



Systematic review of stereotactic body radiotherapy in stage III non-small cell lung cancer

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Abstract: Despite adequate treatment, 50% of stage III locally advanced inoperable non-small cell lung cancer (NSCLC) patients have a locoregional relapse. Local control on early stages on the contrary, is as high as 85–90% with stereotactic body radiotherapy (SBRT). The addition of SBRT to conventional chemoradiation or its use in monotherapy in stage III NSCLC is a novel strategy to decrease local failure that has been explored by various authors. This is a systematic review of studies using SBRT in inoperable stage III NSCLC. Search results obtained 141 articles of which only 6 original studies were pointed as relevant. Three of these studies were prospective, of which 2 were phase I dose-escalation studies and remaining 3 were retrospective. In summary, SBRT outcomes on 134 patients were included. Median dose in the SBRT treatment was 22.5 Gy in 2 to 7 fractions. Obtained global toxicity was 3.7% grade 5 and 14.17% grade 3. Dose-escalation studies proposed a 2 fraction SBRT schedule of 20–24 Gy, obtaining a 78% local control rate at 1 year and an OS of 67%. Initial improvement in local control with this innovative therapeutic strategy has led to ongoing phase II and III clinical trials that will evaluate the efficiency of SBRT in stage III NSCLC clinical scenario.

Keywords: Stereotactic body radiotherapy (SBRT); stereotactic ablative radiotherapy (SABR); locally advanced non-small cell lung cancer (NSCLC); stage III

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Introduction

Stage III unresectable non-small cell lung cancer (NSCLC) represents approximately 20% (1) of all patients diagnosed with NSCLC. For years, the standard treatment has been thoracic radiotherapy 60–66 Gy in 30–33 daily fractions with concomitant cisplatin based chemotherapy (2), offering an overall survival rate at 5 years between 15–25% (3). Nowadays, consolidation with Durvalumab represents the new standard of care in patients with PD-L1 \geq 1%

and no progression after chemoradiation (4). However, intrathoracic progression in the Durvalumab arm showed just a little difference with the placebo arm, 36.6% *vs.* 48.1%. Therefore in stage III clinical scenario, local relapse continues being a mayor challenge.

Specifically, local relapse in stage III NSCLC can vary from 20% to 50% (5). Dose escalation with conventional radiotherapy to the lung tumor is related to higher local control but also to a higher toxicity. In that sense, the RTOG 0617 (6) study was a game-changer, as it

demonstrated how, higher doses to organs at risk like the heart, were fundamental to explain the toxicity seen at dose escalation studies.

On the other hand, stereotactic body radiotherapy (SBRT) encompasses a technique that can deliver high dose conformal radiation through multiple radiation beams with steep dose gradients in 3–8 fractions. In early stage NSCLC, SBRT studies have demonstrated local control rates as far as 94% 3 years post-treatment (7,8). Nevertheless, in very central lesions or tumors with mediastinal lymph node infiltration, grade 3 or higher toxicity can reach 46% (9).

Consequently, using dose escalation with SBRT technique to improve local control in stage III NSCLC seems an attractive strategy. Scientific literature available on the topic as far as dose to deliver, toxicity profile and possible concomitant treatments to combine is scarce. This systematic review summarizes the current scientific evidence on the use of SBRT in locally advanced inoperable NSCLC (stage III).

Material and methods

A systematic review on the literature was performed using PubMed-Medline, Embase and Scopus databases. Relevant articles on SBRT usage in inoperable stage III NSCLC were identified using the following terms in the Medical Subject Heading (MeSH):

(SBRT or SABR or stereotactic [MeSH Terms]) AND (NSCLC or Carcinoma or Non small cell lung or Non-small-cell Lung or Lung carcinoma or Non-small-cell Lung Carcinoma or Nonsmall Cell lung Carcinoma or Nonsmall Cell Lung Cancer or Non-Small-Cell Lung Carcinoma or Non Small Cell Lung Carcinoma or Non-Small Cell Lung Cancer [MeSH Terms]) AND (Stage III [MeSH Terms]).

Search syntax was adapted to Embase and Scopus databases in order to find relevant articles on the topic. We included studies up to December 2019.

