Lung Cancer 130 (2019) 67–75

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Radical consolidative treatment provides a clinical benefit and long-term survival in patients with synchronous oligometastatic non-small cell lung cancer: A phase II study

Oscar Arrieta[a,*], Feliciano Barrón[a], Federico Maldonado[a], Luis Cabrera[a,b], José Francisco Corona-Cruz[a], Monika Blake[a], Laura Alejandra Ramírez-Tirado[a], Zyanya Lucia Zatarain-Barrón[a], Andrés F. Cardona[c,d,e], Osvaldo García[a], Osvaldo Arén[f], Jaime De la Garza[a]

[a] Thoracic Oncology Unit, National Cancer Institute (INCan), San Fernando #22, Sección XVI, Tlalpan, CP 14080, Mexico City, Mexico
[b] Médica Sur Oncology Center, Mexico
[c] Clinical and Traslational Oncology Group, Clínica del Country, Bogotá, Colombia
[d] Foundation for Clinical and Applied Cancer Research- FICMAC, Bogotá, Colombia
[e] Clinical Research and Biology Systems Department, Universidad El Bosque, Bogotá, Colombia
[f] Centro de Investigación Clínica Bradford Hill, Santiago, Chile

ARTICLE INFO

Keywords:
NSCLC
Oligometastatic
Survival
Radical consolidative therapy
Radiotherapy
Surgery

ABSTRACT

Objectives: Evidence is rapidly accumulating for the use of radical consolidative treatment (RCT) for patients with oligometastatic non-small cell lung cancer (NSCLC). Nonetheless, published studies have several limitations, including a selection of patients whose favorable characteristics might dictate therapeutic success, as well as scarce prospective data regarding overall survival (OS). The objective of this study was to determine whether RCT increases OS in patients with oligometastatic NSCLC.
Materials and methods: In this prospective, single-arm phase II study, we sought to evaluate the efficacy of RCT in patients with oligometastatic NSCLC in terms of OS. Patients with pathologically confirmed stage IV NSCLC who presented ≤5 synchronous, any-site metastases (including central nervous system [CNS] metastases), as assessed by PET-CT, were included. All patients received four initial cycles of systemic treatment. Following, those with stable disease/partial response received RCT to the primary site and metastases. The response to RCT was evaluated with PET-CT. The primary end-point was OS. Secondary end-points included progression-free survival (PFS) and best response by PET-CT. The study is registered in clinicaltrials.gov (NCT02805530).
Results: Thirty-seven patients were included in the analysis. The mean age was 55.8 years (range: 33–75 years). At diagnosis, 43.2% of patients presented with CNS metastases. Following RCT, 19 (51.4%) patients achieved a complete-response (CR) by PET-CT, while 18 (48.6%) had a non-complete response (NON-CR). The median OS was nonreached (NR) and was positively affected by CR on PET-CT (NR *vs.* 27.4 [95% CI: 16.4–38.3]; $p = 0.011$). The median PFS was 23.5 months (95% CI: 13.6–33.3) and was positively affected by CR on PET-CT (NR *vs.* 14.3 [95% CI: 11.7–16.9]; $p < 0.001$; HR: 0.19 [0.07-0.52]; $p = 0.001$).
Conclusion: Patients with oligometastatic NSCLC who undergo RCT have a high response rate and favorable OS. Patients with a CR by PET-CT have significantly longer OS, rendering this an important potential prognostic marker.

1. Introduction

Despite the major advances seen in the last decades in terms of therapeutic strategies, lung cancer (LC) remains the leading cause of cancer-related deaths worldwide, claiming approximate 2.07 million lives per year [1–3]. Facing the LC epidemic has been challenging; however, a steady decline in death rates has been observed since the 1990s, with a combined decrease of 45% in the time span from 1990 to

* Corresponding author at: Thoracic Oncology Unit and Laboratory of Experimental Oncology, National Cancer Institute (INCan), San Fernando #22, Section XVI, Tlalpan, Mexico City, CP 14080, Mexico.
E-mail address: ogar@unam.mx (O. Arrieta).

https://doi.org/10.1016/j.lungcan.2019.02.006
Received 23 October 2018; Received in revised form 30 January 2019; Accepted 6 February 2019

2015 [4]. Although these numbers seem encouraging, this reduction has mostly been the direct result of a decrease in tobacco use and implementation of smoking cessation strategies throughout the world [4]. On the other hand, patients who already have the disease are most often diagnosed within the advanced setting, with ≥75% of patients presenting stage IIIB-IV disease [5,6]. This limits therapeutic options, and patients are faced with a dim prognosis, with rapid progression and a poor response to therapy [7,8].

Treatment for stage IV non-small cell lung cancer (NSCLC) is in constant change; currently, several studies have suggested the use of chemotherapy (CT) plus immunotherapy (IO) or IO alone as first-line treatment for patients without a targetable genomic alteration and in concordance with Programmed Death-Ligand 1 (PD-L1) expression. However, this strategy is usually reserved for patients and regions that can afford and have access to these medications [9]. Meanwhile, patients who do not have access to IO still receive platinum-based CT, with a 5-year survival (SV) that ranges from 5% to 18% [10,11]. On the other hand, it is now recognized that stage IV disease is not a homogeneous entity, and we can identify particular subgroups of patients with different biological behaviors. One of these subgroups is the so-called "oligometastatic NSCLC" subgroup that comprises patients with up to 5 metastases [12].

Recently, evidence stemming from several phase II studies has demonstrated a higher progression-free survival (PFS) with the use of radical consolidative treatment (RCT) among patients with oligometastatic disease [13,14]. Nonetheless, this approach remains somewhat controversial due to the scarce availability of prospective evidence alongside other limitations [15]. For example, many of the available studies include patients with clinical characteristics that are likely to impact their outcomes, such as a specific pattern of dissemination (excluding liver or central nervous system [CNS] metastases), known to confer a poor prognosis [16]. Additionally, there is a discrepancy in terms of what constitutes oligometastatic disease, including presentation (synchronous *vs.* metachronous) and regarding the number of metastases (≤5 *vs.* ≤3) [17,18]. This has raised the question of whether the favorable prognosis seen in currently published trials stems from a selection of patients with a less aggressive tumor biology as a confounding factor [16,19]. Supplementary Table 1 highlights findings in previously conducted prospective trials.

Another limitation is the lack of imaging or biological markers to predict which patients will reap the most benefit from these interventions [17]. An interesting option in this regard is the use of PET-CT as an imaging tool to perform the baseline and subsequent evaluation of patients. PET-CT has shown to be the best available imaging method to detect occult metastases and can offer metabolic information (with prognostic significance) to evaluate the response to treatments [20,21].

To date, there is little published data in terms of the prospective assessment of overall survival (OS) in patients with oligometastatic NSCLC who undergo RCT, raising the question of whether RCT will be a valuable intervention in the long term [16].

The compelling evidence towards the benefit of radical treatment of oligometastatic disease has derived in the inclusion of this strategy in the treatment guidelines by the European Society for Medical Oncology (ESMO) since 2012 [18]. The recommendation states that patients with one to three synchronous metastases at diagnosis may reap benefits from local consolidative therapy following systemic therapy; nonetheless, the level of evidence for this recommendation in the last version released (2018) is merely IIIB, and the guidelines recommend these patients be assessed by a multidisciplinary tumor board and, preferably, be included in clinical trials [22].

