

بسم الله الرحمن الرحيم

**Sudan University of Science and
Technology
College of Graduate Studies**

***Evaluation of Adjuvant Whole Brain
Radiotherapy After Stereotactic
Radiosurgery of Brain Metastases***

تقييم العلاج الاشعاعي التعزيزي لكامل المخ بعد الجراحة الاشعاعية
للسرطانات المنتقلة الى المخ

***A Thesis Submitted for Partial Fulfillment
with Requirement of Master Degree in
Medical Physics***

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Dedication

*To my mother , my father , my
great teachers
my sisters , and my brothers .*

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Acknowledgement

*The creation of this thesis rely not only on me ,
but also to a large extent on a network of
dedicated people who are responsible for the
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Abbreviations

SRS	Stereotactic Radiosurgery
WBRT	Whole brain radiotherapy
RCT	Randomized controlled trial
BM	Brain metastasis
MMSE	Mini-mental status
examination	
PCI	Prophylactic cranial
irradiation	

HVLT-R Hopkins verbal learning test-
revised

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Abstract (in English)

Stereotactic radiosurgery is frequently used either alone or together with whole brain radiotherapy to treat brain metastases. Some studies reported better results with combination of WBRT+SRS, while others reported that WBRT didn't enhance the effect of SRS.

The aim of this meta-analysis is to determine whether WBRT+SRS or SRS alone will result in better clinical outcomes for patients with brain metastases .

The meta-analyses were done using an online effect size calculator -based on the reference(practical meta-analysis) by David.B Wilson- on the following outcomes : survival rate, local tumor recurrence rate, new distant

brain metastases recurrence rate, and the neurologic radiation toxicity rate .

It is found that : the local tumor recurrence and the new distant brain metastases recurrence rates had been reduced in the WBRT+SRS group with Odds Ratios of 0.36 and 0.44 respectively; but the neurologic radiation toxicity rate was higher in the WBRT+SRS group with an Odds Ratio of 3.84 . And there was no significant difference in one year survival rate between the two groups with an Odds Ratio of 0.54 .

It is concluded that: the WBRT reduces the local tumor recurrence and new brain metastases recurrence; but worsens the neurocognitive function in the patients. On other hand, the addition of WBRT to SRS didn't improve the survival for patients with brain metastases.

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Abstract (in Arabic)

الجراحة الإشعاعية (لما لوحدها او مصحوبة بعلاج شعاعي- لكامل- المخ-) تستخدم- لعلاج السرطانات- المتنقلة- في- المخ- - بعض الدراسات- بينت- ان- الجراحة الاشعاعية مصحوبة بعلاج شعاعي- لكامل- المخ- تعطي- نتائج علاجية لفضل- - بينما- اوضح البعض- الاخر- ان- استخدام- العلاج- الاشعاعي- لكامل- المخ- مع الجراحة الاشعاعية لا يحسن- تأثيرها-

في- هذه الدراسة- - الهدف- هو تحديد- ما- اذا كانت- الجراحة- الاشعاعية لوحدها او الجراحة الاشعاعية مصحوبة بعلاج شعاعي- لكامل- المخ- سيعطي- نتائج علاجية لفضل- بالنسبة- للمرضى- الذين- يعانون- من- . اورام- سرطانية متنقلة- في- المخ-

في- هذه الدراسة- - باستخدام- حاسبة (موصولة بشبكة الانترنت-)- تستخدم- لحساب- المقادير- الاحصائية - اجريت- التحليلات- المتعددة- على- المخرجات- الآتية :- معدل- النجاة- - معدل- رجوع الورم- السرطاني- في-

موضع العلاج, معدل رجوع الورم السرطاني في مواضع جديدة في المخ - و معدل ظهور تأثيرات إشعاعية على الخلايا العصبية لقد وجد ان :- معدلات رجوع الورم السرطاني في موضع العلاج و في مواضع جديدة في المخ تنخفض عند استخدام الجراحة الاشعاعية مصحوبة بعلاج اشعاعي لكامل المخ - حيث كانت نتيجة النسب الاحتمالية 0.44 هي و 0.44 على التوالي - و لكن معدل ظهور تأثيرات اشعاعية في الخلايا العصبية يرتفع عند استخدام الجراحة الاشعاعية مصحوبة بعلاج اشعاعي لكامل المخ - حيث كانت نتيجة النسبة الاحتمالية لها 3.84 - كما وجد انه ليس هنالك فرق كبير في معدل النجاة بين مجموعتي المرضى المعالجنين بأي من المعالجتين - حيث كانت نتيجة النسبة الاحتمالية لمعدل النجاة 0.54 هي في هذه الدراسة - لقد خلص الى ان :- العلاج الاشعاعي لكامل المخ - المصاحب للجراحة الاشعاعية - يخفض حالات رجوع الورم السرطاني - لكنه يزيد الاضرار في الوظائف الحيوية العصبية لدى المرضى - من ناحية اخرى - ان العلاج الاشعاعي لكامل المخ - عندما يضاف للجراحة الاشعاعية لا يحسن معدل النجاة بالنسبة للمرضى ذوي السرطانات المتنقلة في المخ .

Chapter one

1-1 Introduction :

The main treatment options available for brain metastases patients are surgery, whole brain radiotherapy, chemotherapy and stereotactic radiosurgery (SRS) .

The late toxicities of WBRT have been well documented.

Moreover, patients with longer survival times ultimately have an increased chance of experiencing WBRT-related toxicity . As such, an approach (such as SRS) of eliminating or delaying WBRT in patients with brain metastases would potentially improve cognitive outcomes in these patients .

Stereotactic radiosurgery (SRS) is a form of external beam radiation therapy which targets a tumor from many different directions so the beams of radiation converge on the tumor.