The articles found on the systematic review were independently examined by two investigators (OLA and ANM). Interesting articles related to the topic that were found outside the initial systematic review were included. Discrepancies between the reviewers were analyzed together and a consensus was reached.

Included studies for the review were those that administered SBRT as a boost after or before conventional chemoradiotherapy, those that administered SBRT in monotherapy and reviews on the administration of SBRT in inoperable stage III NSCLC. Studies that did not report

administered doses or that did not include outcomes such as toxicity, progression free survival or local control were excluded. Articles that were not published in English or did not have the complete text available were also excluded.

This systematic review has been carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*Figure 1*). To measure quality of the studies the NIH quality-measure tool for this purpose was used available at <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>.

Results

Systematic review on the three databases above mentioned extracted 141 studies, 11 of which met inclusion criteria (5,10–19) (*Figure 1*). Two studies were reviews (5,15), one did not include clinical data (17), two studies had preliminary results (11,12), 3 were prospective studies and another 3 were retrospective. For quantitative and qualitative analysis 6 articles were fully reviewed (*Table 1*).

In the studies that met the inclusion criteria, a total of 134 patients affected of stage III inoperable NSCLC were treated with SBRT some time during the therapeutic strategy. These studies were carried out between 2008 and 2019 in different centers, majority of them in United States, and one in China. In relation to the design of the studies included, 3 studies had a prospective design, 2 of which were phase I. The remaining 3 were retrospective series. Sample size for each study and results are described in *Table 1*.

Out of the 6 original studies that considered SBRT administration in stage III NSCLC, 1 employed SBRT in monotherapy (10) and the other 5 employed SBRT as a dose escalation technique in the context of conventional chemoradiotherapy (13,14,16,18,19).

Studies that administered SBRT as a dose intensification technique had a median dose in the conventional radiotherapy of 50.4 Gy in a median of 28 fractions. Additionally, the median dose in the SBRT boost was 22.25 Gy delivered in 2 to 7 fractions.

Systemic treatment employed for conventional chemoradiotherapy was platinum-based. One of the studies included FDG PET-CT scan as a tool for contouring the gross tumor volume (GTV) for the boost. The rest of the studies relied on CT scans to delineate the GTV. Three studies included the primary tumor and the affected lymph nodes in the SBRT therapeutic volume. The remaining two, on the contrary, included the primary tumor but not the lymph nodes. Reported

