

## Additional radiation boost to whole brain radiation therapy for brain metastases in small cell lung cancer- A Phase II Study

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**Abstract:** Background: Radiation boost has been used effectively in combination with WBRT in various schedules as an effective and possible therapy option in small cell lung cancer (SCLC) with brain metastases. The present phase II single institution study was aimed to evaluate the efficiency of additional radiation boost to whole brain radiation therapy for brain metastases (BMs) in SCLC at Department of Clinical Oncology, Faculty of Medicine, Tanta university Hospital. Patients and Methods: 36 patients, their ages >18 years with brain metastases in SCLC, adequate hepatic, renal and hematologic function, no less than one assessable lesion, and a Karnofsky performance status  $\geq 70\%$  were participated. After confirming the BMs, WBRT plus a radiation boost were done for all patients. The total dose of administered WBRT was 30Gy (given in 10 daily doses, each dose equal 3Gy/day). The booster radiation doses was given throughout 3D-CRT simultaneous integrated boost WBRT. The administered radiation dose was 3.5–5Gy/daily for 10 doses (Total 35–50Gy) varied according to the diameter of BMs. Results: The median period of follow-up was 14 months (range, 1 - 90 months). Median OS time was 13.5 months. The 6-, 12-, and 24-month OS intervals were reached 84.5, 62.7, and 21.5%, respectively. Higher Karnofsky performance status, solitary BMs,  $\leq 2$  cm maximum diameter of the largest BMs tumor, absence of progressive extracranial disease, asymptomatic BMs showed a statistically significant better overall survival in univariate analysis. In multivariate analysis, only,  $\leq 2$  cm maximum diameter of the largest BMs tumor, none progressive extracranial disease, and asymptomatic BMs were independently related to this end point. Conclusion: Additional radiation boost to whole brain radiation for treatment of small cell lung cancer metastases in brain appeared to offer beneficial effects on overall survival.

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### 1. Introduction

Small-cell lung cancer (SCLC) metastases in the brain (BM) are a general trouble for affected patients [1]. The standard treatment of patients with small-cell lung cancer (SCLC) metastases in the brain is known as whole brain radiotherapy (WBRT). Yet, it has modest efficiency and available in complete expected information for WBRT, in addition to local therapies like stereotactic radio surgery (SRS) [2].

Regimens that are used in the treatment of SCLC BMs, including WBRT, had at least equivalent overall survival in retrospective studies [3-11]. Previous trials reported activity of combination of WBRT with radiation boost in the control of SCLC metastasis in the brain [12, 13].

Currently, individuals with SCLC brain metastasis is WBRT, regardless of the number of BM [1, 14, 15]. Previous retrospective studies along the last three decades was low and depending mainly on and is analogically logical by earlier PCI studies [8, 16- 19].

Earlier randomized studies established that the treatments with SRS plus WBRT could enhance the overall survival rate of patients complaining from

metastatic tumor in the brain [13, 20]. The dose appreciation approach has also been studied successfully with the combination of WBRT with an additional radiation boost to produce an effective and viable treatment option for patients with SCLC with BMs [12]. Sun et al [12], treated metastatic SCLC in brain of patients with WBRT with/or without a radiation boost, They concluded that it is a practicable therapy choice to elevate the survival rate suffering from SCLC metastatic in brain of patients treated with WBRT plus a radiation boost [12].

Based on these data, we carried out, this current phase II single institution study designed with a target to estimate the efficiency of WBRT combined with a radiation boost in brain metastatic SCLC patients.

### 2. Patients and Methods

#### Patient Selection

Between January 2008 and March 2017, 36 patients over the age of 18 years with histologically confirmed brain metastases (BMs) in small cell lung cancer (SCLC) were subjected to this study, at Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital.

Eligible patients were required to have at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) Group criteria [21], a Karnofsky performance status (KPS) of  $\geq 70$ , adequate bone marrow reserve, adequate renal and hepatic function. Prior chemotherapy and radiotherapy for initial limited-stage (LS) SCLC prior to study entry were allowed. All our patients received WBRT plus a boost of radiation after confirmation of BMs.

