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Highlights:

- In favourable unresectable stage III NSCLC, SBRT may improve local regional control
- Most studies report definitive tumor and nodal SBRT, or tumor SBRT boost
- Across the studies, median OS span from 10 to 52 months and grade 4-5 AE from 0 to 13.3%
- A biologically effective dose higher than 112.3 Gy may increase locoregional control
- Future trials should detail their OAR dose constraints and include immune therapies

Stereotactic body radiation therapy in unresectable stage III non-small cell lung cancer: a systematic review

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Stereotactic body radiation therapy in unresectable stage III non-small cell lung cancer: a systematic review

Abstract

In unresectable stage III non-small cell lung cancer (NSCLC), the standard of care for most fit patients is concurrent chemotherapy with normofractionated radiotherapy (NFRT), followed by durvalumab consolidation. Nevertheless, almost half of patients will present locoregional or metastatic intrathoracic relapse. Improving locoregional control thus remains an important objective. For this purpose, stereotactic body radiotherapy (SBRT) may be a relevant treatment modality. We performed a systematic review of the literature that evaluate the efficacy and safety of SBRT in this situation, either instead of or in addition to NFRT. Among 1788 unique reports, 18 met the inclusion criteria. They included 447 patients and were mainly prospective (n=10, including 5 phase 2 trials). In none, maintenance durvalumab was administered. Most reported SBRT boost after NFRT (n=8), or definitive tumor and nodal SBRT (n=7). Median OS varied from 10 to 52 months, due to the heterogeneity of the included populations and according to treatment regimen. The rate of severe side effects was low, with less than 5% grade 5 toxicity, and mainly observed when mediastinal SBRT was performed without dose constraints to the proximal bronchovascular tree. It was suggested that a biologically effective dose higher than 112.3 Gy may increase locoregional control. SBRT for selected stage III NSCLC bears potential to improve loco-regional tumor control, but at present, this should only be done in prospective clinical trials.

Keywords: unresectable non-small cell lung cancer; stage III; stereotactic body radiation therapy

Introduction

Lung cancer is the leading cause of cancer death worldwide with an estimated 1.8 million deaths per year [1], mainly represented by non-small cell lung cancers (NSCLC). Approximately one third of patients is diagnosed with locally advanced disease (LA) [2]. Many of these patients have unresectable disease or are medically inoperable. The definition of unresectable stage III NSCLC varies and may include technically resectable disease [3]. There is consensus that the overall survival (OS) of most patients is similar whether treated locally with surgery or radiotherapy. Because most patients with LA have tumor or lymph nodes invading and/ or abutting large blood vessels, the esophagus or large airways, standard fractionation doses of about 2 Gy to total doses of around 60 Gy have been given and are the current standard of care [4]. The addition of consolidative durvalumab has shown to improve the OS, with median OS increasing from 29.1 to 47.5 months, and an absolute 5-year OS gain of 9.5% [5].

Nevertheless, local control (LC) remains challenging. Data prior to the durvalumab maintenance reported that local regional control was independently correlated to long-term survival [6]. At the time of treatment, overall response rate currently remains between 50 and 70%, with less than 5% complete response [7–10]. At 1 year, local-regional failure was reported around 15% [11]. The vast majority were in-field and marginal relapses (n=5/10 and n=4/10, respectively) and associated with distant progression (n=9/10) [11]. In patients who do not experience distant relapse, 10% and 35% will present in-field and out-of-field recurrence, respectively [12]. Furthermore, in-field recurrence is associated with shorter OS ($p < 0.001$) [13].

Because of the improvement of RT techniques, increasing the dose may potentially be beneficial. Intensity-modulated radiotherapy (IMRT) is associated with fewer severe pneumonitis and lower cardiac doses [14]. A higher normofractionated dose in a smaller and more conformal volume may improve LC and overall response rate in this indication [15].

Stereotactic body radiation therapy (SBRT) allows an accurate high dose delivery in a short overall treatment time. In early-stage NSCLC, this translated into higher LC rate [16], reduced oesophageal toxicity and improved quality of life [17]. It should be acknowledged that not only the radiation dose was higher in the SBRT arms, but also PTV margins were highly reduced. It may also be relevant to better spare organs at risk (OAR) since a quarter of patients will present intrathoracic-only recurrence [12] and may receive a second course of RT, or another metastasis-directed therapy [18]. In addition to these potential advantages, the immunomodulatory effects of SBRT may also improve immunotherapy efficacy in locally advanced disease [19,20]. Nevertheless, stage III NSCLC is a heterogeneous population in terms of tumor size, location, nodal involvement, and patient characteristics. Because of the potential to increase LC with reduced toxicity of SBRT compared to conventional radiotherapy, we systematically reviewed the literature of SBRT in stage III node-positive NSCLC.

Material and methods

Data sources and study selection

A systematic review of the literature was performed using PubMed, Scopus, Embase and Web of Science databases, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines. The search was performed on October 11th, 2022. Search terms included synonyms of, and words related to “lung cancer”, “stereotactic body radiotherapy” and “stage III”. Research was restricted to English and French languages but there was no restriction regarding the date of publication. The full search strategy is reported in Supplementary materials. In case of several publications for the same study, all were considered for this qualitative review.