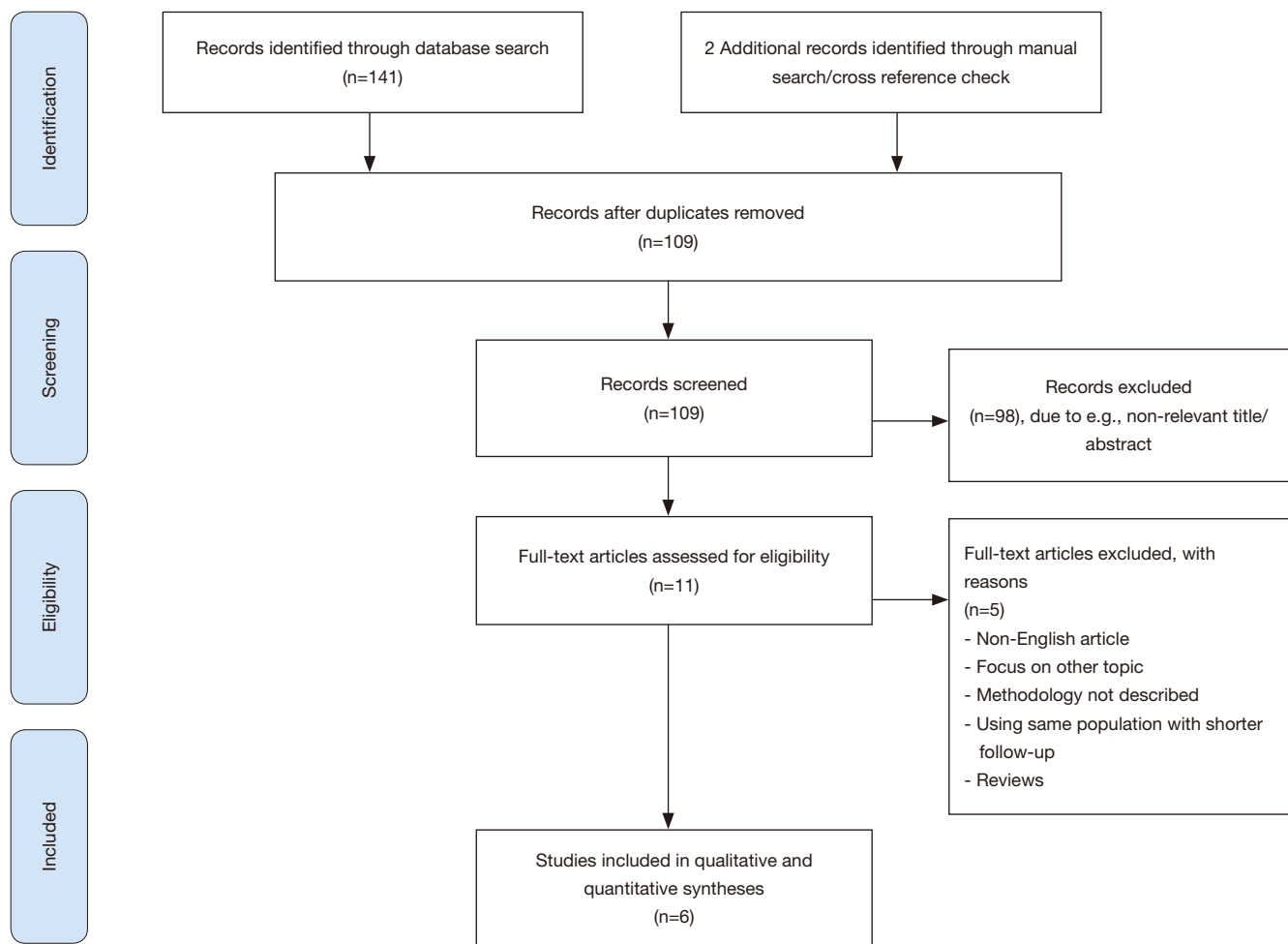


Figure 1 PRISMA flow diagram.

median follow-up was 18.75 months. Median local control was 76%. As far as toxicity is concerned, 12% of patients experienced grade 3 or higher toxicity.

The phase I dose-escalation study by Hepel *et al.* included 12 patients (13). Primary objective was to obtain dose limiting toxicity (DLT) for toxicity such as pneumonitis, oesophageal fistula, cardiac toxicity, bone fractures or dermatitis. Four dose schedules are described, from 16 to 28 Gy administered in 2 fractions and incrementing dose per fraction by 4 Gy in each cohort. Following its primary objective (DLT), 3 patients per cohort-dose were included using a classical 3×3 trial design.

Patients on Hepel's study underwent chemoradiotherapy previously at a dose of 50.4 Gy in 28 fractions. Most common systemic treatment to combine with radiation was 2 cycles of cisplatin and etoposide every 3 weeks or

carboplatin-taxol weekly for 6 weeks. After conventional chemoradiotherapy, a CT scan was obtained to address the remaining tumor in order to plan SBRT treatment that would be administered 1 to 4 weeks after.

In this case, both the remaining primary tumor and lymph nodes were included in the treatment field. Four dose cohorts were reached, where grade 3 or superior toxicity was not observed. 42% of the patients received consolidation chemotherapy for 2 more cycles.

With a median follow-up of 15.5 months, local control the first year was 78% and 100% in 6 patients who received 24 Gy or higher doses. Overall survival of the whole study was 67%. One patient on the 24 Gy cohort experienced grade 5 toxicity in peribronchial vasculature.

The other phase I dose-escalation study published in 2017 by Higgins *et al.* (14) included 19 patients and its primary

