

The role of prophylactic radiotherapy in prevention of brain metastasis

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Abstract:

Introduction:

Despite of these side effects, many studies concluded that the benefits of prophylactic brain radiation in prevention and delaying the spread of cancer overcome its harmful effects. This review aimed to evaluate the literature assessing the role of prophylactic radiotherapy in prevention of metastasis to the brain tissues, measure its incidence and the overall survival rates in patient with lung cancer to provide evidence-based data

Methods:

Electronic search was performed in Medline using Pubmed resulted in 107 eligible studies. The titles and abstracts of all these articles, was screened and based on this reading studies excluded due to irrelevancy or duplication.

Results:

Search of the literature identified total of 107 studies, after exclusion of irrelevant, duplicated and review studies, five studies were included in the review as they met the inclusion criteria. The included studies pointed to assess the effect of prophylactic radiotherapy in avoidance of brain metastasis. All included studies were randomized controlled trials. Total numbers of 1399 patients were recruited in the included studies. Age of patients range from 39 up to 84 years old or more. Small-cell lung cancer was the primary cancer in three of the included studies. One of the included studies assessed patients with non-small cell lung cancer and one study included patients with small cell anaplastic bronchogenic carcinoma.

Conclusions:

The use of prophylactic radiotherapy is effective in reduction of incidence of brain metastasis, but it had no role in rising of the overall survival.

Keywords: Brain, tumor, radiation, radiotherapy, prophylaxis

Introduction:

The incidence of the secondary brain metastasis is associated with poor prognosis in most cases^(1, 2). Several studies reported short duration of survival after diagnosis of brain metastasis. In spite of development of treatment procedures in patients with brain metastasis, the high mortality rates remain a serious barrier to upgrade survival rates^(3, 4).

Prophylactic radiotherapy was used to prevent metastasis of primary lesions to the brain tissues. Many randomized control trials were conducted to measure the effect of the prophylactic radiation in prevention of brain metastasis and improvement of the survival rate⁽⁵⁻⁹⁾. Small cell lung cancer is characterized by high metastasis rates, especially to the brain⁽¹⁰⁾. It was also noted that non-small lung cancer metastasis to the brain is a common problem that affect the quality of life and the survival rate^(11, 12). In spite

of high prevalence of brain metastasis, there is an ongoing debate about the importance of prophylactic radiation of brain, doubts about its toxicity and impact on survival rates^(13, 14). Deterioration of the brain functions and memory loss and intelligent deficit are serious side effects of radiation when used as a prophylaxis to prevent brain metastasis^(6, 8). Despite of these side effects, many studies concluded that the benefits of prophylactic brain radiation in prevention and delaying the spread of cancer overcome its harmful effects.

This review aimed to evaluate the literature assessing the role of prophylactic radiotherapy in prevention of metastasis to the brain tissues, measure its incidence and the overall survival rates in patient with lung cancer to provide evidence-based data. These data can help the healthcare providers and improve the quality of treatment benefits of prophylactic brain radiation

in prevention and delaying the spread of cancer overcome.

Methods:

Electronic search was performed in Medline using Pubmed with search strategy "brain metastasis" and radiotherapy and (mortality or death or survival or cure) (filters= clinical trials and custom date from 1992 till now). The titles and abstracts of all these articles, was screened and based on this reading studies excluded due to irrelevancy or duplication. This review was registered using Prospero (Registration of Systematic Reviews in University of York).

Results:

Search of the literature identified total of 107 studies, after exclusion of irrelevant, duplicated and review studies, five studies were included in the review as they met the inclusion criteria. The included studies pointed to assess the effect of prophylactic radiotherapy in avoidance of brain metastasis.

All included studies were randomized controlled trials. Total number of 1399 patients were recruited in the included studies. Age of patients range from 39 up to 84 years old or more. Small-cell lung cancer was the primary cancer in three of the included studies ^(5, 6, 8). One of the included studies assessed patients with non-small cell lung cancer ⁽⁷⁾ and one study included patients with small cell anaplastic bronchogenic carcinoma ⁽⁹⁾.