Inclusion criteria were as follows: published articles or meeting abstracts; observational or interventional studies with or without control group; included patients >18 years, with stage

III NSCLC considered non-surgical candidate by the authors; treated with curative intent external beam radiotherapy at least partially delivered by highly hypofractionated RT (defined as $D_{max}(PTV) \geq 5$ Gy); reported dose and fractionation; reported LC, time to local failure or local recurrence-free survival. Exclusion criteria were: letters and commentaries; cohorts not reporting data on any of the relevant outcomes; unclear disease staging; cohorts pooling results between various stages if stage III represented $< 2/3$ cases.

Abstracts screening and full-papers review were independently performed by 2 reviewers (BA and WW), and disagreements were addressed by discussion.

Data extraction

For study characteristics, first author, year of publication, study design, funding source and population overlap with another included study were extracted. For cohort characteristics, the number and proportion of stage III patients, inclusion and exclusion criteria, median follow-up, median age, tumor size, treatment characteristics of NFRT and SBRT, LC data, disease-free survival (DFS) or metastatic-free survival (MFS), OS, and grade ≥ 3 ($G \geq 3$) toxicities according to the classification used in each study were extracted.

Quality assessment

The risk of bias of the final studies was examined by both reviewers using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series [21]. Categories were judged by summing the results: $< 60\%$, 60 to 80% and $> 80\%$ yes was high risk, medium risk and low risk of bias, respectively.

Results

Identified studies and quality assessment

Databases search yielded 1788 unique citations. All titles and abstracts were retrieved and screened. Among the 28 records selected for full-text eligibility assessment, 18 met inclusion criteria [22–39] ([Figure 1](#)). The characteristics of included studies are summarized in [Table 1](#). They included 447 patients (range 3-49) and were mainly prospective (phase 2 trials, n=5; phase 1 trials and prospective cohorts, both n=3). Most reported SBRT series delivered a tumor boost after NFRT (n=5), or gave definitive tumor and nodal SBRT (n=7). None administered immune therapy. All but one studies presented medium (n=3) or low risk (n=14) of bias ([Table 2](#)). The remaining study was a communication abstract, and its results were subsequently completed [27,29].

SBRT Boost after NFRT

Most included studies reported tumor and nodal NFRT followed by a SBRT boost to the primary tumor (n=5) or both tumor and nodes (n=3). This regimen allows for CCRT, with well-known efficacy and safety, while thereafter increasing the dose to the tumor.

In 5 publications, the SBRT boost was delivered to the primary tumor only, in 2 or 3 fractions [23,24,27,29,30]. Salazar et al. delivered 22.5Gy in 3 fractions (biologically equivalent dose with alpha/beta ratio of 10 (BED_{10}), 92.5 Gy) in patients who could safely receive SBRT after 45 Gy NFRT [23]. They achieved a median OS (mOS) of 15 months [23]. Feddock et al., updated by Kumar et al., delivered 19.5-20Gy in 2 fractions (BED_{10} of 102-110Gy) in patients with tumor ≤ 5 cm and without persistent nodal disease after NFRT [24,27,29]. They achieved a mOS of 27.6 and 15.6 months in stage II-IIIA and stage IIIB, respectively [24,27,29] and reported 14.3% $G \geq 3$ radiation pneumonitis (RP) and 5.7% late haemoptysis (n=2/35). Doyen et al. reported similar results in a dose-escalation phase I trial, with median tumor size at SBRT of 39.5mm and a median of 1 N2 station involved. After 46

Gy-NFRT, they concluded that 33 Gy in 3 fractions is safe and can be recommended, which achieves an overall BED₁₀ of 110.6 Gy [30]. One patient in 3x12Gy group and another one in 3x11Gy group presented grade 5 haemoptysis and grade 4 oesophageal fistula, respectively.

To increase dose on the whole gross disease, a few publications performed SBRT boost on both primary tumor and involved nodes in case of limited and favourable nodal locations. In patients with tumor volume <120cc and node volume <60 cc after NFRT, Hepel et al. reported higher locoregional control when SBRT dose ≥ 24 Gy in 2 fractions (BED₁₀ ≥ 112.3 Gy; 1y-LC 100% vs 50%, p=0.02) [26]. After 44 Gy NFRT, Higgins et al. reported that the maximum tolerated dose was 30 Gy in 5 fractions (BED₁₀ 100.8 Gy) [28]. However, since it led to 3 dose-limiting toxicities, they recommended 2 fractions of 10 Gy (BED₁₀ 92.8 Gy) [28]. Most of the included patients had 2 (53%) N1-N2 stations involved, with a small primary tumor (median, 2.7cm). In these dose-escalation phase I trials, radiation doses to the mediastinum have been reported to induce 8-15% of lethal AE [26,28]. Nevertheless, these toxicities were experienced in absence of dose constraints to the proximal bronchovascular tree, and in the high-dose groups. In contrast, in patients with median tumoral diameter of 5 cm (range 2.4-9.5 cm) mostly staged N2 (63%), Karam et al. did not observe any late grade 4-5 AE after 5x5 Gy [25]. This may have been underestimated by the short median follow-up of 14 months [25].