The goal of SRS is to precisely deliver a high dose to the target volume in a single fraction to destroy or stop the growth of a lesion without adversely affecting surrounding tissue . Normal tissues are protected both by selectively targeting only the abnormal lesion and by using cross-firing techniques to minimize the exposure of the adjacent anatomy . In that way, the amount of radiation needed to destroy tumor cells is delivered directly to the tumor, and the amount of exposure to the area surrounding

the tumor is limited . So, With SRS, high doses of radiation can be delivered with sub-millimeter accuracy .

Therefore, Stereotactic radiosurgery (SRS) is appropriate for brain metastases patients who have fewer than five brain metastases all of which have a diameter of less than 4 cm. And it is frequently used, either alone or together with whole-brain radiation therapy to treat brain metastases from solid tumors .

Although randomized trials have favored adding whole-brain radiation therapy to stereotactic radiosurgery for most end points, recently , there is a published meta analysis demonstrated a survival disadvantage for patients treated with whole brain radiation therapy and stereotactic radiosurgery compared with patients treated with stereotactic radiosurgery alone { Saghal, 2015 } . and so , Certain experts and radiation oncology groups have proposed replacing whole-brain radiation therapy with stereotactic radiosurgery alone for the management of brain metastases.

Unfortunately, soon after that meta-analysis was published , use of whole-brain radiation therapy in managing brain metastases has become controversial among radiation oncologists.

However, this situation creates conflict for radiation oncologists who believe that there are enough high level of evidence for the effectiveness of whole-brain radiation therapy in the treatment of brain metastasis .

Thus , to remedy this controversy we have to make further studies .

1-2- THE PROBLEM OF THE STUDY

Brain metastases are the most common cause of malignant brain tumours in adults. And they occur in 20–40% of patients with systemic cancer ; 30–40% present with a single metastasis {Andrews, et.l , 2004}.

Although whole brain radiation therapy (WBRT) has been used to treat brain metastases together with Stereotactic Radiosurgery , a recent trend promotes the use of Stereotactic Radiosurgery-alone .

However, the data in this area is controversial and may not be reliable due to early evaluation of these end points after Whole Brain Radiotherapy with a limited number of patients .

So , in patients with brain metastases, it is unclear whether adding up-front whole brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) has better clinical outcomes compared with SRS alone .

1-3- THE GENERAL OBJECTIVE

To determine whether SRS alone or WBRT combined with SRS will result in better clinical outcomes for patients with brain metastases .

1-4- THE SPECIFIC OBJECTIVES

- To assess the survival , tumor recurrence rate , and the functional preservation rate resulted from the SRS used alone for treatment of brain metastases .

- To assess the survival , tumor recurrence rate , and the functional preservation rate resulted from the use of WBRT combined with SRS for treatment of brain metastases .

Chapter two

Literature Review

2-1- Theoretical background :-

The brain metastases are the spread of a primary tumor to the brain . They can occur due to any tumor in any - wherever the site of this tumor - and they have the characteristics and histology of the primary tumor , where if the brain metastases resulted from a lung cancer , these metastases will still lung cell cancer ; but in the brain .

Therefore the treatment of the brain metastases depends mainly on the primary tumor histology .

One of the increasingly used treatment options for brain metastases is the radiotherapy including Whole Brain Radiation Therapy and Stereotactic Radiosurgery .

Whole Brain Radiation Therapy :-

Is giving electromagnetic ionizing radiation to the entire brain using a traditional external beam radiation therapy equipment(Linac or Co₆₀ machine).

It is often used alone in patients with poor prognosis and in cases of unresectable brain metastases couldn't be treated with

stereotactic radiosurgery ; due to their sizes or their number .
And recently , it has been used as adjuvant therapy after surgery or stereotactic radiosurgery in order to treat the microscopic lesions not targeted with SRS dose ; because they were not seen by the radiology studies , where these lesions are just cancer cells in the normal-appearing brain but don't form a mass and therefore they were not seen by the radiology studies , and by adding the WBRT to SRS even these microscopic lesions will be treated , leading to reduce the risk of tumor recurrence . Thus , the clinical aim of adding WBRT to SRS is to kill all the cancer cells , but with note this will be in cost of sparing the surrounding healthy tissues .

Stereotactic Radiosurgery :-

Is a form of external beam radiation therapy which targets a tumor from many different directions, so the beams of radiation converge on the tumor.

The goal of SRS is to precisely deliver a high dose of radiation the tumor in a single session , with minimal dose (should be kept below the tolerable doses) to the surrounding healthy tissues.

So , SRS can be defined as a highly precise administration of a high radiation dose to the tumor site in a single session .

Thus , with SRS a high radiation dose can delivered to the tumor with sub-millimeter accuracy ; therefore SRS is used alone or together with WBRT to treat the fewer than five small brain metastases , while for larger in number and size brain

metastases SRS beams will converge on each other leading to increase the dose to the surrounding healthy tissues beyond the tolerable doses ; therefore SRS is not used for larger brain metastases .

And due to the high accuracy of SRS , therefore SRS is often suggested to be used alone with the clinical aim is To avoid the potential side effects associated with WBRT .

There are many techniques used for delivering of the SRS dose

(i) **Gamma knife :-**

is a radiosurgical device that has been associated with radiosurgery for the past four decades. Despite great technological advances during this time, the fundamental design and principles of the gamma unit have not changed much since the late 1960s. The unit incorporates 201 Co₆₀ sources housed in the central body of the unit. These sources produce 201 collimated beams directed to a single focal point at a source to focus distance of about 40 cm. The final definition of the circular beam field size is provided by one of four helmets delivering circular fields .

The main components of the gamma unit are:

- A radiation unit with an upper hemispherical shield and a central body
- An operating table and sliding cradle
- A set of four collimator helmets providing circular beams at the isocentre

- A control unit.

(ii) Linac based stereotactic radiosurgery :-

Such as X knife and Cyber knife .

1- X knife :-

Is a radiosurgical device that uses a standard isocentric linac with tight mechanical and electrical tolerances, modified for radiosurgery. It requires a head frame for immobilizing the patient's head .