Patients with earlier prophylactic cranial irradiation (PCI) prior to the detection of BMs, extracranial metastases at time of study entry, second malignant disease, and pregnant women were considered ineligible.

All patients provided written informed consent prior to enrolment into the study. The Ethics Committee at our Faculty of Medicine, Tanta University granted protocol approval.

### Treatment

Eligible patients received chemo-radiotherapy for initial LS SCLC. All our patients received intravenous infusion of cisplatin 30 mg/m<sup>2</sup> on days 1-3 or carboplatin 500mg day 1 combined with etoposide 100mg from days 1 - 5 of a 3-week cycle. Before chemotherapy infusion, hydration, adequate anti-emetic therapy, antacids and steroids were ensured for all patients. Growth factor (G-CSF) and antibiotic were administered in some cases, based upon clinical judgment. Patients were designed to receive treatment for 6 cycles unless disease progression or unacceptable toxicity occurred.

Adequate hematological and organ functions recovery should be ensured before each treatment session. Dose reduction was allowed according to clinical judgment.

Thoracic radiotherapy was delivered by linear accelerator photon beams. All patients received sequential or concurrent 3D conformal radiotherapy (3D-CRT). For all patients, the gross tumor volume (GTV) included the tumor and metastatic lymph nodes. The tumor bed and the draining area of metastatic lymph nodes before chemotherapy, which was expanded from the GTV by a 5mm uniform margin were defined as the clinical target volume (CTV). The planning target volume (PTV) was outlined with a 5–10mm margin to the CTV. The radiation dose was 50–63Gy in 25–30 fractions, 1.8–2 Gy per fraction at one fraction per day.

After confirming the BMs, all patients underwent WBRT plus a radiation boost. WBRT was performed with linear accelerators photon beams using opposed lateral fields with a total dose of 30Gy (3Gy per fraction administered in 10 fractions at one fraction per day). The additional radiation boost was administered using 3D-CRT simultaneous integrated

boost WBRT. The GTV encompassed contrast-enhancing tumor on MRI, the PTV of metastases was defined as the 3mm margin to the GTV. The administered radiation dose was 35–50Gy in 10 fractions with 3.5–5Gy per fraction and one fraction per day. We treated BMs less than 1 Cm in maximum diameter with a prescription of 50Gy; BMs larger than 1 Cm but smaller than 3 Cm with 40 Gy; and BMs larger than 3Cm and less than 4 Cm with 35Gy. The prescription of dose fractionation was based on previous clinical trials [22, 23].

### Patient and Treatment Evaluation

All patients had a complete medical history and physical examination before entering the study. Furthermore, a complete blood count and liver and renal function tests were conducted before entry into the study. Gadolinium-enhanced brain MRI or computed tomography (CT) scans were used to detect BMs. Abdomino-pelvic and chest computed tomography (CT) scans, as well as brain MRI every 3 months or when disease progression was suspected. After therapy, patients were followed every 3 months for the first 2 years and every 6 months thereafter.

### Study Endpoints

The primary endpoint of this study was the overall survival, which was defined as the time between the date of BM diagnosis and the date of death or last follow up.

### Statistical analysis:

The date of final analysis was April 2019. Overall survival was calculated according to the Kaplan-Meier method [24], with SPSS [Statistical package] (version 19.0). Mean and standard deviation were estimates of quantitative data. The 95% confidence intervals (95% CIs) were calculated with the exact method. Statistical significance was assessed by the log-rank test. All *P* values were two-tailed; a value of 0.05 was considered significant.

## 3. Results

### Patients Characteristics

A total of 36 patients were enrolled in this phase II trial from January 2008 and March 2017 at Clinical Oncology Department, Tanta University Hospital. The characteristics of all eligible patients are shown in Table 1. The ages of patients participating in the current study was averaged 59 years (range, 35–70 years), 66.67% (24/36) of who were male. Sequential CRT was received by 66.7% (24/36) of patients.