In this prospective, open-label, phase II clinical trial, we evaluated the efficacy of RCT in patients with oligometastatic NSCLC in terms of OS. Additionally, we identified key factors that can impact the long-term prognosis for advanced-stage oligometastatic disease.

2. Methods

2.1. Study design

This is a prospective, open-label, single-arm, phase II study that enrolled patients from two large cancer reference centers in Mexico City, designed to evaluate the safety and efficacy of RCT as part of a multimodal treatment of patients with oligometastatic NSCLC who were assessed with FDG PET-CT before and after RCT of the primary lung tumor and/or oligometastatic disease.

This protocol is registered in clinicaltrials.gov (NCT02805530). The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulatory requirements and laws. The study was approved by the institutional review board and independent ethics committee (015/023/ICI and CEI/957). All patients provided written, informed consent.

2.2. Study population

The patients included in the study were male or female, 18 years of age or older, with pathologically confirmed stage IV NSCLC (according to the 7th edition of the American Joint Committee on Cancer staging system), and presented with synchronous oligometastatic disease, defined as those presenting ≤5 metastatic sites (any site metastases, including the central nervous system [CNS]), and synchronous metastases, defined as those identified within the first month of the diagnosis of the primary tumor. Baseline PET-CT and brain imaging were mandatory for inclusion in the study. Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) score ≤2 and adequate organ function (including an absolute neutrophil count of 1.5 cells $\times 10^9$/L, platelet count of 100 cells $\times 10^9$/L, white blood count of 3 cells $\times 10^9$/L, and hemoglobin 10 g/dL or higher within 3 weeks of study entry, a total bilirubin level less than or equal to 1.5 × the upper limit of normal (ULN), alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase less than or equal to 2.5 × ULN or less than or equal to 5·0 × ULN if liver metastases were present).

Key exclusion criteria included patients with a contraindication for receiving platinum-based chemotherapy, or targeted therapy; patients with concurrent uncontrolled diseases; patients with malignant pleural or pericardial effusion, previous treatments with chemotherapy, tyrosine kinase inhibitors (TKI) or radiotherapy to the primary site; pregnant or lactating women; and patients with concomitant malignant diseases, except for inactive basal cell carcinoma of the skin, or carcinoma *in situ* of the cervix, when completely resected.

2.3. Study treatment

The study scheme is shown in Fig. 1. All patients received four initial cycles of systemic treatment. Patients with metastases at sites other than the CNS received first-line systemic treatment, which included TKIs for patients who were detected with an actionable driver mutation (*EGFR* mutation or *ALK* translocation), and platinum-based chemotherapy for the remaining patients included in the trial. The choice of a specific TKI or a chemotherapy scheme was at the discretion of the treating physician. Patients with synchronous CNS metastases were evaluated in less than one week from the diagnosis by the multidisciplinary tumor board to define the initial treatment. Patients who required immediate local therapy for CNS metastases could receive radiotherapy. After 4 cycles of treatment, patients who had a complete response or those who progressed were excluded from the trial. Patients with stable disease or a partial response were evaluated by a multidisciplinary tumor board (including specialists in thoracic oncology, radiology, radiotherapy and thoracic surgery) to establish the type of radical treatment to the primary tumor and metastases. Radical treatment to the primary tumor and metastases included surgery,

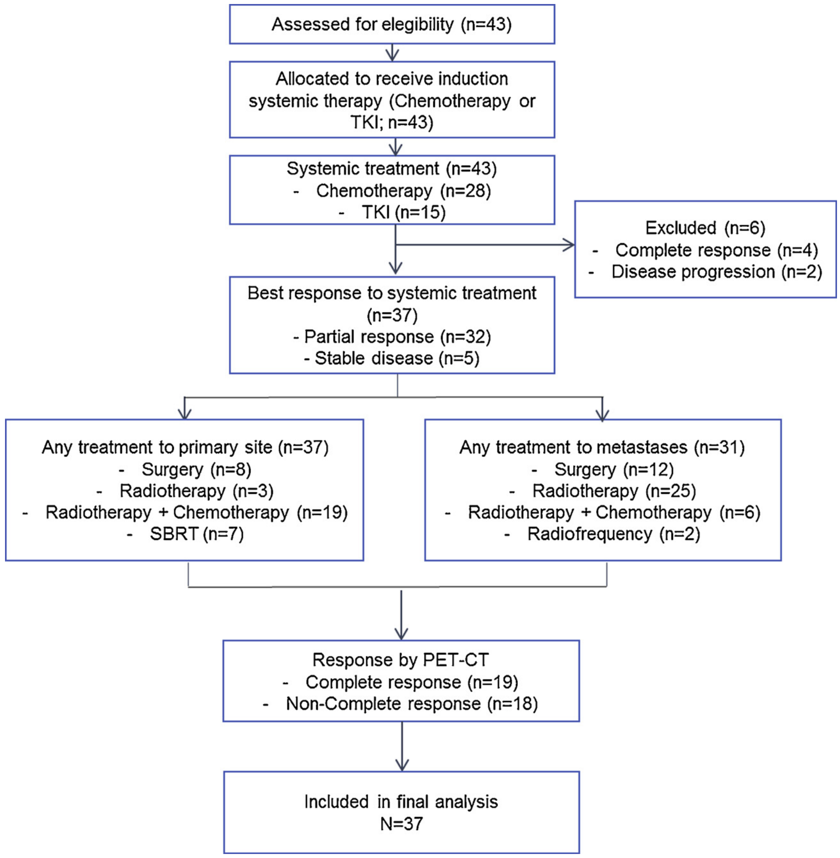

Fig. 1. CONSORT diagram.

radiotherapy (RT [choice of dose fractioning regimen was made by the attending radiotherapist, with curative intent when possible]), chemoradiotherapy (CRT), stereotactic body radiation therapy (SBRT) or radiofrequency ablation (RFA). Each of these options could be used alone or as a combination strategy depending on each patient, with a clear intent to reach a complete response.

Maintenance therapy was permitted and was administered at the discretion of the treating physician following a predefined set of standard of care options included in the most recent version of the national guidelines [6].

2.4. Assessments

Safety was assessed by monitoring adverse events (AEs) graded according to the National Cancer Institute (NCI, Bethesda, MD, EE.UU.) CTCAE, 4.0. Standard laboratory hematologic and blood chemistry parameters were assessed at baseline, upon the first administration of chemotherapy or TKIs, and until the end of the 4th cycle of treatment. Two dose reductions were allowed in patients who had grade 3 toxicity events; treatment was restarted when toxicity improved to grade 2.

Disease progression was followed with imaging (FDG PET-CT) every 6–8 weeks after RCT during the first 12 months and at the discretion of the treating physician thereafter. Progressive disease was defined according to the Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 [23] and the PET Response Criteria in Solid Tumors 1.0 (PERCIST) [24,25], as observed by two independent attending physicians. Progressive disease was further defined as per progression pattern into nonoligo (i.e., systemic) progression (development of lesions outside a previously visualized lesion site by PET-CT, not susceptible to local treatment) or oligo-progression/local progression (primary tumor or new lesions that are susceptible to local treatment or an increase $>$ 20% of the lesion volume from the last PET-CT).