The modifications on a linac - to be used for SRS - consist of :

- Supplementary collimation .
- A remotely controlled motorized table or treatment chair rotation .
- Table brackets or a floor stand for immobilizing the stereotactic frame .
- Interlocked readouts for angular and height position of the table .

2 - Cyber knife :-

Is a form of frameless stereotactic radiosurgery using a specialized . miniature linac with a robotic arm , it uses a mask along with skull based . tracking allowing the robot to follow the target .

The CyberKnife stereotactic radiosurgery system broadens the range . of stereotactic radiosurgery and offers the following improvements over . standard radiosurgical techniques :

- It allows frameless radiosurgery .
- It monitors and tracks the patient's position continuously and uses on-line images for finding the exact position of the target .
- It aims the radiation beam into the on-line determined target position and achieves a dose delivery accuracy of the order of 1 mm

2-2- Previous studies :-

Stereotactic radiosurgery is a widely accepted treatment for a number of medical conditions. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology for Central Nervous System Cancers (2012) notes the use of SRS with primary brain tumors and brain metastases.

Multiple randomized trials (Kondziolka et al., 1999 ; Li et al., 2000 ; Andrews et al., 2004 ; Aoyama et al., 2006 ; Aoyama et al., 2007 ; chang et al.,2009 ; Kocher et al.,2011 ; Lei Duan et al., 2014) and a number of nonrandomized or case series studies evaluated the safety and efficacy of SRS with or without WBRT and microsurgery for patients with brain metastases .

SRS was associated with good local tumor control and reduction in brain recurrence, although impact on survival was only seen in patients with good prognostic indicators and limited extracranial disease. In the reviewed studies, tumor control, recurrence rates, and overall survival varied widely depending on the type of tumor and the extent of disease, as well as other patient factors. Some

studies reported better results with combination therapy (surgical excision, WBRT, and stereotactic radiosurgery), while others reported that addition of WBRT did not enhance the effect of stereotactic radiosurgery.

The National Comprehensive Cancer Network released a 2008 practice guideline for central nervous system cancers and noted that SRS may be used for a limited number of small, deep, non-symptomatic lesions, but that surgery may be more appropriate for larger, more symptomatic lesions. Patients with greater than 4 metastatic lesions should be treated with WBRT with or without SRS in selected cases { Radiosurgery practice guideline report . 2008}.

The first prospective trial looking at the utility of an SRS boost was published in 1999 by Kondziolka et al. This single-institution RCT included patients with 2–4 metastases measuring ≤ 2.5 cm and a KPS ≥ 70 . There were 14 patients in the WBRT arm and 13 in the WBRT plus SRS arm. The two groups were well matched with regard to patients factors . The primary endpoint was local control with secondary endpoints including time to progression and median survival. The study was halted at the 60% accrual point after interim evaluation revealed improved median time to progression (36 versus 6 months) and local failure rate (8% versus 100%) for patients in the WBRT plus SRS arm. Because of the small number of patients, there was insufficient power to assess differences in median survival.

Li et al. in 2000 reported their results of a three arm prospective cohort study examining patients with either small-cell or nonsmall-cell lung cancer with a single brain metastasis measuring ≤ 4.5 cm . Seventy lung cancer patients with newly diagnosed single brain metastasis were treated with either WBRT alone ($n = 29$), or SRS alone ($n = 23$), or the combination of both ($n = 18$). Groups were well matched with regard to gender, age, extent of extracranial disease, histology, and KPS scores. Multiple endpoints, including survival, freedom from local progression, freedom from new brain metastasis, local control, KPS, and cause of death, were measured and compared using univariate and multivariate analyses. Analysis revealed improved median survival ($P < 0.0001$), local control ($P = 0.004$), and median time to progression ($P < 0.0001$) in the WBRT plus SRS arm. However, the comparison between SRS alone and SRS plus WBRT groups indicated that adding WBRT only improved freedom from distant failure.

Andrews et al. 2004 : -

IN 2004 , Radiation Therapy Oncology Group (RTOG) directed a randomized trial (*Lancet* 2004; 363: 1665-72) , where they enrolled 333 Patients with one to three newly diagnosed brain metastases were randomly allocated either whole brain radiation therapy (WBRT) or WBRT followed by stereotactic radiosurgery boost. Patients were stratified by number of metastases and status of extracranial disease. Primary outcome was survival; secondary outcomes were tumour response and local rates,

overall intracranial recurrence rates, cause of death, and performance measurements.

They found that : The Univariate analysis showed that there was a survival advantage in the WBRT and stereotactic radiosurgery group for patients with a single brain metastasis (median survival time 6.5 vs 4.9 months, $p=0.0393$). Patients in the stereotactic surgery group were more likely to have a stable or improved Karnofsky Performance Status (KPS) score at 6 months' follow-up than were patients allocated WBRT alone (43% vs 27%, respectively; $p=0.03$). By multivariate analysis, survival improved in patients with an RPA class 1 ($p<0.0001$) or a favourable histological status ($p=0.0121$) .

Thus , they concluded that : WBRT and stereotactic boost treatment improved functional autonomy (KPS) for all patients and survival for patients with a single unresectable brain metastasis .

Aoyama et al. 2006 : -

Aoyama. H and his participants enrolled a randomized controlled trial (Aoyama. H. et al. JAMA . 2006) of 132 patients with 1 to 4 brain metastases, each less than 3 cm in diameter, enrolled at 11 hospitals in Japan between October 1999 and December 2003 .

Their aim was To To determine if WBRT combined with SRS results in improvements in survival, brain tumor control, functional preservation rate, and frequency of neurologic death .

