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REVIEW

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Examining the survival benefit of radiation therapy on leptomeningeal carcinomatosis and identifying factors associated with survival benefit of whole-brain radiation therapy

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Abstract

Today, there are no conclusive data on the survival benefit from radiation therapy for leptomeningeal carcinomatosis (LMC) patients. The purpose of this article is mainly two folds: first, to report the survival benefit of radiation therapy (RT) in LMC patients with breast or lung as primary cancer and second, to identify the factors of LMC patients that had survival benefit from whole brain radiation therapy (WBRT).

Systematic literature review was performed. Search terms included 'Leptomeningeal', 'prognostic factors' and 'lung' or 'breast'. Literatures were included if patient profile was reported. Specifically, age, median survival, diagnosis time line, type of cancer, received treatments, performance score, and systemic disease were sought after. Literature were excluded if they were a) case reports, b) written in language other than English, or c) not including patient profile.

For LMC patients with primary breast cancer, 7 studies were found since 1991 that met searching criteria. Factors which would allow breast cancer-caused LMC patients to benefit from WBRT with survival are identified with statistical significance. They include Karnofsky (KPS) >60, Intrathecal (IT) chemotherapy, systemic therapy, hormonal receptor status and severity of systemic disease. Patients who met aforementioned criteria and received WBRT had longer median survival (17 weeks vs 11.9 weeks, $P = 0.015$). Similarly, 10 studies were found that met searching criteria for non-small cell lung cancer (NSCLC) caused LMC. Beneficial factors for NSCLC-caused LMC are identified. They include IT chemotherapy, KPS > 60, and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment. Patient who met these criteria had longer median survival when received WBRT (17.6 weeks vs 12.2 weeks, $p = 0.0412$).

KEYWORDS

breast cancer, leptomeningeal carcinomatosis, lung cancer, whole brain radiation therapy (WBRT)

1 | INTRODUCTION

The prevalence of leptomeningeal carcinomatosis (LMC) is reported to be approximately 5% of all patients with cancer.[1] LMC is a detrimental complication of cancer involving the central nervous system (CNS). Without treatment, the median survival from diagnosis is 4–6 weeks, and with treatment, it is doubled to 8–12 weeks.[2–5] The incidence of LMC has been increasing for the past several decades. Such increase is partially due to: (i) improved diagnostic modalities, including high-resolution magnetic resonance imaging and computed tomography, and (ii) improved cancer treatment.[6] Paradoxically, with cancer treatment improvement, the risk of LMC increases, as the chance for cancer cells to invade the subarachnoid space is increased over time. Today, there is no clear standard of care to treat LMC

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patients. Due to the relatively short median survival, a careful weighing between prolonging life while worsening the quality of life and maintaining the pain-free quality of life without prolonging life needs to be evaluated and discussed with the patient.

As of today, intrathecal (IT) chemotherapy is the mainstay of LMC treatment.[7,8] The most common method is using the Ommaya reservoir and directly injecting chemotherapeutic agents into the cerebrospinal fluid (CSF). Many have reported that IT has survival benefit for the good-risk patient group.[9–11] Radiation therapy (RT), often used in conjunction with the IT, is used to target symptomatic sites and to relieve mass effect.[12] However, the effectiveness of RT on overall survival has not been as conclusive as IT treatment. This is partially due to poor prognosis with a short median survival. Such a combination, along with rapid deterioration of neurological functions, makes randomized trials very challenging. Therefore, RT is mainly considered to be supplemental therapy to IT. For the past decades, multiple retrospective studies were published with conflicting conclusions on the survival benefit of RT. This is mainly because multiple factors contribute to not only clinical progression, but also survival. Therefore, it is important to take such complex dynamics into account when treating/assessing LMC patients.

The purpose of the present review is twofold. The first purpose is to examine the effectiveness of RT in prolonging the survival of LMC patients. Second is for different primary cancers, to identify constituting factors that would allow LMC patients to have survival benefit when treated with RT. Differentiating factors for breast cancer and lung cancer are crucial as treatment planning, including RT changes. Based on identified factors, a general algorithm for breast cancer and lung cancer will be devised.

