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Systematic Review

Prognostic factors for overall survival of stage III non-small cell lung cancer patients on computed tomography: A systematic review and meta-analysis

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ABSTRACT

Introduction: Prognosis prediction is central in treatment decision making and quality of life for non-small cell lung cancer (NSCLC) patients. However, conventional computed tomography (CT) related prognostic factors may not apply to the challenging stage III NSCLC group. The aim of this systematic review was therefore to identify and evaluate CT-related prognostic factors for overall survival (OS) of stage III NSCLC.

Methods: The Medline, Embase, and Cochrane electronic databases were searched. After study selection, risk of bias was estimated for the included studies. Meta-analysis of univariate results was performed when sufficient data were available.

Results: 1595 of the 11,996 retrieved records were selected for full text review, leading to inclusion of 65 studies that reported data of 144,513 stage III NSCLC patients andcompromising 26 unique CT-related prognostic factors. Relevance and validity varied substantially, few studies had low relevance and validity. Only four studies evaluated the added value of new prognostic factors compared with recognized clinical factors. Included studies suggested gross tumor volume (meta-analysis: HR = 1.22, 95%CI: 1.05–1.42), tumor diameter, nodal volume, and pleural effusion, are prognostic in patients treated with chemoradiation. Clinical T-stage and location (right/left) were likely not prognostic within stage III NSCLC. Inconclusive are several radiomic features, tumor volume, atelectasis, location (pulmonary lobes, central/peripheral), interstitial lung abnormalities, great vessel invasion, pit-fall sign, and cavitation.

Conclusions: Tumor-size and nodal size-related factors are prognostic for OS in stage III NSCLC. Future studies should carefully report study characteristics and contrast factors with guideline recognized factors to improve evidence evaluation and validation.

Cancer is a major cause of mortality and a societal burden, which poses a medical challenge to this day [1]. Lung cancer is one of the most common types of cancer with respect to incidence [2]. The relatively low survival of lung cancer in conjunction with treatment induced toxicity emphasizes the importance of considering prognosis before making treatment decisions [1–7]. Stage III non-small cell lung cancer (NSCLC) compromises a particularly difficult subgroup in this regard, because it represents a heterogeneous group of patients. Trials conducted in the last decade show improved survival outcomes compared to older trials, resulting from introduction of PET-CT and MRI for optimal staging ('stage migration') and from improvements in surgical treatment, radiotherapy, and introduction of immunotherapy. Still, only a proportion of all patients benefit from these intensive multimodality treatment schemes and a significant proportion experiences toxicity. This is the challenge presented to multidisciplinary boards: balancing the chance of disease curation and quality of life, making treatment decisions while taking into account risk factors as individual prognostic factors. Current guidelines acknowledge several prognostic factors including stage at diagnosis, performance status, gender, and weight loss [8]. Prognostic factors can also be derived by medical imaging modalities. Of all modalities used in diagnosis and staging of NSCLC, computed tomography (CT) is most commonly used [9]. CT, typically used to obtain information on tumor size and location, is integral for determination of clinical T-stage and N-stage [9,10]. In recent years an abundance of articles considering factors for overall survival (OS) that can be measured by CT has been published [11–21]. In order for these CT-related prognos-

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tic factors to become applicable in clinical practice, a clear overview should be created. Other common outcomes are progression-free and disease-free survival. We note these outcomes are mainly of interest for comparing treatment efficacy. OS is arguably the most relevant outcome from a patient perspective, therefore this review focusses specifically on OS. For these reasons, the aim of this study was to systematically review and appraise the evidence on CT-related prognostic factors for OS of stage III NSCLC patients, and to synthesize the evidence with a meta-analysis where possible.

Methods

Search strategy

This study was pre-registered in the PROSPERO registration of systematic reviews (registration number/ID 160936). The Medline (via PubMed), Embase, and Cochrane electronic databases were searched for literature (last queried on 30-09-2019). The search terms consisted of terms reflecting domain, determinant, and outcome of the research question. The complete queries are available in Appendix B.

Study selection

Studies retrieved by this search term were screened on title and abstract using the online screening tool Abstrackr [22]. A blinded pilot title/abstract screen of 100 articles was completed by 2 independent reviewers (MvL, WA), conflicts were resolved via consensus by the 2 reviewers. During the following full text review selected publications, reviews, and editorials were screened for cross-references. Original studies discussing the effect of a prognostic factor for OS that can be measured on CT prior to treatment allocation of stage III NSCLC patients were included. Excluded were studies not including stage III NSCLC patients, considering no CT-related prognostic factors for stage III NSCLC patients, written in a language other than English, French, German, or Dutch, and studies that explicitly stated consisting of only pathological staged patients ($n = 17$), because initial treatment decisions can only be based on clinical stage [9]. The utilized TNM-staging system was used as a relevance criterion. Additionally, when multiple studies explicitly stated use of the same patient cohort, the publication with the most recent data was included. Finally, results of multivariable analyses of studies containing a stage III patient number per variable below 5 or containing variables measured after treatment initiation ($n = 6$), were excluded from analysis.

Data collection

Data was extracted from the inclusions with a data extraction sheet based on the Cochrane Handbook [23], which was piloted for 2 randomly selected publications. After some adjustments were made during a consensus meeting (MvL, WA, JV), the final version (Appendix D) was used to extract data regarding baseline characteristics, treatment, prognostic factors, outcome measures, and general study information, including the utilized TNM-staging system edition. Where the utilized edition was not specified, an estimate was made based on both inclusion period and references of the article. In cases where outcome measures were reported as model coefficient, the hazard ratio was calculated by exponentiating the model coefficient.

Risk of bias assessment

A grading system for critical appraisal was designed, based on the SIGN and TRIPOD [24,25], to separately assess relevance and validity of included publications on outcome level. After piloting for 4 random inclusions, some adjustments were made during a consensus meeting (MvL, WA, JV), giving rise to the final version (Appendix C), which was used to assess both relevance and validity of all inclusions.

Statistics

A meta-analysis was performed on model coefficients from univariate models of prognostic factors when three or more studies reported at least either: the HR and associated standard error, HR and p-value, or a confidence interval. When the reported HR was numerically identical to either the upper bound or lower bound of the confidence interval (e.g. due to rounding), this study was excluded from the meta-analysis.

As the Cox proportional hazards model models the hazards as log-hazard ratios, we log-transformed all hazard ratios, standard errors, and confidence intervals before pooling. When not directly reported, the standard error of the log-HR was recalculated using the range of the log-HR confidence interval (upper minus lower) divided by 3.92 (which is the number of standard deviations included in the 95% confidence interval). If the absolute difference between the upper and the lower was less than 0.05 (leading to numerical inaccuracies due to rounding), or when the CI was not reported but the p-value was, we recalculated the standard error using the p-value. For this calculation we assumed that the p-value was calculated based on a Chi-square distribution with one degree of freedom on the Wald-statistic, which is the default method for calculating the p-value in most statistical software packages. For continuous prognostic factors, the log-HR was standardized to a similar unit of measurement. As the included studies ranged a wide period of inclusion times, different TNM staging methods, and different treatment modalities, we used a random-effects model to pool results, utilizing the Paule-Mandel method for estimating between study variance τ [26]. In addition, between study heterogeneity was estimated using Higgin's & Tompson's I^2 [27]. We did not perform meta-regression, nor did we perform the Egger's test for publication bias as the number of studies was <10 for each comparison [28]. The meta-analysis was performed in R, version 3.6.3, using packages 'meta' and 'dmetar' [29,30].

Results

A total of 11,996 records were retrieved (519 duplicates; Fig. 1), consisting of 10,108 results on Medline, 1863 on Embase, and 25 on Cochrane. The 1595 publications selected for full text review yielded 53 original publications, 8 reviews and 3 editorials. After searching cross-references, a total of 65 original publications were included.

The 65 inclusions reported data of 144,513 stage III NSCLC patients (112,082 reported stage IIIA, 31,888 IIIB, and 53 IIIC; Table 1). These studies yielded a total of 26 unique CT-related prognostic factors. Most studies had a retrospective cohort study design; nine studies reported a prospective cohort study design [14,20,31–37]. In studies reporting follow-up duration, median follow-up ranged from 10 to 70.8 months. Thirty inclusions explicitly stated using a clinical staging method [12,14,16,21,31,33,36,38–60], while a combination of clinical and pathological staging was used in 3 studies [61–63]. The remaining 32 studies did not specify the staging method [11,13,15,17,18,20,32,34,35,37,64–85]. More recent staging systems TNM6 (2002, $n = 9$), TNM7 (2009, $n = 23$), and TNM8 (2017, $n = 3$) were used in 35 publications [11–13,15,16,33,35,36,38,39,42,46,47,49,51,52,54–57,59,61–63,65,66,68,72,73,75,76,78,80,81,85]. Use of less recent staging systems, such as TNM4 [48,67] and TNM5 [14,43,74,79], was stated in 6 inclusions. In

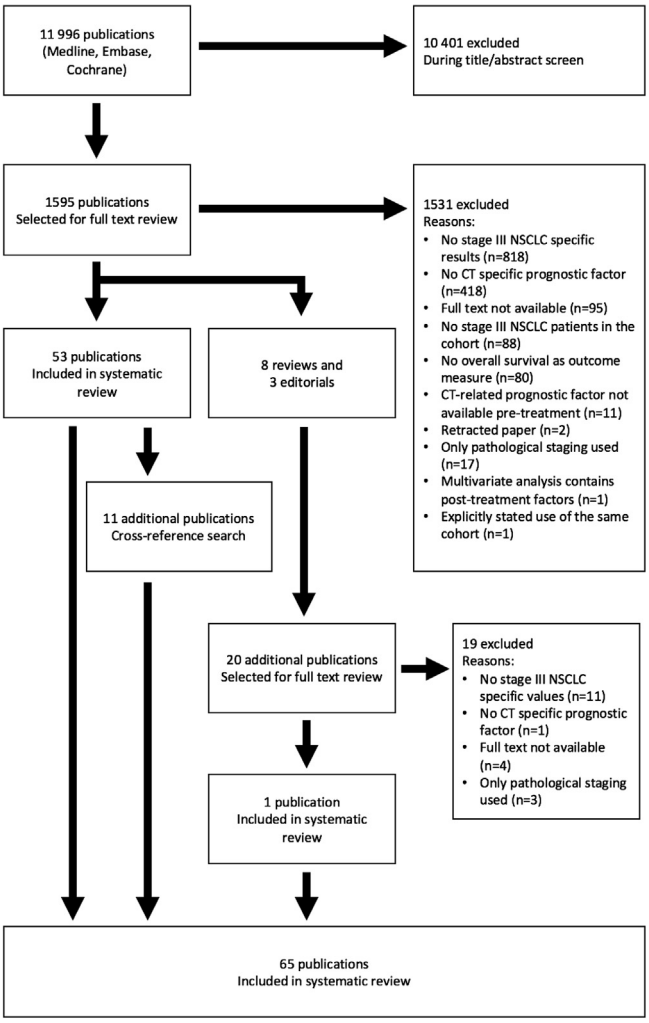

Fig. 1. Flow chart of study selection: Flow chart of study selection from the Medline, Embase, and Cochrane database. *Abbreviations:* CT: Computed tomography, NSCLC: Non-small cell lung cancer.

critical appraisal, studies that made use of the less recent staging systems were considered to be less relevant. The remaining 24 publications did not explicitly report the utilized staging system.

The stage III cohort generally consisted of multiple histological types with a majority of squamous cell carcinoma and adenocarcinoma patients, except for 2 studies which consisted solely of adenocarcinoma [17] or squamous cell carcinoma [51] patients and 10 studies in which histological type was not reported specifically for stage III patients [14,31,33,35,39,74] or at all [20,50,64,70]. Stage III patients were treated exclusively with chemotherapy and/or radiotherapy in 39 studies [11–13,15,18,20,21,31,32,34–36,41,45,47,48,51,53–56,58–60,64,65,67,70–72,74,76,77,80–85], while surgery was an option in 25 publications [14,16,17,33,37–40,42–44,46,49,50,52,57,61–63,66,68,73,75,78,79]. A single study did not report treatment modalities [69].

Finally, it should be taken into account that 4 studies made use of the Surveillance, Epidemiology, and End Results (SEER) database with a similar inclusion period and studied the same prognostic factor, indicating that their data is likely to overlap [49,68,69,78]. Overlap of recruitment period and measured prognostic factors was also present in 5 cohort studies that took place at the MD Anderson Cancer Center [11,35,41,65,76], and 2 at the Stanford University School of Medicine [64,70] and National Cancer Center Hospital East [45,52]. The results of studies with presumed overlapping data, taking the individual relevance and validity of the studies into consideration, were treated as results of a single study in data analysis.

The score for relevance ranged from low to high. Five publications were considered to have a high and 8 a low relevance, 52 a medium (Appendix Figure C.3, Table C.3). Low relevance was assigned due to a lack of explicit description of patient characteristics in the stage III cohort [32,50,69], or pronounced discrepancies with the standard stage III population [17,61–63,85]. Most studies ($n = 62$) were estimated to have a medium validity. Two studies were assessed to have a high validity [13,71] and 1 study had an estimated low validity, as it did not report confidence interval (CI) or p-values [11]. In Appendix C results of critical appraisal are described in more detail.