Prophylactic cranial irradiation (PCI) was used in all of the included studies ⁽⁵⁻⁹⁾. All of the included studies measured the incidence of brain metastasis. In one study the incidence of brain metastasis in the PCI group was less than the control group during the first two years and after 5 years of follow up ⁽⁶⁾. In another study the incidence of brain metastasis was 44% in the PCI group and 51% in the control group ⁽⁸⁾. Another author reported incidence of brain metastasis of 7.7% in the PCI group and 18% in the observational group ⁽⁷⁾.

Figure (1): Prisma diagram of the included studies in the systematic review

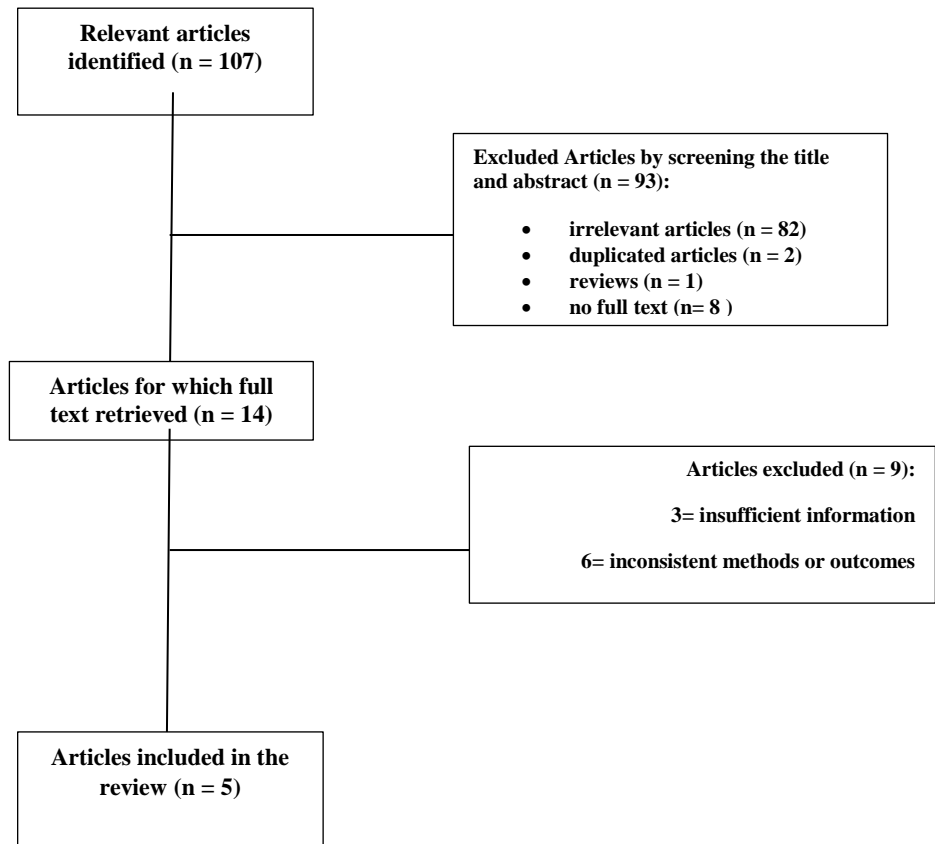


Table (1): Summary of the findings of the included studies

Study	Study design	Sample size	Age of patients (Mean and Range)	Type of primary cancer	Radiotherapy technique used for prevention of metastasis	Incidence of brain metastasis (%)	Incidence of another metastasis (%)	Duration from radiotherapy until incidence of brain metastasis	Effect of prophylactic radiotherapy	Overall survival
Arriagada <i>et al.</i> ⁽⁶⁾	A randomized controlled trial	511	Mean±SD= 56 ± 9	SCLC	(PCI)	37% in control group (no PCI), 20% in the PCI group, 5 years brain metastasis, 59% in control group (no PCI), 43% in the PCI group	26% in control group (no PCI), 32% in the PCI group, 5 years metastasis, 53% in control group (no PCI), 50% in the PCI group	Within the first 2 years	PCI decreased the risk of brain metastasis and death	3 years survival= 18% in control group (no PCI), 26% in the PCI group, 5 years survival=15% in control group (no PCI), 18% in the PCI group
Laplanche <i>et al.</i> ⁽⁸⁾	A randomized clinical trial	221	Less than 70 years Mean 58 ±9 in PCI group 57±9 in control group	SCLC	(PCI)	44% (C.I=32–57%) in the PCI group 51% C.I= 38–63%) in the control group.	53% in the PCI group 58% in the control group	4 years	No significant difference between the two groups in the incidence of brain metastasis and survival	22% in the PCI group 16% in the control group
Gore <i>et al.</i> ⁽⁷⁾	A randomized clinical trial	356	Range (39-84), Median 63 in the PCI group and 62 in the observational group	NSCLC	(PCI)	7.7% in the PCI group 18.0% in the observational group	3.3% in the PCI group 10.7% in the observational group	1 year	PCI decreased the rate of brain metastasis but did not improve the overall survival or disease-free survival	6 months survival=74% in PCI group, 69.7% in the observational group, 12 months survival=56.4% in PCI group, 51.2% in the observational group