Sequential tumor SBRT and nodal NFRT

Two other trials evaluated sequential full-dose tumor SBRT and nodal-only NFRT. The main advantage of this strategy is to perform ablative dose on the tumor while limiting hypofractionation and its severe toxicity risks to mediastinal structures. In a phase 2 trial including peripheral tumors ≤ 5 cm, Martel-Lafay et al. performed standard dose nodal CCRT, followed by 54Gy in 3 fractions tumor SBRT (BED₁₀ 151.2Gy) [31]. They achieved a

promising mOS of 51.6 months, with only one grade 3 RP. Nevertheless, the patients were highly selected, having a performance status of 0-1, presenting primary tumor of 10 to 36 mm (median, 19 mm) peripherally located, without progression after CCRT and without $G\geq 3$ toxicity. The main advantage is to perform the ablative dose soon before IO initiation. Nevertheless, the primary tumor was treated only by chemotherapy during the first weeks.

On the other hand, two retrospective studies reported an inverted sequence associating 4-fraction primary tumor SBRT followed by nodal NFRT. In 3 patients of their larger NSCLC cohort, Chi et al. observed neither local failure or death at 2 years, nor $G\geq 3$ AE [22]. In patients with small, isolated lesion (GTV, median 6.4cc) distant from the nodal involvement, Kim et al. performed tumoral SBRT and 60 Gy nodal NFRT thereafter [32]. They achieved good local and distant results at 2 years with few grade 3-4 AE (n=3/21).

Definitive SBRT

After these first positive signals, definitive SBRT on both primary tumor and involved nodes was evaluated [33–39]. Most trials performed altered SBRT regimens to compensate the contraindication or non-eligibility for concurrent chemotherapy [33–37]. In these unfit populations with median age of 63 to 73 years, they reported limited mOS of 10 to 22 months. Wang et al. and Arciadiacono et al. observed no $G\geq 3$ AE [33,36,37]. Nevertheless, Cong et al. reported two patients with previous coronary disease who have died of heart failure and myocardial infarction, possibly related to SBRT, while one patient experienced G3 RP [34,35].

Since a majority of patients will fail because of distant metastases [5,40], the hypothesis was made that combining both chemotherapy and definitive SBRT may be beneficial in fit patients. Kubicek et al. recently performed definitive SBRT and 4 cycles of full-dose chemotherapy in patients with tumor <8cm (median, 4.5cm) and 3 or fewer involved nodes

(median, n=1) [38,39]. It has to be noted that the dose to lymph nodes was reduced to 40-50 Gy in 5 fractions. Critical mediastinal OAR should not receive >105% of dose, with specific dose constraints to non-adjacent walls of esophagus (5mL <27.5Gy), great vessels (10mL <47Gy) and trachea (4mL <18Gy). They achieved a mOS of 27.2 months with 100% LC and 19% regional nodal failure at 2 years. Two (9.1%) patients experienced late $G\geq 3$ AE, including one (4.5%) G5 haemoptysis.

Discussion

Despite significant progress in the management of locally advanced NSCLC, LC remains to be improved. A relevant way could be to use the technical innovations of RT and integrate SBRT into the management of these patients, either instead of, or in addition to, NFRT. This recent modality of treatment achieves higher dose in smaller and more conformal volumes, while decreasing treatment duration and its logistical burden for both patients and caregivers. Our review highlights that various treatment sequences, doses and volumes may be considered in stage III NSCLC patients with tumor <5 cm, with promising long-term results. Contrasting with other schedules, standard nodal CCRT followed by full dose tumoral SBRT achieved a mOS of 52 months [31]. The mOS varied widely, mostly from 10 to 28 months, due to the heterogeneity of the included populations and according to treatment regimens. These results are similar to what is expected in this situation, with a mOS of 29.1 months of the selected population of the PACIFIC trial CCRT group [5]. Most have been shown to be very well tolerated. Nevertheless, grade 5 toxicity rate was observed, mainly in comorbid patients or in absence of dose constraints on proximal bronchovascular tree during mediastinal SBRT, but usually remained <5% even in those cases. A decision tree can be suggested ([Figure 2](#)), based on inclusion criteria, on dose and volumes of published phase I and II trials. Since trials

evaluating SBRT boost reported various inclusion criteria, with important dose and volume heterogeneity, no clear recommendation can be made whether to perform this additional dose on primary tumor only or on involved nodes as well. These high dose treatments should therefore be conducted in experienced centers, preferably in clinical trials, and with a risk-adapted fractionation strategy.

Focus may particularly be on increasing control of the primary tumor since primary local failures are twice as frequent as regional recurrences [41,42]. Mediastinal SBRT can lead to significant lethal AE [43,44], particularly in this population with important overall target volume [26,28]. To avoid these critical AE, dose constraints must be predefined on proximal bronchovascular tree [26,28,45]. In case of SBRT boost, dose summation should be done for considering the different fractionations and without underestimating the biological delivered dose, scaling each dose to equivalent dose in 2 Gy fraction (EQD2) or BED.