2.5. Outcomes

The primary end-point was OS. Secondary end-points included PFS, safety, best response by PET/CT and patterns of failure. PFS was defined as the time from the start of any treatment until disease progression, death or the last follow-up. OS was defined as the period since the pathological diagnosis of NSCLC until the last follow-up or death.

2.6. Statistical analysis

The present study was designed to assess the OS of patients who received immediate RCT delivered to oligometastatic sites after first-line systemic therapy. A Simon 2-stage design was used to determine the sample size. Considering a 2-year OS of 30%, as reported in the literature (at the time of study design) for stage IV NSCLC, and setting the hypothesis of a 2-year OS of 50% with the new treatment, the required number of patients is 40 (with $\alpha = 0.05$ and $\beta = 0.20$). For descriptive purposes, continuous variables were summarized as arithmetic means with standard deviations, while categorical variables were summarized as frequencies and percentages. The median OS and PFS were estimated using the Kaplan-Meier method, whereas the log-rank test was used for making comparisons among subgroups. The Brookmeyer-Crowley method was used to calculate the 95% confidence intervals (CI) for the Kaplan-Meier estimates of PFS and OS, and the Wald method was used to calculate the CIs of the hazard ratios (HRs). All variables were dichotomized for survival analyses. Statistical significance was determined as $p \leq 0.05$ using a two-tailed test. An interim analysis was planned and reviewed by an independent committee appointed by INCan after 35 events for safety and futility. Annual review by this committee was performed for safety and to assess trends in the outcomes that would affect the continuity of the trial. SPSS software version 21 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

3. Results

3.1. Patient characteristics

Between June 2015 and December 2017, 355 stage IV NSCLC patients were evaluated. Among these, 43 patients met the criteria for oligometastatic disease. All 43 oligometastatic patients were assessed for eligibility and were allocated to receive systemic treatment (either platinum-based chemotherapy or TKIs). All patients were staged by PET-CT and brain magnetic resonance imaging (MRI). Six patients were excluded from the initial study population (four achieved a complete response, and two had progressive disease). Among the 37 patients included, 37.8% (14/37) were female, the mean age at diagnosis was 55.8 years (Standard Deviation [SD]: 10.6), 45.9% (17/37) had a positive smoking history and 24.3% (9/37) reported wood-smoke exposure. Most patients (94.6%; 35/37) presented with nonsquamous histology, while 5.4% (2/37) had squamous histology. Of patients with adenocarcinoma, 40.5% (15/37) harbored an *EGFR* mutation and 1 patient (2.7%) had an *ALK* rearrangement. Patients presented with 3 or more metastases in 35.1% of the cases, while 14 patients (37.8%) had a single metastasis at the time of diagnosis. The three most common metastatic sites were the CNS (16; 43.2%), contralateral lung (15; 40.5%) and bone (16; 43.2%) (Table 1).

3.2. Treatment characteristics

After receiving 4 cycles of the first-line therapy of choice (platinum-based chemotherapy: 26; TKI: 11), we identified a partial response in 86.5% (n = 32) of patients, while 13.5% showed (n = 5) stable disease. All 37 patients received RCT. Among those, 100% received treatment to the primary site (any treatment alone or in combination as previously described), which included surgery (n = 8), RT (n = 3), CRT (n = 19) and SBRT (n = 7). Furthermore, 31 patients (83.8%) required additional treatment for metastases to any site, including surgery (n = 12), RT (n = 25), CRT (n = 6) and RFA (n = 2).

After the completion of treatment, the response was assessed with PET-CT; 19 patients (51.4%) achieved a complete response (CR), and 18 (48.6%) had a partial response (NON-CR) (Fig. 1) (Table 2).

Maintenance treatment was administered in 26 (70.3%) patients. Maintenance treatment schemes included TKI for 13 patients (35.1%) and pemetrexed on 13 cases (35.1%). During follow up, disease progression was identified in 22 patients (59.5%); 12 (54.5%) had an oligo-/local pattern of progression, while 10 (45.5%) displayed non-oligo progression. Among those who progressed, 15 patients (40.5%) received second-line treatment at progression.

Table 1
Patient characteristics (n = 37).

		n (%)
Sex		
	Male	23 (62.2)
	Female	14 (37.8)
Age		
	Mean (SD)	55.8 (10.6)
Smoking exposure		
	Never smoker	20 (54.1)
	Ever smoker	17 (45.9)
Wood-smoke exposure		
	Present	9 (24.3)
	Absent	28 (75.7)
Histology		
	Non-squamous	35 (94.6)
	Squamous	2 (5.4)
Oncodriver mutation		
	Absent	21 (56.8)
	Present	16 (43.2)
No. of metastases		
	One	14 (37.8)
	Two	10 (27)
	Three or more	13 (35.1)
Metastatic sites		
	CNS	16 (43.2)
	Bone	16 (43.2)
	CL lung	15 (40.5)
	Lymphatic nodes	11 (29.7)
	Adrenal glands	3 (8.1)
	Liver	1 (2.7)
	Subcutaneous tissue	1 (2.7)

Table 2
Treatment characteristics.

	n(%)
LOCAL disease treatment	37 (100)
Primary LOCAL systemic treatment regimens	
TKI	11 (29.7)
Platinum doublet chemotherapy	26 (70.3)
Platinum + Paclitaxel	11 (42.3)
Platinum + Pemetrexed	14 (53.8)
Platinum + Gemcitabine	1 (3.8)
Response to primary LOCAL systemic treatment	
Partial response	32 (86.5)
Stable disease	5 (13.5)
METASTATIC disease treatment	
Present	31 (83.8)
Primary/Metastases treatment N (%)/N (%)	
Chemoradiation	19 (51.4) /6 (19.4)
Surgery	8 (21.6) / 12 (38.7)
SBRT	7 (18.9) / 0 (0)
Radiotherapy	RFA2 (8.1) / 25 (80.6) 3(8.1) /25 (80.6)
RFA	0 (0) / 2 (6.5)
PET/CT response to radical consolidative therapy	
Complete response	19 (51.4)
NON-complete response	18 (48.6)

3.3. Survival outcomes

The median follow up was 32.5 months. The median PFS for the entire population was 23.5 (95% CI: 13.6–33.3) months (Fig. 2A). There were no differences in the PFS by gender, age, tobacco or wood-smoke exposure, or *EGFR* mutation status. For patients with an actionable mutation, the median PFS was 17.9 months (95% CI: 10.8–25.1) vs. 23.5 months (95% CI: NR) for those without an actionable mutation p = 0.341; HR: 1.49 [95%: 0.65–3.47]; p = 0.347) (Fig. 2B).

For patients who achieved a metabolic complete response (CR) by PET-CT, the median PFS was not reached; on the other hand, for those who did not achieve a metabolic complete response (NON-CR), the median PFS was 14.3 months (95% CI: 11.7–16.9). The HR for progression in patients with CR vs. NON-CR was 0.19 (95% CI: 0.07-0.52; $p < 0.001$) (Fig. 2C).