Table 1 Prospective and retrospective studies that met inclusion criteria

Author/year	Study	N	SBRT sequence	Median dose NFRT	CCT	Time**	Median dose SBRT	Test for targeting	Target boost	Toxicity \geq G3	Mean FU _m	LC	OS
Salazar et al. 2008	Retrospec.	30	Boost	45 Gy (1.8 Gy/ Fr)	No	NA	22.5 Gy (7.5 Gy/Fr)	NA	PT	0%	NA	82%	19%
Karam et al. 2013	Retrospec.	15	Boost	50.4 Gy (45–60 Gy)	Yes	25 [7–97]	25.25 Gy (range, 20–30) (5 Gy/Fr)	CT	PT + ELN	12.5%	14	76%	NR
Hepel et al. 2016	Phase I	12	Boost	50.4 Gy/28 Fr	Yes	7–28	G1: 8 Gy \times 2 Fr; G2: 10 Gy \times 2 Fr; G3: 12 Gy \times 2 Fr; G4: 14 Gy \times 2 Fr	CT	PT + ELN	8%	15.5	78% 1 y	67% 1 y
Higgins et al. 2016	Phase I	15	Boost	44 Gy/22 Fr	Yes	1–3	G1: 9 Gy \times 2 Fr; G2: 10 Gy \times 2 Fr; G3: 6 Gy \times 5 Fr; G4: 7 Gy \times 5 Fr	CT	PT + ELN	20%	22	59% 1 y	39% OS
Kumar et al. 2017	Prospec.	42	Boost	60 Gy/30 Fr	Yes	30	19.5 Gy (6.5 Gy/Fr) vs. 20 Gy (10 Gy/2 Fr)	PET/TC	PT	11.9%	25.2	63.5% 1 y	19.2% vs. 26.4%
Cong et al. 2019	Retrospec.	20	Monotherapy	0	No	–	35 Gy (5 Fr)	NA	PT + ELN	9.8%	17	61.2%	18%

** , days after CCT. NFRT, normofractionated radiation therapy; CCT, concomitant chemotherapy; NA, not available; MST, median survival time; PT, primary tumor; ELN, enlarged lymph node; LC, local control; NR, not reached.

objective was also to determine the maximal tolerated dose (MTD). Four dose cohorts were designed: 18 Gy (9 Gy \times 2 Fr), 20 Gy (10 Gy \times 2 Fr), 30 Gy (6 Gy \times 5 Fr) and 35 Gy (7 Gy \times 5 Fr). In a similar manner, 3 patients per dose-cohort were included. They all underwent conventional chemoradiotherapy previously at a dose of 44 Gy in 2 Gy fractions concurrent to weekly carboplatin (45–50 mg/m²) and paclitaxel (AUC 2).

Consolidation chemotherapy was at the discretion of the clinician and 73% received it. The third dose cohort (6 Gy \times 5 Fr) had a grade 5 tracheo-esophageal fistula that derived in death of the patient. Another 2 patients at the fourth dose cohort (7 Gy \times 5 Fr) presented grade 3 or higher toxicity: one grade 5 hemoptysis and one grade 3 hypoxia. With these findings, authors conclude that the save dose range would be 20 Gy in 2 fractions.

Residual disease in this case was measured with CT scans and SBRT was delivered to the primary tumor and the remaining lymph nodes. Local control rate was 59% the first year and overall survival was 39%.

The third and last prospective study was published in 2017 by Kumar *et al.* (16). Patients with inoperable stage IIB (4p) and IIIA–B (38p) were included. Median follow-up was 25 months. Primary objective of the study was to determine the safety or toxicity profile of an SBRT boost. All patients received conventional chemoradiotherapy (59.4–60 Gy with standard 180–200 cGy fractions). In this case, PET-CT was achieved 1 month after termination of chemoradiotherapy, and the remaining disease was included in the SBRT boost. 2 dose cohort were designed: 10 Gy \times 2 fractions for tumors in the periphery (28p) and 6.5 Gy \times 3 fractions for central tumors (14p). Boost did not include lymph nodes. The median time between chemoradiotherapy and SBRT delivery was 2.9 months. One-year local control of the study was 63.6%. Toxicity rate was 11.9% grade 3 with no grade 4 or higher toxicity.

Out of the three retrospective studies that met the selection criteria, the study by Cong stands out due to its innovative therapeutic approach (10). In this case, SBRT is administered in monotherapy for stage III NSCLC with a Cyberknife at a median dose of 35 Gy in 5 fractions. Primary tumor and lymph nodes were both included in the treatment volume. Median follow-up time was 17 months with a local control rate of 61%. Grade 3 toxicity or higher was 9.8%.