1.1 | LMC management overview

Figure 1 shows the simplified treatment algorithm for LMC patients. Such an algorithm was derived from National Comprehensive Cancer Network guidelines shown in detail in Figure 2.[13] Once the diagnosis of LMC is made, the patient is further stratified into either poor-risk or good-risk groups, as shown. For poor-risk groups, the therapy is mainly supportive with palliative therapy. In contrast, for the good-risk group patients, the goal is to control the cancers by aggressively treating the patients. Treatment goals include improving or stabilizing the neurological function, improving the quality of life, or prolonging life.[14] Achieving any of the three listed treatment goals would be considered as such treatment being effective. For patients who are receiving whole-brain RT (WBRT), it is recommended to cover the meningeal space, including the lamina cribrosa and basilar cistern.[14]

1.2 | CSF flow study, RT and survival benefit

Before the intra-CSF chemotherapy is started, a CSF flow study is recommended, as shown in Figure 1. As cancerous cells invade the subarachnoid space, they can block the CSF outflow. More than 50% of LMC patients are reported to have CSF flow abnormality, and as high as 70% has been reported by Grossman et al.[15] As outflow is disturbed, hydrocephalus develops and intracranial pressure can be elevated. This explains why >50% of LMC patients report headache as their chief complaint.[16] More importantly, without normal CSF flow, intra-CSF chemotherapy is not recommended due to the possibility of developing neurotoxicity. Intra-CSF chemotherapy relies on normal CSF flow to be distributed throughout the entire neuraxis. CSF flow obstruction will cause toxic chemotherapeutic agents to build up within the subarachnoid space, a phenomenon described as "protected site effect" by Glantz et al., and cause more toxicity than benefit.[17] It has been reported that such toxicity affects the survival of LMC patients.[18] In order to assess CSF flow, either technetium or indium-DTPA is used.[19] Once the dye is injected, images are taken in such an order that certain compartments should be clear of dye with the elapse of time. Typically, dyes reach the basilar cisterna, lumbosacral sac, and leave the entire ventricle within 10 min, 2 h, and 24 h, respectively.[15,17,20]

The sensitivity, selectivity, and accuracy of CSF flow study is >99%, whereas detecting flow abnormality using magnetic resonance imaging or computed tomography is 60% and 30%, respectively.[21] Once the flow abnormality is detected, focal RT is used to correct the obstruction.[22] The localized spot is mapped to the brain scan images and radiation is used to treat the obstruction. Glantz et al.[17] and Chamberlain et al.[23] reported survival benefit of RT in LMC patients with flow abnormality. Table 1 summarizes the finding of Glantz et al.[17] Similar findings have been reported in Grossman et al.[15] and Chamberlain et al.[24]

RT, hence, indirectly provides survival benefit by resolving the obstruction and by allowing effective IT treatment to take place. CSF flow study has been incorporated as part of the LMC treatment guidelines. Based on the aforementioned findings, the diagnostic and survival algorithm for CSF outflow abnormality can be designed as shown in Figure 2. If the obstruction is corrected, which is shown in the red box from Figure 2, survival benefit can result.

1.3 | Breast cancer-caused LMC

Breast cancer is the most common solid tumor causing LMC, as it comprises 35% of total solid tumor-based LMC patients.[4,6,25] The breast cancer-caused LMC rate has been increasing for the past decade, mainly due to improvement in breast cancer treatments.[1,26] For breast cancer, tumor cells directly invading the subarachnoid space is thought to be the most likely cause of dissemination to the meninges.[27,28] The median survival of patients with breast cancer is the highest compared with other primary cancers, at 9–30 weeks.[10,29,30] Most common histological types and biological subtypes for breast cancer LMC are lobular and triple-negative, respectively.[31–33] This is contrary to the fact that the most common biological subtype in the general breast cancer population is luminal A.[31] A summary of breast cancer-caused LMC is summarized in Table 2.