In early-stage NSCLC, increasing radiation dose to $BED_{10} > 100$ Gy improves local control and prognosis [46,47]. A dose-threshold of $BED_{10} > 112.3$ Gy has been reported in stage III disease [26]. Nevertheless, a dose-response relationship is not as clear when performing moderately hypofractionated or normofractionated RT. A recent meta-analysis of randomized controlled trials (RCT) reported that higher RT doses were associated with poorer survival in case of concurrent chemotherapy [48]. This negative correlation may be due, at least in part, to the increased side effects. In RTOG 0617 dose escalation trial, high-volume centers achieved significantly longer PFS and OS compared to low-volume centers (11.4 vs 9.7 months, and 26.2 vs 19.8 months, respectively) [49]. Therefore, these higher dose treatments should be conducted in experienced centers. On the other hand, in absence of chemotherapy a positive association between higher RT dose and OS was observed (median survival ratio 1.13; 95%CI 1.04-1.22) [48]. This less pronounced dose-response relationship in advanced- compared to early-stage disease may also be due to their specific pattern of recurrence. Indeed, stage I-II diseases present

fewer recurrence and a lower propensity for distant relapse [49]. These important differences can explain the central role of local control through delivering higher dose in early-stage disease.

On top of the efficacy, steeper dose-gradient and smaller treated volumes with SBRT may better preserve OAR. In early-stage NSCLC, the SPACE randomized trial reported fewer RP (19% *vs* 34%) and esophagitis (8 *vs* 30%) after SBRT than after CCRT [17]. Furthermore, evidence is emerging suggesting that lymphopenia negatively affect prognosis [50–52] and may be reduced when limiting bone marrow and circulating blood irradiation [50]. By limiting dose to these unusual thoracic OAR, SBRT limits severe lymphopenia [51] and may improve prognosis compared to conventional RT.

A prerequisite to increase treatment conformity is accurate target volume definition. PET/CT not only allows this more precise delineation but also reduces interobserver variability, particularly in case of atelectasis or central location [53,54], and improve nodal and metastatic staging [55,56]. PET PLAN, a RCT, showed the non-inferiority of isotoxic dose escalation in pre-treatment FDG-PET selected volume compared to conventional CT-based strategy [57]. This metabolic-based method tended to reduce local regional failure (2-year rate: 20% *vs* 39%, respectively) [57]. In the PET-boost trial, patients received 66 Gy in 24 fractions, with a randomization of simultaneous integrated boost ≥ 72 Gy either on the entire tumor or to the 50% maximum standardized uptake value area on pretreatment PET/CT [58]. This strategy led to higher LC but increased severe AE, with 9 (11.7%) grade 5 haemoptysis and oesophageal fistulae.

Per- and post-treatment persistent metabolic activity may also be associated with poorer outcomes [59,60]. PET/CT can thus be a surrogate of radioresistant area to perform a radiation boost on per-treatment FDG-avid volume. This strategy was reported by Kong et al. first in a single arm and then in a randomized phase II trials [61,62]. They escalated dose up to 80 Gy in

30 fractions on residual tumor on mid-treatment FDG-PET, with median pre-treatment GTV of 98cc (range 6-597). However, the adaptive treatment did not significantly increase OS, PFS or local-regional tumor progression free survival [62]. Another comparison of FDG-PET/CT-adapted radiotherapy with standard regimen is ongoing in RTEP7 randomized phase II-III trial (NCT02473133). In this trial, dose is escalated to 74 Gy on the persistent FDG-avid volume at 42 Gy during CCRT.

In addition to improving volume selection, SBRT may be of particular interest to some selected subpopulations. First, this highly accurate technique can be performed even in presence of severe impaired lung function [63]. Second, in elderly or comorbid patients that are ineligible to sequential or CCRT [64], SBRT might compensate the local regional loss of disease control. In a meta-analysis of RCT, it was reported that in absence of chemotherapy a higher RT dose improved OS [48]. There was no upper dose threshold above which there was no further benefit.

More than just a volume selection, the better understanding of the molecular tumor biology may improve patient selection. A non-randomized phase 2 trial reported that patients with hypoxic tumors, defined as 18F-fluoromisonidazole PET/CT-positive, have shorter PFS and OS [65]. However, spatial dose adaptation using RT boost on hypoxic areas did not improve the prognosis. It has recently been reported that mutations of KEAP1-NFE2L2 [66–68] or KRAS [68–71], and high NOTCH activity [72] confer poorer prognosis and a radioresistant phenotype. The latter may be overcome by higher radiation dose [70]. Nevertheless, preclinical data suggest that KRAS-mutated tumors may present greater radioresistance at higher doses [68]. Other prognostic factors predictive of treatment response are emerging, such as tumor aneuploidy [73], activation of the serine/glycine biosynthesis pathway [74,75] and proteome-based classification[76]. To improve treatment-personalization, a 10-gene-expression-based radiation-sensitivity index was developed to derive individual genomic adjusted radiation dose (GARD) [77]. This may identify patients who could benefit from highly hypofractionated dose

escalation [78]. In parallel, development of image-based deep learning may predict LC to optimize RT dose prescription [79]. Combining multiple “omic” approaches will probably improve efficacy and safety prediction [80].