Their findings were that : The median survival time and the 1-year actuarial survival rate were 7.5 months and 38.5% (95% confidence interval, 26.7%-50.3%) in the WBRT_SRS group and 8.0 months and 28.4% (95% confidence interval, 17.6%-39.2%) for SRS alone ($P=.42$). The 12-month brain tumor recurrence rate was 46.8% in the WBRT_SRS group and 76.4%for SRS alone group ($P_.001$). Salvage brain treatment was less frequently required in the WBRT_SRS group ($n = 10$) than with SRS alone ($n = 29$) ($P_.001$). Death was attributed to neurologic causes in 22.8% of patients in the WBRT_SRS group and in 19.3% of those treated with SRS alone ($P=.64$). There were no significant differences in systemic and neurologic functional preservation and toxic effects of radiation .

And they concluded that : Compared with SRS alone, the use of WBRT plus SRS did not improve survival for patients with 1 to 4 brain metastases, but intracranial relapse occurred considerably more frequently in those who did not receive WBRT.

Consequently, salvage treatment is frequently required when up-front WBRT is not used .

Aoyama et al. 2007 : -

Aoyama .H and his participants enrolled a prospective randomized controlled trial (Aoyama H, et al. Int J Rdiat Oncol Biol Phys. 2007) of 132 patients with 1 to 4 brain metastases , with the aim , To determine how the omission of whole brain raditherapy affects the neurocognitive function of patients have been treated with stereotactic radiosurgery) . And to achieve this objective , they assessed the neurocognitive function using the Mini-Mental State Examination .

Their findings were that : there were statistically significant differences for tumor volume , extent of tumor , age , and karnofsky performance status ; and there were improvements of ≥ 3 points in Mini-Mental State Examination of 9 WBRT+SRS patients and 11 SRS-alone patients ; and the 12- ,24- ,and 36-months actuarial free rate of 3-point drop in the MMSE was (76.1% , 68.5% , 14.7% in WBRT+SRS group , and 59.3% , 51.9% , and 51.9% in SRS-alone group , respectively ; and the average duration until deterioration was 16.5 months in the WBRT+SRS group and 7.6 months in the SRS-alone group . And finally , in the interpretation of the results , they concluded that : For most brain metastatic patients , control of the brain tumor is the most important factor for stabilizing the neurocognitive function. However, the long term adverse effects of WBRT on the neurocognitive function might not be negligible .

Chang EL, et al. Lancet Oncol. 2009 : -

Chang EL and his participants enrolled a randomized controlled trial (Chang EL, et al. Lancet Oncol. 2009) of 58 patients with brain metastases , and they stratified the patients by recursive partitioning analysis class, number of brain metastases, and radioresistant histology .

Their primary end point was neurocognitive function:objectively measured as a significant deterioration (5 point drop) in hopkins verbal learning test-revised (HVLTR) total recall at 4 months .

Their findings were that : the WBRT+SRS group patients were more likely to show a decline in learning and memory function (mean posterior probability of decline 52%) at 4 months than the SRS alone group patients (mean posterior probability of decline 24%) . At 4 months there were 4 deaths (13%) in the SRS alone group , and 8 deaths (29%) in the WBRT+SRS group . 73% of patients in WBRT+SRS group were free from CNS recurrence at 1 year , compared with 27% of patients who received SRS alone . In the SRS+WBRT group , one case of grade 3 toxicity was attributed to radiation treatment ; and in SRS alone group , one case of grade 3 toxicity and 2 cases of grade 4 toxicity were attributed to radiation treatment .

In the interpretation of the results , they concluded that : patients treated with WBRT+SRS were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group of patients who received SRS alone . Initial treatment with a combination of SRS and close clinical

monitoring is recommended as the preferred treatment strategy to better preserve learning and memory in patients with brain metastases .

Kocher et al. 2011 : -

Kocher et al. in 2011 compared patients with 1–3 brain metastases, excluding small-cell lung cancer, and stable extracranial disease that were randomized to an observational cohort or WBRT cohort following initial treatment with either SRS or surgery. Of the 199 patients in the radiosurgery group, 100 patients were allocated to observation, and 99 were allocated to WBRT. Among patients treated with surgery or SRS initially, there was no significant difference ($P = 0.71$) in the time to performance status decline for the observation group (10 months) versus the WBRT group (9.5 months). Similarly, overall survival times were not significantly different ($P = 0.89$) between the observation and WBRT arms (10.9 versus 10.7, resp.). They concluded adjuvant WBRT reduces intracranial relapses and neurologic deaths but fails to improve the duration of functional independence and overall survival after SRS or surgical treatment of cerebral metastases .

Lei Duan et al. 2014 : -

Lei Duan with a group of researchers directed Meta analysis (published at Asian Pacific Journal of Cancer Prevention, Vol 15, 2014) , with the aim To evaluate the effect of whole brain radiation (WBRT) combined with stereotactic surgery (SRS) versus stereotactic radiosurgery alone for patients with brain metastases . where They perform a statistical analyses for 4 randomized controlled trials including 903 patients .

Their findings were that : there were a statistically significant lowering of the local recurrence rate (OR=0.29, 95%CI: 0.17~0.49), new brain metastasis rate (OR=0.45, 95%CI: 0.28~0.71) and symptomatic late neurologic radiation toxicity rate (OR=3.92, 95%CI: 1.37~11.20) in the WBRT+SRS group . And no statistically significant difference existed in the 1-year survival rate (OR=0.78, 95%CI: 0.60~1.03) .

They concluded that : The results indicate that whole brain radiotherapy combined with stereotactic radiosurgery has advantages in local recurrence and new brain metastasis rates, but stereotactic radiosurgery alone is associated with better neurological function. However, as the samples included were not large, more high-quality, large-sample size studies are necessary for confirmation .

Chapter three

MATERIALS AND METHODS

A literature search was carried out for Randomized Controlled Trials comparing SRS alone versus WBRT and SRS boost for the initial management of adult patients with newly diagnosed brain metastases (single or up to 4).