At time of study entry, the median KPS was 80%, and more than half of the patients (55.6%) had a KPS of  $\leq 80\%$ . Median time between primary diagnosis of small cell lung cancer (SCLC) to inclusion was 11 months (range, 6–23 months). Most of the patients (55.6% {20/36}) had multiple brain metastases (Table 1).

**Table 1. Patients', tumors' and treatment Characteristics (N = 36)**

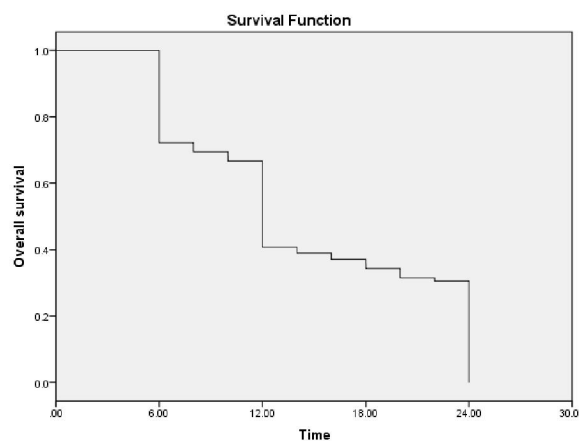
| <b>Patient Characteristics</b>                           | <b>No.</b> | <b>%</b> |
|--|------------|----------|
| <b>Sex</b>   |            |          |
| Male   | 24         | 66.7     |
| Female   | 12         | 33.3     |
| <b>Age, years</b>  |            |          |
| Median   | 59         |          |
| Range  | 35-70      |          |
| <b>Karnofsky performance status</b>                      |            |          |
| Median   | 80         |          |
| 70   | 6          | 16.67    |
| 80   | 14         | 38.89    |
| 90   | 11         | 30.56    |
| 100  | 5          | 13.89    |
| <b>Smoking history</b>                                   |            |          |
| Yes  | 26         | 72.2     |
| No   | 10         | 27.8     |
| <b>Number of BMs</b>                                     |            |          |
| Single metastasis  | 8          | 22.2     |
| 2-3  | 10         | 27.8     |
| >3   | 18         | 50       |
| <b>Interval from diagnosis of SCLC to BMs (month)</b>    |            |          |
| Median   | 11         |          |
| Range  | 6- 23      |          |
| <b>Maximum diameter of the largest tumor (cm)</b>        |            |          |
| ≤2   | 19         | 52.8     |
| >2   | 17         | 47.2     |
| <b>Progressive extracranial disease status</b>           |            |          |
| No   | 30         | 83.3     |
| Yes  | 6          | 16.7     |
| <b>Symptomatic BMs</b>                                   |            |          |
| No   | 24         | 66.7     |
| Yes  | 12         | 33.3     |
| <b>Prior radiotherapy- chemotherapy (CRT) before BMs</b> |            |          |
| Sequential CRT   | 24         | 66.7     |
| Concurrent CRT   | 12         | 33.3     |

### Treatment

After confirming the BMs, all patients underwent WBRT combined with a booster radiation. WBRT was performed with linear accelerators photon beams by means of contrasting lateral fields by a dose of 3Gy/day for 10 days. The additional radiation boost (3-5 Gy/day for 10 days) was administered using 3D-CRT simultaneous integrated boost WBRT. The booster dose was given and differ according to the size of BMs;50Gy for BMs less than 1 Cm, 40 Gy for BMs 1-3Cm and 35Gy for BMs 3-4 Cm.

### Survival

The median period of follow-up was 14 months (range, 1 - 90 months). Median OS time was 13.5 months. The 6-, 12-, and 24-month OS rates were 84.5, 62.7, and 21.5% respectively, (Fig. 1).



**Fig 1. Kaplan–Meier curve of overall survival. Median overall survival time was 13.5 months.**

Higher Karnofsky performance status, solitary BMs,  $\leq 2$  cm maximum diameter of the largest BMs tumor, absence of progressive extracranial disease, asymptomatic BMs showed a statistically significant better overall survival in univariate analysis (Table 2).