In the 65 inclusions, 26 individual CT-related prognostic factors for OS of stage III NSCLC patients were described. These 26 factors were divided in 5 categories: Radiomic features (Homogeneity, Kurtosis, Standard deviation, Entropy, Skewness, Mean HU, Largest axial slice average, Average, Largest axial slice uniformity, Busyness, Infomc1, Sosvariance), Size-related prognostic factors excluding T-stage (Tumor diameter, Tumor volume, Gross Tumor Volume), T-stage, Nodal factors (Lymph node volume, Lymph node diameter), and Other CT-related prognostic factors (Atelectasis, Location, Cavitation, Cavitary wall thickness, Interstitial lung abnormalities, Great vessel invasion, Pit-fall sign, Pleural effusion).

Two inclusions studied radiomic features, yielding 12 individual prognostic factors (Table 2) [11,12]. Both studies consisted of stage IIIA and IIIB patients treated with concurrent chemoradiation with a similar distribution of histological subtypes to other inclusions. The association between homogeneity, kurtosis, standard deviation, entropy, skewness, and mean Hounsfield unit (HU) and OS was studied in a single publication. Entropy and skewness were calculated from the HU-histogram. Entropy reflects irregularity in HU-values, while skewness reflects asymmetry of the histogram. While homogeneity, kurtosis, and standard deviation were not significant on univariate analysis, entropy, skewness, and mean HU were significant in both univariate and multivariable analysis [12]. In the second study, 8 radiomic features were measured on either contrast enhanced or 4D-CT scans giving rise to average intensity projection and expiratory phase images. Considering the diverse measurement techniques (LoG, IHIST, GRAD, NGTDM, COM), outcomes of 12 unique factors were reported as coefficients in a model for OS. This model was reported to be significantly better than the model containing solely conventional prognostic factors. However, metrics regarding individual statistical significance were not reported, meaning that while included factors are likely to be significant, their individual prognostic value remains uncertain. It should also be noted that the first study did not specify the utilized software, meaning that comparability of the 2 studies is decreased [11]. In summary, both inclusions indicated radiomic features with potential, including entropy, skewness, mean HU, largest axial slice average, largest axial slice uniformity, HU kurtosis, HU infomc1, HU standard deviation, and HU sosvariance, which should be validated in larger cohorts.

Three size-related prognostic factors were found across 38 inclusions (Table 3): Tumor diameter [16,32,34,38,45,48–52,57,58,60,68,69,78,83], Tumor volume [16,18,66,67,71,73,80,81], and Gross Tumor Volume (GTV) [11,13,15,18,21,35,41,47,54,64,65,70,73,74,76,77,80]. Tumor volume and GTV were considered unique prognostic factors, as GTV encompasses both the volume of the primary tumor and involved lymph nodes [11,13,15,18,41,64,65], where tumor volume includes only primary tumor volume [13,16,66,67,71].

Tumor diameter (the longest diameter of the primary tumor in the transverse plane) was tested as a prognostic factor for OS in 17 inclusions [16,32,34,38,45,48–52,57,58,60,68,69,78,83]. These

Table 1
Study characteristics.

7Study citation (PMID)	Study duration (start – end date)	Country	Source of data	Study design	CT-related prognostic factor	Number of stage III participants	TNM staging system used (estimation)	Treatment of the stage III NSCLC participants	NSCLC histological subtypes present	Outcome measure (follow-up)
Huo X, 2017 (29441096)	2005–2011	China	Cohort (The Second Hospital of Tianjin Medical University)	Retrospective	T-stage, Tumor diameter	Clinical stage: IIIA (26), IIIB (156)	NR (TNM6 or TNM7)	Iodine-125 seed implantation and chemotherapy	Squamous cell carcinoma (113), Adenocarcinoma (62), Not specified (7)	Median follow-up: 23 months
Li M, 2004 (15541820)	1994–1998	Japan	Cohort (Hospital of Jiangsu University)	Prospective	Pit-fall sign	Clinical stage: IIIA (10), IIIB (6)	TNM5	Surgery	Not specified for stage III; Overall study population: Squamous cell carcinoma (11), Adenocarcinoma (90), Large cell carcinoma (1), Adenosquamous cell carcinoma (1)	NR
Yilmaz U, 2018 (29559214)	2008–2015	Turkey	Cohort (Dr Suat Seren Chest Disease and Surgery Training and Research Hospital)	Retrospective	T-stage	Clinical stage: IIIA (20), IIIB (49), IIIC (10)	TNM8	Concurrent chemoradiotherapy	Squamous cell carcinoma (58), Not specified (21)	Median follow-up: 20.7 months
Firat S, 2002 (12243808)	1983–1991	USA	Cohort (4 RTOG-studies)	Retrospective	Tumor diameter	Clinical stage: IIIA (69), IIIB (43)	NR (TNM2 or TNM3)	Radiotherapy	Squamous cell carcinoma (79), Not specified (33)	NR
Lee HY, 2012 (22265854)	2004–2009	South Korea	Cohort (Samsung Medical Center)	Retrospective	Tumor diameter	Clinical stage: IIIAN2 (205)	TNM7	Neoadjuvant chemoradiotherapy and surgery	Squamous cell carcinoma (82), Adenocarcinoma (112), Large cell/ neuroendocrine carcinoma (6), Pleiomorphic carcinoma (1), Not specified (4)	Median follow-up: 19.2 months
Ahn SY, 2015 (26020832)	2006–2011	South Korea	Cohort (Seoul National University College of Medicine)	Retrospective	CT texture features (Homogeneity, Kurtosis, Standard deviation, Entropy, Skweness, Mean attenuation of primary tumors)	Clinical stage: IIIA (45), IIIB (53)	TNM7	Concurrent chemoradiotherapy	Squamous cell carcinoma (40), Adenocarcinoma (28), Not specified (30)	NR
Ryu JS, 2014 (24550423)	2002–2010	South Korea	Cohort (Inha University Hospital)	Retrospective	Pleural effusion	Clinical stage: IIIA (227), IIIB (248)	TNM7	Concurrent/sequential chemoradiotherapy (stage IIIA and IIIB), (neoadjuvant chemotherapy and surgery (stage IIIA), or cytotoxic chemotherapy (stage IIIB)	Not specified for stage III; Overall study population: Squamous cell carcinoma (863), Adenocarcinoma (1004), Not specified (194)	NR
Koo TR, 2014 (25498887)	2001–2009	South Korea	Cohort (Seoul National University College of Medicine)	Retrospective	Gross tumor volume, T-stage	NR Stage: IIIA (49), IIIB (108)	TNM7	Concurrent chemoradiotherapy	Squamous cell carcinoma (86), Adenocarcinoma (52), Large cell carcinoma (2), Not specified (17)	Median follow-up: 24.4 months

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Table 1 (*continued*)

7Study citation (PMID)	Study duration (start – end date)	Country	Source of data	Study design	CT-related prognostic factor	Number of stage III participants	TNM staging system used (estimation)	Treatment of the stage III NSCLC participants	NSCLC histological subtypes present	Outcome measure (follow-up)
Gensheimer MF, 2017 (28830717)	2006–2015	USA	Cohort (Stanford University School of Medicine)	Retrospective	Gross tumor volume	NR Stage: IIIA (36), IIIB (41)	NR (TNM6 or TNM7)	Concurrent chemoradiotherapy, or radiotherapy	NR	Median follow-up: 14 months
Fried DV, 2016 (26176655)	2008–2013	USA	Cohort (University of Texas MD Anderson Cancer Center)	Retrospective	T-stage, Gross tumor volume	NR Stage: IIIA (107), IIIB (88)	TNM7	Radiotherapy (and chemotherapy)	Squamous cell carcinoma (89), Not specified (106)	Median follow-up (surviving patients): 37 months
Fried DV, 2014 (25220716)	2004–2012	USA	Cohort (University of Texas MD Anderson Cancer Center)	Retrospective	Gross tumor volume, CT texture features (Average, Kurtosis, Busyness, Infomc1, Standard Deviation, Uniformity, Sosvariance on CE, AVG or T50 CT)	NR Stage: IIIA (45), IIIB (46)	TNM7	Concurrent chemoradiotherapy (and adjuvant chemotherapy)	Squamous cell carcinoma (46), Not specified (45)	Median follow-up (surviving patients): 59 months
Alexander BM, 2011 (20605346)	2000–2006	USA	Cohort (Brigham and Women's Hospital/Dana-Farber Cancer Institute)	Retrospective	Tumor volume, Nodal volume	NR Stage: IIIA (46), IIIB (61)	TNM6	Concurrent chemoradiotherapy (and surgery)	Squamous cell carcinoma (27), Adenosquamous carcinoma (38), Large cell carcinoma (4), Not specified (38)	Median follow-up: 15 months
Sibley GS, 1995 (7493826)	1987–1992	USA	Cohort (Micheal Reese Hospital)	Retrospective	Tumor volume, Atelectasis, T-stage	NR Stage: IIIA (18), IIIB (19)	TNM4	Radiotherapy (and chemotherapy)	Squamous cell carcinoma (23), Adenocarcinoma (6). Large cell carcinoma (2), Not specified (6)	Median follow-up: 18.9 months
Soussan M, 2013 (23306807)	2009–2011	France	Cohort (Avicenne University Hospital)	Retrospective	Tumor diameter, Tumor volume	Clinical stage: IIIA (23), IIIB (9)	TNM7	Induction chemotherapy and radiotherapy or surgery	Squamous cell carcinoma (16), Adenocarcinoma (12), Large cell carcinoma (4)	Median follow-up: 19 months
Watanabe Y, 2016 (27663793)	1998–2007	Japan	Cohort (National Cancer Center Hospital Tokyo)	Retrospective	Cavitary wall thickness	NR Stage: III (28)	NR (TNM5 or TNM6)	Surgery	Adenocarcinoma (28)	NR
Basaki K, 2006 (16226400)	1997–2003	Japan	Cohort (Hirosaki University Hospital)	Retrospective	T-stage, Gross tumor volume, Tumor volume, Nodal volume, Location	NR Stage: IIIA (30), IIIB (41)	NR (TNM5 or TNM6)	Radiotherapy (and chemotherapy)	Squamous cell carcinoma (56), Adenocarcinoma (12), Large cell carcinoma (2), Adenosquamous carcinoma (1)	Median follow-up: 34 months
Hyun SH, 2014 (23948859)	2003–2007	South Korea	Cohort (Samsung Medical Center)	Retrospective	T-stage	Pathological & clinical stage: IIIA (194)	TNM7	Surgery (and adjuvant chemotherapy and/or radiotherapy)	Squamous cell carcinoma (74), Adenocarcinoma (100), Large cell carcinoma (6), Not specified (14)	Median follow-up: 54 months
William WN, 2009 (19318668)	1998–2003	USA	Cohort SEER database	Retrospective	Tumor diameter	NR Stage: IIIB (22091)	TNM6	Surgery and/or radiotherapy	Squamous cell carcinoma (5725), adenocarcinoma (6841), Large cell carcinoma (1410), Bronchialveolar carcinoma (482), Not specified (6169)	NR
Morgensztern D, 2012 (22982648)	1998–2003	USA	Cohort SEER database	Retrospective	Tumor diameter	NR Stage: IIIA (6327), IIIB (5988)	NR (TNM7)	NR	Squamous cell carcinoma (3920), Adenocarcinoma (3500), Large cell carcinoma (768), Not	Median follow-up: 10 months