For patients with normal CSF outflow, IT therapy has shown survival benefit for breast cancer-caused LMC patients.[10,17,29,30,34] In contrast, the survival benefit of RT on breast cancer LMC patients has not been clearly established. In order to study the benefit of RT on the overall survival of LMC patients with primary breast cancer, seven studies meeting the search criteria were found dating from 1991 to 2013. All seven papers discussed RT as a treatment modality, and discussed

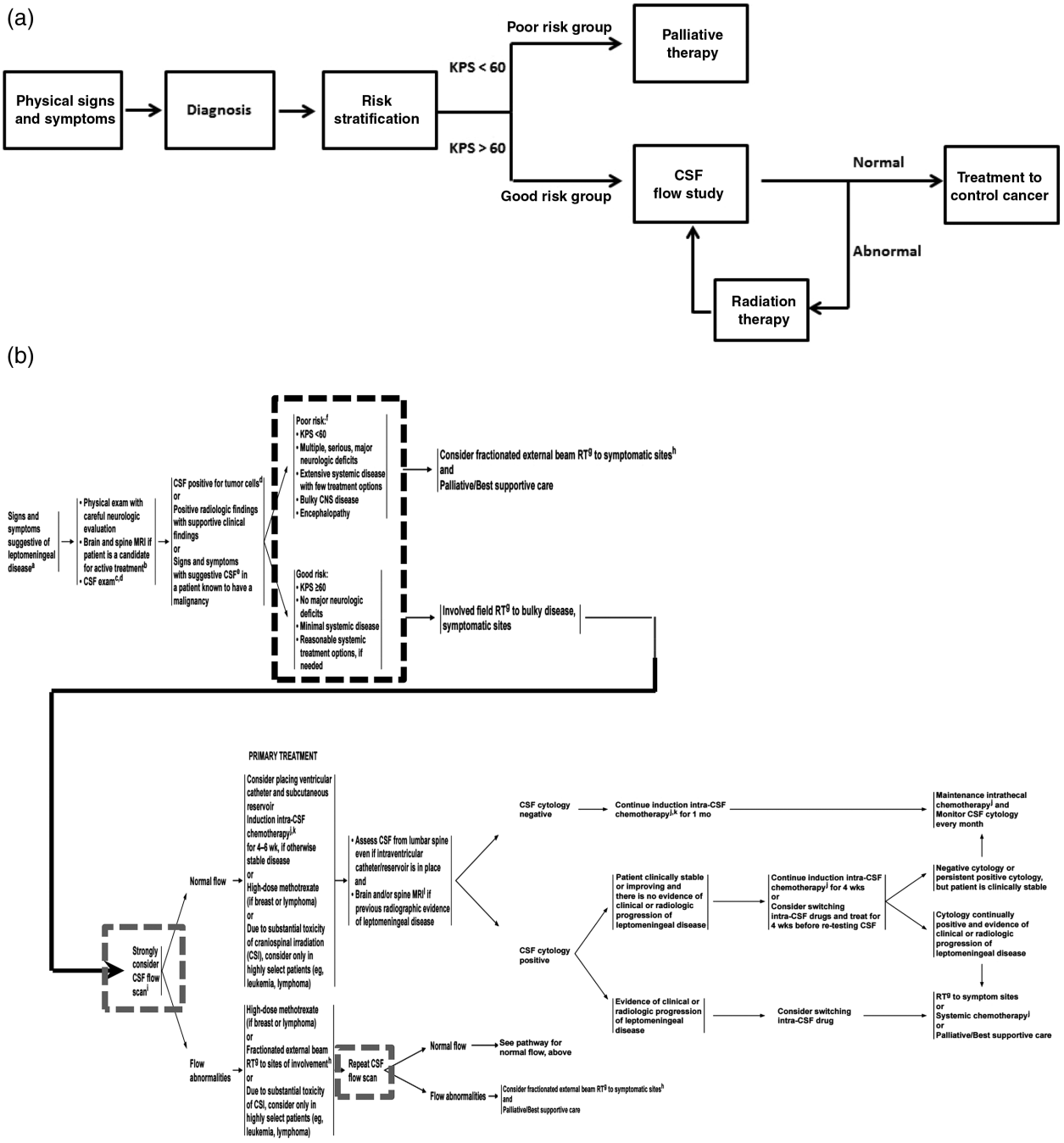


FIGURE 1 Treatment Overview. (a) Simplified algorithm of the leptomeningeal carcinomatosis treatment. (b) Complete algorithm of the leptomeningeal carcinomatosis treatment from the National Comprehensive Cancer Network. CSF, cerebrospinal fluid; KPS, Karnofsky Performance Scale