For patients with oligo-/local progression, the median PFS was 15.0 months (95% CI: 10.9–19.2); conversely, patients with nonoligo progression showed a median PFS of 10.8 months (95% CI: 8.2–13.5) (p = 0.009). The HR for nonoligo vs. oligo-/local pattern of progression was 3.30 (95% CI: 1.26–8.64; p = 0.015) (Fig. 2D) (Table 3).

The median OS for the entire population was not reached (Fig. 3A). We did not observe any significant differences in terms of OS according to age, sex, tobacco or wood smoke exposure, number of metastases at diagnosis, presence of baseline CNS metastases or presence of a driver mutation (Fig. 3B). On the other hand, patients with a metabolic CR had a longer OS than those with NON-CR (NR vs. 27.4 [95% CI: 16.4–38.3]; p = 0.011) HR: 0.21 [95% CI: 0.06-0.79]; p = 0.216); however, this difference was not statistically significant. (Fig. 3C). Finally, patients with an oligo-/local progression pattern had a significantly improved OS compared with those with a nonoligo progression pattern (NR vs. 21.1 [95% CI: 13.7–28.6) p = 0.001) HR: 6.53 [95% CI: 1.75–24.4];

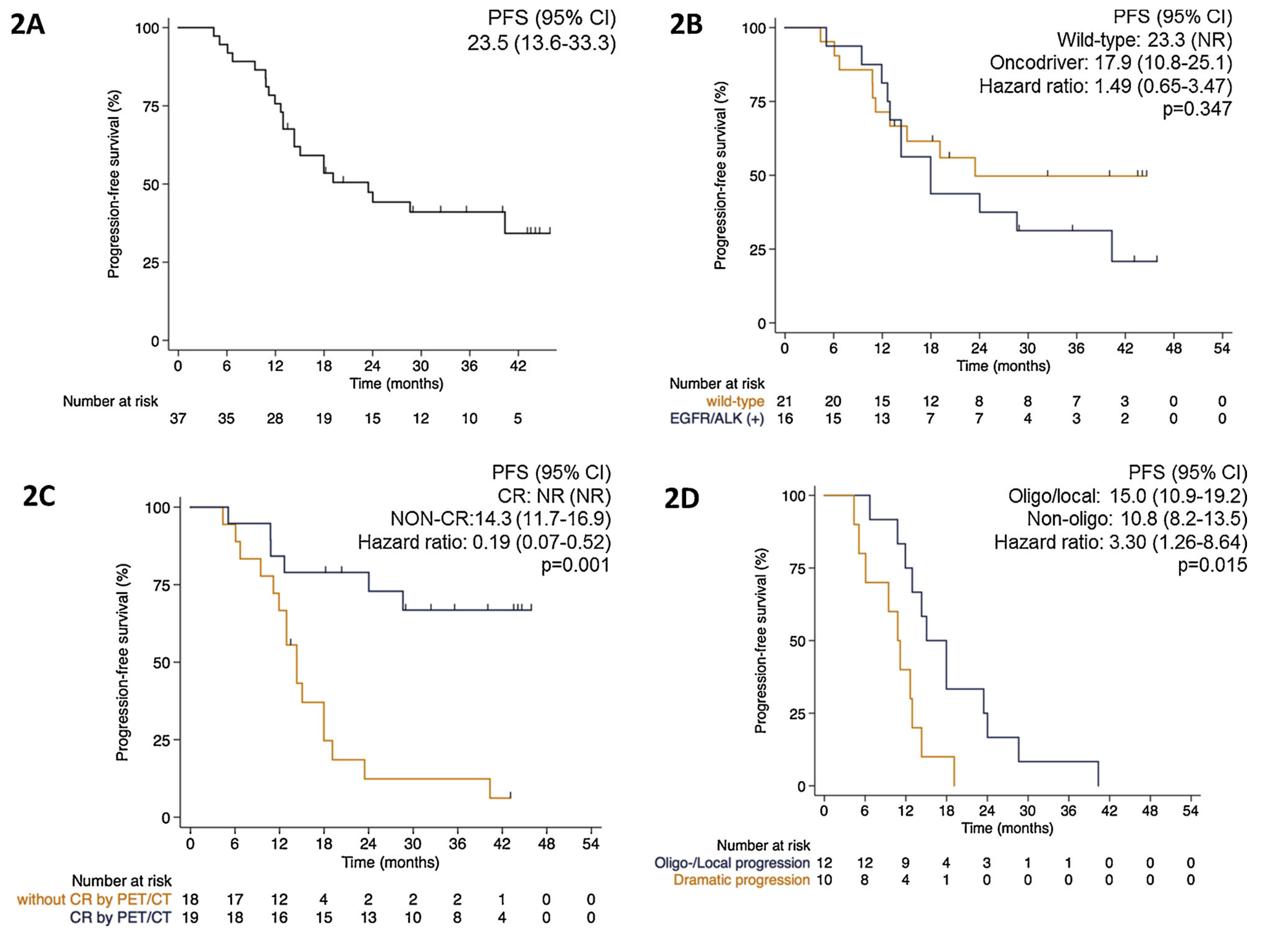

Fig. 2. Progression-free survival for the entire population (2 A). Progression-free survival in patients with driver mutations compared with wild type (2B). Progression-free survival for patients with a complete metabolic response compared with those with a noncomplete metabolic response (2C). Progression-free survival for patients with nonoligo progression vs. oligo/local progression pattern (2D).

p = 0.005) (Fig. 3D).

3.4. Safety

In terms of safety, no treatment-related deaths were observed from the start of the study until the last follow up. Most patients (70.3%) experienced an adverse event (AE); however, most were grade 1 or 2 and included adverse events related to RT to the chest or CNS. The most frequent grade 1 AEs included headache and nausea, which were present in 6 of the 34 patients (17.6% in both cases) who received RT as part of their treatment. The most frequent grade 2 AE was nausea in patients receiving RT (n = 5/34; 14.7%), while the other grade 2 AEs observed included hyporexia, dizziness, vomiting, asthenia and dysphagia. Eight grade 3 AEs were detected and included one case of pneumonitis in a patient undergoing SBRT; however, the event resolved favorably. Finally, only 1 grade 4 AE was observed throughout the course of the study, which was severe hemorrhage in a patient undergoing radiofrequency ablation, the patient was admitted to the intensive care unit and was monitored closely until discharge. A detailed list of all AEs that were recorded throughout the study can be found in Supplementary Table 2.

4. Discussion

For many years, the extent of disease and staging systems have been the most important prognostic factors and basis for cancer treatment guidance. The International Association for the Study of Lung Cancer (IASLC) acknowledges that some patients with oligometastatic disease are now receiving more aggressive local therapy in addition to systemic treatment, and this has been considered for their new staging system [26].

The role of radical treatment in a single organ (e.g., CNS, adrenal gland or liver) has been previously studied. However, aside from radical treatment of a single brain metastasis, no survival benefit has been found in phase 3 trials, limiting the use of radical treatment as common practice; nonetheless, the lack of a clear definition of the term oligometastases has produced a great array of information [18]. As a direct result, currently published studies on this topic present a very heterogeneous population [16]. However, despite methodological limitations, it is striking to see that conclusions are similar across the current body of evidence: radical consolidative treatment improves clinical outcomes in oligometastatic NSCLC patients (Supplementary Table 1).