									specified (4127)	
Hyun SH 2015 (26295651)	2008–2013	South Korea	Cohort (Samsung Medical Center)	Retrospective	T-stage	Clinical stage: IIIA (161)	NR (TNM6 or TNM7)	Surgery (and adjuvant chemotherapy and/or radiotherapy)	Squamous cell carcinoma (56), Adenocarcinoma (92), Not specified (13)	Median follow-up (surviving patients): 20 months
Bulbul Y, 2010 (20636252)	2006–2008	Turkey	Cohort (Farabi Hospital)	Prospective	Atelectasis/ Obstructive pneumonitis	NR stage: IIIA (8), IIIB (32)	NR (TNM6 or TNM7)	Sequential chemoradiotherapy	NR	NR
Wald P, 2017 (28843360)	2012–2016	USA	Cohort (The Ohio State University Wexner Medical Center)	Retrospective	T-stage, Gross tumor volume	Clinical stage: IIIA (39), IIIB (13)	NR (TNM7)	Concurrent chemoradiotherapy (and induction/consolidative chemotherapy)	Squamous cell carcinoma (30), Adenocarcinoma (19), Not specified (3)	Median follow-up: 19.3 months
Xiang ZL, 2012 (22929048)	2005 – NR	USA	Cohort (University of Texas MD Anderson Cancer Center)	Retrospective	Gross tumor volume	Clinical stage: III (84)	NR (TNM6 or TNM7)	Concurrent chemoradiotherapy	Squamous cell carcinoma (38), Adenocarcinoma (34), Not specified (12)	Median follow-up: 19.2 months
Wu J, 2016 (27212196)	2005–2009	USA	Cohort (Stanford University School of Medicine)	Retrospective	Gross tumor volume	NR Stage: IIIA (12), IIIB (20)	NR (TNM6 or TNM7)	Radiotherapy (and chemotherapy)	NR	Not specified for stage III, Entire cohort: Median follow-up: 20.2 months
Elsayad K, 2018 (29623466)	2013–2017	Germany	Cohort (University Hospital Münster)	Retrospective	Gross tumor volume	NR stage: IIIA (26), IIIB (13), IIIC (11)	TNM8	Radiotherapy (and chemotherapy)	Squamous cell carcinoma (22), Adenocarcinoma (25), Other (3)	Median follow-up: 10 months
Jie Y, 2017 (NA)	2009–2012	China	Cohort (Shangdong Cancer Hospital)	Retrospective	T-stage, Tumor volume, Location	NR Stage: IIIA (35), IIIB (43)	NR (TNM7)	Concurrent chemoradiotherapy	Squamous cell carcinoma (33), Adenocarcinoma (34), Not specified (11)	Median follow-up: 24.5 months
Shien K, 2015 (NA)	1999–2011	Japan	Cohort (Okayama University Hospital)	Retrospective	Location	Clinical stage: IIIA (44), IIIB (32)	TNM7	Surgery and induction chemoradiotherapy	Squamous cell carcinoma (30), Adenocarcinoma (43), Adenosquamous cell carcinoma (1), Large cell carcinoma (2)	Median follow-up: 64 months
Crvenkova S, 2015 (NA)	2005–2008	Macedonia	Cohort (University Clinic of Radiotherapy and Oncology Skopje)	Prospective	Tumor diameter	NR stage: IIIB (85)	NR (TNM6 or TNM7)	Concurrent/sequential chemoradiotherapy	Squamous cell carcinoma (56), Adenocarcinoma (16), Large cell carcinoma (5), Not specified (8)	Median follow-up: 36 months
Saga T, 2015 (NA)	2010–2014	Japan	Cohort (Cancer Institute Hospital)	Prospective	T-stage	Clinical stage: IIIA (12), IIIB (11)	NR (TNM7)	Concurrent/sequential chemoradiotherapy	Not specified for stage III, Overall study population: Squamous cell carcinoma (11), Adenocarcinoma (19), Large cell carcinoma (8)	NR
Li J, 2009 (NA)	1998–2004	China	Cohort (Hospital of Jiangsu University)	Retrospective	T-stage	Clinical stage: IIIA (91)	TNM5	Surgery and neo adjuvant chemotherapy and/or radiotherapy	Squamous cell carcinoma (40), Adenocarcinoma (44), Large cell carcinoma (4), Undifferentiated NSCLC (3)	Median follow-up: 43 months
Dong X, 2016 (NA)	2007–2010	China	Cohort (Shangdong Cancer Hospital)	Retrospective	T-stage, Location	NR stage IIIA (24), IIIB (34)	TNM6	Concurrent chemoradiotherapy	Squamous cell carcinoma (30), Adenocarcinoma (25), Not specified (3)	Median follow-up: 60 months
Agrawal V, 2017	2003–2013	USA	Cohort (Brigham	Retrospective	T-stage, Gross tumor	NR Stage:	TNM7	Concurrent	Squamous cell carcinoma	Median

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Table 1 (*continued*)

7Study citation (PMID)	Study duration (start – end date)	Country	Source of data	Study design	CT-related prognostic factor	Number of stage III participants	TNM staging system used (estimation)	Treatment of the stage III NSCLC participants	NSCLC histological subtypes present	Outcome measure (follow-up)
(28426673)			and Women's Hospital/Dana-Farber Cancer Institute)		volume, Tumor volume	IIIA (61), IIIB (12)		chemoradiotherapy and surgery	(16), Adenocarcinoma (48), Not specified (9)	follow-up: 36 months
Phernambucq ECJ, 2012 (22659960)	2003–2010	The Netherlands	Cohort (VU University Medical Center)	Retrospective	Tumor cavitation	Clinical stage: IIIA (36), IIIB (51)	NR (TNM6 or TNM7)	Concurrent chemoradiotherapy (and surgery)	Squamous cell carcinoma (37), Adenocarcinoma (28), Large cell carcinoma	NR
Chaft JE, 2013 (23857398)	2005–2011	USA	Cohort (Memorial Sloan-Kettering Cancer Center)	Prospective	Tumor cavitation	Clinical stage: IIIA (34)	TNM6	Neoadjuvant chemoradiotherapy, adjuvant immunotherapy and surgery	Not specified for stage III; Overall study population: Adenocarcinoma (45), Large cell carcinoma (4), Adenosquamous carcinoma (1)	Median follow-up: 29 months
Chang JY, 2017 (28727865)	2009–2011	USA	Cohort (University of Texas MD Anderson Cancer Center)	Prospective	Tumor diameter, Location	NR stage: IIIA (30), IIIB (34)	NR (TNM7)	Concurrent chemoradiotherapy	Squamous cell carcinoma (28), Adenocarcinoma (25), Not specified (11)	Median follow-up: 27.3 months
Naito Y, 2008 (18520801)	2000–2004	Japan	Cohort (National Cancer Center Hospital)	Retrospective	Tumor diameter	Clinical stage: IIIA (26), IIIB (47)	NR (TNM5 or TNM6)	Concurrent chemoradiotherapy	Squamous cell carcinoma (28), Adenocarcinoma (29), Not specified (16)	Median follow-up: 35 months
Shumway, 2011 (21676484)	1999–2010	USA	Cohort (The University of Chicago)	Retrospective	T-stage	Clinical stage: IIIA (44), IIIB (9)	TNM6	Concurrent chemoradiotherapy and surgery	Squamous cell carcinoma (19), Adenocarcinoma (22), Large cell carcinoma (2), Not specified (10)	Median follow-up: 19 months
Nguyen QN, 2015 (26028228)	2006–2010	USA	Cohort (University of Texas MD Anderson Cancer Center)	Prospective	Gross tumor volume	NR stage: IIIA (70), IIIB (43)	TNM6	Concurrent chemoradiotherapy	Not specified for stage III; Overall study population: Squamous cell carcinoma (59), Not specified (75)	Median follow-up: 56.4 months
Etiz D, 2002 (12095548)	1991–1998	USA	Cohort (Duke University Medical Center)	Retrospective	Gross tumor volume	NR stage: IIIA (47), IIIB (64)	TNM5	Concurrent chemoradiotherapy (and induction/adjuvant chemotherapy)	Not specified for stage III; Overall study population: Squamous cell carcinoma (66), Adenocarcinoma (33), Large cell carcinoma (20), Not specified (31)	Median follow-up: 13.2 months
Akcam TI, 2015 (NA)	2005–2011	Turkey	Cohort (Dr Suat Seren Chesr Disease and Surgery Training and Research Hospital)	Retrospective	T-stage, Location	NR stage: IIIA (74), IIIB (37)	TNM7	Surgery and adjuvant chemotherapy	Squamous cell carcinoma (59), Adenocarcinoma (50), Large cell carcinoma (2)	Mean follow-up: 31.8 months
Zhou R, 2018 (NA)	2005–2013	USA	Cohort (University of Texas MD Anderson Cancer Center)	Retrospective	T-stage, Gross tumor volume	NR stage: IIIA (234), IIIB (257)	TNM6	Concurrent chemoradiotherapy (and induction/adjuvant chemotherapy)	Squamous cell carcinoma (182), Not specified (309)	NR

Park YJ, 2015 (NA)	2009–2011	South Korea	Cohort (Ansan Hospital)	Retrospective	Gross tumor volume	Clinical stage: IIIA (8), IIIB (23)	TNM7	Concurrent chemoradiotherapy	Squamous cell carcinoma (20), Adenocarcinoma (9), Not specified (2)	NR
Oberije C, 2015 (25936599)	2002–2011	The Netherlands	Cohort (MAASTRO clinic)	Prospective	T-stage, Nodal volume	Clinical stage: IIIA (199), IIIB (349)	TNM6	Concurrent/sequential chemoradiotherapy	Squamous cell carcinoma (164), Adenocarcinoma (81), Large cell carcinoma (190), Not specified (113)	Median follow-up: 66 months
Warner A, 2016 (26867890)	1995–2010	Europe, USA, Asia	Cohort (13 institutions)	Retrospective	Gross tumor volume	NR stage: IIIA (366), IIIB (650), IIINR (143)	NR (TNM5 or TNM6)	Concurrent chemoradiotherapy	Squamous cell carcinoma (338), Adenocarcinoma (289), Large cell carcinoma (145), Not specified (473)	Median follow-up: 43.5 months
Hayakawa K, 1996 (8765179)	1976–1989	Japan	Cohort (Gunma University Hospital)	Retrospective	T-stage, Tumor diameter Location	Clinical stage: IIIA (81), IIIB (60)	TNM4	Radiotherapy (and chemotherapy)	Squamous cell carcinoma (104), Adenocarcinoma (24), Large cell carcinoma (13)	NR
Mao Q, 2018 (29554790)	2004–2009	USA	Cohort SEER database	Retrospective	Tumor diameter, Location	NR stage: IIIA (1809)	TNM7	Surgery and/or radiotherapy	Squamous cell carcinoma (444), Adenocarcinoma (1294), Large cell carcinoma (71)	Median follow-up: 39 months
Pang Z, 2017 (29268415)	2004–2011	USA	Cohort SEER database	Retrospective	Tumor diameter, Location	Clinical stage: IIIA (98700)	TNM7	Surgery and/or radiotherapy	Squamous cell carcinoma (21748), Adenocarcinoma (32175), Not specified (37251)	NR
Broderick SR, 2016 (26410162)	1998–2010	USA	Cohort NCDB	Retrospective	T-stage, Tumor diameter	Clinical stage: IIIA (542)	NR (TNM7)	Surgery and neoadjuvant/adjuvant chemoradiotherapy	NR	NR
Hwang IG, 2008 (18623378)	1997–2003	South Korea	Cohort (Samsung Medical Center)	Retrospective	T-stage	NR stage: IIIA (68)	TNM5	Surgery and neoadjuvant concurrent chemoradiotherapy	Adenocarcinoma (41), Not specified (27)	Median follow-up: 61.8 months
Topkan E, 2018 (29887509)	2007–2013	Turkey	Cohort (Baskent University Medical Faculty)	Retrospective	Tumor diameter, Tumor cavitation	Clinical stage: IIIA (154), IIIB (635)	TNM7	Concurrent chemoradiotherapy	Squamous cell carcinoma (789)	Median follow-up: 22.9 months
Hishida T, 2014 (24203815)	1993–2008	Japan	Cohort (National Cancer Center Hospital)	Retrospective	Tumor diameter, Location	Clinical stage: IIIA (97)	TNM6	Surgery (and adjuvant chemotherapy and/or radiotherapy)	Squamous cell carcinoma (25), Adenocarcinoma (52), Large cell carcinoma (6), Adenosquamous carcinoma (7), Not specified (7)	Median follow-up: 70.8 months
Horinouchi H, 2012 (23004347)	1999–2003	Japan	Cohort (National Cancer Center Hospital)	Retrospective	T-stage	Clinical stage: IIIA (50), IIIB (61)	NR (TNM5 or TNM6)	Concurrent chemoradiotherapy	Squamous cell carcinoma (26), Adenocarcinoma (71), Large cell carcinoma (6), Adenosquamous carcinoma (1), Not specified (7)	NR
Betticher DC, 2006 (16622435)	1997–2000	Switzerland	Multicenter	Prospective	T-stage, Nodal enlargment	NR stage: IIIA (75)	NR (TNM5)	Surgery and neo adjuvant chemotherapy and/or radiotherapy	Squamous cell carcinoma (32), Adenocarcinoma (23), Large-cell carcinoma (9), Not specified (11)	Median follow-up: 60 months
Kanzaki H, 2016 (27125214)	2006–2012	Japan	Cohort (Shikoku Cancer Center Hospital)	Retrospective	T-stage, Gross tumor volume	Clinical stage: III (111)	TNM7	Concurrent/sequential chemoradiotherapy or radiotherapy	Squamous cell carcinoma (45), Adenocarcinoma (48), Large cell carcinoma (5), Not specified (13)	Median follow-up: 52.2 months
Lee VHF, 2016	2006–2012	Hong Kong	Cohort (Li Ka	Retrospective	Gross tumor volume,	NR stage:	TNM7	Concurrent	Squamous cell carcinoma	Median

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Table 1 (*continued*)