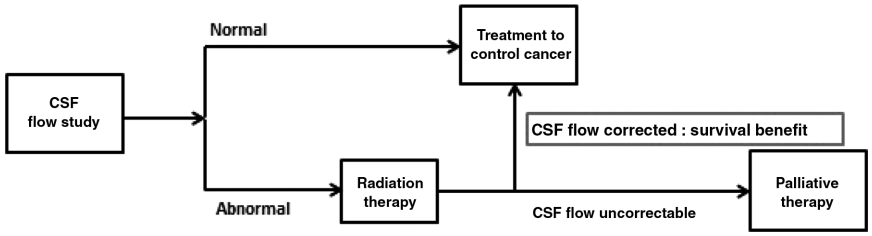


FIGURE 2 Cerebrospinal fluid (CSF) flow abnormality correction with radiation therapy and survival benefit

TABLE 1 Survival benefit after cerebrospinal fluid flow correction with radiation therapy

Flow Status	Survival
Normal ($n = 13$)	6.9 months
Abnormal but corrected with RT ($n = 9$)	13 months
Abnormal but uncorrectable ($n = 9$) RT, radiation therapy.	0.7 months

TABLE 2 Summarizing the breast cancer-type leptomeningeal carcinomatosis

Prevalence (among solid tumor LMC)	35%
Median survival	9–30 weeks
Most common histological subtype	Lobular
Most common biological subtype	Triple negative
Most common treatment for OS	IT chemotherapy

IT, intrathecal; LMC, leptomeningeal carcinomatosis; OS, overall survival.

prognostic factors for LMC patients with breast cancer. Table 3 summarizes the seven studies and the patient demographics for each study.

As can be seen from Table 3, just two studies by Rudnick et al.[35] and Niwinski et al.[31] showed survival benefit with WBRT. These two studies were compared with the other five studies. Table 4 shows the comparison of patients who experienced survival benefit with WBRT. Statistically significant factors include Karnofsky Performance Scale (KPS) score, IT chemotherapy, systemic therapy, hormonal receptor status, and severity of systemic disease. Patients that benefited from WBRT had longer median survival of 17 weeks compared with 11.9 weeks, with statistical significance ($P = 0.015$). Patients in the benefited group used more multimodality treatments, including intra-CSF, systemic, and WBRT (53% vs 33%). Also, the systemic metastatic involvement was substantially lower in the benefited group (46% vs 67%). Based on Table 4, an algorithm can be created for those who can potentially benefit with longer survival from the RT (gray box), as shown in Figure 3.

1.4 | Lung cancer-caused LMC

Lung cancer is the second most common cause of LMC from solid tumors, comprising approximately 20%.[36] Without treatment, survival is 4–6 weeks. With treatment, survival can be extended to 16–24 weeks.[20] Non-small cell lung cancer (NSCLC) is the most common cause, constituting >80 % of LMC patients.[37] For NSCLC-caused LMC, retrograde flow to the vertebral and paravertebral venous system with an increased intrathoracic pressure is believed to be the most common cause of gaining access to the subarachnoid space.[27,28] The most common histological type is adenocarcinoma, making up >85% of lung cancer-caused LMC. Current treatment modalities for NSCLC-caused LMC includes IT chemotherapy, systemic therapy, RT, and epidermal growth factor tyrosine kinase inhibitor (EGFR-TKI). Like breast cancer-caused LMC, there is no standard treatment protocol at present. A summary of lung cancer-caused LMC is shown in Table 5.

IT chemotherapy has consistently shown survival benefit for patients with NSCLC-caused LMC.[38–41] For the past decade, adding EGFR-TKI targeted therapy to the treatment has shown substantial improvement in survival consistently. Nakamura et al.[42] showed patients receiving the EGFR-TKI regimen had a median survival of 13 months compared with 4 months for those without EGFR-TKI treatment.[42] Similar results were reported from Morris et al.,[39] Lee et al.,[40] and Xu et al.[43] In contrast, the survival benefit from RT has been reported with inconsistent conclusions. In order to make a more concrete conclusion on the survival benefit of RT of LMC patients with primary lung cancer, 10 studies from 1998 to 2015 were reviewed. All 10 studies included WBRT as a treatment modality and discussed prognostic factors for LMC patients with NSCLC. Table 6 summarizes the results.

