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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

# Brain metastasis as exclusion criteria in clinical trials involving extensive-stage small cell lung cancer

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## Abstract

**Background** The American Society of Clinical Oncology and Friends of Cancer Research submitted recommendations to the FDA to reduce barriers in clinical trial participation. They proposed the removal of several specific exclusion criteria, including brain metastasis. Clinical trials involving small cell lung cancer (SCLC) have varying exclusion criteria regarding brain metastasis.

**Methods** We completed an online search of clinicaltrials.gov for the query "SCLC, extensive stage." The trials were classified into a group of strict exclusion, allowed only if treated, allowed without treatment, or undefined. Relationships between status of brain metastasis in exclusion criteria and study characteristics (trial status, trial design, sponsor, location, and treatment groups) were investigated by Chi-squared test. The trends of exclusion status were investigated by a comparison against the variable time.

**Results** Of the 204 eligible trials, 32 strictly excluded any form or history of CNS metastases, 129 allowed patients that are undergoing or have undergone CNS-specific therapy, 9 allowed patients without any CNS-specific therapy, and 34 did not mention any criteria involving CNS metastases. Studies conducted outside the United States and with single systemic therapy were associated with strict exclusion of brain metastasis ($p = 0.026$ and 0.039, respectively). The proportion of clinical trials with strict exclusion has remained around 15% for the past few decades.

**Conclusion** Non-US and single systemic therapy studies are more commonly associated with strict exclusion of brain metastasis in ES-SCLC trials. The strict exclusion of brain metastases in clinical trials has remained relatively constant for the past few decades.

**Keywords** Brain metastasis · Clinical trials · Small cell lung cancer · Exclusion criteria

## Introduction

Small cell lung cancer (SCLC) is one of two histological classifications of lung cancer accounting for 10–15% of lung cancers. While it is less prevalent, it is considered the more aggressive form of lung cancer. Patients diagnosed with limited-stage and extensive-stage SCLC have a 5-year relative survival rate of only 29% and 3%, respectively (American Cancer Society 2019). The poor prognosis of SCLC highlights the need for more effective therapeutic interventions.

The American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (FOCR) has submitted recommendations to the FDA to reduce barriers of entry into clinical trials (ASCO 2018; Kim et al. 2017; Lichtman et al. 2017; Lin et al. 2017). They proposed the removal of several specific items commonly listed as exclusionary, such as previous cancer history, organ dysfunction, brain metastasis, and HIV. This is related to ES-SCLC trials as patients with a history of brain metastases are often excluded from these cancer treatment trials. The exclusion of these patients is not only detrimental to study progression but potentially unnecessary. A study recently conducted by the Response Assessment in Neuro-Oncology (RANO) group has suggested that including patients with stable or treated brain metastases is "justified in majority of cases and may speed the development of effective therapies" (Lin et al. 2013).

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Contrary to the recent push for less exclusion, we hypothesize that brain metastasis exclusion criteria have been intensified over the past few decades. In this study, we examine ES-SCLC clinical trials by detailing their exclusion criteria and other variables through a systematic search of the website clinicaltrials.gov. The website is a comprehensive database containing all ongoing and past clinical trials with specific enrollment details for each study. Through analysis of the data, we intend to document statistics and patterns of brain metastasis exclusion criteria in ES-SCLC clinical trials that will help the FDA and future investigators design more inclusive trials that yield greater power and generate more generalizable data.