7Study citation (PMID)	Study duration (start – end date)	Country	Source of data	Study design	CT-related prognostic factor	Number of stage III participants	TNM staging system used (estimation)	Treatment of the stage III NSCLC participants	NSCLC histological subtypes present	Outcome measure (follow-up)
(24710123)			Shing Faculty of Medicine)		Tumor volume, Nodal volume	IIIA (18), IIIB (25)		chemoradiotherapy (and induction/adjuvant chemotherapy)	(9), Adenocarcinoma (25), Not specified (9)	follow-up: 41.5 months
Casiraghi M, 2019 (30446406)	1998–2015	Italy	Cohort (European Institute of Oncology, Milan)	Retrospective	Location	Pathological & clinical stage: IIIA (233)	TNM7	Surgery and neo adjuvant chemotherapy and/or radiotherapy	Squamous cell carcinoma (89), Adenocarcinoma (117), Large cell carcinoma (3), Adenosquamous carcinoma (8), Pleomorphic carcinoma (9), Carcino-sarcoma (1), Not specified (6)	Median follow-up: 24 months
Higo H, 2019 (30793176)	2012–2015	Japan	Cohort (Okayama University Hospital)	Retrospective	Interstitial lung abnormalities	Clinical stage: III (71)	TNM7	Chemoradiotherapy	Squamous cell carcinoma (25), Adenocarcinoma (40), Not specified (6)	NR
Kim E, 2019 (30266585)	2006–2013	South Korea	Cohort (SMG-SNU Boramae Medical Center)	Retrospective	T-stage	Clinical stage: IIIA (72), IIIB (58)	TNM7	Concurrent chemoradiotherapy	Squamous cell carcinoma (64), Adenocarcinoma (44), Not specified (22)	Mean follow-up: 51.3 months
Dieleman EMT, 2018 (30055239)	2005–2015	The Netherlands	Cohort (AMC)	Retrospective	Tumor volume, Nodal volume	NR stage: IIIA (116), IIIB (38)	TNM7	Concurrent chemoradiotherapy	Squamous cell carcinoma/ Large cell carcinoma (118), Adenocarcinoma (36)	Median follow-up: 22 months
Yoo GS, 2019 (30544255)	1996–2015	South Korea	Cohort (Samsung Medical Center)	Retrospective	Great vessel invasion	NR Stage: IIIA (13), IIIB (24)	NR (TNM7)	Concurrent chemoradiotherapy	Squamous cell carcinoma (21), Adenocarcinoma (11), Not specified (5)	Median follow- up: 17 months
Pusceddu C, 2019 (31289539)	2010–2013	Italy	Cohort (Oncological Hospital A. Businco)	Retrospective	Tumor diameter	NR stage: IIIB/C (53)	NR (TNM8)	Microwave ablation	Squamous cell carcinoma (13), Adenocarcinoma (51), Large cell carcinoma (1)	Median follow-up: 21.5 months
Konert T, 2019, (31367906)	2010–2014		Multicenter	Retrospective	T-stage	NR stage: IIIA (145), IIIB (53), IIIC (32)	NR (TNM8)	Concurrent/sequential chemoradiotherapy or radiotherapy	Squamous cell carcinoma (90), Adenocarcinoma (97), Large cell carcinoma (15), Not specified (28)	Median follow-up: 15 months
Maniwa T, 2018 (30746228)	2006–2013	Japan	Cohort (12 thoracic surgery departments belonging to the Thoracic Surgery Study Group of Osaka University)	Retrospective	T-stage, Tumor diameter	Clinical stage: IIIA (92), IIIB (2)	TNM7	Surgery and adjuvant chemotherapy	Adenocarcinoma (65), Not specified (29)	Median follow-up: 56.5 months
Tao X, 2019 (31179087)	2007–2016	China	Cohort (Fudan University Shanghai Cancer Center)	Retrospective	T-stage, Location	Pathological & clinical stage: IIIA (603)	TNM8	Surgery and neoadjuvant/adjuvant chemoradiotherapy	Squamous cell carcinoma (135), Adenocarcinoma (425), Adenosquamous carcinoma (26), Not specified (17)	Median follow-up: 31.98 months
Kim DY, 2019 (31591865)	2004–2016	South Korea	Cohort (Seoul National University Bundang Hospital)	Retrospective	T-stage	NR stage IIIA (56), IIIB (26)	TNM7	Chemoradiotherapy	Squamous cell carcinoma (52), Adenocarcinoma (16), Not specified (14)	Median follow-up (surviving patients): 20.1 months

Table 2
Summary of findings radiomics and other CT-related prognostic factors.

Radiomic feature related prognostic factor	Study citation (First author, year (PMID))	Description texture measurement	Description prognostic factor groups	Number of patients	OS	Univariate analysis (estimate (95% CI))	Multivariable analysis (estimate (95% CI)	Factors corrected for in multivariable analysis
Homogeneity	Ahn SY, 2015 (26020832)	CE-CT	>0.03 vs ≤0.03	54/44	Mean (months): 24.8/Median (months): 23.0	$p = 0.483$		
Kurtosis	Ahn SY, 2015 (26020832)	CE-CT	>9.932 vs ≤9.932	49/49	Mean (months): 25.3/Median (months): 21.0	$p = 0.488$		
	Fried DV, 2014 (25220716)	CE-CT; IHIST	Continuous	91			HR: 0.978	
		T50-CT; GRAD	Continuous	91			Not included in model	
Standard deviation	Ahn SY, 2015 (26020832)	CE-CT	>36.411 vs ≤36.411	43/55	Mean (months): 26.0/Median (months): 21.0	$p = 0.295$		
	Fried DV, 2014 (25220716)	AVG-CT; LoG	Continuous	91			HR: 1.024	
Entropy	Ahn SY, 2015 (26020832)	CE-CT	≤4.445 vs >4.445	23/75	Mean (months): 29.8/Median (months): 20.0	$p = 0.030$	HR: 2.31 (1.031–5.226) $p = 0.040$	Skewness, Mean HU
Skewness	Ahn SY, 2015 (26020832)	CE-CT	≤−2.374 vs >−2.374	38/60	Mean (months): 28.1/Median (months): 19.0	$p = 0.021$	HR: 1.92 (1.013–3.642) $p = 0.046$	Entropy, Mean HU
Mean HU	Ahn SY, 2015 (26020832)	CE-CT	≤43.448 vs >43.448	49/49	Mean (months): 26.8/Median (months): 17.0	$p = 0.030$	HR: 1.93 (1.074–3.454) $p = 0.028$	Entropy, Skewness
Largest axial slice average	Fried DV, 2014 (25220716)	CE-CT; LoG; Sigma = 1	Continuous	91			HR: 1.15	
		T50-CT; LoG; sigma = 1.5	Continuous	91			HR: 0.923	
Average	Fried DV, 2014 (25220716)	CE-CT; LoG; Sigma = 1	Continuous	91			Not included in model	
Largest axial slice uniformity	Fried DV, 2014 (25220716)	AVG-CT; LoG; Sigma = 1	Continuous	91			HR: 1.54	
		AVG-CT; LoG; sigma = 2.5	Continuous	91			HR: 1.73	
		T50-CT; LoG; Sigma = 1.5	Continuous	91			Not included in model	
Busyness	Fried DV, 2014 (25220716)	CE-CT; NGTDM	Continuous	91			Not included in model	
Infomc1	Fried DV, 2014 (25220716)	CE-CT, COM	Continuous	91			HR: 12.2	
Sosvariance	Fried DV, 2014 (25220716)	T50-CT; COM	Continuous	91			HR: 1.0011	
Other CT-related prognostic factor	Study citation (First author, year (PMID))	Description prognostic factor groups	Number of patients	OS	Univariate analysis (estimate (95% CI))	Multivariable analysis (estimate (95% CI)	Factors corrected for in multivariable analysis	
Atelectasis/ Obstructive pneumonitis	Sibley GS, 1995 (7493826)	None vs <50% vs >50%	21/5/11.	Median (months): 18.3/19.5/19.8 1y survival rate (%): 61/100/91 2y survival rate (%): 45/0/28	$p = 0.98$			
	Bulbul Y, 2010 (20636252)	Negative vs Positive (Stage IIIA & IIIB patients)		Median (months): 14.5/9.8 1y survival rate (%): 67.2/40.0	$p = 0.032$			
		Negative vs Positive (Stage IIIB patients)		Median (months): 13.9/9.3 1y survival rate (%): 72.2/35.8	$p = 0.044$			
Interstitial lung abnormalities	Higo H, 2019 (30793176)	Positive vs Negative			$p = 0.49$			

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Table 2 (*continued*)

Radiomic feature related prognostic factor	Study citation (First author, year (PMID))	Description texture measurement	Description prognostic factor groups	Number of patients	OS	Univariate analysis (estimate (95% CI))	Multivariable analysis (estimate (95% CI)	Factors corrected for in multivariable analysis
Location	Dong X, 2016 (27322376)	Right vs Left	40/18		HR: 1.756 (0.718–1.958) $p = 0.637$			
	Basaki K, 2006 (16226400)	Right vs Left	41/30	Median (months): 14/12 2y survival rate (%): 18/29	Not significant			
		Hilar vs Upper vs Middle-lower	33/29/9	Median (months): 15/12/9 2y survival rate (%): 29/20/0	Not significant			
	Pang Z, 2017 (29268415)	Left vs Right	35946/58435		HR: 1.006 (0.992–1.020) $p = 0.406$			
	Casiraghi M, 2019 (30446406)	Right vs Left	130/103		HR: 0.98 (0.72–1.33) $p = 0.89$			
	Jie Y, 2017 (NA)	Central vs Peripheral	37/41		HR: 1.464 (0.871–2.463) $p = 0.151$			
	Tao X, 2019 (31179087)	Cental vs Peripheral	128/475		HR: 1.08 (0.74–1.57) $p = 0.6843$			
	Shien K, 2015 (NA)	Non-lower lobe vs Lower lobe	58/18	5y survival rate (%): 77.0/37.9	$p = 0.022$			
	Chang JY, 2017 (28727865)	Left lung or right lower lobe vs Right middle or right upper lobe				HR: 1.90 (1.03–3.50) $p = 0.04$	KPS, Overall stage, Tumor size	
	Akcam TI, 2015 (NA)	Upper lobe vs Middle lobe vs Lower lobe	64/3/44			HR: 1.538 (0.968–2.445) $p = 0.069$	Age, Histology, T-stage, Multi-single station	
	Hayakawa K, 1996 (8765179)	Upper lobe vs Superior segment of the lower lobe vs Lower lobe vs Main or intermediate bronchus	83/19/28/11	Median (months): 13.5/16/12/9.5 2y survival rate (%): 25/42/12/0 5y survival rate (%): 16/5/4/0	$p = 0.032$			
		Upper lobe + Superior segment of the lower lobe vs Lower lobe	102/28			HR: 1.51 (1.12–2.04) $p = 0.0085$	Age, Gender, PS, Histology, Tumor size, T-stage, N-stage, Total dose, Field size	
		Upper lobe + Superior segment of the lower lobe vs Main or intermediate bronchus	102/11			HR: 2.28 (1.24–4.16) $p = 0.0085$	Age, Gender, PS, Histology, Tumor size, T-stage, N-stage, Total dose, Field size	
	Mao Q, 2018 (29554790)	Main bronchus vs Upper lobe	22/1043	Median (months): 36.0/40.0	HR: 0.856 (0.427–1.714) $p = 0.660$			
		Main bronchus vs Middle lobe	22/84	Median (months): 36.0/42.0	HR: 0.697 (0.418–1.162) $p = 0.167$			
		Main bronchus vs Lower lobe	22/602	Median (months): 36.0/34.0	HR: 0.665 (0.374–1.181) $p = 0.164$			
		Main bronchus vs Overlap lobe	22/39	Median (months): 36.0/28.0	HR: 0.790 (0.472–1.321) $p = 0.368$			
	Hishida T, 2014 (24203815)	Upper lobe vs Middle or lower lobe	29/16	5y survival rate (%): 29.2/12.5	$p = 0.208$			

Pit-fall sign	Li M, 2004 (15541820)	Negative vs Positive (Stage III patients)	10/6.	5y survival rate (%): 25.0/50.0	$p = 0.470$		
		Negative vs Positive (Stage IIIA patients)	7/3.	5y survival rate (%): 14.3/33.3	$p = 0.579$		
		Negative vs Positive (Stage IIIA patients)	3/3.	5y survival rate (%): 66.7/66.7	$p = 0.886$		
Pleural effusion	Ryu JS, 2014 (24550423)	No pleural effusion vs Minimal pleural effusion (Stage IIIA patients)	197/30	Median (months): 17.7/10.6	HR: 2.12 (1.39–3.23) $p = 0.0003$	HR: 1.62 (0.95–2.94)	Gender, Age, Smoking habit, CCI score, ECOG, Weight loss, Hemoglobin, Albumin, Alkaline phosphatase, Calcium, Histology, EGFR mutation, Tumor size, N stage, Number of organs effected by metastasis, PET, Treatment
		No pleural effusion vs Minimal pleural effusion (Stage IIIB patients)	189/59	Median (months): 14.5/7.8	HR: 1.65 (1.22–2.21) $p < 0.0001$	HR: 1.57 (1.08–2.28)	Gender, Age, Smoking habit, CCI score, ECOG, Weight loss, Hemoglobin, Albumin, Alkaline phosphatase, Calcium, Histology, EGFR mutation, Tumor size, N stage, Number of organs effected by metastasis, PET, Treatment
Cavitary wall thickness	Watanabe Y, 2016 (27663793)	≤4.5 mm ('thin') vs >4.5 mm ('thick')	7/21.		$p = 0.96$		
Cavitation	Phernambucq ECJ, 2012 (22659960)	Positive vs negative	16/71.	Median (months): 9.9/16.3	$p = 0.09$		
	Chaft JE, 2013 (23857398)	Positive vs negative		3y survival rate (%): 57/44	$p = 0.48$		
	Topkan E, 2018 (29887509)	Positive vs negative	694/95.	Median (months): 24.1/15.7	$p < 0.001$	HR: 1.54 (1.37–1.71) $p < 0.001$	Overall stage, Weight loss status, Anemia
Great vessel invasion	Yoo GS, 2019 (30544255)	Aortic arch	4	2y survival rate (%): 75.0	$p = 0.065$	HR: 0.058 (0.002–2.25) $p = 0.127$	Age, Gender, PS, Histology, N-stage
		Descending aorta	3	2y survival rate (%): 33.3	$p = 0.189$	HR: 3.60 (0.30–43.02) $p = 0.312$	Age, Gender, PS, Histology, N-stage
		Pulmonary artery	13	2y survival rate (%): 51.9	$p = 0.883$	HR: 0.53 (0.074–3.73) $p = 0.520$	Age, Gender, PS, Histology, N-stage
		Superior vena cava	10	2y survival rate (%): 62.5	$p = 0.579$	HR: 0.16 (0.008–3.31) $p = 0.235$	Age, Gender, PS, Histology, N-stage
		Heart	11	2y survival rate (%): 24.5	$p = 0.218$	HR: 1.94 (0.24–15.75) $p = 0.537$	Age, Gender, PS, Histology, N-stage