TABLE 3 Summary of breast cancer patients with leptomeningeal carcinomatosis published in the past 20 years

	Boogerd (1991)	Jayson (1994)	Fizazi (1996)	Rudnick (2007)	Gauthier (2010)	De Azevedo (2011)	Niwanski (2013)
No. patients	44	35	68	67	91	60	118
Median age (years)	57	45	52	49	53	46	49
Median survival	12	11	9.5	16	14	13	18
time from BR to LMC (months)	38	20	30	27	22	17.9	25
KPS score >60	NA	NA	34	41	NA	47	80
KPS score <60	NA	NA	34	26	NA	12	38
Intra-CSF Chemo	44	1	41	57	80	41	93
systemic	20	NA	42	41	72	13	80
WBRT	22	8	18	33	26	22	66
WBRT benefit on OS	No	No	No	Yes	No	No	Yes
Ductal carcinoma	NA	NA	29	23	52	47	54
Lobular	NA	NA	29	22	23	13	32
ER/PR-positive	17	NA	13	37	60	28	49
Systemic metastasis	28	NA	47	29	67	47	57
Most common	Bone	NA	Bone	Bone	Bone	Bone	Bone

BR, brain radiation; CSF, cerebrospinal fluid; ER, estrogen receptor; KPS, Karnofsky Performance Scale; LMC, leptomeningeal carcinomatosis; NA, not available; PR, progesterone receptor; WBRT, whole-brain radiation therapy.

TABLE 4 Analysis of factors associated with survival benefit of whole-brain radiation therapy

	WBRT with survival benefit (2 studies)	WBRT without survival benefit (5 studies)	*P*-value
No. patients	185	207	
Median age	49	50.6	0.68
Median survival (weeks)	17	11.9	0.015
Time from BR to LMC (months)	26	25.5	0.94
KPS score >60	121 (65%)	109 (52%)	0.01
KPS score <60	64 (34%)	97 (46%)	0.0137
Intra-CSF Chemo	150 (81%)	127 (61%)	<0.0001
systemic	121 (65%)	90 (43%)	<0.0001
WBRT	99 (53%)	70 (33%)	<0.0001
Ductal carcinoma	77 (41%)	76 (36%)	0.55
Lobular	54 (29%)	42 (20%)	0.49
ER/PR-positive	86 (46%)	41 (19%)	0.01
Systemic metastasis	86 (46%)	140 (67%)	<0.0001

BR, brain radiation; CSF, cerebrospinal fluid; ER, estrogen receptor; KPS, Karnofsky Performance Scale; LMC, leptomeningeal carcinomatosis; PR, progesterone receptor; WBRT, whole-brain radiation therapy.

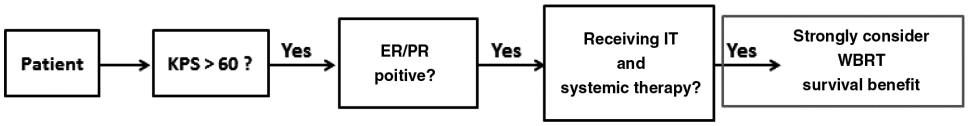


FIGURE 3 Algorithm for recommending radiation therapy for survival benefit based on seven studies. ER, estrogen receptor; KPS, Karnofsky Performance Scale; PR, progesterone receptor; IT, intrathecal; WBRT, whole-brain radiation therapy

TABLE 5 Summarizing the leptomeningeal carcinomatosis with primary lung cancer

Prevalence (among solid tumor LMC)	20%
Median survival	12–18 weeks
Most common histological subtype	NSCLC
Most common cytology	Adenocarcinoma
Most common treatment for OS	Intrathecal

LMC, leptomeningeal carcinomatosis; NSCLC, non-small cell lung cancer; OS, overall survival.

Of the 10 studies, five reported survival benefit with WBRT. Table 7 shows the comparison of LMC patients who experienced survival benefit with WBRT.

Statistically significant factors include IT chemotherapy, performance score, and EGFR TKI treatment. The median survival was higher among patients who benefited longer survival with WBRT (17.6 weeks vs 12.2 weeks). The performance score was substantially better for those who benefited the longer survival with WBRT. Not surprisingly, the group with benefited survival from WBRT had a substantially higher percentage treated with EGFR-TKI (36% vs 18%). Based on such findings, a general algorithm for a patient with LMC with NSCLC who can potentially experience survival benefit from WBRT (gray box) can be created, as shown in Figure 4.