## Methods

This study is a systematic review of ES-SCLC clinical trials that are available online through a search of clinicaltrials.gov for the query "Small Cell Lung Cancer, extensive stage". Trials were excluded if they specifically required the presence of brain metastasis or did not specifically state ES-SCLC in condition or disease. The following data were recorded for each trial: NCT identifier, trial title, ES-SCLC specificity, study start date, trial status, trial phase, sponsor, location, treatment, metastasis status, publication status, and publication link. NCT identifier, trial title, study start date, trial phase, and sponsor were copied directly from the data available from the search results. ES-SCLC specificity (Yes or No) was determined by finding whether the trial was focused only on ES-SCLC or if it included other types of cancers. Trial status (Category 1 or 2) was categorized into not yet recruiting or recruiting (ongoing) studies; category 2 included unknown, terminated, active-not recruiting, completed, or withdrawn (finished) studies. The location variable was determined by the sites being located in the US, international, both, or unlisted. The treatment type (chemotherapy, targeted therapy, immunotherapy, antiangiogenic therapy, combination therapy, other) was determined through a search of the intervention via google or a drug bank. Metastasis status was determined by looking in the enrollment criteria section of the search results and determining whether it was strictly excluded (no presence or history of brain metastasis allowed), allowed with CNS-specific therapy (allowed if controlled or treated), allowed without CNS-specific therapy (allowed even if uncontrolled) and undefined (no mention of brain metastasis in exclusion criteria). Publication status (published, unpublished, ongoing) was conducted via a search of PubMed for its clinical title and NCT identifier.

Tables were generated by determining how the trials were distributed among each variable: Trial status, trial design, sponsor, location, treatment, and brain metastasis. A separate table was generated by determining the proportion of trial characteristics falling in each exclusion criteria group. Chi-squared analysis was performed on six variables: trial status, trial design, sponsor, location, treatment, and publication status; a $p$ value $< 0.05$ was considered significant. A final graphical figure was produced comparing the proportions of exclusion status in blocks of 5 years starting from 1995 and ending in 2019.

## Results

The query resulted in 214 studies as of June 11, 2019. Ten studies were excluded primarily due to the study requiring presence of brain metastases or focusing on the radiation treatment of brain metastases.

Table 1 is a summary of the trial characteristics. Trials that were completed were much more common that those that are still ongoing (82.8% vs. 17.2%). Trials were more often in Phase II or beyond than before Phase II (73.5% vs 26.5%). Majority of the trials used combination therapy (68.6%) as the intervention. Concerning brain metastases, the "allowed with CNS-specific therapy" group was by far the most common, accounting for 63.2% of the total trials. In general, the ES-SCLC specific trials had proportions extremely similar to that of the total column. However, in contrast, Non ES-SCLC specific trials had a much larger proportion of NIH sponsored trials (27.6% vs. 11.3%), much smaller proportion of industry sponsored trials (10.3% vs. 25.0%) and many more studies located in the US (63.8% vs. 45.6%) as compared to the total.

Table 2 shows the distribution of metastasis exclusion status among each of the subcategories of trial characteristics. In all cases except one, the allowed with CNS-specific therapy group was the most prevalent within each subcategory. In contrast, the allowed without CNS-specific therapy was the least prevalent in each subcategory.

Table 3 is the Chi-squared analysis of six trial characteristics against enrollment criteria. Evaluation of location (including US and excluding US) and treatment type (Combination vs Single Systemic Treatment) against whether it was excluded or allowed yielded statistically significant $p$ values of 0.026 and 0.039, respectively. There is a non-significant trend that ongoing (Category 1) trials are strictly excluding at a higher rate ($p = 0.117$). There is no association between pivotal (phase II–III and III) and non-pivotal trials in strict exclusion ($p = 0.859$, data not shown).