In this study, we assessed the efficacy of RCT in patients with oligometastatic NSCLC and using PET-CT to stage and evaluate the response.

The strengths of this current study include that the population was not limited to patients with favorable clinical characteristics. We included patients with up to 5 metastatic sites, at any age, with any histological pattern. Importantly, we did not exclude patients with known unfavorable prognostic factors, such as liver or CNS metastases [27].

Our results show that, after a median follow up of 32.5 months, the median OS has not been reached. Other prospective studies on this topic (Supplementary Table 1) have reported a median OS of 41.2 months

Table 3
Factors associated with PFS and OS.

	N	# progression (events)	Progression-free survival		# deaths (events)	Overall survival	
			Median [95% CI], mo	p-Value		Median [95% CI], mo	p-Value
Overall	37	22	23.5 (13.6 – 33.3)		13	NR (NR)	
Gender							
Male	23	14	23.5 (5.8 – 41.1)		10	NR (NR)	
Female	14	8	17.9 (6.1 – 29.8)	0.709	3	NR (NR)	0.106
Age							
< 60 yrs	25	14	28.6 (3.2 – 54.1)		8	NR (NR)	
60+ yrs	12	8	5.2 (4.2 – 24.5)	0.179	5	35.5 (NR)	0.575
Tobacco exposure							
Absent	20	14	17.9 (10.9 - 24.9)		7	NR (NR)	
Present	17	8	23.5 (NR)	0.501	6	NR (NR)	0.667
Wood-smoke exposure							
Present	9	5	40.3 (0.0 – 94.9)		3	NR (NR)	
Absent	28	17	7.1 (5.2 – 33.1)	0.415	10	NR (NR)	0.774
No. of metastases at diagnosis							
1 to 2	24	13	20.0 (0.0 – 48.4)		8	NR (NR)	
3+	13	9	6.1 (6.1 – 29.9)	0.370	5	NR (NR)	0.682
CNS metastases at diagnosis							
Present	16	12	12.6 (7.9 – 17.4)		8	27.4 (NR)	
Absent	21	10	28.6 (NR)	0.065	5	NR (NR)	0.079
EGFR mutation status							
EGFR (+)	15	11	17.9 (13.3 – 22.6)		5	NR (NR)	
wild-type	22	11	24.0 (NR)	0.383	8	NR (NR)	0.579
Oncodriver mutation							
wild-type EGFR/ALK (-)	21	10	23.5 (NR)		8	NR (NR)	
EGFR/ALK (+)	16	12	17.9 (10.8 – 25.1)	0.341	5	NR (NR)	0.415
Complete response (PET-CT)							
without CR by PET/CT	18	16	14.3 (11.7 – 16.9)		10	27.4 (16.4 – 38.3)	
CR by PET/CT	19	6	NR (NR)	**< 0.001**	3	NR (NR)	**0.011**
Pattern of progression							
Oligo- /Local progression	12	12	15.0 (10.9 – 19.2)		3	NR (NR)	
Nonoligo progression	10	10	10.8 (8.2 – 13.5)	**0.009**	10	21.1 (13.7 - 28.6)	**0.001**
i							
0	5	3	40.3 (0.0 – 88.4)		1	NR (NR)	
1-3	32	19	19.1 (8.1 – 30.1)	0.660	12	39.9 (35.5 – 45.5)	0.106
N							
0-1	13	7	40.3 (14.1 – 66.6)		5	44.5 (40.1 – 48.9)	
2-3	24	15	15.1 (9.3 – 20.8)	0.232	8	39.9 (31.9 – 48.1)	0.065

[28] and 13.5 months [29]. Several considerations in the trial design and setting can explain these differences, including the definition of oligometastatic disease, as well as inclusion during or after systemic therapy. For example, the initial study by De Ruysscher et al. included patients who received radical treatment concurrently with radiotherapy, thereby avoiding the selection bias towards patients with a better prognosis when eliminating patients who progress to initial systemic therapy [29]. Another difference is the number of metastases allowed for inclusion. In the study by De Ruysscher et al., patients with fewer than 5 metastases were included, although 87% of patients had a single metastasis compared with the results of the study by Gomez et al. [30] that included patients with ≤3 metastases. Interestingly, another recently published study by Iyengar et al. which included patients with up to 5 sites of metastases in addition to the primary also reported an NR OS when treated radically with stereotactic ablative radiotherapy, highlighting the role of newer and safer techniques in this disease setting [31]. In our study, we included patients with up to 5 metastases, and, similarly, the median OS was not reached. It is important to consider that this is the first study to assess RCT in Latin America; thus, the outcomes must also be interpreted in terms of our regional setting. Patients in Mexico are known to have a higher incidence of EGFR mutations (34%), which can be seen in this study, and a lower frequency of KRAS mutations (15.9%), compared with Caucasian populations; both of these variations have been extensively documented and reviewed elsewhere [32]. Additionally, we could identify several characteristics that are likely to impact OS, identifying subgroups with different prognoses. For example, patients with a metabolic CR, as well as those with an oligo-/local pattern of progression, have not reached a median OS compared with their counterparts with NON-CR and those with a nonoligo pattern of progression, with a median OS of 27.4 and 21.1 months, respectively. These results are interesting and raise new hypotheses, suggesting that this specific approach to oligometastatic disease is beneficial, including staging by PET-CT, treating with RCT and assessing the metabolic response thereafter. Interestingly, the pattern of progression was an important prognostic factor, and, therefore must be documented in every patient so that good-prognosis cases can be differentiated from those with a poor prognosis early during the course of treatment. This is an essential consideration, particularly in practices that do not seek a wide array of molecular abnormalities early during the course of the disease, and in settings where access to targeted therapy and immunotherapy might be challenging and reserved for specific cases.

Notably, our data, along with data from previously published studies, imply the possibility of improving our current definition of oligometastatic disease, by characterizing the variables that, in this subset of patients, appear to improve outcomes to RCT. In doing so, we can propose that these patients be offered RCT as standard-of-care early on in their treatment [22]. This is a bold suggestion; however, evidence accumulates regarding the beneficial effects in terms of the survival with offering patients more aggressive treatment approaches; in the case of our study, this benefit was not dependent on the number of metastases present at baseline.