The search terms used were : whole brain radiotherapy, metastases tumor of brain or brain metastases or brain metastasis, stereotactic radiotherapy or stereotactic radiosurgery. In addition, the references of included studies and of review articles were reviewed to identify additional articles not found by the initial search.

The inclusion criteria were as follows:

- any randomized controlled trial on the treatment of brain metastases using WBRT combined SRS and SRS alone that has been published .
- included participants 18 years of age or older .
- patients definitely diagnosed as having brain metastases as study subjects.

3-1-DATA EXTRACTION

The eligible studies were reviewed for study characteristics and clinical relevance . The following information were extracted onto standardized data collection forms: author, trial title and year of

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publication, study design, number of participants and their characteristics.

3-2-Study Design

This study is a Meta-Analysis for clinical trials. Initially , 96 articles were reviewed under the search strategy and data extraction methods. Duplicated studies were removed . Non-clinical randomized studies and irrelevance studies were excluded by reading the title and abstract .

Finally 3 largest randomized controlled clinical trials conducted to-date : the Asian trial by Aoyama et al. ,2006; the North American trial by Chang et al. ,2009; and the European trial by Kocher et al. ,2011 ; were included . A total of 364 patients were evaluated for this meta-analysis. .

Note : Importantly, for the RCT by Kocher et al, the treatment arms randomizing to surgery alone versus surgery followed by WBRT were excluded for this analysis, and only the data from the SRS alone versus WBRT and SRS boost randomization were included.

3-3-THE OUTCOMES

The meta analyses were applied separately on the following outcomes :

1-year survival rate, local recurrence rate, symptomatic late neurologic radiation toxicity rate , and new brain metastases rate

3-4-STATISTICAL ANALYSIS

Heterogeneity between studies was anticipated due to different methods of analysis, different lag exposures, and population

differences. Meta-analyses was done using an online effect size calculator based on the reference: Practical Meta-Analysis, by David B. Wilson, { David.B Wilson , 2001} .

The data were analyzed using logged odds ratio (**OR** logged) and finally converted into the combined odds ratio (OR) , judging values of (OR) less than 0.5 to suggest significant difference that addition of WBRT had reduce the specific clinical outcome , and values more than 1.5 to suggest significant difference that addition of WBRT had increase the specific clinical outcome .

Statistical heterogeneity between studies was evaluated using the Q test and the I^2 statistic, judging values of I^2 less than 25% to be minimal, less than 50% to be moderate, and 50% or greater to be substantial.

Where Q and I^2 were calculated by the following equations, {David.B Wilson,2001}

$$Q = \{ \sum [W_i \times (OR_{log_i})^2] \} - \frac{[\sum (W_i \times OR_{log_i})]^2}{\sum W_i} \quad \text{---- (1)}$$

$$\text{and } I^2 = \frac{Q - (N - 1)}{Q} \times 100\% \quad \text{----}$$

(2)

Where :

N is the number of the studies

OR_{log_i} is the logged adds ratio in the study (i)

W_i is the weight assigned to study (i) , which is given by

$$W_i = 1/V_i$$

----- (3)

[V_i is the within study variance for study (i)]

Then : If there was no statistically significant heterogeneity in a given set of data, the fixed effects model was used for meta-analysis , where the combined logged adds ratio (**OR** logged)_c could be calculated by the following equation

$$(\text{OR logged})_c = \frac{\sum [W_i \times (\ln \log i)]}{\sum W_i} \quad \text{-----(4)}$$

And finally, (**OR** logged)_c was converted into the combined odds ratio (OR) as following

$$(\text{OR}) = e^{(\ln \log)_c}$$

----- (5)

While , If the results of trials showed heterogeneity, the random effects model was used , where the weight W_i would be adjusted to include the between study variance (T) as following :

$$*W_i = 1 / (V_i + T)$$

----- (6)

$$\text{Where , } T = \frac{Q - (N - 1)}{\sum W_i - \frac{\sum (W_i^2)}{\sum W_i}}$$

----- (7)

Then , the combined logged adds ratio (**OR** logged)_c could be calculated by the following equation, {11}

$$(\text{OR logged})_c = \frac{\sum [i W_i \times (i \log i)]}{\sum W_i}$$

----- (8)

And finally, $(\text{OR logged})_c$ was converted into the combined odds ratio (OR) according to equation (5) as following

$$(\text{OR}) = e^{(\text{logged})_c}$$

Chapter four

Results

Of the 3 RCTs, the pooled analysis for Survival rate could only be performed on data from the Aoyama and Chang studies, and yielded no significant difference in Survival between the groups (table 2) with an OR of 0.54.

For local recurrence rate, and new brain metastases rate, the analysis was performed on data from all the 3 studies. and the results showed that there were significant differences favoring WBRT and SRS boost in reducing the local recurrence rate of the treated brain metastases (table 4) with an OR of 0.36, and in reducing distant new brain metastases rate with an OR of 0.44. For the secondary outcome, symptomatic late neurologic radiation toxicity rate, the analysis was performed on data from Aoyama study and Chang study. And the results showed that, there was a significant difference between the two groups with an OR of 3.84 (table 8).