Consolidation durvalumab is now a standard of care [81] and its efficacy may be improved if initiated early after NFRT [5,82]. Nevertheless, plasmatic cytokine changes are different after SBRT and IMRT, which could lead to a different immune response [19]. An important issue is that none of the reviewed trials administered consolidation durvalumab, thus an optimal timing cannot be formally recommended. Nevertheless, since synergistic association has already been reported between SBRT and IO [20,83], we suggest that regimes delivering tumor SBRT shortly before durvalumab initiation should be preferred. A promising and original hybrid regimen has been proposed by Peulen et al. [84]. After 21 fractions of 2.42 Gy (60 Gy equivalent dose in 2 Gy fractions), they reported the dosimetric feasibility of performing 3 more fractions on the nodes with a simultaneous integrated boost of 3x18Gy SBRT on the primary tumor.

Further studies are needed to clarify the place of SBRT in stage III NSCLC. First, comparisons with the standard normofractionated regimen are still needed, particularly for nodal irradiation. To the best of our knowledge, no phase III trial are ongoing. Second, durvalumab maintenance after CCRT is the new standard of care in this clinical scenario [85]. However, to date, no publication reported efficacy and safety of SBRT in this setting. Results of an ongoing single-arm phase II trial (NCT03589547) are awaited. They evaluate the benefit of a 2-fractions SBRT consolidation at the beginning of the durvalumab maintenance. Nevertheless, systemic treatment may continue to evolve. The COAST phase II trial recently reported that the addition of oleclumab or monalizumab (anti-CD73 and anti-NKG2A, respectively) may improve PFS (HR <0.45) compared to the PACIFIC regimen alone. PACIFIC-9 (NCT05221840) will further evaluate these combinations in a phase III trial. Future

trials evaluating innovative systemic combinations [86] should also consider the opportunity to include a radiotherapy experimental part.

Conclusion

Unresectable stage III NSCLC patients with tumor < 5cm may safely be treated using SBRT either instead of, or in addition to, NFRT. Biologically effective dose should be higher than 112.3 Gy, and dose constraints to proximal bronchovascular tree and oesophagus should be strictly respected. Further studies are needed to include immunotherapy (ie durvalumab) maintenance. At the same time, including SBRT in future trials of systemic treatment may be considered.

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Table 1. Characteristics of included studies

Reference	Design	N	mFU	ChT	NFRT	Interval	SBRT			LC	OS	Tox G \geq 3	Restrictions
					dose / #	NFRT- SBRT	Prior PET-CT	Target	Dose / #				
<i>SBRT Boost after NFRT</i>													
Salazar et al., 2008 [23]	Retro.	30	44	No	45 Gy / 25#	NA	No	T	22.5Gy / 3# (70%-IDL)	73% (IIIA), 47% (IIIB)	Median: 15 months	No G \geq 3 toxicity	-
Feddock et al., 2013 [24] †	Prospec.	35	13	Yes	59.4 Gy / 33#	2 months	Yes	T	Periph.: 20Gy / 2# Medial: 19,5Gy / 3#	82.9%	NA	N=5 G3 RP N=2 late G5 haemoptysis	T \leq 5cm and no persistent node after NFRT
Karam et al., 2013 [25]	Retro.	16	14	Yes	50.4 Gy / 28#	20 days	No	T&N	25Gy / 5#	At 1y: 76%	At 1y: 78%	No G4-5 toxicity	-
Hepel et al., 2016 [26]	Phase 1 (n=2 centers)	12	15.5	Yes	50.4 Gy / 28#	7-30 days	No	T&N	16-28Gy / 2#	At 1y: 78%	At 1y: 67%	N=1 late G5 haemoptysis	T <120cc and N<60cc after NFRT
Kumar et al., 2016 [27] †	Prospec. Meeting	43	15	Yes	59.4 Gy / 33#	NA	Yes	T	Periph.: 20Gy / 2# Medial: 19,5Gy / 3#	76.7%	Median: 26.5 (IIIA) and 17.4	NA	T \leq 5cm and no persistent node after NFRT

											months		
											(IIIB)		
Higgins et al. 2017 [28]	Phase 1 (n=2 centers)	19	13	Yes	44 Gy / 22#	NA	No	T&N	18-20Gy / 2# or 30-35Gy / 5#	3y-LRFS: 59%	At 3y: 39%	All in 5# cohorts: N=1 G3 RP N=1 G5 haemoptysis N=1 G5 tracheoesophageal fistula	T ≤8cm, N1-2 ≤5cm
Kumar et al., 2017 [29]	Prospec.	37	25.2	Yes	59.4 Gy / 33#	86.1 days	Yes	T	Periph.: 20Gy / 2# Medial: 19,5Gy / 3#	At 3/5y: 29.8% / 17%	Median: 27.6 (II/IIIA) and 15.6 months (IIIB)	N=5 G3 RP N=2 late G5 haemoptysis	T ≤5cm and no persistent node after NFRT
Doyen et al., 2018 [30]	Phase 1 (n=2 centers)	26	37.1	Yes	46 Gy / 23#	21 days	No	T	21-36Gy / 3#	2y-LC / LRFS: 70.3% / 55.5%	At 2y: 50.8%	N=1 late G4 oesophageal fistula N=1 late G5 haemoptysis	T <5cm after NFRT