Unfortunately, virtually all late-stage NSCLC patients undergoing treatment will show progressive disease at some point. Therefore, it is imperative that we can detect such an event early in its course and convene the most beneficial way of approaching it, while keeping in

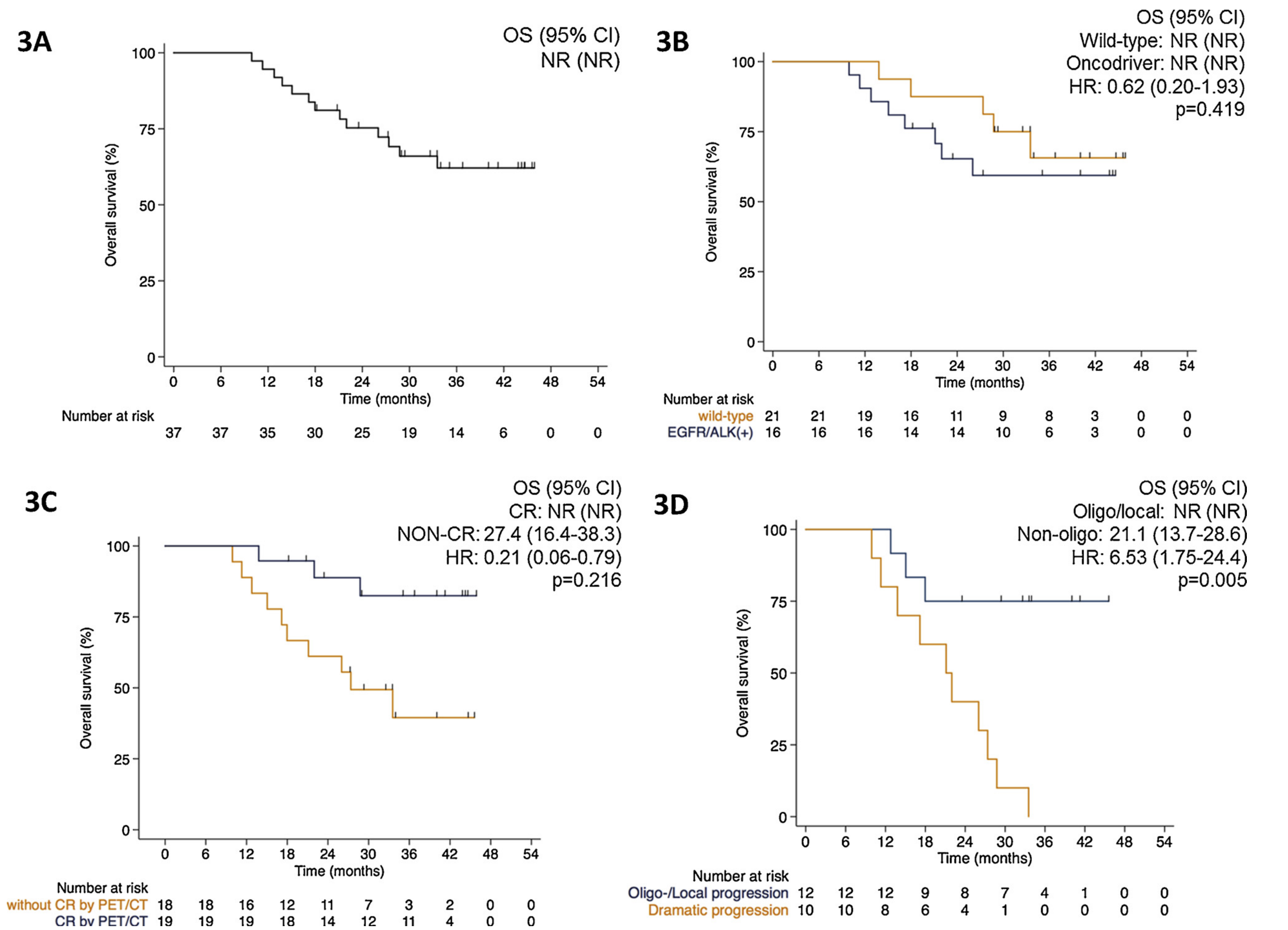

Fig. 3. Overall survival for the entire population (3 A). Overall survival in patients with driver mutations compared with the wild type (3B). Overall survival for patients with a complete metabolic response compared with those with a noncomplete metabolic response (3C). Overall survival for patients with nonoligo progression vs. oligo/local progression pattern (3D).

mind patient safety and quality of life. By providing metabolic information on the activity of tumor cells, 18-FDG PET-CT has become a powerful tool in assessing treatment response. It is well established that significant differences are found in the pre/posttreatment SUVmax of patients who respond to CRT compared with those who do not have a response [33,34]. As such, a baseline PET-CT should be mandatory in patients who must undergo RCT, and the results from this study suggest that using PET-CT as a follow-up imaging tool is also beneficial in patients with oligometastatic NSCLC.

Finally, it is important to note that this combination of factors, the use of PET-CT staging, RCT, and assessment of metabolic response after therapy, has increased the survival outcomes of RCT compared with that in previously published studies. In the recent update of the trial by Gómez et al., the authors report a median PFS in the RCT group of 14.2 months; however, the patients in our cohort had a median PFS of 23.5 months, which might be the result of improved staging by PET-CT only and an opportune identification of progressive disease, coupled with early intervention to address it.

Although the results are encouraging, there are some limitations in this trial. First, all the patients were from the same geographic region; therefore, a larger, multicenter and region-wide study must be staged to include a more robust sample size and assess the reproducibility across patients with diverse ethnic backgrounds and environmental exposure. Additionally, it is important to note that PET-CT can give false positives. In this trial, all PET-CT studies were evaluated by a nuclear medicine specialist and discussed by a panel of thoracic oncology experts. Therefore, to the best of our knowledge, all patients were true positives to oligometastatic disease. Nonetheless, it is important to note that we do not routinely assess metastases for histology, unless the panel of experts was clinically suspicious of a second primary, which was not the case with any of the patients in this study. Furthermore, as in previous trials, initial systemic therapy was chosen at the discretion of the treating physician. Finally, an important limitation is a limited availability within our setting of last generation targeted therapy agents, the use of which might improve outcomes for certain patient subgroups.

5. Conclusions

Our study supports the use of radical consolidative therapy in patients with oligometastatic NSCLC. We render PET-CT as an optimal tool to evaluate the response in patients with advanced NSCLC, as a metabolic CR predicts long-term survival outcomes in patients undergoing RCT. This difference in terms of prognosis for patients with CR vs. NON-CR should be explored in future studies to assess if different management, for example, maintenance immunotherapy, could benefit patients with a dimmer prognosis.

Competing interests

Dr. Arrieta reports personal fees from Pfizer, grants and personal fees from Astra Zeneca, grants and personal fees from Boehringer Ingelheim, personal fees from Lilly, personal fees from Merck, personal fees from Bristol Myers Squibb, and grants and personal fees from

Roche, outside the submitted work. Dr. Cardona reports grants from Merck Sharp & Dohme, Boehringer Ingelheim, Roche, Bristol-Myers Squibb and The Foundation for Clinical and Applied Cancer Research – FICMAC.; others from Pfizer, Boehringer Ingelheim, Astra Zeneca, MSD, BMS, Celldex, Roche; and personal fees from Merck Sharp & Dohme, Boehringer Ingelheim, Roche, Bristol-Myers Squibb, Pfizer, Novartis, Celldex Therapeutics, Foundation Medicine, Eli Lilly and Foundation for Clinical and Applied Cancer Research – FICMAC., outside the submitted work. All other authors have no competing interests to declare.

Funding

None.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.02.006.