**Table 1** Trial characteristics

| | Total, *N* (%) | ESSCLC specific, *N* (%) | Not ESSCLC specific, *N* (%) |
|---|---|---|---|
| Trial status | | | |
| Category 1 (not yet recruiting or recruiting) | 35 (17.2) | 24 (16.4) | 11 (19.0) |
| Category 2 (unknown/terminated/active-not recruiting/completed/withdrawn) | 169 (82.8) | 122 (83.6) | 47 (81.0) |
| Trial design/type | | | |
| Phase I/I–II | 54 (26.5) | 32 (21.9) | 22 (37.9) |
| Phase II/II–III/III/IV/NA | 150 (73.5) | 114 (78.1) | 36 (62.1) |
| Sponsor | | | |
| Other (organization/university/investigator) | 58 (28.4) | 43 (29.5) | 15 (25.9) |
| NIH | 23 (11.3) | 7 (4.8) | 16 (27.6) |
| Industry | 51 (25.0) | 45 (30.8) | 6 (10.3) |
| Other/industry | 32 (15.7) | 24 (16.4) | 8 (13.8) |
| Other/NIH | 38 (18.6) | 26 (17.8) | 12 (20.7) |
| Other/NIH/industry | 2 (1.0) | 1 (< 1) | 1 (1.7) |
| Location | | | |
| US only | 93 (45.6) | 56 (38.4) | 37 (63.8) |
| International only | 58 (28.4) | 46 (31.5) | 12 (20.7) |
| US and International | 37 (18.1) | 33 (22.6) | 4 (6.9) |
| Unlisted | 16 (7.8) | 11 (7.5) | 5 (8.6) |
| Treatment | | | |
| Chemotherapy | 17 (8.3) | 11 (7.5) | 6 (10.3) |
| Targeted therapy | 26 (12.7) | 14 (9.6) | 12 (20.7) |
| Immunotherapy | 3 (1.5) | 2 (1.4) | 1 (1.7) |
| Antiangiogenic | 2 (1.0) | 0 | 2 (3.4) |
| Combination | 140 (68.6) | 110 (75.3) | 30 (51.7) |
| Other | 16 (7.8) | 9 (6.2) | 7 (12.1) |
| Brain metastasis | | | |
| Strict exclusion | 32 (15.7) | 21 (14.4) | 11 (19.0) |
| Allowed with CNS-specific treatment | 129 (63.2) | 91 (62.3) | 38 (65.5) |
| Allowed without CNS-specific treatment | 9 (4.4) | 6 (4.1) | 3 (5.2) |
| Undefined | 34 (16.7) | 28 (19.2) | 6 (10.3) |
| Total | 204 | 146 | 58 |

Table 4 is the distribution of the proportion of trials falling in each exclusion category over time. Figure 1 is a stacked bar graph representation of the data in Table 4. The proportion of clinical trials with strict exclusion (blue) ranged from 11.9 to 20.0% when evaluated over the past 25 years in blocks of 5 years.

## Discussion

A previous study investigating non-small cell lung cancer (NSCLC) clinical trials found that those trials similarly have varying exclusion criteria concerning CNS-related comorbidities such as brain metastases (McCoach et al. 2016). Due to the lack of SCLC clinical trial review studies as well as the RANO–ASCO–FOCR proposal, we became interested in finding the trends and current status of exclusion of brain metastases in ES-SCLC trials.

While exclusion criteria are undoubtedly necessary to reduce confounding variables and ultimately protect the patient from harm, many argue that testing therapies in a restricted patient population results in a lack of generalizability. While the results of the trial may have statistical significance, the intervention of the trial may have little clinical significance as it is unable to be applied to the "diverse patient populations seen in routine practice" (ASCO 2018).