Nodal NFRT followed by tumoral SBRT

Martel-Lafay et al., 2021 [31]	Phase 2 (n=12 centers)	25	58	Yes	66 Gy / 33#	3-4 weeks	No	T	54 Gy / 3#	At 6 months: 79%	Median: 51.6 months	N=1 acute G3 RP	T ≤5cm, >2cm from mediastinum
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Tumoral SBRT followed by nodal NFRT

Chi et al., 2016 [22] *	Retro.	3	23.7	Yes	63 Gy / 35#	NA	Yes	T	40-50Gy / 4#	At 2y: 100%	At 2y: 100%	No G≥3 toxicity	-
Kim et al., 2018 [32]	Retro.	21	12	Yes (57%)	60 Gy / 33#	8 days	Yes	T	54 Gy / 4#	2y-LRFS: 74.2%	At 2y: 60.5%	N=1 acute G3 oesophagitis N=1 acute G3 RP N=1 acute G4 RP	-

Definitive SBRT

Wang et al., 2015 [33]	Retro.	49	25	No	-	-	No	T&N	48 Gy / 12# (50%-IDL)	At 3y: 95.5%	Median: 22 months	No G≥3 toxicity	Aged ≥65 Unfit for ChT
Cong et al., 2019 [34] ‡	Retro.	20	17	NA	-	-	No	T&N	35Gy / 5# (68- 75%-IDL)	At 1y: 61.2%	Median: 17 months	N=1 G3 RP N=2 G5 cardiac toxicity	Unfit for CCRT Ultracentral tumor
Cong et al., 2019 [35] ‡	Retro.	15	16.5	Yes (40%)	-	-	No	T&N	31-36Gy / 5-6#	At 1y: 60.8%	Median: 17 months	N=1 G3 RP	Unfit for CCRT

												N=2 G5 cardiac toxicity	Ultracentral squamous cell tumor
Arcidiacono et al., 2020 [36]	Phase 2 Meeting	25	9	Yes (85%)	-	-	Yes	T&N	40Gy / 5#	84% Median LRFS: 8 months	Median: 10 months	No G≥3 toxicity	Unfit for ChT
Arcidiacono et al., 2022 [37]	Phase 2 Meeting	27	19	No	-	-	Yes	T&N	40Gy / 5#	74%	NA	No G≥3 toxicity	Aged ≥70 Unfit for ChT
Kubicek et al., 2020 [38] *	Phase 2 Meeting	22	23.1	Yes	-	-	Yes	T&N	Periph.: 60Gy / 3# Central: 50Gy / 5# N: 40-50Gy / 5#	100%	Median: 27.2 months	N=6 G3 acute toxicity N=2 late G≥3 toxicity	T <8cm, ≤ 3 N+
Kubicek et al., 2022 [39]	Phase 2	22	23.1	Yes	-	-	Yes	T&N	Periph.: 60Gy / 3# Central: 50Gy / 5# N: 40-50Gy / 5#	100%	Median: 27.2 months	N=6 G3 acute toxicity N=1 late G3 RP N=1 late G5 hemoptysis	T <8cm, ≤ 3 N+

† Updated: Kumar et al., 2017; ‡ Population overlap; * among the 29 patients treated by image-guided radiotherapy ; * Updated: Kubicek et al., 2022

Abbreviations: #, fractions; ChT, chemotherapy; CCRT, chemoradiotherapy; IDL, isodose line; LC, local control; LRFS, local recurrence-free survival; Meeting., meeting abstract; mFU, median follow-up; N, node(s); NFRT, normofractionated radiation therapy; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; Prospec., prospective; Retro., retrospective; RP, radiation pneumonitis; SBRT, stereotactic body radiation therapy; T, tumor

Table 2. Quality assessment of included studies using Joanna Briggs Institute Critical Appraisal Checklist for Case Series