References

[1] L.A. Torre, R.L. Siegel, A. Jemal, Lung cancer statistics, in: A. Ahmad, S. Gadgeel (Eds.), Lung Cancer and Personalized Medicine: Current Knowledge and Therapies, Springer International Publishing, Cham, 2016, pp. 1–19.
[2] C.A. Ridge, A.M. McErlean, M.S. Ginsberg, Epidemiology of lung cancer, Semin. Intervent. Radiol. 30 (2) (2013) 93–98.
[3] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA: Cancer J. Clin. 68 (6) (2018) 394–424.
[4] F. Islami, L.A. Torre, A. Jemal, Global trends of lung cancer mortality and smoking prevalence, Transl. Lung Cancer Res. 4 (4) (2015) 327–338.
[5] H. Lemjabbar-Alaoui, O.U. Hassan, Y.W. Yang, P. Buchanan, Lung cancer: biology and treatment options, Biochim. Biophys. Acta 1856 (2) (2015) 189–210.
[6] O. Arrieta, E. Guzman-de Alba, L.F. Alba-Lopez, A. Acosta-Espinoza, J. Alatorre-Alexander, J.F. Alexander-Meza, S.R. Allende-Perez, S. Alvarado-Aguilar, M.E. Araujo-Navarrete, L.M. Argote-Greene, C.A. Aquino-Mendoza, A.M. Astorga-Ramos, H. Austudillo-de la Vega, A. Aviles-Salas, L.J. Barajas-Figueroa, N. Barroso-Quiroga, M. Blake-Cerda, P.A. Cabrera-Galeana, G. Calderillo-Ruiz, A.D. Campos-Parra, A.M. Cano-Valdez, D. Capdeville-Garcia, G. Castillo-Ortega, C. Casillas-Suarez, P. Castillo-Gonzalez, J.F. Corona-Cruz, M.E. Correa-Acevedo, S.S. Cortez-Ramirez, J.A. de la Cruz-Vargas, J.G. de la Garza-Salazar, M.D. de la Mata-Moya, M.E. Dominguez-Flores, H.R. Dominguez-Malagon, L.M. Dominguez-Parra, A. Dominguez-Peregrina, J. Duran-Alcocer, M.I. Enriquez-Aceves, A. Elizondo-Rios, M.D. Escobedo-Sanchez, P.E. de Villafranca, A. Flores-Cantisani, J.P. Flores-Gutierrez, F. Franco-Marina, E.E. Franco-Gonzalez, R.A. Franco-Topete, H. Fuentes-de la Pena, S. Galicia-Amor, D. Gallardo-Rincon, A. Gamboa-Dominguez, J. Garcia-Andreu, C.M. Garcia-Cuellar, M.C. Garcia-Sancho-Figueroa, R. Garcia-Torrentera, R. Gerson-Cwilich, A. Gomez-Gonzalez, L. Green-Schneeweiss, R. Guillen-Nunez Mdel, H. Gutierrez-Velazquez, C. Ibarra-Perez, E. Jimenez-Fuentes, P. Juarez-Sanchez, A. Juarez-Ramiro, J. Kelly Garcia, R. Kuri-Exsome, J.M. Lazaro-Leon, E. Leon-Rodriguez, S. Llanos-Osuna, S. Llanos-Osuna, U. Loyola-Garcia, J.S. Lopez-Gonzalez, F.J. Lopezy de Antunano, M.A. Loustaunau-Andrade, E.O. Macedo-Perez, L. Machado-Villarroel, M. Magallanes-Maciel, L. Martinez-Barrera, J. Martinez-Cedillo, G. Martinez-Martinez, A. Medina-Esparza, A. Meneses-Garcia, A. Mohar-Betancourt, J. Morales Blanhir, J. Morales-Gomez, D. Motola-Kuba, M.P. Najera-Cruz, C. Nunez-Valencia Cdel, M.A. Ocampo-Ocampo, M.D. Ochoa-Vazquez, C.A. Olivares-Torres, A. Palomar-Lever, M. Patino-Zarco, R. Perez-Padilla, Y.R. Pena-Alonso, A.R. Perez-Romo, M. Aquilino Perez, P.M. Pinaya-Ruiz, M.A. Pointevin-Chacon, J.J. Poot-Braga, R. Posadas-Valay, M. Ramirez-Marquez, I. Reyes-Martinez, J. Robledo-Pascual, J. Rodriguez-Cid, C.E. Rojas-Marin, E. Romero-Bielma, J.E. Rubio-Gutierrez, J.A. Saenz-Frias, M.A. Salazar-Lezama, K. Sanchez-Lara, R. Sansores Martinez, P. Santillan-Doherty, J. Alejandro-Silva, J.L. Tellez-Becerra, V. Toledo-Buenrostro, L. Torre-Bouscoulet, L. Torecillas-Torres, M. Torres, V. Tovar-Guzman, J.G. Turcott-Chaparro, J.J. Vazquez-Cortes, M.E. Vazquez-Manriquez, N. Vilches-Cisneros, J.F. Villegas-Elizondo, M.M. Zamboni, J. Zamora-Moreno, J.W. Zinser-Sierra, National consensus of diagnosis and treatment of nonsmall cell lung cancer, Rev. Invest. Clin. 65 (Suppl. 1) (2013) S5–84.
[7] N.A. Howlader, M. Krapcho, et al., SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site, April (2017) https://seer.cancer.gov/csr/1975_2014/.
[8] O. Arrieta, A. Carmona, L.A. Ramirez-Tirado, D. Flores-Estrada, E.O. Macedo-Perez, J.N. Martinez-Hernandez, J.F. Corona-Cruz, A.F. Cardona, J. de la Garza, Survival of patients with advanced non-small cell lung cancer enrolled in clinical trials, Oncology 91 (4) (2016) 185–193.
[9] L.E. Raez, A.F. Cardona, E.S. Santos, H. Catoe, C. Rolfo, G. Lopes, C. Barrios, L.A. Mas, C. Vallejos, Z.L. Zatarain-Barron, C. Caglevic, O. Arrieta, The burden of lung cancer in Latin-America and challenges in the access to genomic profiling, immunotherapy and targeted treatments, Lung Cancer 119 (2018) 7–13.
[10] J.H. Schiller, D. Harrington, C.P. Belani, C. Langer, A. Sandler, J. Krook, J. Zhu, D.H. Johnson, G. Eastern Cooperative Oncology, Comparison of four chemotherapy regimens for advanced nonsmall-cell lung cancer, N. Engl. J. Med. 346 (2) (2002) 92–98.
[11] K. Kelly, J. Crowley, P.A. Bunn Jr, C.A. Presant, P.K. Grevstad, C.M. Moinpour, S.D. Ramsey, A.J. Wozniak, G.R. Weiss, D.F. Moore, V.K. Israel, R.B. Livingston, D.R. Gandara, Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial, J. Clin. Oncol. 19 (13) (2001) 3210–3218.
[12] A. Ashworth, G. Rodrigues, G. Boldt, D. Palma, Is there an oligometastatic state in nonsmall cell lung cancer? A systematic review of the literature, Lung Cancer 82 (2) (2013) 197–203.
[13] K.S. Albain, J.J. Crowley, M. LeBlanc, R.B. Livingston, Survival determinants in extensive-stage nonsmall-cell lung cancer: the Southwest Oncology Group experience, J. Clin. Oncol. 9 (9) (1991) 1618–1626.
[14] D. Li, X. Zhu, H. Wang, M. Qiu, N. Li, Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic nonsmall cell lung cancer? A meta-analysis, J. Thorac. Dis. 9 (2) (2017) 310–317.
[15] O. Arrieta, C. Villarreal-Garza, J. Zamora, M. Blake-Cerda, M.D. de la Mata, D.G. Zavala, S. Muniz-Hernandez, J. de la Garza, Long-term survival in patients with nonsmall cell lung cancer and synchronous brain metastasis treated with whole-brain radiotherapy and thoracic chemoradiation, Radiat. Oncol. 6 (2011) 166.
[16] M. Brighenti, F. Petrelli, S. Barni, B. Conti, E. Sarti, M. Ratti, S. Panni, R. Passalacqua, M. Bersanelli, Radical treatment of oligometastatic nonsmall cell lung cancer: Ready for prime time? Eur. J. Cancer 79 (2017) 149–151.
[17] S. Li, R. Zhu, D. Li, N. Li, X. Zhu, Prognostic factors of oligometastatic nonsmall cell lung cancer: a meta-analysis, J. Thorac. Dis. 10 (6) (2018) 3701–3713.
[18] F.B.S. Novello, R. Califano, T. Cufer, S. Ekman, M. Giaj Levra, K. Kerr, S. Popat, M. Reck, S. Senan, G.V. Simo, J. Vansteenkiste, S. Peters, Metastatic nonsmall-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 27 (Suppl. 5) (2016) v1–v27.
[19] L. Boreta, S.S. Yom, Is there a benefit to locally consolidative therapy for oligometastatic nonsmall cell lung cancer? Ann. Transl. Med. 5 (5) (2017) 108.
[20] S. Kligerman, S. Digumarthy, Staging of nonsmall cell lung cancer using integrated PET/CT, AJR Am. J. Roentgenol. 193 (5) (2009) 1203–1211.
[21] B. Hochhegger, G.R. Alves, K.L. Irion, C.C. Fritscher, L.G. Fritscher, N.H. Concatto, E. Marchiori, PET/CT imaging in lung cancer: indications and findings, J. Bras. Pneumol. 41 (3) (2015) 264–274.
[22] D. Planchard, S. Popat, K. Kerr, S. Novello, E.F. Smit, C. Faivre-Finn, T.S. Mok, M. Reck, P.E. Van Schil, M.D. Hellmann, S. Peters, E.G. Committee, Metastatic nonsmall cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 29 (Suppl._4) (2018) iv192–iv237.
[23] L.H. Schwartz, S. Litiere, E. de Vries, R. Ford, S. Gwyther, S. Mandrekar, L. Shankar, J. Bogaerts, A. Chen, J. Dancey, W. Hayes, F.S. Hodi, O.S. Hoekstra, E.P. Huang, N. Lin, Y. Liu, P. Therasse, J.D. Wolchok, L. Seymour, RECIST 1.1-Update and clarification: from the RECIST committee, Eur. J. Cancer 62 (2016) 132–137.
[24] S.J. Min, H.J. Jang, J.H. Kim, Comparison of the RECIST and PERCIST criteria in solid tumors: a pooled analysis and review, Oncotarget 7 (19) (2016) 27848–27854.
[25] J.H. O, M.A. Lodge, R.L. Wahl, Practical PERCIST: a simplified guide to PET response criteria in solid tumors 1.0, Radiology 280 (2) (2016) 576–584.
[26] P. Goldstraw, K. Chansky, J. Crowley, R. Rami-Porta, H. Asamura, W.E. Eberhardt, A.G. Nicholson, P. Groome, A. Mitchell, V. Bolejack, S. International Association for the Study of Lung Cancer, A.B. Prognostic Factors Committee, I. Participating, S. International Association for the Study of Lung Cancer, B. Prognostic Factors Committee Advisory, I. Participating, The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer, J. Thorac. Oncol. 11 (1) (2016) 39–51.
[27] Y. Ren, C. Dai, H. Zheng, F. Zhou, Y. She, G. Jiang, K. Fei, P. Yang, D. Xie, C. Chen, Prognostic effect of liver metastasis in lung cancer patients with distant metastasis, Oncotarget 7 (33) (2016) 53245–53253.
[28] D. Gomez, C. Tang, J. Zhang, G.R. Blumenschein, M. Hernandez, J.J. Lee, R. Ye, Local Consolidative Therapy (LCT) improves Overall Survival (OS) compared to maintenance therapy/observation in oligometastatic Nonsmall Cell Lung Cancer (NSCLC): final results of a multicenter, randomized, controlled phase 2 trial, Int. J. Radiat. Oncol. Biol. Phys. 2 (2018) (2018 ASTRO Annual Meeting Late-breaking Abstract Selection).
[29] D. De Ruysscher, R. Wanders, L.E. Hendriks, A. van Baardwijk, B. Reymen, R. Houben, G. Bootsma, C. Pitz, L. van Eijsden, A.C. Dingemans, Progression-free survival and overall survival beyond 5 years of NSCLC patients with synchronous oligometastases treated in a prospective phase II trial (NCT 01282450), J. Thorac. Oncol. 13 (12) (2018) 1958–1961.
[30] D.R. Gomez, G.R. Blumenschein Jr., J.J. Lee, M. Hernandez, R. Ye, D.R. Camidge, R.C. Doebele, F. Skoulidis, L.E. Gaspar, D.L. Gibbons, J.A. Karam, B.D. Kavanagh, C. Tang, R. Komaki, A.V. Louie, D.A. Palma, A.S. Tsao, B. Sepesi, W.N. William, J. Zhang, Q. Shi, X.S. Wang, S.G. Swisher, J.V. Heymach, Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic nonsmall-cell lung cancer without progression after first-line systemic therapy: a multicenter, randomised, controlled, phase 2 study, Lancet Oncol. 17 (12) (2016) 1672–1682.