Outcomes concerning radiomic features and other CT-related prognostic factors in univariate and multivariable analysis of the included studies. Estimates are reported with 95% confidence interval and *p*-value when available. Used statistical models are: Cox proportional hazard model, log-rank test (LR). Abbreviations: AVG: Average intensity projection image, CCI: Charlson comorbidity index, CE-CT: Contrast enhanced computed tomography, CI: Confidence interval, COM: Co-occurrence matrix, ECOG: Eastern cooperative oncology group, EGFR: Epidermal growth factor receptor, GRAD: Absolute gradient, HR: Hazard ratio, HU: Hounsfield unit, IHIST: Histogram, LoG: Laplacian of Gaussian filter, NGTDM: Nearest gray tone difference matrix, OS: Overall survival, PET: Positron emission tomography, PMID: PubMed identification number, T50: Expiratory image.

Table 3
Summary of findings size-related prognostic factors.

Size-related prognostic factors	Study citation (First author, year (PMID))	Description prognostic factor groups	Number of patients	OS	Univariate analysis (estimate (95% CI))	Multivariable analysis (estimate (95% CI)	Factors corrected for in multivariable analysis
Gross tumor volume (GTV)	Koo TR, 2014 (25498887)	$\leq$50 cm^3 vs >50 cm^3	33/124	3y survival rate (%): 65.7/28.4	$p < 0.001$		
		Continuous		Median (months): 25.5; 3y survival rate (%): 36.4	HR: 1.001 (1.000–1.002) $p = 0.019$		
	Basaki K, 2006 (16226400)	<85 mL vs >85 mL	36/35	Median (months): 18/11; 2y survival rate (%): 34/10	$p = 0.0003$	HR: 1.05 (1.02–1.09) $p < 0.01$	PS, 2 Gy equivalent dose, Age, Chemotherapy, Histology, T-stage, N-stage
	Xiang ZL, 2012 (22929048)	<96.6 cm^3 vs $\geq$96.6 cm^3	42/42		HR: 1.764 (0.866–3.592) $p = 0.118$		
	Etiz D, 2002 (12095548)	<97 cm^3 vs $\geq$97 cm^3				$p = 0.006$	Age, Gender, KPS, Weight loss, N-stage, Total dose (6 Gy), Fractionation schedule, Chemotherapy
	Park YJ, 2015 (NA)	$\geq$90 cm^3 vs <90 cm^3		Median (months); 15.8/13.0	$p = 0.670$		
	Warner A, 2016 (26867890)	$\geq$100 cm^3 vs <100 cm^3			OR: 2.53 (1.53–4.18) $p < 0.001$	OR: 2.61 (1.10–6.20) $p = 0.029$	FEV
		Continuous (50 cm^3)	1245	Median (months): 20.94; 1y survival rate (%): 70.6%; 2y survival rate (%): 45.1; 3y survival rate (%): 31.5; 4y survival rate (%): 26.8; 5y survival rate (%): 22.0	OR: 1.08 (1.00–1.17) $p = 0.053$	OR: 1.04 (0.93–1.17) $p = 0.475$	FEV
	Wu J, 2016 (27212196)	<median vs > median	16/16		HR: 2.75 (1.13–6.72) $p = 0.020$	HR: 1.00 (0.99–1.00) $p = 0.410$	High-risk tumor volume, Overall stage, KPS
	Gensheimer MF, 2017 (28830717)	Continuous	77	Median (months): 23; 2y survival rate: 46%	HR: 1.33 (0.94–1.90) $p = 0.110$		
	Fried DV, 2016 (26176655)	Continuous	195			HR: 1.252, $p = 0.01$	Overall stage, T-stage, Induction chemotherapy, Age, Gender, KPS, Co-occurance matrix energy, Solidity
	Fried DV, 2014 (25220716)	Continuous	91			HR: 1.0024	Age, ECOG, Histology, Gender, Texture features (Average, Kurtosis, Busyness, Infomc1, Standard Deviation, Uniformity, Sosvariance on CE, AVG or T50 CT)
	Wald P, 2017 (28843360)	Continuous	53	2y survival rate (%): 53.9	HR: 1.00 (1.00–1.01) $p = 0.983$		
	Elsayad K, 2018 (29623466)	Continuous	50	Median (months): 20; 2y survival rate (%): 46	HR: 1.002 (1–1.004), $p = 0.06$		
	Agrawal V, 2017 (28426673)	Continuous	73	Median (months): 78; 1y survival rate (%): 85; 3y survival rate (%): 68	HR: 1.00 (0.99–1.00) $p = 0.72$		
	Nguyen QN, 2015 (26028228)	Continuous	113	Median (months): 30.4	HR: 1.437 (1.531–1.7918) $p = 0.00124$	HR: 1.474 (1.177–1.845) $p = 0.007$	Age
	Zhou R, 2018 (NA)	Continuous	491	Median (months): 21; 1y survival rate (%): 85.5; 2y survival rate (%): 61.2; 3y survival rate (%): 44.5; 4y survival rate (%): 37.0; 5y survival rate (%): 31.6	HR: 1.00 (1.000–1.004) $p = 0.042$		

	Kanzaki H, 2016 (27125214)	Continuous (10 mL)	111	Median (months): 21.7; 5y survival rate (%): 22.6	HR: 1.02 (1.00–1.04) $p = 0.013$		
	Lee VHF, 2016 (24710123)	Continuous	43	Median (months): 37.8	$p = 0.059$	$p = 0.049$	Stage, SUV, Nodal volume
Tumor volume	Sibley GS, 1995 (7493826)	<100 cm^3 vs 100–200 cm^3 vs >200 cm^3	6/7/8	Median (months): 41/11.3/25.5; 1y survival rate (%): 67/43/75; 2y overall survival rate (%): 67/29/49	$p = 0.55$		
	Basaki K, 2006 (16226400)	<52 cm^3 vs >52 cm^3	36/35	Median (months): 18/10; 2y survival rate (%): 34/9	$p = 0.00008$	HR: 1.05 (1.02–1.09) $p < 0.01$	Nodal volume, PS, 2 Gy equivalent dose, Age, Chemotherapy, Histology, T-stage, N-stage
	Jie Y, 2017 (NA)	<50.8 cm^3 vs ≥50.8 cm^3	39/39		HR: 0.667 (0.393–1.131) $p = 0.133$	HR: 0.633 (0.357–1.124) $p = 0.118$	T-stage, N-stage AUC CSH, SUVmax, MTV, TLG
	Soussan M, 2013 (23306807)	Continuous	32	Median (months): 18	NS		
	Alexander BM, 2011 (20605346)	Continuous (by 10 cm^3 increase) – All participants	107	Median (months): 23	HR: 1.01 $p = 0.47$		
		Continuous (by 10 cm^3 increase) – Only chemoradiation paricipants	76	Median (months): 15	HR: 1.02 $p = 0.16$	HR: 1.03 (1.01–1.06) $p < 0.01$	Gender, Nodal volume
	Agrawal V, 2017 (28426673)	Continuous	73	Median (months): 78; 1y survival rate (%): 85; 3y survival rate (%): 68	HR: 1.00 (0.99–1.00) $p = 0.52$		
	Lee VHF, 2016 (24710123)	Continuous	43	Median (months): 37.8	$p = 0.064$	$p = 0.069$	GTV, Stage, SUV
	Dieleman EMT, 2018 (30055239)	Continuous	154	Median (months): 36.1; 1y survival rate (%): 79, 2y survival rate (%): 61, 3y survival rate (%): 52, 5y survival rate (%): 40	HR: 1.001 (0.999–1.002) $p = 0.27$		
Tumor diameter	Huo X, 2017 (29441096)	<3.0 cm vs 3.0–5.0 cm vs 5.1–7.0 cm	62/37/83	1y survival rate (%): 93.54/83.78/72.93; 3y survival rate (%): 42.64/23.45/11.19; 5y survival rate (%): 17.50/4.47/0	$p < 0.001$		
	Firat S, 2002 (12243808)	<7cm vs ≥7 cm	47/37		$p = 0.16$		
	Lee HY, 2012 (22265854)	≤4.2 cm vs >4.2 cm			HR: 0.95 (0.57–1.59) $p = 0.844$		
	Crvenkova S, 2015 (NA)	≤5cm vs >5 cm	32/47	Median (months): 20/13	$p < 0.001$		
	William WN, 2009 (19318668)	<4.5 cm vs >4.5 cm (T4 Satelite patients)	1495/544	Median (months): 27/11; 2y survival rate (%): 52/24; 5y survival rate (%): 31/14		HR: 1.52 (1.32–1.75) $p < 0.001$	Age, Gender, Ethicity, Histology, N-stage, Initial treatment modality
		<4.5 cm vs >4.5 cm (T4 Invasive patients)	2256/3758	Median (months): 12/10; 2y survival rate (%): 28/20; 5y survival rate (%): 12/9		HR: 1.24 (1.16–1.32) $p < 0.001$	Age, Gender, Ethicity, Histology, N-stage, Initial treatment modality
		<4.5 cm vs >4.5 cm (T4 Pleural effusion patients)	2651/2454	Median (months): 6/4; 2y survival rate (%): 15/9; 5y survival rate (%): 3/2		HR: 1.29 (1.21–1.38) $p < 0.001$	Age, Gender, Ethicity, Histology, N-stage, Initial treatment modality
	Morgensztern D, 2012 (22982648)	0.1–3.0 cm vs 3.1–5 cm	3499/4245		HR: 1.13 (1.08–1.18) $p < 0.001$		
		0.1–3.0 cm vs 5.1–7 cm	4245/2646		HR: 1.27 (1.21–1.34) $p < 0.001$		
		0.1–3.0 cm vs 7.1–20 cm	2646/1926		HR: 1.41 (1.33–1.50) $p < 0.001$		
		0.1–3.0 cm vs 3.1–5 cm (Stage IIIA patients)		Median (months): 13/11; 1y survival rate (%): 50.3/43.9; 2y survival rate (%): 27.7/22.4; 3y survival rate (%): 17.1/13.2;		HR: 1.11 (1.04–1.19) $p = 0.001$	Age, Gender, Ethnicity, Histology, Overall stage

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Table 3 (*continued*)