As far as the retrospective work of Salazar *et al.* (18), SBRT was delivered in different NSCLC clinical scenarios, including metastasis. In summary, 30 patients were stage

Questions for Assessment	Hepel et al.	Higgins et al.	Kumar et al.
Was the study question or objective clearly stated?	😊	😊	😊
Were eligibility/selection criteria for the study population prespecified and clearly described?	😊	😊	😊
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	😊	😊	😊
Were all eligible participants that met the prespecified entry criteria enrolled?	😊	😊	😊
Was the sample size sufficiently large to provide confidence in the findings?	😊	😊	😊
Was the test/service/intervention clearly described and delivered consistently across the study population?	😊	😊	😊
Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	😊	😊	😊
Were the people assessing the outcomes blinded to the participants' exposures/interventions?	😞	😞	😞
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	😊	😊	😊
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	😊	😊	😊
Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	😊	😊	😊
If the intervention was conducted at a group level did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	😞	😞	😞

😊 Yes; 😞 No.

Figure 2 Study Quality assessment tool for before-after studies with no control group.

III and were included in this review. They received conventional radiotherapy total dose 45 Gy in 25 fractions and SBRT boost in 3 fractions of 7.5 Gy each to the primary tumor (excluding lymph nodes). Obtained local control by stages was: 73% in stage IIIA and 47% in stage IIIB. Information about systemic therapy was not available. No grade 3 or higher toxicity was detected.

Finally, the retrospective study by Karam *et al.* (19) included 16 patients, all stage III. Conventional chemoradiotherapy was delivered with a median total dose of 50.4 Gy. In order to identify the SBRT volume during treatment, 4 fiducial markers were placed prior to simulation. Median follow-up reached 14 months, with an overall survival at 1 year of 78%. Local and regional control were 76% and 79% respectively. Toxicity was not graded accurately, although information on one patient developing hemoptysis and another pneumonitis is given.

The overall quality of the studies was measured using the NIH “Study quality assessment tools”. Specifically, “before-after studies with no control group” was used to measure the prospective studies, and the “quality case series studies” was


























used to measure the retrospective studies (see *Figures 2,3*).

Discussion

Standard treatment for stage III inoperable NSCLC remains conventional chemoradiotherapy; systemic therapy being platinum-based and radiation doses going up to 60–66 Gy in 2 Gy daily fractions (4,20).

The primary objective of this systematic review was to establish first clinical experiences and the existing scientific evidence supporting the use of SBRT in inoperable stage III NSLCL as a tool to decrease local failure. Six relevant studies were found. After careful examination, two principal therapeutic strategies were identified: on one hand, the use of SBRT as a boost after conventional chemoradiation, and on the other, the use of SBRT in monotherapy in those patients that are not good candidates for conventional chemoradiation.

Interestingly, SBRT treatment volume design differs from study to study. Sometimes it includes just the primary tumor in order to reduce toxicity, and in other cases, it

Questions for Assessment	Salazar et al.	Karam et al.	Cong et al.
Was the study question or objective clearly stated?			
Was the study population clearly and fully described, including a case definition?			
Were the cases consecutive?	NA	NA	
Were the subjects comparable?			
Was the intervention clearly described?			
Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?			
Was the length of follow-up adequate?			
Were the statistical methods well-described?			
Were the results well-described?			

☺ Yes; ☹ No. NA, not available.

Figure 3 Quality assessment tool for case series studies.

includes positive lymph nodes too instead.

SBRT volume

Stage III NSCLC disease is characterized by lymph node involvement in the mediastinum. The administration of SBRT in this stage poses an important risk of toxicity due to proximity of critical organs like bronchi, esophagus, large vessels and the heart. Classically, central lung lesions have been defined as those at a distance of 2 cm or less from the mediastinum or principal bronchi (21). In studies that used SBRT to central lesions in early stages, grade 3 or higher toxicity was reported as 9% (22). Nevertheless, treatment volumes did not include positive lymph nodes. Up to date, SBRT administration to treat lymph nodes has been anecdotic and doses to administer are therefore not clear (23).

In our systematic review, 5 out of 7 studies used SBRT technique as a dose-intensification method after concurrent chemoradiotherapy. In these studies, initial disease-volume is reduced with conventional treatment in order to pursue a safer SBRT treatment volume. Two studies (Salazar and Kumar *et al.*) include solely the primary tumor in the intention to treat volume. Grade 3 toxicity reported by these authors is 0% and 11.9% respectively. Remaining

studies include the involved lymph nodes in the SBRT volume as well as the primary tumor and grade 3 toxicity reported varies from 8% to 20%.