[31] P. Iyengar, Z. Wardak, D.E. Gerber, V. Tumati, C. Ahn, R.S. Hughes, J.E. Dowell, N. Cheedella, L. Nedzi, K.D. Westover, S. Pulipparacharuvil, H. Choy, R.D. Timmerman, Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial, JAMA Oncol. 4 (1) (2018) e173501.

[32] O. Arrieta, A.F. Cardona, C. Martin, L. Mas-Lopez, L. Corrales-Rodriguez, G. Bramuglia, O. Castillo-Fernandez, M. Meyerson, E. Amieva-Rivera, A.D. Campos-Parra, H. Carranza, J.C. Gomez de la Torre, Y. Powazniak, F. Aldaco-Sarvide, C. Vargas, M. Trigo, M. Magallanes-Maciel, J. Otero, R. Sanchez-Reyes, M. Cuello, Updated frequency of EGFR and KRAS mutations in nonsmall-cell lung cancer in Latin America: the Latin-American consortium for the investigation of lung cancer (CLICaP), J. Thorac. Oncol. 10 (5) (2015) 838–843.

[33] I. Bahce, C.G. Vos, C. Dickhoff, K.J. Hartemink, M. Dahele, E.F. Smit, R. Boellaard, O.S. Hoekstra, E. Thunnissen, Metabolic activity measured by FDG PET predicts pathological response in locally advanced superior sulcus NSCLC, Lung Cancer 85 (2) (2014) 205–212.

[34] Y. Yamamoto, Y. Nishiyama, T. Monden, Y. Sasakawa, M. Ohkawa, M. Gotoh, K. Kameyama, R. Haba, Correlation of FDG-PET findings with histopathology in the assessment of response to induction chemoradiotherapy in nonsmall cell lung cancer, Eur. J. Nucl. Med. Mol. Imaging 33 (2) (2006) 140–147.