Size-related prognostic factors	Study citation (First author, year (PMID))	Description prognostic factor groups	Number of patients	OS	Univariate analysis (estimate (95% CI))	Multivariable analysis (estimate (95% CI)	Factors corrected for in multivariable analysis
				5y survival rate (%): 8.6/7.2			
		0.1–3.0 cm-5.1–7 cm (Stage IIIA patients)		Median (months): 11/9; 1y survival rate (%): 43.9/38.9; 2y survival rate (%): 22.4/16.5; 3y survival rate (%): 13.2/11.3; 5y survival rate (%): 7.2/5.6		HR: 1.15 (1.07–1.24) $p = 0.0001$	Age, Gender, Ethnicity, Histology, Overall stage
		0.1–3.0 cm vs 7.1–20 cm (Stage IIIA patients)		Median (months): 9/8; 1y survival rate (%): 38.9/35.2; 2y survival rate (%): 16.5/14.5; 3y survival rate (%): 11.3/9.1; 5y survival rate (%): 5.6/3.7		HR: 1.15 (1.05–1.26) $p = 0.002$	Age, Gender, Ethnicity, Histology, Overall stage
		0.1–3.0 cm vs 3.1–5 cm (Stage IIIB patients)		Median (months): 11/10;1y survival rate (%): 43.8/40.1;2y survival rate (%): 22.4/18.7;3y survival rate (%): 13.3/10.0;5y survival rate (%): 8.3/4.9		HR: 1.09 (1.01–1.19) $p = 0.02$	Age, Gender, Ethnicity, Histology, Overall stage
		0.1–3.0 cm vs 5.1–7 cm (Stage IIIB patients)		Median (months): 10/9; 1y survival rate (%): 40.1/35.1; 2y survival rate (%): 18.7/15.4; 3y survival rate (%): 10.0/9.3; 5y survival rate (%): 4.9/5.7		HR: 1.11 (1.04–1.20) $p = 0.003$	Age, Gender, Ethnicity, Histology, Overall stage
		0.1–3.0 cm vs 7.1–20 cm (Stage IIIB patients)		Median (months): 9/8; 1y survival rate (%): 35.1/31.6; 2y survival rate (%): 15.4/13.6; 3y survival rate (%): 9.3/8.7; 5y survival rate (%): 5.7/5.4		HR: 1.10 (1.01–1.19) $p = 0.02$	Age, Gender, Ethnicity, Histology, Overall stage
	Chang JY, 2017 (28727865)	≤7cm vs >7 cm				HR: 2.39 (1.07–5.31) $p = 0.03$	KPS, Overall stage, Tumor location
	Naito Y, 2008 (18520801)	<5cm vs ≥5 cm	33/40			HR: 0.862 (0.473–1.569) $p = 0.626$	Age, Gender, PS, Overall stage, Smoking status, Histology, Body weight loss
	Hayakawa K, 1996 (8765179)	≤5cm vs >5 cm	44/97	Median (months): 18.5/11.5; 2y survival rate (%): 35/18; 5y survival rate (%): 19/7	$p = 0.008$	HR: 1.41 (0.93–2.14) $p = 0.10$	Age, Gender, PS, Histology, T-stage, N-stage, Location, Total dose, Field size
	Pang Z, 2017 (29268415)	≤3 cm vs 3–5 cm			HR: 1.184 (1.161–1.207) $p = 0.009$	HR: 1.115 (1.093–1.136) $p < 0.001$	Age, Gender, Histology, Location, Differentiation, Surgery type, Therapy
		≤3 cm vs 5–7 cm			HR: 1.332 (1.304–1.361) $p < 0.001$	HR: 1.256 (1.228–1.283) $p < 0.001$	Age, Gender, Histology, Location, Differentiation, Surgery type, Therapy
		≤3 cm vs >7 cm			HR: 1.476 (1.680–1.745) $p < 0.001$	HR: 1.361 (1.329–1.394) $p < 0.001$	Age, Gender, Histology, Location, Differentiation, Surgery type, Therapy
	Topkan E, 2018 (29887509)	≤5 cm vs >5 cm	246/543	Median (months): 25.3/22.4	$p = 0.04$		
	Hishida T, 2014 (24203815)	≤3 cm vs >3 cm	7/38.	5y survival rate (%): 68.6/15.0	$p = 0.106$		
	Pusceddu C, 2019 (31289539)	<4 cm vs ≥4 cm	26/39		$p = 0.03$		
	Maniwa T, 2018 (30746228)	≤3 cm vs >3 cm				HR: 1.42 (0.73–2.87) $p = 0.31$	Single/Multiple N2, Histology
	Soussan M, 2013 (23306807)	Continuous	32	Median: 18 months	NS		
	Mao Q, 2018 (29554790)	Continuous (mm)	1809		HR: 1.010 (1.008–1.012) $p < 0.001$	HR: 1.011 (1.008–1.014) $p < 0.001$	Age, Gender, Location, Histology, Grade, Lymph node number, Positive lymph nodes, Visceral

					pleural invasion, Surgery type, Therapy
Broderick SR, 2016 (26410162)	Continuous	542		HR: 1.00 (0.997–1.002) $p = 0.836$	Age, Gender, Ethnicity, Income, Facility type, T-stage, Charlson/Deyo score, Neoadjuvant therapy, Right pneumonectomy

Outcomes concerning size-related prognostic factors in univariate and multivariable analysis of the included studies. Estimates are reported with 95% confidence interval and p-value when available. Used statistical models and tests are: Cox proportional hazard model, logistic regression, log-rank test (LR), binary proportion test. Abbreviations: AUC-CSH: Area under the curve of cumulative SUV histograms, AVG: Average intensity projection images, CE: Contrast enhanced, CI: Confidence interval, ECOG: Eastern cooperative oncology group, GTV: Gross tumor volume, Gy: Gray, HR: Hazard ratio, (K)PS: (Karnofsky) performance status, MTV: Metabolic tumor volume, OR: odds ratio, OS: Overall survival, PMID: PubMed identification number, SD: Standard deviation, SUV: Standardized uptake volume, T50: Expiratory phase images, TLG: Total lesion glycolysis, y: Year.

studies had diverse characteristics. Of the 5 studies that consisted solely of stage IIIA patients receiving surgery, 3 did not find significance in univariate and multivariable analysis [38,49,50,52,57,78]. The 2 studies that did find significance were derived from the SEER database with a similar inclusion period, meaning they may contain overlapping data. Taking this into account, the majority of included analyses indicate tumor diameter is not prognostic for this patient subgroup. Significance was reported in 3 of the 6 studies consisting of stage IIIA and IIIB patients receiving chemoradiation [34,45,48,51,58,60]. However 2 of the studies that respectively reported insignificance in univariate and multivariate analysis used an older version of the TNM-staging system (TNM2/3 and TNM4) and were therefore less comparable with the other studies. This implies tumor diameter is a prognostic factor for stage IIIA/B patients treated with chemoradiation. Three studies consisting of stage IIIA and IIIB patients that did not specify treatment [69] or included surgery as treatment modality [16,57], decreasing their comparability to the other 6, respectively reported significance in univariate and multivariable analysis, and insignificance in univariate and multivariate analyses. The final 3 studies found significance in univariate and multivariable analysis, consisting exclusively of stage IIIB/C patients, who received chemoradiation [32], surgery [68], or microwave ablation in their respective studies [83]. While Morgensztern et al. (2012) [69] also did a subgroup analysis for stage IIIB patients, it should be taken into consideration that both William et al. (2009) [68] and Morgensztern et al. (2012) [69] extracted data from the SEER database using the same inclusion period, and are therefore likely to have overlapping data. Therefore, included data indicates tumor diameter is prognostic for stage IIIB NSCLC patients, as all included analyses indicated significance.

Tumor volume was studied in 8 publications [16,18,66,67,71,73,80,81], which were relatively comparable, with exception of 3 studies, including Alexander et al. (2011) [66], which consisted of cohorts where surgery was a treatment option [16,66,73]. In these 3 studies, 2 of which were conducted at the same institution with overlapping inclusion period, tumor volume was insignificant in univariate analysis [16,66,73]. However, Alexander et al. (2011) [66] did a subgroup analysis for patients receiving only chemoradiation, which was comparable in characteristics to the other 5 studies [18,67,71,80,81]. In these studies significance was reported in 1 out of 5 univariate [18], and 2 out of 4 multivariable analyses [18,66]. Nevertheless, it should be taken into consideration that one of the studies which reported insignificance made use of version 4 of the TNM staging system, and was therefore perceived as less relevant in data analysis. Therefore included data is too heterogeneous to make firm conclusions regarding tumor volume as a prognostic factor for stage III NSCLC patients receiving chemoradiation.

The prognostic effect of GTV was studied in 17 inclusions [11,13,15,18,21,35,41,47,54,64,65,70,73,74,76,77,80]. GTV was significant in 8 out of 16 univariate and 7 out of 9 multivariable analyses. It should, however, be taken into consideration that 1 study, which reported insignificance in univariate analysis, had surgery as a treatment option [73], complicating its comparison with other inclusions. Other than this, the cohorts of included studies seemed to correspond concerning treatment and composition of stage. Two publications that reported significance and insignificance in univariate analysis respectively were conducted at the same institution with a similar recruitment period [64,70]. Chance of overlapping data was also present in 5 other studies [11,35,41,65,76], 4 of which reported significance in univariate and multivariable analyses, and 1 insignificance in univariate analysis.

The univariate results of eligible inclusions for GTV were pooled in a meta-analysis (Fig. 2A). Warner et al. (2016) [77]

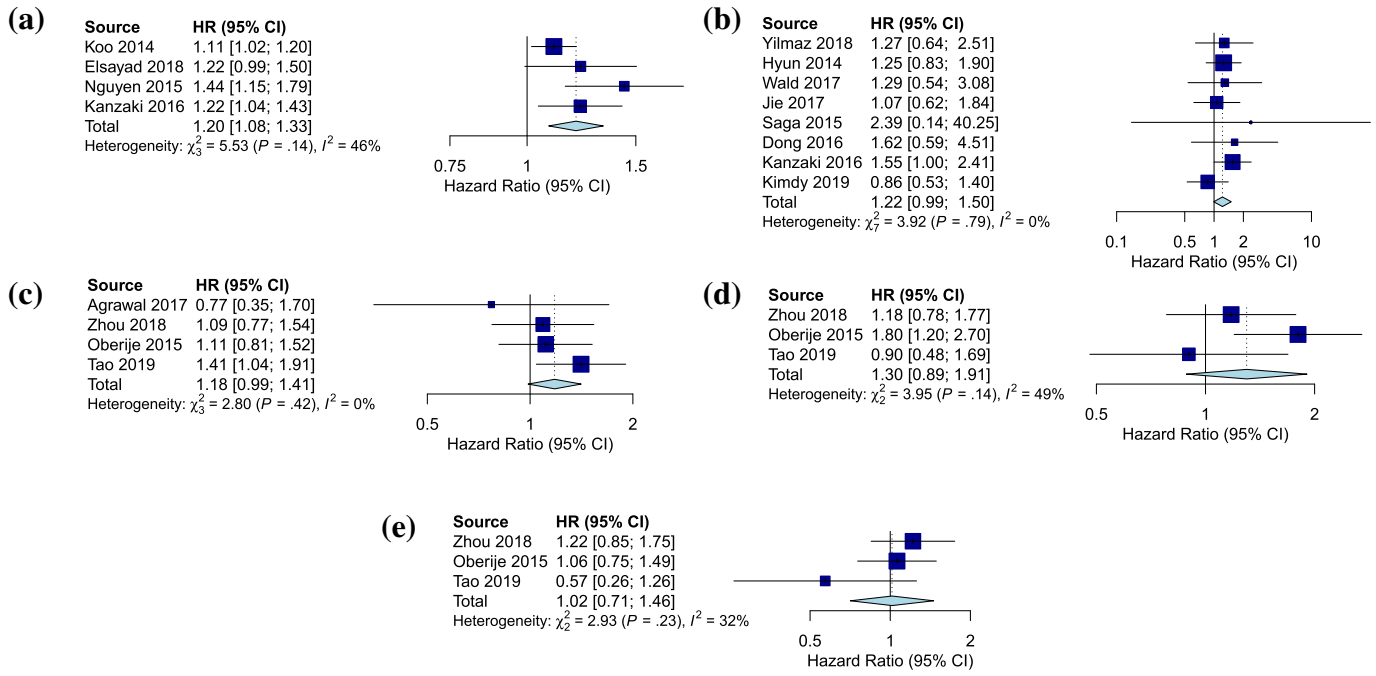

Fig. 2. Forest plot outcome meta-analysis: Forest plots of the outcome of the meta-analysis of: (A) GTV, (B) T1-2 vs T3-4, (C)T1 vs T2, (D) T1 vs T3, and (E) T1 vs T4. In (A) while the results from Gensheimer et al. [64] were included in the meta-analysis, the weight of the study was 0.0% due to the high variance. We excluded these results from the forest plot because they made visual comparison of the other studies impossible.

was excluded as it reported an Odds Ratio from a logistic regression, as opposed to a HR. Three studies were excluded from the meta-analysis as the reported point estimate of the HR coincided numerically with either the upper or lower bound on the confidence interval [21,73,76]. Lee et al. (2016) [80] was excluded as it did not report the point estimate or the confidence interval. The five remaining inclusions had no reason to suspect overlapping patient cohorts [13,15,35,54,64]. None of these studies included surgery as a treatment option. Three inclusions did not report the unit of measurement for GTV [13,15,64]. For these studies, the unit of measurement was inferred from the reported median or mean tumor volume. The estimated heterogeneity between these studies was substantial (I^2 = 50.2%, τ = 0.12). The pooled estimate for the HR of GTV measured in units of 100 cm^3 for overall survival is HR = 1.22 (95% CI 1.05–1.42, p = 0.008). Considering this evidence, along with the observation that it was significant in majority of multivariable analyses even when comparability of the studies and potential overlapping data was taken into account, it is likely that Gross Tumor Volume is a prognostic factor.