**Table 2** Percentages of trial characteristic subcategories falling within each exclusion status group

| | Total, *N* | Strict exclusion, *N* (%) | Allowed with CNS-specific treatment, *N* (%) | Allowed without CNS-specific treatment, *N* (%) | Undefined, *N* (%) |
|---|---|---|---|---|---|
| Trial status | | | | | |
| Category 1 (not yet recruiting or recruiting) | 35 | 8 (22.9) | 18 (51.4) | 1 (2.9) | 8 (22.9) |
| Category 2 (unknown/terminated/active-not recruiting/completed/withdrawn) | 169 | 24 (14.2) | 111 (65.7) | 8 (4.7) | 26 (15.4) |
| Trial design/type | | | | | |
| Phase I/I–II | 54 | 9 (16.7) | 36 (66.7) | 2 (3.70) | 7 (13.0) |
| Phase II/II–III/III/IV/NA | 150 | 23 (15.3) | 93 (62.0) | 7 (4.70) | 27 (18.0) |
| Sponsor | | | | | |
| Other (organization/university/investigator) | 58 | 10 (17.2) | 32 (55.2) | 2 (3.4) | 14 (24.1) |
| NIH | 23 | 6 (26.1) | 16 (69.6) | 1 (4.3) | 0 |
| Industry | 51 | 4 (7.8) | 32 (62.7) | 4 (7.8) | 11 (21.6) |
| Other/industry | 32 | 8 (25.0) | 21 (65.6) | 0 | 3 (9.4) |
| Other/NIH | 38 | 4 (10.5) | 27 (71.1) | 1 (2.6) | 6 (15.8) |
| Other/NIH/industry | 2 | 0 | 1 (50.0) | 1 (50.0) | 0 |
| Location | | | | | |
| US only | 93 | 12 (12.9) | 70 (75.3) | 3 (3.2) | 8 (8.6) |
| International only | 58 | 13 (22.4) | 30 (51.7) | 1 (1.7) | 14 (24.1) |
| US and international | 37 | 4 (10.8) | 20 (54.1) | 4 (10.8) | 9 (24.3) |
| Unlisted | 16 | 3 (18.8) | 9 (56.3) | 1 (6.3) | 3 (18.8) |
| Treatment | | | | | |
| Chemotherapy | 17 | 3 (17.6) | 9 (52.9) | 1 (5.9) | 4 (23.5) |
| Targeted therapy | 26 | 5 (19.2) | 16 (61.5) | 2 (7.7) | 3 (11.5) |
| Immunotherapy | 3 | 0 | 2 (66.7) | 0 | 1 (33.3) |
| Antiangiogenic | 2 | 0 | 2 (100) | 0 | 0 |
| Combination | 140 | 18 (12.9) | 97 (69.3) | 6 (4.3) | 19 (13.6) |
| Other | 16 | 6 (37.5) | 3 (18.8) | 0 | 7 (43.8) |
| Total | 204 | 32 (15.7) | 129 (63.2) | 9 (18.4) | 34 (16.7) |

With the vast differences in exclusion among those with brain metastases, there is a lack of a uniform set of standards to be enrolled in these trials (Lin et al. 2013). As a result, it becomes much more difficult for future researchers to draw conclusions and compare results of the different trials as each trial excludes a different set of patients. In addition, setting exclusion criteria removes a large proportion of eligible patients with ES-SCLC, and the clinical trials are struggling to enroll enough patients to produce results with enough power (Lin et al. 2017).

Excluding cases with brain metastasis also makes assessing intracranial efficacy of investigational treatment impossible. Agents with potential CNS-penetrating agents can only be appropriately evaluated when brain metastasis are allowed for enrollment. A successful example is a recent phase III trial of alectinib, an oral inhibitor of ALK-driven NSCLC, where the investigational agent showed a CNS response rate of 81% in a population with 40% brain metastasis at baseline (Peters et al. 2017). We, therefore, believe brain metastasis should not be always an exclusionary factor in oncology clinical trials.

Our Chi-squared analysis suggests that there is evidence that clinical trials involving certain types of treatments and in certain locations are excluding patients with brain metastases at a higher rate. A future follow-up investigation of location and treatment could prove beneficial in increasing rates of inclusion. Despite a non-significant trend that ongoing studies have a higher rate of strict exclusion compared to completed studies ($p = 0.117$), graphical evidence suggests that the proportion of clinical trials with strict exclusion has remained relatively constant (around 15%) for the past few decades.

Currently, it is still difficult to assess whether the RANO–ASCO–FOCR proposal submitted in 2017 on

**Table 3** Chi-squared analysis of trial characteristics and enrollment criteria

| | Strict exclusion | Allowed | Total | Chi-square *p* value |
|---|---|---|---|---|
| Trial status | | | | 0.117 |
| Category 1 (not yet recruiting or recruiting) | 8 | 19 | 27 | |
| Category 2 (unknown/terminated/active-not recruiting/completed/withdrawn) | 24 | 119 | 143 | |
| Trial design/type | | | | 0.947 |
| Phase I/I–II | 9 | 38 | 47 | |
| Phase II/II–III/III/IV/NA | 23 | 100 | 123 | |
| Sponsor | | | | 0.351 |
| Industry | 4 | 36 | 40 | |
| Other (organization/university/investigator) | 10 | 34 | 44 | |
| NIH | 6 | 17 | 23 | |
| Combination of industry, NIH, and other | 12 | 51 | 63 | |
| Location | | | | 0.026 |
| Including US | 16 | 97 | 113 | |
| Excluding US | 13 | 31 | 44 | |
| Treatment | | | | 0.039 |
| Combination | 18 | 103 | 121 | |
| All others (single systemic treatment) | 14 | 35 | 49 | |
| Publication status | | | | 0.208 |
| Published | 14 | 50 | 64 | |
| Unpublished | 13 | 77 | 90 | |
| Ongoing | 5 | 11 | 16 | |