2 | DISCUSSION

To our knowledge, this is the first synthesized literature review analyzing factors that have statistical significance in regard to survival benefit of RT in LMC patients. Many retrospective studies have been published with different conclusions on the relationship between RT and its survival benefit. Such conflicting results are not surprising given the nature of retrospective study, the complex treatment regimen of LMC patients, and the varying degree of prognostic factors associated with patient populations in different studies. Therefore, systematic review of published studies to investigate the inconsistent conclusions on survival benefit of RT and identifying factors that lead to the discrepancy would benefit clinicians in providing optimal treatment to LMC patients.

The role of RT for LMC patients is twofold. The first role is to facilitate a successful treatment course of IT chemotherapy by correcting CSF outflow obstruction, which exists in >50% of LMC patients.[15] The second role is to relieve symptoms and mass effects. RT has shown survival benefit in both categories.[17,31,40]

Indirect survival benefit of RT by correcting CSF outflow obstruction is reported by multiple studies.[15,17,44] In study by Glantz et al., patients who started with abnormal CSF flow and corrected with RT ($n = 9$) had longer median survival than those with normal CSF flow ($n = 13$) with statistical significance (13 months vs 7 months).[17] In addition to correcting obstruction, performance and extent of systemic disease involvement were reported to have contributed to longer survival compared with normal-flow patients. However, in the same study, patients with CSF outflow abnormality that was not correctable with RT ($n = 9$) had a much shorter median survival compared with those corrected (13 months vs 0.7 months). Among the uncorrectable population, just two out of nine patients had significant performance degradation with cranial nerve involvement compared with the

TABLE 6 Summary of non-small cell lung cancer patients with leptomeningeal carcinomatosis published in last 20 years

	Chamberlain (1998)	Chuang (2008)	Park (2010)	Nakamura (2012)	Morris (2012)	S Lee (2013)	Xu (2015)	Umemura (2012)	Gwak (2011)	Riess (2014)
No. patients	32	34	50	67	125	149	108	91	105	30
Median age (years)	57	60	62.5	64	59	58	61	62	56	58
Median survival (weeks)	20	5.1	22	17	12	14	21	14	12	12
Time-to-diagnosis (months)	7	7.1	10.2	12	15	11.1	12	12.2	17	16.4
Adenocarcinoma	24	32	42	67	97	135	85	83	101	30
Intra-CSF	32	2	48	37	7	109	42	27	59	2
systemic	20	20	22	37	20	29	59	51	53	21
WBRT	9	10	27	29	46	67	49	21	18	19
WBRT Survival	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No
ECOG PS ≤2	32	17	35	37	63	129	87	52	50	14
ECOG >2		17	15	30	62	20	21	39	55	16
EGFR-TKI	0	0	14	37	9	24	42	51	29	21

CSF, cerebrospinal fluid; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR-TKI, epidermal growth factor tyrosine kinase inhibitor; WBRT, whole-brain radiation therapy.

outflow-corrected group. Otherwise, the performance characteristics and systemic involvement were very similar between two groups. Hence, there is a clear survival benefit if CSF outflow obstruction can be corrected. Therefore, it is important to emphasize how RT plays a vital role in allowing IT chemotherapy to work properly, which is the mainstay of LMC treatment today. Today, the National Comprehensive Cancer Network guidelines strongly recommend a CSF flow study once a LMC patient is categorized into the good-risk group.

For LMC patients from breast cancer, seven studies were identified that met our search criteria. Two of seven studies concluded that WBRT has survival benefit. Using survival benefit with WBRT as a variable, two groups were created. Group 1 ($n = 185$) was from two studies that showed survival benefit, and group 2 ($n = 207$) from studies that did not show survival benefit with the WBRT.[31,35] Group 1 had a longer median survival compared with group 2 (17.6 vs 12.2 weeks) with statistical significance. Factors that showed statistical significance between group 1 and group 2 included KPS >60, IT chemotherapy, systemic treatment, WBRT, and the severity of systemic disease including metastases to other organs.