Rubenstein <i>et al.</i> ⁽⁵⁾	A randomized clinical trial	197	36% < 65 years and 64% More than or equal 65	SCLC	(PCI)	28%	41%	Not reported	PCI have accomplished a significant reduction in the incidence of brain metastasis with little toxicity.	1-year survival= 68% in the PCI group and 33% in the observational group, 2 years survival= 46% in the PCI group and 13% in the observational group
Hansen <i>et al.</i> ⁽⁹⁾	A randomized controlled trial	114	Range= 42-70 years old Median= 60 years old	Small Cell Anaplastic Bronchogenic Carcinoma	6 MeV linear accelerator	21.7%	Not reported	210 - 300 days	No difference was observed between the two groups of patients in survival time, response rate, duration of response, or relapse pattern, including the frequency of brain metastasis	21 patients survived after 18 months of follow up

SD: Standard deviation, SCLC: Small cell lung cancer, NSCLC: Non-small cell lung cancer, PCI: Prophylactic cranial irradiation

Discussion:

Rubenstein *et al.* reported that 28% of patients underwent PCI have developed brain metastasis⁽⁵⁾. Hansen *et al.* found an incidence of 21.7% of brain metastasis in the included patients⁽⁹⁾.

Regarding the duration from radiotherapy until incidence of brain metastasis, the minimum duration was one year as found by Gore *et al.*⁽⁷⁾. The findings of Arriagada *et al.* study elaborated the early occurrence of brain metastasis within the first two years⁽⁶⁾. The brain metastasis occurred after 4 years as found by Laplanche *et al.*⁽⁸⁾. Hansen *et al.* reported the occurrence of brain metastasis between 210-300 days⁽⁹⁾. One study did not report the time of onset for brain metastasis⁽⁵⁾.

Metastasis to sites other than brain was reported in four of the included studies. Arriagada *et al.* reported 32% metastasis to other sites in the PCI group and 26% in control group⁽⁶⁾. Laplanche *et al.* found the incidence of metastasis to sites other than the brain to be 53% in the PCI group and 58% in the control group⁽⁸⁾. Gore *et al.* reported the incidence of metastasis to sites other than the brain to be 3.3% in the PCI group and 10.7% in the observational group⁽⁷⁾. Rubenstein *et al.* reported in their study that; 41% of metastasis was to sites other than the brain⁽⁵⁾. Hansen *et al.* did not report the incidence of metastasis in other sites⁽⁹⁾.