Although survival was not significantly different, older age, male sex, smokers, shorter interval from diagnosis of SCLC to development of BMs and concurrent CRT showed a trend for poor overall survival in our study.

In multivariate analysis, only,  $\leq 2$  cm maximum diameter of the largest BMs tumor, none progressive

extracranial disease, and asymptomatic BMs were independently related to this end point (Table 3).

#### 4. Discussion

The incidence of small cell lung cancer (SCLC) representing approximately 20% of all lung tumor cases. It spread earlier in the progress of its normal history rather than non-small cell pulmonary tumor and the symptoms practically is more severe. At the beginning of diagnosis the incidence of brain metastasis is mainly about 10% of cases, and frequency is elevated during the course of disorder to reach to 40-50% of cases. [25].

**Table 2. Univariate analysis of correlation between patients', tumors' and treatment characteristics with OS**

| Patient Characteristics                                  | No.   | %     | Median OS (months) | P value |
|--|-------|-------|--------------------|---------|
| <b>Sex</b>   |       |       |                    |         |
| Male   | 24    | 66.7  | 13                 | 0.352   |
| Female   | 12    | 33.3  | 14                 |         |
| <b>Age, years</b>  |       |       |                    |         |
| Median   | 59    |       |                    | 0.295   |
| Range  | 35-70 | 52.8  | 14                 |         |
| < 65   | 19    | 47.2  | 12                 |         |
| $\geq 65$  | 17    |       |                    |         |
| <b>Karnofsky performance status</b>                      |       |       |                    |         |
| Median   | 80    |       |                    | 0.018*  |
| 70   | 6     | 16.67 | 6                  |         |
| 80   | 14    | 38.89 | 12                 |         |
| 90   | 11    | 30.56 | 14                 |         |
| 100  | 5     | 13.89 | 15                 |         |
| <b>Smoking history</b>                                   |       |       |                    |         |
| Yes  | 26    | 72.2  | 13                 | 0.327   |
| No   | 10    | 27.8  | 14                 |         |
| <b>Number of BMs</b>                                     |       |       |                    |         |
| Solitary BMs   | 8     | 22.2  | 15                 | 0.013*  |
| 2-3  | 10    | 27.8  | 13                 |         |
| >3   | 18    | 50    | 7                  |         |
| <b>Interval from diagnosis of SCLC to BMs (month)</b>    |       |       |                    |         |
| Median   | 11    |       |                    | 0.278   |
| Range  | 6- 23 | 47.2  | 12                 |         |
| $\leq 10$  | 17    | 52.8  | 14                 |         |
| >10  | 19    |       |                    |         |
| <b>Maximum diameter of the largest tumor (cm)</b>        |       |       |                    |         |
| $\leq 2$   | 19    | 52.8  | 15                 | 0.027*  |
| >2   | 17    | 47.2  | 10                 |         |
| <b>Progressive extracranial disease status</b>           |       |       |                    |         |
| No   | 30    | 83.3  | 14.5               | 0.021*  |
| Yes  | 6     | 16.7  | 8                  |         |
| <b>Symptomatic BMs</b>                                   |       |       |                    |         |
| No   | 24    | 66.7  | 15                 | 0.031*  |
| Yes  | 12    | 33.3  | 9                  |         |
| <b>Prior radiotherapy- chemotherapy (CRT) before BMs</b> |       |       |                    |         |
| Sequential CRT   | 24    | 66.7  | 14                 | 0.421   |
| Concurrent CRT   | 12    | 33.3  | 13.5               |         |