In general, KPS score is a strong prognostic factor for all cancer treatments.[45] All seven studies reported KPS >60 to be a positive prognostic factor for overall survival regardless of the survival benefit from the WBRT. KPS score is directly related to the status of the involvement, and a recent study showed that there is a correlation between high KPS score and survival benefit from WBRT for patients with CNS metastasis.[46,47] Therefore, higher-performing patients benefiting more from WBRT treatment is predictable to a certain degree. Multimodality treatment (IT + RT + systemic) was another factor. Group 1 received more triple modality treatment than group 2 (55% vs 33%). Multiple studies report a synergistic effect when multiple treatment modalities are combined. Systemic chemotherapy and targeted therapy help eradicate disease in systemic sites that IT cannot reach due to the blood–brain barrier. Also, RT can provide deeper penetration into CNS tissue compared with IT, whose penetration is limited to approximately 2–3 mm.[48] The extent of metastasis to other organs also played a significant role in whether patients would experience survival benefit or not from WBRT. Group 1 had substantially lower systemic metastasis compared with group 2 (46% vs 67%). The explanation for such results aligns with the KPS score. A low KPS score often correlates with more extensive systemic involvement.[49] Hence, it is not surprising that factors contributed to WBRT survival benefit included both the KPS score and the severity of systemic involvement with statistical significance.

For LMC patients with NSCLC primary, 10 studies were identified. Factors that showed statistical significance with WBRT survival benefit were KPS score, WBRT, IT chemotherapy, and EGFR-TKI treatment. KPS score and IT chemotherapy share the same rationale with breast cancer patients. For the past decade, the use of EGFR-TKI for NSCLC whose mechanism involves activating mutations in exons 19 and 21,[50] has shown substantial survival benefit.[39,40] When EGFR-TKI is combined with WBRT, synergistic effects have been reported with survival benefit for patients with NSCLC with brain metastasis.[51,52] A study from Welsh et al. showed increased survival by 11.8 months when treated with EGFR-TKI with WBRT.[51] It is believed that WBRT injures

TABLE 7 Analysis of factors associated with survival benefit of whole-brain radiation therapy

	WBRT with survival benefit (5 studies)	WBRT with no survival benefit (5 studies)	*P*-value
No. patients	465	326	
Median age (years)	61.5	60.4	
Median survival (weeks)	17.6	12.2	0.0412
Time-to-diagnosis (months)	14.24	12.5	0.56
Adenocarcinoma	412 (87%)	284 (87%)	0.94
Intra-CSF	226 (49%)	102 (31%)	<0.0001
systemic	198 (43%)	134 (41%)	0.29
WBRT	193 (41%)	102 (31%)	0.0063
ECOG PS ≤2	340 (73%)	176 (54%)	<0.0001
ECOG >2	125 (26%)	150 (46%)	<0.0001
EGFR-TKI	168 (36%)	59 (18%)	<0.0001

CSF, cerebrospinal fluid; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR-TKI, epidermal growth factor tyrosine kinase inhibitor; WBRT, whole-brain radiation therapy.

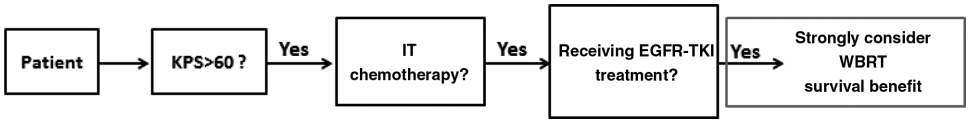


FIGURE 4 Algorithm for recommending radiation therapy for survival benefit based on 10 studies for leptomeningeal carcinomatosis non-small cell lung cancer. EGFR-TKI, epidermal growth factor tyrosine kinase inhibitor; KPS, Karnofsky Performance Scale; IT, intrathecal; WBRT, whole-brain radiation therapy

the blood–brain barrier, and allows better penetration and higher concentration of EGFR-TKI agents into CNS parenchyma.[43,53,54]

3 | CONCLUSION

The role of RT and its survival benefit for LMC patients are reviewed. Factors that are associated with WBRT survival benefit are systemically derived and extensively discussed. Though multiple factors are identified, KPS score seems to be the single most important prognostic factor that governs the survival benefit associated with WBRT. Algorithms for LMC patients with breast or lung cancer are devised. Such algorithms can serve as a general guideline to assess the patient profile that can potentially have survival benefit by receiving WBRT.

CONFLICT OF INTEREST

The authors declare that they had read the article and there are no competing interests.

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