**Table 4** Exclusion status of trials per half decade

| Date range | Strict exclusion, % | Allowed, % | Undefined, % |
|---|---|---|---|
| 1995–1999 ($N=15$) | 20.0 | 66.7 | 13.3 |
| 2000–2004 ($N=42$) | 11.9 | 76.2 | 11.9 |
| 2005–2009 ($N=53$) | 15.1 | 73.6 | 11.3 |
| 2010–2014 ($N=33$) | 15.2 | 54.5 | 30.3 |
| 2015–2019 ($N=61$) | 18.0 | 63.9 | 18.0 |

increasing the eligibility of patients with treated/stable brain metastasis has made any impact. From Fig. 1, we can see that the proportion of trials that allowed brain metastasis patients increased from 54.5% in 2010–2014 to 63.9% in 2015–2019, but it is difficult to conclude it was due to the proposal.

We acknowledge this study has its limitations. Clinicaltrials.gov has strict guidelines for registry of trials conducted in the US. However, this does not pertain to studies overseas, and they may be registered into different trial registries. Therefore, the trials found in clinicaltrials.gov overrepresent studies conducted in the US. Information that is available at clinicaltrials.gov may not be comprehensive when compared to available data in published articles and recent trials registered in clinicaltrials.gov may provide more information than do previous studies. Nevertheless, we hope our data will still help researchers who conduct future trials in ES-SCLC.

## Conclusion

Studies are enrolling patients with stable/treated brain metastases at the highest rate and unstable/untreated brain metastases at the lowest rate. Non-US and single systemic therapy studies are more commonly associated with strict exclusion of brain metastasis in ES-SCLC trials. The strict exclusion of brain metastases in clinical trials has remained relatively constant (around 15%) for the past few decades.

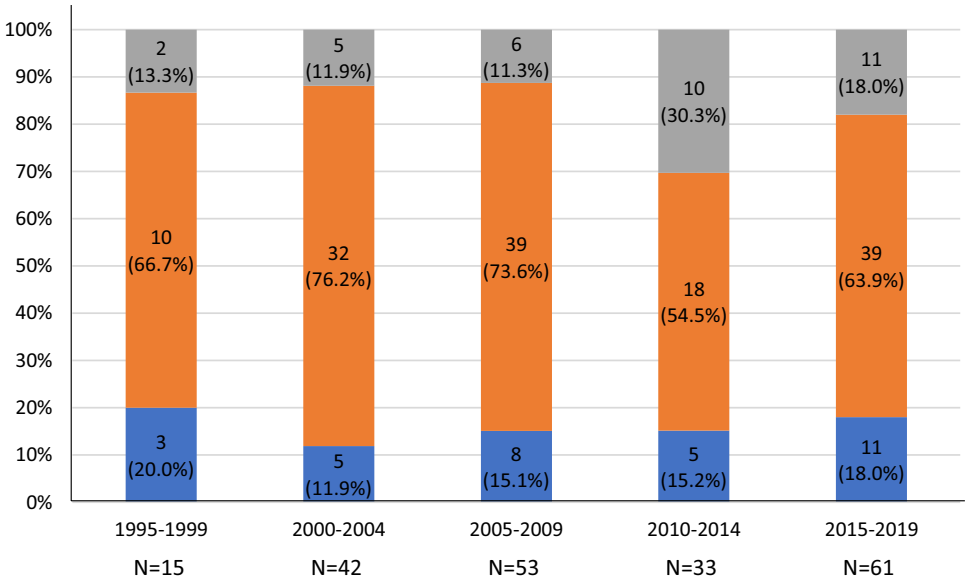


**Fig. 1** The number and percentage of each exclusion category is included in each bar. Blue bars; strict exclusion, orange bars; allowed, gray bars; undefined

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## Compliance with ethical standards

**Conflict of interest** All authors declared no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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