Regarding the effect of prophylactic radiotherapy, it was noted that PCI decreased the risk of brain metastasis in three of the included studies⁽⁵⁻⁷⁾. Arriagada *et al.* reported that the use of PCI decreased both death and risk of brain metastasis⁽⁶⁾. Gore *et al.* found that the PCI decreased the rate of brain metastasis but did not improve the overall survival or disease-free survival⁽⁷⁾. While, Laplanche *et al.* concluded that no significant difference was between the PCI and the control groups in the incidence of brain metastasis and survival⁽⁸⁾. Similarly, Hansen *et al.* reported no difference of prophylactic radiation in the response duration and degree, survival time, frequency of brain metastasis and the relapse pattern⁽⁹⁾.

The overall survival was calculated in all included studies. Arriagada *et al.* found 26% of patients in PCI group survived for 3 years while only 18% of control group survived for this period. They reported that 5 years survival rate

to be 18% in the PCI group and 15% in control group⁽⁶⁾. Laplanche *et al.* found an overall survival of 22% in the PCI group and 16% in the control group⁽⁸⁾. The 6 months survival and 12 months survival rates were measured by Gore *et al.* as they reported 6 months survival of 74% and 69.7% in PCI group and the observational group, respectively. While, they found 12 months survival rate of 56.4% and 51.2% in the PCI group and observational group, respectively⁽⁷⁾. Rubenstein *et al.* measured the 1 and 2 years overall survival rates and they found one year survival rates of 68% and 33%, and the two years survival rates of 46% and 13%, for PCI and observational groups, respectively⁽⁵⁾. Hansen *et al.* found that only 21 patients survived after 18 months of follow up⁽⁹⁾.

Prophylactic radiation is thought to be effective in prevention of brain metastasis and improving survival rates. This review aimed to assess all trials that measured the effect and benefits of using radiation therapy as a prophylactic treatment to prevent metastasis to the brain in patients with lung cancer. It aims at providing of evidence-based conclusion about its benefits and importance.

All patients recruited in the included studies were adult diagnosed with primary lung cancer included both small cell and non-small cell lung cancer⁽⁵⁻⁹⁾. A prophylactic radiation to prevent brain metastasis was used in all included studies. The follow up aimed to assess the survival rate, the incidence of brain metastasis and the time taken until development of brain metastasis.

A study found that 28% out of 197 patients with small cell lung cancer developed brain metastasis⁽⁵⁾. Metastasis to other sites than brain occurred to 41% of the studied patients. This study concluded that the incidence of brain metastasis showed significant reduction after use of prophylactic radiation. Furthermore, it was noted the presence of a low risk of toxicity that followed using radiation as a prophylaxis of brain metastasis⁽⁵⁾. Gore *et al.* reported that only 7.7% of the included patients with non-small lung cancer developed brain metastasis after one year compared to 18% of observational group⁽⁷⁾. Metastasis to other sites occurred in both groups. According to these results Gore *et al.* concluded that incidence of brain metastasis decreased after the application of prophylactic

radiation ⁽⁷⁾. Similarly, **Arriagada *et al.*** ended up with the consistent results ⁽⁶⁾. While one study reported development of brain metastasis in less than one year after the prophylactic radiation ⁽⁹⁾. Moreover, it was noted that out of 114 patient received prophylactic radiation, 21.7% developed brain metastasis. In this study the author did not find significant variations between the patients who received the prophylactic radiation and the other group. Similar study done by Laplanche *et al.* ended up with consistent results, as they found that the incidence of brain metastasis after 4 years of the follow up revealed no considerable variations between the treatment and the observational groups ⁽⁸⁾.

Regarding the overall survival rate after using radiation therapy as a prophylaxis to prevent metastasis to the brain, only one study found that the use of prophylactic radiation decreased the death rate ⁽⁶⁾. Other included studies did not find significant differences between the treatment and the control groups ^(5, 7-9). Finally, we concluded that the use of prophylactic radiotherapy is effective in reduction of incidence of brain metastasis, but it had no role in rising of the overall survival.

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