Reference	Clear inclusion criteria	Reliable measure	Valid measure	Consecutive inclusion	Complete inclusion	Clear demographic characteristics	Clear initial clinical characteristics	Clear outcomes and follow-up	Site demographic information	Appropriate statistical analysis
Salazar, 2008	+	+	+	+	+	?	?	+	+	?
Feddock, 2013	+	+	+	+	+	+	+	+	+	+
Karam, 2013	+	+	?	+	+	+	+	?	+	+
Hepel, 2016	+	+	+	+	+	+	+	+	+	+
Kumar, 2016	+	+	+	?	?	−	−	−	+	+
Higgins, 2017	+	+	+	+	+	+	+	+	+	+
Kumar, 2017	+	+	+	+	+	+	+	+	+	+
Doyen, 2018	+	+	+	?	?	+	+	+	+	+
Martel-Lafay, 2021	+	+	+	+	+	+	+	+	+	+
Chi, 2016	?	+	+	+	+	−	−	+	+	+
Kim, 2018	+	+	+	+	+	+	+	+	+	+
Wang et al, 2015	+	+	+	+	+	+	+	+	+	+
Cong, 2019	+	+	+	+	+	+	+	+	+	+
Cong, 2019	+	+	+	+	+	+	+	+	+	+
Arcidiacono, 2020	?	+	+	?	?	?	+	+	+	+
Arcidiacono, 2022	+	+	+	+	+	+	+	?	+	−
Kubicek, 2020	+	+	+	+	+	−	−	+	+	+
Kubicek, 2022	+	+	+	+	+	?	+	+	+	+