**Table 3. Multivariate analysis of correlation between patients', tumors' and treatment characteristics with OS**

| Patient Characteristics                                  | No. | %     | HR of death (95% CI) | P value |
|--|-----|-------|----------------------|---------|
| <b><i>Karnofsky performance status</i></b>               |     |       |                      |         |
| Median   | 80  | 16.67 |                      |         |
| 70   | 6   | 38.89 | 0.536                | 0.324   |
| 80   | 14  | 30.56 | (0.184 – 2.530)      |         |
| 90   | 11  | 13.89 |                      |         |
| 100  | 5   |       |                      |         |
| <b><i>Number of BMs</i></b>                              |     |       |                      |         |
| Solitary BMs   | 8   | 22.2  | 0.857                | 0.217   |
| 2-3  | 10  | 27.8  | (0.327 – 1.523)      |         |
| >3   | 18  | 50    |                      |         |
| <b><i>Maximum diameter of the largest tumor (cm)</i></b> |     |       |                      |         |
| ≤2   | 19  | 52.8  | 0.518                | 0.034*  |
| >2   | 17  | 47.2  | (0.109 – 0.941)      |         |
| <b><i>Progressive extracranial disease</i></b>           |     |       |                      |         |
| No   | 30  | 83.3  | 0.498                | 0.007*  |
| Yes  | 6   | 16.7  | (0.249 – 0.762)      |         |
| <b><i>Symptomatic BMs</i></b>                            |     |       |                      |         |
| No   | 24  | 66.7  | 0.397                | 0.027*  |
| Yes  | 12  | 33.3  | (0.198 – 0.574)      |         |

Exposure the patients suffering from brain cancer metastasis to whole brain radiation treatment (WBRT) still the golden therapy in SCLC irrespective of the size or number of BM [26, 27]. WBRT is still approved as a good scheme for treating of BM in SCLC even in cases of limited, solitary or multiple lesions of BMs may be attributed to primary anxieties concerning the possibility for diffuse CNS progression [12, 28]. Whereas, fears about a single natural history of SCLC BM in continue to initiative endorsements for WBRT even between subjects with restricted BM [29]. There are documents to contest the postulation of poorer efficacy with SRS in treatment of SCLC.

The frequency of extracranial disease metastasis at the onset or shortly after diagnosis of disease, appeared in 60% and 95% of SCLC metastasis in the patient's brain [30]. Due to the violent systemic nature of SCLC, such patients suffering from SCLC were omitted from contribution in this trial that is exploring substitutes to conventional WBRT. Therefore, due to exclusion of SCLC from this study, limited number of patients have been accompanied to attendant the therapy progress patients in this group and to challenge the prevailing perspective that conventional WBRT alone is the only efficient therapy for SCLC metastatic in the brain. Thus, this analysis of only 36 SCLC patients assessed a group of LS-SCLC individuals who had not complained from metastases

in the extracranium before BMs diagnosis in those patients. After confirmation of BMs diagnosis the patients were subjected for treatment, with WBRT plus a radiation boost. Significant favorable survival outcomes were observed, which compare favorably with the other studies of conventional WBRT alone [3- 11].

Thirty-six patients in our series underwent WBRT plus a radiation boost. 13.5 months and one and two-year was the median survival rate for the entire group, OS rates were 62.7, and 21.5% respectively. These results were comparable with that reported by Andrews et al. [13] who demonstrated in his series of 24 SCLC patients with 1 to 3 BMs that a survival benefit was observed in patients with BM for WBRT plus SRS boost arm, than for WBRT alone ( $p = 0.039$ ).

In addition, our results of WBRT plus a radiation boost regimen were comparable with that of the WBRT plus a radiation boost arm in Sun et al., study [12]. Sun et al., described a single-institution retrospective trials of 82 subjects that treated with WBRT alone ( $n = 49$ ) or combined with a booster doses of radiation ( $n = 33$ ) and their results were lower than of WBRT combined with a radiation boost protocol [12]. He demonstrated that, the median OS in the WBRT group ( $n = 49$ ) was 8.5 months, while the OS in the WBRT combined with boost

group (n = 33) was 13.4 months. The OS rate was significantly higher (p=0.004) in groups treated with WBRT plus boost (84.5, 62.7, and 21.5%) than that treated with WBRT alone (59.8, 29.9, 9.6%) after, 6-, 12-, and 24-month, respectively. This was similar to that mentioned in our patients who received WBRT plus a radiation boost (The median period of follow-up was 14 months, median OS time was 13.5 months, the 6-, 12-, and 24-months OS rates were 84.5, 62.7, and 21.5% respectively).