Imaging technique to determine the GTV

Choice of imaging technique in the design of the GTV differs from study to study. Residual disease identification after conventional chemoradiotherapy is fundamental to make an impact in locoregional control and most probably, on overall survival. In this regard, just one study (16) included PET-CT at one-month completion of chemoradiotherapy to determine the residual disease.

At present, the standardization of radiomics in PET scans and the study of its prognostic value for lung cancer has been studied (24). Whether PET can be an independent prognosis factor in lung cancer in order to select patients for treatment intensification after chemoradiation is also currently under consideration (25).

Dose election

In the studies previously mentioned, median dose for SBRT was 22.25 Gy with a number of fractions ranging from 2 to 7. Two studies are phase I dose-escalation

studies. Higgins (14) reported an MTD at 6 Gy \times 5 Fr dose after conventional chemoradiation of 44 Gy 2 Gy/fraction. Authors conclude that 20 Gy in 2 fractions of 10 Gy is safer.

Nevertheless, in the other phase I study by Hepel (13), local control is higher when dose is equal or higher than 24 Gy in 2 fractions, and in contrast, toxicity is lower (8% versus 15.78%). The gain in local control in the Hepel study (78% *vs.* 59%) could be related to the biological effective dose administered (BED), which is superior: 126.7 versus 112.3 Gy.

On the other hand, locoregional control is not specified in the different dose cohorts, so concluding which dose per fraction is best for this objective is difficult. In this regard, Kumar *et al.* (16) concluded that local and regional control are similar in the different schemes evaluated: 10 Gy \times 2 Fr *vs.* 6.5 Gy \times 3 Fr. However, data in this study has given us much thought. To start, local failure in the 6.5 Gy \times 3 cohort and 10 Gy \times 2 cohort is 14% and 21% respectively. Meanwhile, biological effective dose for each cohort goes as follows: BED₁₀ 32.2 versus 40 Gy. In conclusion, the higher BED cohort has a worse local failure, the opposite of what is generally accepted. To our understanding, this may be in relation to the immune changes occurring after repeated doses of radiation, favoring the 6.5 Gy \times 3 cohort as seen in mice studies on the topic (26). In addition, ablative doses per fraction of around 10 Gy, have a deleterious effect on interferon activation genes due to the activation of exonuclease TREX1, who is capable of fragmenting the tumor nucleic acid in the dendritic cell and as a result, inhibit cGAS-STING pathway (27,28).

Consolidation after SBRT

In the studies selected, there is a lack of information regarding the use of consolidation systemic therapy. Out of the three studies that do inform on the matter, the proportion of patient receiving this treatment varies from 6% to 73%. In the present, consolidation treatment with immunotherapy is standard of care due to the publication of the PACIFIC TRIAL (29), where durvalumab demonstrated an improved overall survival: 83.1% at 1 year. If we compare OS of SBRT studies and OS of the PACIFIC trial, it is clear that the second is higher. In terms of intrathoracic disease control, the combination of conventional chemoradiotherapy and immunotherapy manages a 60% local control. Whether the combination of triple therapy (conventional chemoradiotherapy + SBRT + durvalumab) is safe or effective is yet to be determined in

future studies. Nevertheless, the combination of multisite SBRT and pembrolizumab has already been tested and toxicity was much lower than expected (30).

As previously explained, according to research on fractionation and cGAS-STING pathway activation, a systemic immune response with SBRT can be obtained at lower radiation doses, and therefore toxicity to the mediastinum organs could be avoided. In addition, the smaller treatment fields achieved with SBRT technique decrease surrounding lymphopenia compared to conventional radiation and overall make this technique safer and more suitable for immune activation and immune combinations.

Toxicity

Toxicity observed throughout the studies is diverse and does not follow a linear relation to dose in most cases. Majority of studies applied dose constraints published previously by other authors that administered lung SBRT. In some cases, like the deceased due to hemoptysis in the Hepel study (13), maximum tolerated doses to the proximal bronchial tree were not established. As a result, an amendment was made for treatment of future patients establishing a new dose constraint to this organ at risk. Other authors (16), adapted fractionation in central lesions to be more conservative. None of the studies report acute irreversible toxicity, although distinction between acute and chronic toxicity is not clear. Higgins group (14) considers acute toxicity whatever is detected in the first 30 days post-SBRT delivery and other groups establish acute toxicity in the first 90 days. In any case, severe toxicity appears late, for which dose-escalation studies are not adequate.