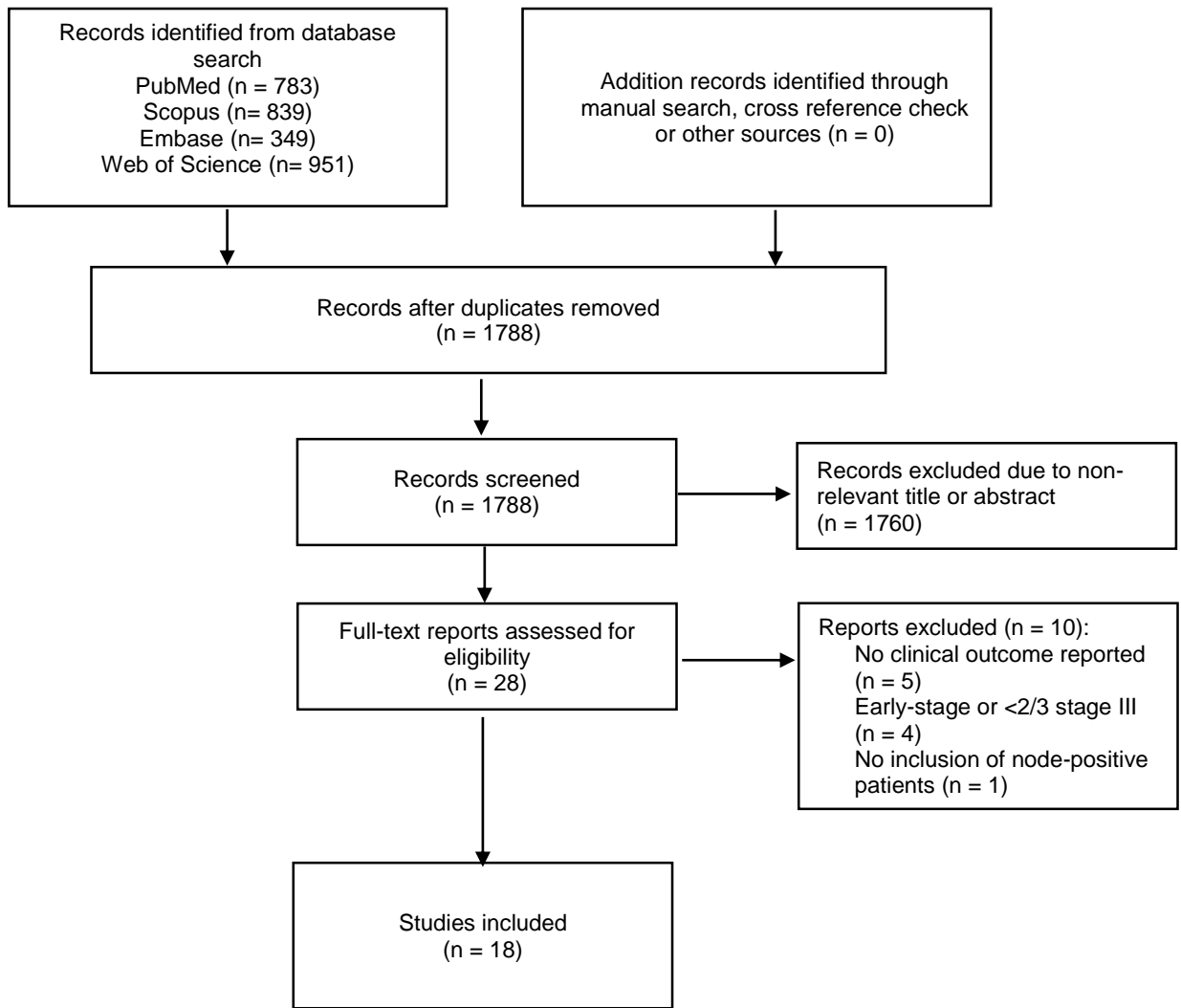


Fig. 1. PRISMA flow diagram

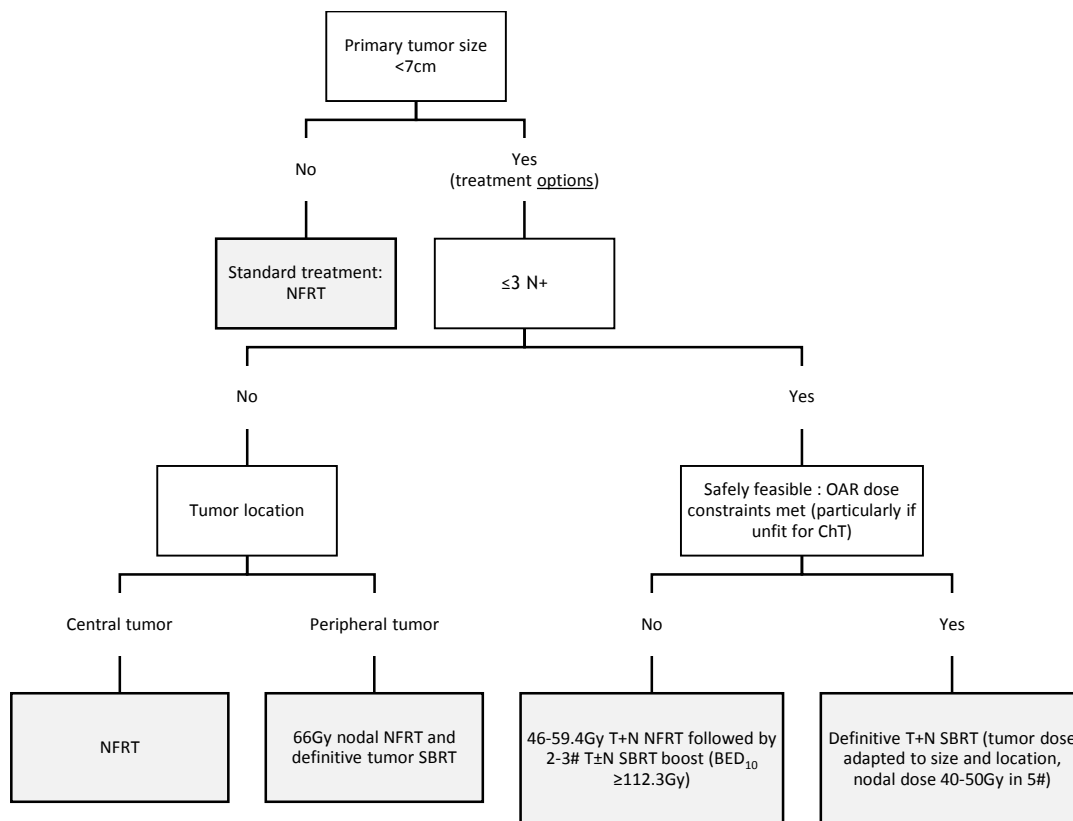


Fig.2. Suggested radiotherapy regimens of stage III non-small cell lung cancers

Abbreviations: #, fractions; ChT, chemotherapy; N+, involved nodes; NFRT, normofractionated radiotherapy; SBRT, stereotactic body radiotherapy; T+N, tumor and nodal

Supplementary materials

Table. Database search method

Database	Search string
PubMed	<p>((Lung Neoplasms[MeSH Terms]) OR (Carcinoma, Non-Small-Cell Lung[MeSH Terms]) OR ("lung carcinoma") OR ("NSCLC") OR ("non small cell lung") OR ("non-small cell lung"))</p> <p>AND (("Stage III") OR ("Stage 3") OR ("Locally") OR ("Locally advanced") OR ("Advanced") OR ("Inoperable") OR ("Unresectable"))</p> <p>AND ((Radiosurgery[MeSH]) OR ("Stereotactic radio*") OR ("Stereotactic body") OR ("SBRT") OR ("SABR"))</p> <p>NOT ("early"[TITLE])</p> <p>AND (("french"[Language]) OR ("english"[Language]))</p>
Scopus	<p>TITLE-ABS-KEY ({lung carcinoma} OR {lung cancer})</p> <p>AND TITLE-ABS-KEY ({stage III*} OR {stage 3*} OR {locally advanced} OR unresect* OR inoperable)</p> <p>AND (TITLE-ABS-KEY (stereotactic PRE/2 radi*) OR TITLE-ABS-KEY (sbrt OR sabr))</p> <p>AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "French"))</p>
Embase	<p>'non small cell lung cancer'/exp</p> <p>AND 'stereotactic body radiation therapy'/exp</p> <p>AND ('stage iii' OR 'stage 3' OR 'locally advanced' OR 'unresectable')</p> <p>AND ([english]/lim OR [french]/lim)</p>

Web of Science	<p>TS = (('lung carcinoma' OR 'NSCLC' OR 'non small cell lung' OR 'non-small cell lung')</p> <p>AND ('Stage III' OR 'Stage 3' OR 'Locally advanced' 'Inoperable' OR 'Unresectable')</p> <p>AND ('Radiosurgery' OR 'Stereotactic radio*' OR 'Stereotactic body' OR 'SBRT' OR 'SABR')) NOT TI=('early')</p>
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