*Outcomes of the meta-analysis

Table 1 : Frequency table of the 1-Year Survival Rate

Study	Group	Survivor	Died	Total
Aoyama	SRS + WBRT	25	40	65
	SRS alone	19	48	67
Chang	SRS + WBRT	6	22	28
	SRS alone	19	11	30

Table 2: the results of the Meta-analysis of 1-Year Survival Rate:

The study	OR logged	variance	weight	Weight*	Odds Ratio (95%CI)
Aoyama	0.457	0.1385	7.22	0.37	1.58(.76, 3.27)
Chang	-1.846	0.3557	2.81	0.34	0.16(.05, 0.51)

Total

OR=0.54

Heterogeneity: $Q = 10.7$, $df=1$, $I^2 = 90\%$

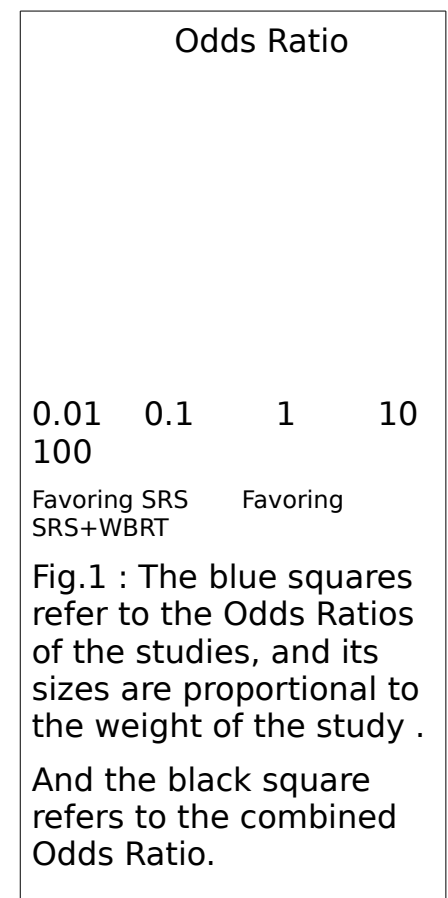


TABLE 3 : Frequency table of the local recurrence

Study	Group	Recurrence	Control	Total
Aoyama	SRS + WBRT	2	63	65
	SRS alone	6	61	67
Chang	SRS + WBRT	0.4	27.6	28
	SRS alone	10	20	30
Kocher	SRS + WBRT	14	85	99
	SRS alone	28	72	100

TABLE 4 .the results of the Meta-analysis of local recurrence Rate:

The study	OR logged	variance	Weight	Odds Ratio (95%CI)
Aoyama	-1.131	0.6989	1.43	0.32(0.06, 1.66)
Chang	-3.541	2.6862	0.372	0.03(0.00, 0.72)
Kocher	-0.86	0.1328	7.53	0.42(0.21, 0.87)

Total

OR=0.36

Heterogeneity: $Q = 2.57$, $df=2$, $I^2= 22\%$

Odds Ratio

0.01 0.1 1 10 100

Favoring SRS +WBRT
Favoring SRS

Fig.2 : The blue squares refer to the Odds Ratios of the studies, and its sizes are proportional to the weight of the study .

And the black square refers to the combined Odds Ratio.

TABLE 5 : Frequency table of the distant new brain metastases recurrence

Study	Group	Recurrence	Controlled	Total
Aoyama	SRS + WBRT	21	44	65
	SRS alone	34	33	67
Chang	SRS + WBRT	8	20	28
	SRS alone	17	13	30
Kocher	SRS + WBRT	26	73	99
	SRS alone	43	57	100

TABLE 5 .the results of the Meta-analysis of distant new brain metastases Rate:

The study	OR Logge d	variance	Weight	Odds Ratio (95%CI)
Aoyama	-0.77	0.1301	07.69	0.46(0.23, 0.94)
Chang	-1.18	0.3107	03.22	0.31(0.10, 0.91)
Kocher	-0.75	0.093	10.75	0.47(0.26, 0.86)

Total

OR=0.44

Heterogeneity: $Q = 0.49, df=2, I^2 = 0\%$

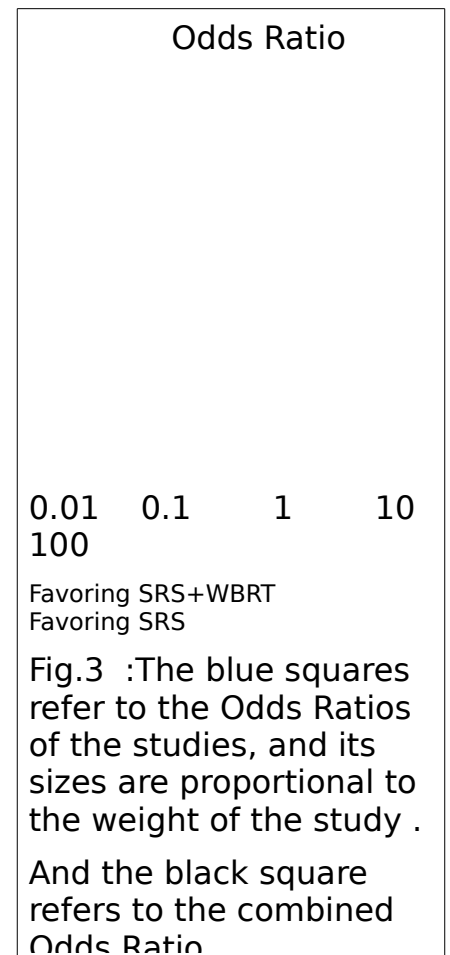


TABLE 7 : Frequency table of the Symptomatic Late Neurologic Radiation Toxicity

Study	Group	Affected	Not affected	Total
Aoyama	SRS + WBRT	7	58	65
	SRS alone	3	64	67
Chang	SRS + WBRT	9	19	28
	SRS alone	2	28	30

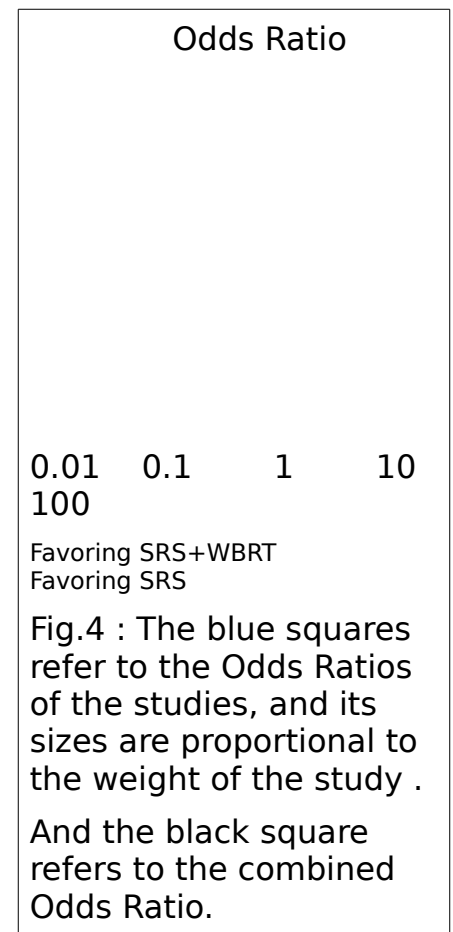
TABLE 8 .the results of the Meta-analysis of Symptomatic Late Neurologic Radiation Toxicity Rate :

