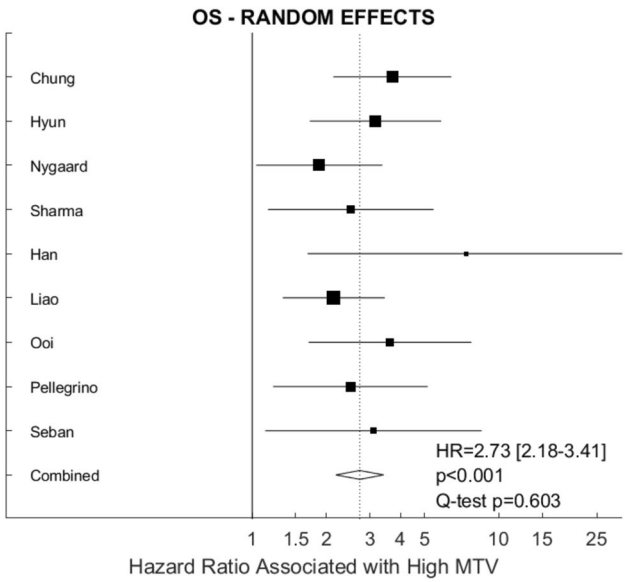

Fig. 3 Association between MTV & OS

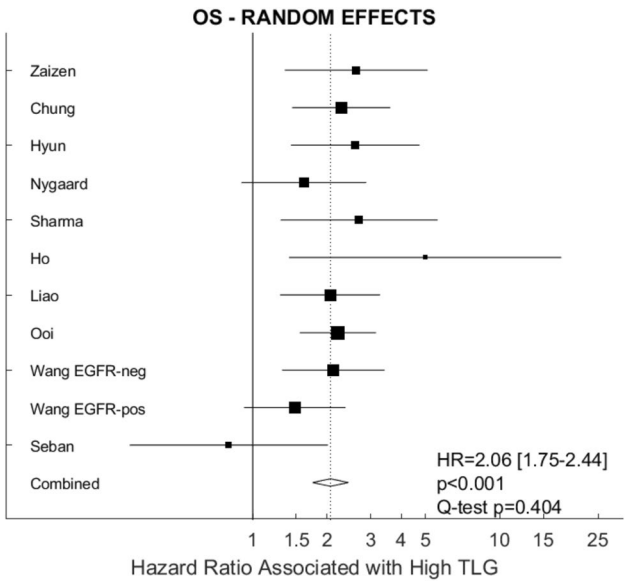

Fig. 5 Association between TLG & OS

concerns that prior findings could be mediated by associations between disease stage and volumetric measures of disease burden. Additionally, we considered primary tumors and regional and distant metastases as components of patients' disease burden, while the previous study focused only on primary lung tumors. Of note, future studies may implement machine learning technique to identify more robust PET-based prognostic variables (e.g., textural features [30]).

Of note, only one study meeting criteria for this analysis utilized immunotherapy as first-line treatment for NSCLC. Our group has begun to examine the value of volume-based PET metrics in our own cohort of patients treated with first-line immunotherapy, and has shown that MTV may be an important prognostic factor for these patients with advanced disease [31]. Additional studies that reflect this current standard of care treatment paradigm for NSCLC are sorely needed to confirm the benefit of PET/CT in the modern treatment era.

Stratification factors employed in recent randomized trials for advanced NSCLC include race, ECOG performance status, tumor histological type, region of enrollment, PD-L1

tumor proportion score (TPS), and choice of chemotherapy [3–8]. The hazard ratios for PFS and/or OS associated with these factors range from 1.23 to 2.94. MTV and TLG, as evidenced by the HR's detailed in our study, are arguably more powerful than many of these prognostic tools. These findings support the use of volume-based measures of disease burden as stratification factors to improve clinical trial efficiency.

Aside from volume-based measures, an additional method of assessing tumor burden in advanced disease is to count the number of sites of metastases. The presence of only a few metastatic sites is termed oligometastatic disease and has been associated with a favorable prognosis. Multiple studies are exploring the role of radical local therapy for oligometastatic cancer patients [32–34]. Future studies with patient-level data are warranted to examine the relationship between volumetric and count-based measures of disease burden, and the merits of each of these metrics as prognostic factors should be compared.

Limitations to this study include the lack of patient-level PET data and the use of variable definitions of high/low MTV and TLG. Of note, sensitivity analyses performed after removing trials with extreme MTV and TLG cutoffs did not yield meaningful changes to the results of our meta-analyses (data not shown). Future analyses with patient-level PET data would allow more refined characterization of the relationship between disease burden measured on PET and NSCLC prognosis.

Conclusion

Baseline PET metrics are powerful prognostic factors for advanced NSCLC patients who are treated with first line therapy. Future studies are needed to examine the prognostic value of PET metrics for patients who receive first-line immunotherapy.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Dr. Berkowitz has no relevant financial or non-financial interests to disclose. Dr. Halmos is a consultant at AstraZeneca, Boehringer Ingelheim, Genentech/Roche, Pfizer, Lilly, Foundation Medicine, Guardant Health, Takeda, Novartis, Merck, Bristol-Myers Squibb, Spectrum Pharmaceuticals and TPT Therapeutics. Dr. Cheng is a consultant at AstraZeneca and Bayer, and she received research grants from Roche/Genentech, Spectrum Pharmaceuticals, and Vaccinex. Mr. Huntzinger is an employee at RefleXion Medical, where he also has stock and stock options. Dr. Ohri is a consultant at Merck and AstraZeneca.

Ethical approval This article does not contain any studies with human or animal subjects performed by any of the authors.

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