Also our results compare favorably with the other studies of WBRT with or without radiation boost which demonstrated significant improvements for the combination WBRT plus boost compared with WBRT alone in patients with metastatic SCLC cancer to the brain [31, 32]. Some investigators [31] evaluated the efficacy of treatment of SCLC patients (n=44) with SRS with/ or without BRT. The results revealed that, WBRT combined with SRS boost was improved significantly OS in patients from 6 months to 14 months post therapy with WBRT plus SRS boost (p = 0.04). Though, this data should be understood carefully due to the decrease in the volume of participated sample (n=6), who were administered WBRT therapy combined with SRS boost group. In a study comprising large of patients (n=4259), Sperduto et al. [32] revised the histories of 299 SCLC metastasis in patient's brain. From the group of 247 subjects were administered WBRT-alone, while 21 subjects were administered WBRT combined with SRS booster radiation dose. The results revealed that OS rate was elevated significantly (15.23 vs. 3.87 months, p = 0.003) in the WBRT combined with SRS boost subjects.

In our analyses, some patients', tumors' and treatment characteristics such as sex, KPS, age, smoking history, extracranial metastases status, symptomatic BMs, maximum diameter of the largest tumor, number of BMs, prior radiotherapy-chemotherapy (CRT) before BMs and interval from diagnosis of SCLC to BMs have been correlated in SCLC patients with BMs with OS. The univariate and the multivariate analyses proposed that progressive extracranial disorder condition, symptomatic BMs, and large size diameter of the cancer were liked significantly with OS. Moreover, in the univariate analysis, the OS was influenced significantly by the KPS and the number of BMs. In other studies, some extrapolative aspects like extracranial metastases status, age, KPS, metachronous disease and the number of BMs, have been recognized in SCLC patients with BMs [12, 31-35]. In Sun et al., study [12], by applying the multivariate analysis (p = 0.795) there was no significant variation in OS rate among patients suffering from different numbers of BMs metastatic lesions (1- 3 and more than 3 BMs) which

was similar to that reported in our study that in the onlyunivariate analysis, the OS was influenced significantly by BMs numbers but not in multivariate analysis (p= 0.217). This was in controversy to the DS-GPA classification, that the BMs numbers can be used as an important predictive element [32] in the multivariate and the univariate analyses. On the other hand, the individuals in the current study were subjected for different treatment regimens, comprising SRS, WBRT, or SRS combined with WBRT or surgical interference, which may cause inappropriate results. Bernhardt et al. [34] retrospectively investigated 229 SCLC BMs patients who exposed to a doses of WBRT, and found in the univariate (p = 0.06) or the multivariate analysis (p = 0.511) that the number of BMs was not a significant predictive factor. Some investigators found in their study that the number of BMs was linked significantly with improvement in the OS (p = 0.011) and local intracranial control (p = 0.027) [36]. The contradicts in this study may be attributed to at least partially, to the differences in the volume of BMs. Therefore, we taken in our consideration to analyze the diameter of tumor in the whole studied group. Comparable to preceding researches [12, 37], there are a correlation between the size of the tumor and the improvement in the rate of OS (small in size of tumor correlated with significant improvement if OS) in both the multivariate and the univariate analyses. Whereas, treatment with WBRT-alone could give active curing for small or subclinical brain metastatic tumor lesions, in the same time, it might have imperfect influence for the large size metastatic lesions in the WBRT-alone arm of these studies [12, 37].

In conclusion, the current results suggest that WBRT plus a radiation boost regimen is an active dose escalation strategy in the control of SCLC metastasis in patients brain. Because the overall survival of the WBRT plus a radiation boost regimen was superior to that in previous studies of WBRT alone, this constitutes a marked advantage over WBRT alone. However, further prospective investigation of this regimen to optimize doses and scheduling is necessary. In addition, further studies are required to elucidate or evaluate the dose escalation-related toxicities and the local intracranial control for individuals treated in WBRT combined with booster radiation doses to help us to refine further the answers to the two most valuable questions: Who to treat? and, what to treat with?

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