The study	OR logged	variance	Weight	Odds Ratio (95%CI)
Aoyama	0.946	0.5091	1.96	2.57(0.64, 10.42)
Chang	1.892	0.6995	1.43	6.63(1.29, 34.16)

Total

OR=3.84

Heterogeneity: $Q = 0.74$,df=, $I^2 = 0\%$



Chapter five

Dissection , conclusions , & recommendations

5-1-Discussion :

Fundamentally, those Randomized Controlled Trials evaluating SRS alone to WBRT plus SRS boost were designed to answer the question of the need for WBRT when local control is optimized by using SRS in each treatment arm. The clinical aim of SRS alone was to avoid the potential side effects associated with WBRT, notably neurocognitive decline.

In this meta-analysis , All the 3 trials evaluated the local recurrence rate, there was no heterogeneity among them ($Q=2.57$, $I^2 = 22\%$), the fixed effects model was used, the results showed that there was a significant statistics difference between the two groups ($OR=0.36$), table (4), Fig.2. Also, All the 3 trials reported the new brain metastases rate, there was no heterogeneity among them ($Q=0.49$, $I^2 = 0\%$), the fixed effects model was used, the results showed that there was a significant statistics difference between the two groups ($OR= 0.44$) , table (6), Fig.3 . Therefore; in this meta-analysis, it was concluded that the addition of WBRT to SRS significantly reduces local tumor recurrence rate , and distant new brain metastases rate .

These results are biologically sound as subclinical microscopic disease in the brain remains untreated without WBRT, resulting in a greater risk of new brain metastases with time. This

observation has been confirmed by Randomized Controlled Trials evaluating prophylactic cranial irradiation (PCI) in lung cancer patients, such as A meta-analysis published by Van der Linden , which indicates that PCI reduces the incidence of brain metastases and prolongs brain metastases-free period.

This reported reduction in local tumor recurrence when adding WBRT to SRS was expected given that the additional dose delivered by the WBRT serves to intensify the SRS dose given to the tumor.

Symptomatic late neurologic radiation toxicity - such as learning decline and memory loss - was reported in two studies :

A randomized control trial (Aoyama et.al , 2007) that tested the neurological function using the strategy of mini-mental status examination (MMSE) indicates that WBRT was effective at preventing the deterioration of neurological function in an early phase after treatment. However, to long-term survivors, WBRT could be a cause of continuous deterioration of neurological function .

Also , (Chang et. al ,2009) evaluated neurocognition using Hopkins Verbal Learning Test - Revised (HVLT -R) which is a validated neurocognitive instrument to determine the impact on the neurocognitive function , and reported that there was a significant improvement in learning and memory function at 4 months in those treated with SRS alone .

The analysis was pooled on the above 2 studies, and there was no heterogeneity between them ($Q=0.74$, $I^2 = 0\%$), the fixed effects

model was used, the results showed that there was a significant statistics difference between the two groups ($OR=3.84$), table (8), Fig.4 . , Therefore; in this meta-analysis, it was concluded that addition of WBRT to SRS significantly increases the late neurologic radiation toxicity rate. thus, favoring SRS alone for better functional preservation rates .

This increase in the neurologic radiation toxicity rate when adding WBRT to SRS was also expected; because the WBRT increases the dose to healthy tissues, as it is delivered to the target with a lower precision compared with SRS ;

; Therefore, It could be concluded that it is the treatment effect of WBRT that affects neurocognition as opposed to the conjecture that brain metastases recurrence is the major source of neurocognitive decline . - this is supported by a published randomized controlled trial on prophylactic cranial irradiation, which reported that a worse learning and memory neurocognitive function was observed after WBRT after PCI , despite the lower incidence of metastases in the PCI arm compared with the controls ,{Gore E , 2005} .

About the main primary end point , the 1-year Survival Rate , there were 2 studies (Aoyama et al., 2006; Chang et al., 2009) that including 190 patients reported the 1-year survival rate, heterogeneity was existed among them ($Q=10.7$, $I^2 = 90\%$), the random effects model was used, the results showed that there

was no significant statistics difference between the two groups (OR=0.54, 95%CI: 0.05 ~ 5.4) , table (2). , Fig.1 .

Although this result was not considered significant (50% improvement could not be detected), but one can consider SRS alone is better ; this could be explained by the adverse effects of WBRT on the neurocognitive function . The results of a similar meta-analysis conducted by Sahgal also favoring SRS with a significant difference; but just for patients of 50 years old and younger,{Sahgal , 2015},where they classify the patients by age as the most important prognostic factor !! . Their way for classification was the big limitation for their study , where the recursive partitioning analysis classification is considered better than classification by age .

In this meta-analysis , it was concluded that there was no significant difference – where it was less than 50% - as well as this difference might not be due to the effects of the WBRT, rather might be due to the prognostic factors of the patients that significantly affect the survival rate , where almost half of the patients in the included studies were different with respect to histology and prognosis .