In the 29 publications studying clinical T-stage, T-stage was divided in several different discrete groups (Table 4) [15,18,21,31,36,37,40,43,46,48,50,53,54,56–59,61,62,65,67,71–73,75,76,79,84,85]. Fourteen publications evaluated its prognostic influence dichotomized in a T3- and T4-stage group and a (T0-) T1- and T2-stage group [15,21,31,48,53,54,56,58,59,61,65,71,72,85]. In this way, T-stage was found to be significant in univariate analysis of 2 studies [54,58] and multivariable analysis of 1 study [48], but insignificant in univariate and multivariable analyses of the other 11 studies [15,21,31,53,56,59,61,65,71,72,85]. However, characteristics of 1 study, which did not report significance in univariate analysis, were different considering study population, consisting of clinically and pathologically staged IIIA patients, and treatment, including surgery. Therefore, these studies cannot be directly compared with the other studies, which were comparable regarding study characteristics (Table 1) [61]. It should also be taken into account that the studies used different versions of the TNM staging system, which considering the changes made in T-stage between TNM6/7/8 further complicates the comparison of the studies.

In order to pool the reported results, the presence of T0 patients was ignored and T0–2 was assumed to be equivalent to T1–2, as the proportion of T0 patients was <2% [54]. Eight inclusions reported a HR and confidence interval for the T-stage 1–2 vs 3–4 comparison with a total of 677 patients (Fig. 2B) [21,31,54,59,61,71,72,85]. There was no indication of heterogeneity between the studies (I^2 = 0.00%, τ = 0.00). The pooled HR was 1.22 (95% CI 0.99–1.50, p-value = 0.06). This result is close to the nominal statistical significance level. As a sensitivity analysis we performed a meta-analysis excluding studies that reported surgery as a treatment option (7 studies, pooled HR 1.21, 95% CI 0.95–1.53, p = 0.12), and restricting to TNM 7 studies (6 studies, pooled HR 1.20, 95% CI 0.96–1.50, p = 0.11), leading to similar results. Taking all this into account, it is unlikely that the univariate clinical T1–2 vs 3–4 comparison holds prognostic value within a stage III cohort. Also, the majority of comparable multivariable analyses found no significant correlation with OS.

Secondly, 8 studies compared T1-stage with T2-stage, T3-stage, and T4-stage. This comparison did not yield significance in any of the reported univariate and multivariable analyses [18,36,48,57,62,67,73,76]. The cohorts of 6 of these studies consisted of stage IIIA and IIIB patients with a relatively comparable distribution. The other 2 studies consisted mainly or only of stage IIIA patients making them less comparable. One of these 2 was estimated to have a low relevance for utilization of both clinical and pathological staging [57,62]. The patients in the 6 other studies received radiotherapy and/or surgery, and had a relatively comparable distribution of histological subtypes to each other and the other inclusions. A further complication for the comparison was the aforementioned use of different versions of the TNM-staging system. However for this comparison no well-defined subgroup for analysis could be performed, due to the heterogeneity of the studies. For the clinical T1 vs T2 comparison (Fig. 2C), four studies were available for meta-analysis [36,62,73,76]. There was no indication of heterogeneity between the studies (I^2 = 0.00%, τ = 0.00).

Table 4
Summary of findings T-stage and lymph node volume.

T-stage and lymph node volume related prognostic factors	Study citation (First author, year (PMID))	Description prognostic factor groups	Number of patients	OS	Univariate analysis (estimate (95% CI))	Multivariable analysis (estimate (95% CI)	Factors corrected for in multivariable analysis
T-stage	Huo X, 2017 (29441096)	T1 + T2 vs T3 + T4	27/155	1y survival rate (%): 96.30/81.10; 3y survival rate (%): 38.23/23.53; 5y survival rate (%): 19.66/7.98	$p = 0.037$		
	Yilmaz U, 2018 (29559214)	T1 + T2 vs T3 + T4	17/62		HR: 1.273 (0.645–2.513) $p = 0.486$	HR: 1.565 (0.765–3.201) $p = 0.220$	PS, Weight loss, N2 disease, N3 disease, Gender, SUVmax
	Koo TR, 2014 (25498887)	T1 + T2 vs T3 + T4	79/78	3y survival rate (%): 43.8/28.7	$p = 0.106$		
	Fried DV, 2016 (26176655)	T1 + T2 vs T3 + T4	97/98			HR: 0.820 $p = 0.31$	Overall stage, Induction chemotherapy, Age, Gender, GTV, KPS, Co-occurrence matrix energy, Solidity
	Hyun SH, 2014 (23948859)	T1 + T2 vs T3 + T4	125/69		HR: 1.254 (0.829–1.898) $p = 0.283$	HR: 1.297 (0.702–2.397) $p = 0.406$	Overall stage, N-stage, ECOG PS, Neoadjuvant chemoradiotherapy, Type of surgery, Chemotherapy, Radiotherapy, SUVmax, MTV
		T1 + T2 vs T3 + T4	125/69			HR: 1.479 (0.825–2.651) $p = 0.188$	Overall stage, N-stage, ECOG PS, Neoadjuvant chemoradiotherapy, Type of surgery, Chemotherapy, Radiotherapy, SUVmax, TLG
	Wald P, 2017 (28843360)	T1 + T2 vs T3 + T4	22/30		HR: 1.29 (0.54–3.08) $p = 0.571$		
	Jie Y, 2017 (NA)	T1 + T2 vs T3 + T4	25/53		HR: 1.069 (0.620–1.844) $p = 0.810$	HR: 1.176 (0.666–2.075) $p = 0.577$	N-stage, CTV, AUC CSH, SUVmax, MTV, TLG
	Saga T, 2015 (NA)	T0 + T1 + T2 vs T3 + T4			HR: 2.39 (0.14–39.71) $p = 0.543$		
	Dong X, 2016 (27322376)	T1 + T2 vs T3 + T4	25/33		HR: 1.625 (0.282–2.173) $p = 0.267$		
	Horinouchi H, 2012 (23004347)	T1 + T2 vs T3 + T4	56/54			HR: 0.91 (0.53–1.61) $p = 0.77$	Age, Gender, Weight loss, Histology, N-stage, Overall stage
	Kanzaki H, 2016 (27125214)	T0 + T1 + T2 vs T3 + T4	59/52		HR: 1.55 (1.00–2.41) $p = 0.048$		
	Hayakawa K, 1996 (8765179)	T1 + T2 vs T3 vs T4	40/58/43	Median (months): 14/13/10; 2y survival rate (%): 28/21/23; 5y survival rate (%): 13/10/9	$p = 0.59$		
		T1 + T2 vs T3 + T4	40/101			HR: 1.30 (1.04–1.61) $p = 0.021$	Age, Gender, PS, Histology, Tumor size, N-stage, Location, Total dose, Field size
	Kim E, 2019 (30266585)	T1 + T2 vs T3 + T4	81/49	3y survival rate (%): 51.8/44.1	$p = 0.238$		
	Kim DY, 2019 (31591865)	T1 + T2 vs T3 + T4	35/47		HR: 0.86 (0.53–1.40) $p = 0.538$		
	Hyun SH 2015 (26295651)	T1 + T2 vs T3	132/29		HR: 2.50 (1.31–4.78) $p = 0.005$		
	Li J, 2009 (NA)	T1 + T2 vs T3	53/38	Median (months): 32/27; 1y survival rate (%): 88.9/86.7; 3y survival rate (%): 44.4/	$p = 0.324$		

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Table 4 (*continued*)

T-stage and lymph node volume related prognostic factors	Study citation (First author, year (PMID))	Description prognostic factor groups	Number of patients	OS	Univariate analysis (estimate (95% CI))	Multivariable analysis (estimate (95% CI)	Factors corrected for in multivariable analysis
				26.7; 5y survival rate (%): 29.2/22.0			
	Betticher DC, 2006 (16622435)	T1 + T2 vs T3	50/25	Median (months): 27.6/57.1	$p = 0.12$		
	Sibley GS, 1995 (7493826)	T1 vs T2 vs T3 vs T4	6/7/11/13	Median (months): unkown/12.1/20.4/19.5; 1y survival rate (%): 67/71/73/84; 2y survival rate (%): 67/29/45/32	$p = 0.52$		
	Basaki K, 2006 (16226400)	T1 vs T2 vs T3 vs T4	4/18/23/26	Median (months): 11/12/13/14; 2y survival rate (%): 28/23/20/23	Not significant	HR: 0.73 (0.51–1.04) $p = 0.08$	Primary tumor volume/Total tumor volume, N-stage, PS, 2 Gy equivalent dose, Age, Chemotherapy, Histology, N-stage
	Agrawal V, 2017 (28426673)	T1 vs T2	18/32		HR: 0.77 (0.35–1.71) $p = 0.53$		
		T1 vs T3 + T4	18/23		HR: 0.40 (0.14–1.10) $p = 0.08$		
	Zhou R, 2018 (NA)	T0 + T1 vs T2	92/175		HR: 1.09 (0.775–1.541) $p = 0.614$		
		T0 + T1 vs T3	92/85		HR: 1.177 (0.785–1.764) $p = 0.431$		
		T0 + T1 vs T4	92/125		HR: 1.217 (0.848–1.747) $p = 0.286$		
	Oberije C, 2015 (25936599)	T0 + T1 vs T2			HR: 1.11 (0.81–1.52) $p = 0.3135$		
		T0 + T1 vs T3			HR: 1.8 (0.92–2.07) $p = 0.3135$		
		T0 + T1 vs T4			HR: 1.06 (0.76–1.50) $p = 0.3135$		
	Tao X, 2019 (31179087)	T1 vs T2	271/239		HR: 1.41 (1.04–1.90) $p = 0.0265$	HR: 1.22 (0.89–1.67) $p = 0.2181$	Age, Gender, Smoking history, Tumor location, Treatment approach, N-stage
		T1 vs T3	271/58		HR: 0.90 (0.48–1.69) $p = 0.7459$	HR: 0.83 (0.43–1.58) $p = 0.5667$	Age, Gender, Smoking history, Tumor location, Treatment approach, N-stage
		T1 vs T4	271/35		HR: 0.57 (0.27–1.31) $p = 0.1872$	HR: 0.51 (0.22–1.21) $p = 0.1290$	Age, Gender, Smoking history, Tumor location, Treatment approach, N-stage
	Maniwa T, 2018 (30746228)	T1 vs T2 + T3 + T4	30/64	5y survival rate (%): 54.0/41.8	$p = 0.39$		
	Hwang IG, 2008 (18623378)	T1 vs T2 + T3	12/56	Median (months): 42.6/41.7	$p = 0.687$		
	Broderick SR, 2016 (26410162)	NR				$p = 0.135$	Age, Gender, Ethnicity, Income, Treatment, Charlson/Deyo score, Tumor size, Neoadjuvant therapy, Right pneumonectomy
	Shumway, 2011 (21676484)	NR			Not significant		
	Akcam TI, 2015 (NA)	NR				HR: 1.201 (1.026–1.405) $p = 0.023$	Age, Histology, Localization, Multi vs single station
	Konert T, 2019, (31367906)	NR		Median (months): 14	$p = 0.053$		

Nodal volume	Alexander BM, 2011 (20605346)	Continuous: by 10 cm^3 increase (All patients)	107	Median (months): 23	HR: 1.09 $p < 0.01$	HR: 1.09 (1.05–1.13) $p < 0.01$	Overall stage, Surgery, Radiation dose
		Continuous: by 10 cm^3 increase (Chemoradiation patients)	76	Median (months): 15	HR: 1.07 $p < 0.01$	HR: 1.09 (1.05–1.14) $p < 0.01$	Gender, Tumor volume
	Basaki K, 2006 (16226400)	<15 cm^3 vs >15 cm^3	35/36	Median: 14/12 months; 2 year survival rate (%): 24/19	Not significant	HR: 1.06 (0.99–1.14) $p = 0.10$	Primary tumor volume, PS, 2 Gy equivalent dose, Chemotherapy, Age, Histology, T-stage, N-stage
	Lee VHF, 2016 (24710123)	Continuous	43	Median (months): 37.8	$p = 0.402$		
	Oberije C, 2015 (25936599)	Continuous (mL)	548		HR: 1.16 (1.14–1.18) $p = 0.0008$		
	Dieleman EMT, 2018 (30055239)	Continuous	154	Median (months): 36.1; 1y survival rate (%): 79; 2y survival rate (%): 61; 3y survival rate (%): 52; 5y survival rate (%): 40	HR: 1.004 (1.00–1.008) $p = 0.033$	HR: 1.007 (1.0–1.012) $p = 0.047$	Gender, Age, Radiation technique
Nodal diameter	Betticher DC, 2006 (16622435)	≤1cm vs >1 cm	14/61	Median (months): 32.5/29.9	$p = 0.47$		

Outcomes concerning T-stage and nodal volume in univariate and multivariable analysis of the included studies. Estimates are reported with 95% confidence interval and *p*-value when available. Used statistical models and tests are: Cox proportional hazard model, log-rank test (LR). Abbreviations: AUC-CSH: Area under the curve of cumulative SUV histograms, CI: Confidence interval, ECOG: Eastern cooperative oncology group, GTV: Gross tumor volume, Gy: Gray, HR: Hazard ratio, (K)PS: (Karnofsky) performance status, MTV: Metabolic tumor volume, NA: Not applicable, NR: Not reported, OS: Overall survival, PMID: PubMed identification number, PS: Performance score, SUV: Standardized uptake volume, TLG: Total lesion glycolysis, Y: year.