In the RTOG 0813 study (31), where SBRT was delivered to central tumors, a time-to-event continual reassessment method (TITE-CRM) (32) design was used that account for this late toxicity. The advantage of this method is it has the ability to calculate MTD without exposing the patient to a higher toxicity.

Out of all the studies in this review that evaluated toxicity, 5 patients presented with grade 5 toxicity and 19 with grade 3 toxicity. The majority of grade 5 toxicities were related to hemoptysis, fistulas or excess dose to proximal bronchial tree and its vasculature.

Quality of the studies

The overall quality of the studies was measured with

Table 2 Ongoing clinical trials found in clinicaltrial.org on Feb 2020 with the keywords “SBRT stage III NSCLC”

	Clinical trial identifier	Interventions	Status	N	Phase	CRT Fr	SBRT Fr	Results
SBRT and CRT combinations	NCT03589547	SBRT-Durvalumab → CRT	Recruiting	25	II	60/30	20/2 Fr	Not available
	NCT02400424	CRT → SBRT peripheral	Active, not recruiting	70	II	66/33 LN	54/3 Fr T	Not available
	NCT01656460	CRT → SBRT	Completed	12	II	50.4/28	16/2 Fr; 20/2; 24/2; 28/2	1 G5 hemoptysis; in Arm 3; 1 G4 late dyspnea in Arm 4
	NCT01933568 N12HYB	CRT + SBRT for peripheral T <5 cm	Completed	15	I	CRT to LN and SBRT to PT concurrent to cisplatin		Not available
	NCT01345851	CRT → SBRT	Active, not recruiting	29	I-II, single group assignment dose-escalation to find MTD	Hypofractionated 10 Fr	5 Fr boost	Not available
	NCT01657617	SBRT → CRT	Completed	35	II	CRT	19.5/3 Fr CT; 20/2 PT	2 G5 hemoptysis; 2 G3 pneumonitis
	NCT02262325	SBRT → CRT	Recruiting	34	II	30 Fr	2 Fr	Not available
SBRT	NCT03727867	TKI + SBRT (EGFR)	Not yet recruiting	300	III	NA	60/8 Fr CT; 50/5 PT	Not available

CRT, conventional chemoradiation; SBRT, stereotactic body radiotherapy; Fr, fractionation in total Gy and number of fractions; LN, lymph nodes; T, tumor; NI, no information; PT, peripheral tumors; CT, central tumors; TKI, tyrosine kinase inhibitor; NA, not applicable.

the NIH tool that was more adequate for each design. Prospective studies were analyzed with the “before-after studies with no control group” (Figure 2) and retrospective studies were analyzed with the “Case Series Studies Tool” (Figure 3). Out of the retrospective studies selected, one study did not have the statistics clearly outlined, another study did not include grades on toxicity, and all 3 studies included heterogeneous population with different disease stages. Only one of the studies specified clearly the patient characteristics. The nature of SBRT treatment on the other hand, did not allow for double blinded design in the prospective studies and the scarce number of patients treated with SBRT does not permit to draw conclusions on the heterogeneous stage III NSCLC population.

Future perspectives

At present, SBRT administration in stage III is being studied in 7 different clinical trials (Table 2). One of them combines SBRT with TKI (NCT03727867). Six phase II studies are ongoing, of which one has already closed recruitment

(NCT01656460). One of these trials (NCT03589547) uses SBRT and Durvalumab as a neoadjuvant strategy before definitive chemoradiation.

Conclusions

Current evidence to administer SBRT in inoperable stage III locally advanced NSCLC is based on two phase I trials. As far as fractionation is concerned, authors establish that 2 fractions of 10 or 12 Gy each are safe after conventional chemoradiation and obtain a local control of around 78%. Hence, increasing biological effective dose above 112.3 Gy seems to have a better local control compared to conventional radiation. Ongoing phase II and III clinical trials will determine the efficacy of this treatment approach and confirm the toxicity in comparison to the standard treatment.

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