Furthermore , the distribution of the patients by age, recursive partitioning analysis (RPA), and number of brain metastases cannot equalize these heterogeneities between the groups. Thus,

the best method to equalize and balance the factors related to the tumor itself is to perform a randomized study in patients with same tumor histology and prognostic factors . Although this is the best way to demonstrate the beneficial or detrimental effect of WBRT, but it is difficult to complete this proposed trial , knowing the fact that even the three nationally randomized trials could enroll only 364 patients , So, further studies should focus on finding best method for classification of the patients .

5-2-Limitations :- This meta-analysis has several limitations :-

Firstly, for the secondary outcome – the neurologic radiation toxicity – the analysis was performed on data from 2 studies those used different neurocognitive tests those are not directly comparable - where the MMSE is not regarded an appropriate measure of neurocognition but of dementia .

Also, Patients were from different countries, as a result, there might be some differences exist among them. Additionally, the radiation dose they received, their age, primary tumor, number of brain metastases and RPA class were totally different, these factors produced potential threats to this meta-analysis. And so, the apparent detrimental effect of adding whole-brain radiation therapy to stereotactic radiosurgery may be the result of inhomogeneous distribution of the patients with respect to histology and prognosis rather than the effect of the treatment itself .

5-3- Conclusions :-

Based on the results of this meta-analysis , it could be concluded that

Addition of whole brain radiation therapy to stereotactic radiosurgery significantly reduces the local tumor recurrence and distant new brain metastases recurrence . but increases the late neurologic radiation toxicity especially the neurocognitive decline such as decline in learning and memory function .

On other hand , the addition of whole brain radiation therapy to stereotactic radiosurgery yields no significant improvement in survival when it is compared to stereotactic radiosurgery alone .

Of note , more studies with large sample sizes should be carried out for confirmation . as well as further studies should be focused on finding the best way for classification of the patients .

5-4- Recommendations :

Finally , (- Because the tumor control is the main goal - and till more studies with large sample sizes are carried out) , It is recommended that :

The patients with 1 to 4 brain metastases all of which have a diameter less than 4 Cm , are preferred to be treated with combination of SRS+WBRT - with taking much care for giving the right doses - and using chemical drugs for treating the potential side effects .

This and more studies should be focused on finding best ways for dose delivery - to reduce the possible effects associated with WBRT - , and on finding better chemical drugs for these effects when they occur .

References :-

- Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;363:1665-1672.
- Aoyama H, Shirato H, Tago M, et al (2006). Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*, **295**, 2483-91.
- Aoyama H, Tago M, Kato N, et al (2007). Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys*, **68**, 1388-95.
- Chang EL, Wefel JS, Hess KR, et al (2009). Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*, **10**, 1037-44
- Gore E (2005). Rtog 0214: a phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small cell lung cancer. *Clin Adv Hematol Oncol*, **3**, 625-6.

- Higgins JPT, Green S, et al (2008). Cochrane handbook for systematic reviews of interventions, version 5.0.2. Chi Chester, West Sussex: The Cochrane Collaboration and John Wiley & Sons.
- Kocher M, Soffiatti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952- 26001 study. *J Clin Oncol* 2010;29:134-141.
- Kondziolka D, Patel A, Lunsford LD, et al. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys* 1999;45: 427-434.
- Lei Duan^{1,2}, Rong Zeng^{1,2}, Ke-Hu Yang , Whole Brain Radiotherapy Combined with Stereotactic Radiotherapy Versus Stereotactic Radiotherapy Alone for Brain Metastases: a Meta-analysis , *Asian Pac J Cancer Prev*, **15 (2)**, 911-915.
- Linskey ME, Andrews DW, Asher AL, et al (2010). The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*, **96**, 45-68.
- Practical meta-analysis , David.B Wilson , 2001 .
- Rades D, Kueter JD, Hornung D, et al (2008). Comparison of stereotactic radiosurgery (SRS). alone and whole brain radiotherapy (WBRT). plus a stereotactic boost (WBRT+SRS). for one to three brain metastases. *Strahlenther Onkol*, **184**, 655-62.

- Radiosurgery Practice Guideline Initiative Stereotactic Radiosurgery for Patients with Metastatic Brain Tumors(radiosurgery Practice Guideline Report # may-2008)
- Sahgal A, Larson D, Knisely J. Stereotactic radiosurgery alone for brain metastases. *Lancet Oncol.* 2015;16:249-50
- Sneed PK, Suh JH, Goetsch SJ, et al (2002).A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys*, **53**, 519-26
- Tsao M, Xu W, Sahgal A (2012). A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer*, **118**, 2486-93.
- Van Der Linden YM, Van Kempen ML, Van Der Tweel I, et al (2001). Prophylactic cranial irradiation in limited disease small-cell lung cancer in complete remission: a retrospective analysis. *Respir Med*, **95**, 235-6.

Appendix-1 : Characteristics of the Included studies :-

Study(year)	Patients		Number of Brain metastases	Radiation dose(Gy)	
	SRS	WBRT+S		SRS	WBRT+S
Aoyama et . 2006	67	RS 65	1 - 4	22~2 5	RS 30
Chang et al. 2009	30	28	1 - 3	19~2 0	30
kocher et al.2011	100	99	1 - 3	19~2 0	30

Study(ye ar)	% single brain metastasi s SRS alone Vs WBRT+S RS	Local Control at 1 year SRS alone Vs WBRT+SRS Vs WBRT+S RS	Distant Control At 2 years SRS alone Vs WBRT+S RS	Overall survival At 1 year SRS alone Vs WBRT+S RS	Neurocognitive Outcomes
Aoyama et al.2006	49% vs. 48%	72.5%vs88. 7%	36.3% vs 58.5%	28.4% vs 38.5%	3 point drop in MMSE (Not significant) Mean Posterior Probability of decline at 4 months: 24% vs 52%
Chang et	60% vs.	67% vs	45% vs	63% vs	
al. 2009	54%	100%	73%	21%	

kocher et al.2011	68% vs. 66%	72% vs 86%	57%vs74 %	Not significant	(Significant) Not reported
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