The pooled HR was 1.18 (95% CI 0.98–1.41, $p = 0.07$). For the comparisons T1 vs T3 and T1 vs T4, three studies were available (Fig. 2D, E) [36,62,76]. There was moderate heterogeneity in the T1 vs T3 studies ($I^2 = 49.4\%$, $\tau = 0.24$), the pooled HR was 1.30 (95% CI 0.89–1.91, $p = 0.18$). For the T1 vs T4 comparison there was also moderate heterogeneity ($I^2 = 31.8\%$, $\tau = 0.22$), the pooled HR was 1.02 (95% CI 0.71–1.46, $p = 0.93$). These results provide additional evidence that T-stage is not prognostic for OS of stage III NSCLC patients.

The effect of clinical T3-stage on OS in comparison to T1- and T2-stage was measured in 3 studies [37,40,43]. These inclusions consisted solely of stage IIIA patients submitted to surgery. While the study populations were comparable to each other, this reduced their comparability to the overall stage III NSCLC population. However, as 2 of these did not explicitly state the utilized TNM-staging system their comparison was complicated. Significance was reported in univariate analysis of 1 publication [43], while the other 2 reported insignificance [40]. Consequently, included data indicates this comparison is not significant for stage IIIA patients receiving surgery.

Finally, 5 studies with alternative or unspecified comparisons reported T-stage to not be statistically significant for OS in univariate and 1 out of 2 multivariable analyses [46,50,75,79,84]. Four of these reported surgery as a possible treatment modality, and, as 2 consisted only of stage IIIA patients, their relevance was lower.

Two prognostic factors specifically concern the involved lymph nodes. Nodal volume was measured in 5 studies (Table 4) [18,36,66,80,81]. Regardless of the presence of patients receiving surgery, nodal volume was found to be significant in univariate and multivariable analysis of 3 studies [36,66,81], but not in univariate and multivariable analysis of the other 2 [18,80]. The studies were comparable to the subgroup analysis for patients who received exclusively chemoradiation, in distribution of stage IIIA/IIIB and histological subtypes. Considering all this, total lymph node volume is likely to be a prognostic factor for stage III patients.

Dichotomized nodal diameter was not found to be significant in univariate analysis of a single study [37]. This study consisted of only stage IIIA patients treated with surgery, and was therefore not representative for the standard stage III population. As this only concerns a single study, no definite conclusions can be drawn.

Prognostic factors that could not be classified as size, nodal, or texture-related, were classified as other CT-related prognostic factors (Table 2). These included 8 unique factors: Atelectasis/Obstructive pneumonitis [20,67], Location [18,34,42,48,49,52,62,63,71,72,75,78], Cavitary wall thickness [17], Cavitation [33,44,51], Interstitial lung abnormalities [55], Great vessel invasion [82], Pit fall sign [14], and Pleural effusion [39].

Atelectasis was studied in 2 inclusions, in 1 as a dichotomous factor [20] and in the other as a discrete variable with more than 2 levels [67]. Atelectasis did not yield significance in univariate analysis as a discrete factor [67], but did as a dichotomous factor [20]. Both the studies consisted of stage IIIA and IIIB patients receiving chemoradiation. The representativeness of the publication that considered atelectasis as a dichotomous factor for the entire stage III NSCLC population cannot be fully assessed, as it did not report the distribution of histological subtype [20]. Additionally, the relevance of publication that considered atelectasis as a discrete factor was decreased, as it made use of an older version of the TNM staging system. Due to these issues in the 2 publications, no concrete conclusion can be made.

Twelve studies reported data on the effect of tumor location on OS in several discrete ways [18,34,42,48,49,52,62,63,71,72,75,78]. Four inclusions compared presence in the right and left lung [18,49,63,72], another 2 between central and peripheral location [62,71]. For both comparisons no significance was reported in univariate analysis. However 1 study for each of the 2 respective com-

parisons was estimated to have a low relevance on behalf of consisting of clinically as well as pathologically staged III patients [62,63]. As a consequence, considering most of the other studies seemed to be representative for the overall stage III NSCLC population [18,71,72], the inclusions give little reason for future research of left/right location. The final comparison was between pulmonary lobes, for which a significant correlation was found in 2 out of 5 univariate [42,48] and 2 out of 3 multivariable analyses [34,48]. It should be noted, however, that in 3 studies which found no significance and 1 which found significance, patients were treated with surgery, decreasing their comparability to the other study cohorts [42,52,78]. Concluding, considering the heterogeneity of the inclusions data, regarding both central/peripheral location and tumor location by lobes remains inconclusive.

Two prognostic factors concern cavitation: appearance of a region with lower density within the tumor mass. Cavitation itself was studied in 3 publications, in which it was reported to be significant in 1 out of 3 univariate analyses and in multivariable analysis [33,44,51]. It should however be noted that 1 study, in which no significance was found, consisted only of IIIA patients treated with surgery. Cavitary wall thickness was reported not to be a significant prognostic factor in a subgroup analysis of a single study for stage III patients treated with surgery [17]. However, this cohort was not representative for the overall stage III population, consisting exclusively of adenocarcinoma patients, and because tumor cavitation is present in less than 25% of lung cancer cases [86]. However, due to the relatively limited data no definite conclusions can be drawn about factors concerning cavitation.

The last four CT-related prognostic factors were measured in single studies. Both interstitial lung abnormalities and great vessel invasion were reported to be not significant as prognostic factors in a stage III NSCLC cohort [55,82]. Pit fall sign, studied in subgroup analyses for stage III NSCLC patients treated with surgery, was not found to be significant. However, these results were based on only 16 stage III patients and should be verified in a larger stage III cohort [14]. The effect of pleural effusion, analyzed in a stage IIIA and IIIB specific manner, was reported to be significant in univariate analysis in stage IIIA patients, and in both univariate and multivariable analysis in stage IIIB patients [39].

Discussion and conclusion

In this systematic review and meta-analysis, 26 unique CT-related prognostic factors were identified for OS in 65 studies comprising 144,513 stage III NSCLC patients. Inclusions indicated T-stage is unlikely to be prognostic for OS of stage III NSCLC patients treated with chemoradiation, as it was found to be insignificant in the majority of analyses [15,18,21,31,36,37,40,43,46,48,50,53,54,56–59,61,62,65,67,71–73,75,76,79,84,85]. Although population characteristics of publications concerning size-related prognostic factors were heterogeneous, there was an indication that GTV, tumor diameter, and nodal volume are prognostic for OS of stage III patients receiving chemoradiation [11,13,15,18,21,32,34–36,41,51,58,64–68,70,71,74,77,80,81,83], but that this may not be the case for tumor volume and diameter in cohorts containing NSCLC patients receiving surgery [16,38,66,68]. This could potentially be explained by the aim of surgery to remove the tumor and involved lymph nodes, which could conceivably undermine size-related prognostic effects [87]. While tumor diameter and volume are related, it is notable that we could not draw any conclusions regarding tumor volume for stage III patients receiving chemoradiation. This was mainly caused by the heterogeneity of the included data, which also hampered the analysis of other factors including atelectasis and location (by pulmonary lobe). The exact extent of heterogeneity in the data is discussed below [16,18,32,34,36–38,45,48–52,58,60,66,68,69,78,80,81]. Furthermore, T-stage, which is partially determined by tumor size as proposed by the international association for the study of lung cancer [88,89], did not seem to hold prognostic value within NSCLC cohorts consisting solely of stage III patients, while GTV and tumor diameter did. A potential explanation is that in cohorts restricted to stage III patients N-stage is dominant in OS of patients with smaller tumors. Additionally restricting the analysis to stage III patients may reduce the variation in T-stage between patients to greater extent than it reduces variation in tumor size, as the T-stage directly influences overall stage. Similarly, a decrease in T-stage necessarily entails an increase in N-stage for stage III patients, lowering the relevance of univariate prognostic models of these factors.

The 2 included studies concerning radiomic features suggest several features (including entropy, skewness, mean HU, largest axial slice average, largest axial slice uniformity, HU kurtosis, HU infomc1, HU standard deviation, and HU sosvariance) have potential prognostic value for stage III NSCLC patients receiving chemoradiation. However, considering this concerned only 2 studies and the vulnerability of radiomic features to difficulties in validation [90,91], we feel this group of prognostic factors warrant separate review. These factors should be validated in a larger cohort [11,12]. Finally, of the other CT-related prognostic factors, location (right/left) is not likely to be a prognostic factor [18,71,72]. Pleural effusion did, however, seem to be a prognostic factor in a single study [39]. No concrete conclusions could be drawn concerning atelectasis, cavitation, and location (by pulmonary lobes, central/peripheral), as evidence was too heterogeneous [18,20,33,42,44,51,67], or for cavitary wall thickness and pit fall sign, as the stage III subgroup of their studies was not representative for the standard stage III NSCLC population [14,17]. More research is warranted to validate these results.

This study presents an overview of prognostic factors for OS of stage III NSCLC patients. Several potential prognostic factors were identified, which could be used to direct future research. Several factors hamper the strength of the conclusions that can be drawn from this systematic review. In 32 studies the utilized staging method (clinical/pathological) was not specified [11,13,15,17,18,20,32,34,35,37,64–80,85]. Three inclusions even compared patients with pathological and clinical stage III [61–63]. We recommend that future studies into prognostic factors are reported according to the TRIPOD reporting guidelines to increase their scientific value and facilitate the use of their results in meta-analysis [24]. Additionally clinical staging is preferred to pathological staging, because, even though in theory pathological stage correlates better to prognosis, ultimately only clinical stage is available for treatment decisions [9,92,93].

Another limitation was that CT-related prognostic factors were not often the primary focus of the included articles. This may have led to relevant articles not being retrieved with the utilized search terms.

We were unable to estimate the risk of publication bias from the provided data due to the low number of studies per prognostic factor. As virtually all studies reported the results on multiple prognostic factors instead of just one, it is less likely that a non-significant result for one of the prognostic factors would have reduced the probability of publication. However, for continuous prognostic factors or prognostic factors with multiple categories, there are several ways to include this variable in the analysis. The way a variable was entered in the analysis (e.g. dichotomized GTV or choosing groups of T-stage for comparison) could be driven by the data and reasons behind these choices were hardly ever reported. This increases the risk of false positive findings.

Additionally, inclusions were found to be heterogeneous in distribution of histological subtypes, stage IIIA/IIIB, and treatment modalities. This limited the analysis of several prognostic factors

including atelectasis [20,67], and location (by pulmonary lobes) [18,42]. It should also be noted that surgery was reported to be a treatment option in 25 of the 65 inclusions [14,16,17,33,37–40,42–44,46,49,50,52,57,61–63,66,68,73,75,78,79]. Considering surgery might influence the relevance of size-related prognostic factors [92,93], these studies may not be comparable to stage III cohorts receiving chemoradiation alone. Finally, OS was measured from distinct time points [12–14,18,21,31–33,35,36,38,40–45,47,48,51,52,59,60,64–66,71–74,77,85]: where some used OS measured from the first day of chemoradiation treatment onwards [12,13,18,32,42–44,55,57,59,60,63–65,71–73,81–85], others measured OS from time of diagnosis [16,20,34,37,39,46,49,50,53,56,61,67–69,78,79]. This complicates comparisons between study cohorts.

Notably, only 6 studies included weight loss in multivariable analysis, even though it is a prognostic factor recognized by guidelines [39,45,51,53,59,74]. Moreover, performance status was included in only 12 of 65 publications [11,18,34,39,45,48,59,61,65,70,74]. The value of new prognostic markers should be evaluated in light of existing ones. It is recommended for future research to explicitly include comparisons with the established prognostic markers weight loss and performance status.

Considering these heterogeneities between the included studies, which hampered our ability to come to strong conclusions concerning both the significance and clinical relevance of the aforementioned prognostic factors, including tumor volume, we suggest future studies report the employed staging system (clinical or pathological, and TNM version), received treatments, presence and handling of missing data, effects sizes, and measures of uncertainty such as confidence intervals. Additionally we advise studies concerning radiomic features to carefully describe the methods used to obtain the results, for reproducibility and future data analysis, specifically in the ways suggested by Zwanenburg et al. (2020) [90] and Welch et al. (2019) [91]. Finally, future studies should compare the measured prognostic factor with those recognized by the clinical guidelines (weight loss and performance status) and validated prognostic factors from other studies.

In conclusion, Gross Tumor Volume, tumor diameter, nodal volume, and pleural effusion are likely to be prognostic factors for OS of stage III patients treated with chemoradiation. Several radiomic features have potential prognostic value. Additionally, the combined evidence strongly indicates that T-stage and location (right/left) are not prognostic for OS within the group of stage III NSCLC patients. Finally, the included evidence concerning tumor volume, atelectasis, location (by pulmonary lobes, central/peripheral), pit fall sign, and cavitation remains inconclusive. Regarding these prognostic factors, more research is needed before firm conclusions can be made and clinically relevant prognostic factors could be used to improve treatment decisions. To improve the evaluation of evidence, future studies should both carefully report the employed staging system, received treatments, effects sizes and measures of uncertainty, and contrast the measured prognostic factor with guideline recognized prognostic factors in addition to those from earlier studies, as presented in this systematic review.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.07.030.

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