Original Article

Focal conformal fractionated radiotherapy *vs.* radiosurgery for lung cancer patients with limited brain metastases

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Background: For lung cancer (LC) patients with limited brain metastases (LBM), radiosurgery (RS) was the current preferred strategy. We aimed to report our experience regarding an alternative strategy (focal conformal fractionated radiotherapy, FCFRT) for these patients in this cohort study.

Methods: We identified LC patients with LBM treated with either FCFRT or RS within 2016–2019 without prior brain local treatment via in-house databases. The characteristics of patients, disease, treatment, and outcome were retrospectively obtained via chart review and peer review. The 1st day of FCFRT or RS was the index date. Overall survival (OS) was calculated from the index date to the last date of contact or death via the Kaplan–Meier method. Log-rank test was used in univariate analyses (UVA) whereas Cox regression method was used in the multivariate analyses (MVA). The incidence of local progression (LP) or distal brain metastases (DBM) was estimated by the competing risk approach with death as the competing risk.

Results: We identified 23 eligible patients. The median dose/fractionation for FCFRT was 36 Gy/10 fractions. The median dose for RS was 20 Gy. The Lung-molGPA prognostic groups' distribution for these two groups was not statistically different. After a median follow-up of 8 months (range, 1–38 months), the OS was not statistically different in UVA [P value 0.9]. The adjusted hazard ratio of death was 0.96 when FCFRT was compared to RS in MVA (95% CI, 0.21–5.22). There was also no statistical significant difference in LP (P value 0.79) or DBM (P value 0.88).

Conclusions: For LC patients with LBM, the OS was not statistically different for definitive FCFRT or RS. There was also no statistical difference in LP or DBM. Further studies should be considered to clarify the indication of FCFRT.

Keywords: Brain metastases (BM); focal conformal fractionated radiotherapy (FCFRT); lung cancer (LC); radiosurgery (RS)

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Introduction

Brain metastases (BM) occurred frequently in cancer patients, with lung cancer (LC) to be the most common primary site (1). For patients with limited BM (LBM), radiosurgery (RS) [such as gamma knife surgery (GKS)] or whole brain radiotherapy (WBRT) was available options according to current treatment guideline although the former was preferred (2). However, some other approaches such as focal fractionated regimens had been studied in the recent years (1).

In the past, the outcome of LC patients with LBM was still poor even treated with RS. In the two randomized controlled trials (RCTs) included in a systematic review published in 2018 (3), the median overall survival (OS) for LC patients with LBM treated with RS was 6.6 or 8.6 months (4,5) respectively, with no benefit of adding WBRT.

Focal conformal fractionated radiotherapy (FCFRT) had been investigated for LBM. When we searched in PubMed using keywords "(((brain metastases) OR (brain metastasis)) AND (conformal) AND ((radiotherapy) OR (radiation therapy))) NOT (whole brain radiotherapy)" in Nov 2019, we identified two relevant studies providing information regarding definitive FCFRT for LBM. Ohtakara and Hoshi had reported median OS 12 months for 24 patients whereas 13.9 months was reported by Lockney *et al.* for 195 patients (6,7). However, both studies were not limited to neither LC nor definitive setting. Furthermore, both studies were not compared with RS.

Due to the sparse literatures regarding FCFRT for LBM as mentioned above, especially for LC patients, we aimed to compare the clinical outcomes of LC patients with LBM treated with either definitive FCFRT or RS via retrospective review of patients treated at our institute. We present the following article in accordance with the STROBE Reporting Checklist (available at http://dx.doi.org/10.21037/apm-19-574).

Methods

Study population

Our study was a cohort study. We identified LC patients with LBM but without prior brain local treatment and treated with FCFRT or GKS (the main RS modality in our institute) within 2016–2019 by using in-house prospectively established databases. Our inclusion criteria included: (I) history of histological confirmation of LC; (II) LBM [defined as 1–4 metastases (8)] confirmed in image studies [magnetic resonance image (MRI) or computed tomography (CT) with/without position emission tomography (PET)]; (III) treated with FCFRT or GKS without prior brain local treatment. The characteristics of patients, disease, treatment, and outcome were retrospectively obtained via chart review and peer review. Our study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of our institute [CMUH106-REC3-119 (CR2)]. All participants gave informed consent before their treatments. We declared the patient's personal data have been secured.

Treatment: FCFRT or GKS

Patients in the FCFRT group were treated with 6- or 10- MV linear accelerators. Standard thermoplastic cast was used for immobilization then patients were simulated with CT in the treatment position. Gross target volume (GTV) was defined as the region of LBM in the simulation CT image, 2–5 mm margin with editing was added to form clinical target volume (CTV) for selected patients. We then added 3–5 mm margin for planning target volume (PTV) to be used in intensity-modulated radiotherapy (IMRT) planning. Image-guided radiotherapy (IGRT) was used in the setup of some patients by their preference [in need of out-of-pocket payment]. Patients in the GKS group were treated with standard stereotactic frame to obtain MRI for target delineation. GKS was delivered via the Leksell Gamma Knife C model (Elekta, Stockholm, Sweden).

Statistical analyses

The 1st day of FCFRT or GKS was the index date. OS was calculated from the index date to the last date of contact or death. Local progression (LP) [or distal brain metastases (DBM)] was calculated from the index date to the 1st date of LP (or DBM) confirmed by imaging work-up or the last date of imaging work-up without LP (or DBM). We excluded those cases with missing information. OS was estimated by Kaplan-Meier method and compared by log-rank test in the univariate analysis (UVA). In order to adjust for potential differences in baseline prognostic factors, we used Cox regression method to adjust for the new and validated Lung-molGPA prognostic groups (LMGPG) in the multivariate analyses (MVA) (8-10). The incidence of LP or DBM was estimated by the competing risk approach with death as the competing risk (11). Chis-square test

Table 1 Patient characteristics distribution for patients in overall survival analysis

Characteristics	FCFRT	GKS	P value
Gender			
Male	8	5	1
Female	6	4	
Histology			
AD	11	9	0.25
Non-AD	3	0	
PST			
No	4	5	0.38
Yes	10	4	
CST			
No	2	1	1
Yes	12	8	
Age			
≥70 y/o	3	3	0.64
<70 y/o	11	6	
KPS			
≤70	2	0	0.58
80	7	4	
90–100	5	5	
ECM			
Without	5	2	0.66
With	9	7	
Gene[†]			
Without	6	1	0.18
With	8	8	
LMGPG			
A2	5	5	0.74
A3	6	4	
N2	2	0	
N3	1	0	

[†], positive *vs*. (negative or unknown) for epidermal growth factor receptor mutation or anaplastic lymphoma kinase fusion oncogene. AD, adenocarcinoma; CST, concurrent systemic therapy; ECM, extra-cranial metastasis; FCFRT, focal conformal fractionated radiotherapy; GKS, gamma knife surgery; GPA, graded prognostic assessment; KPS, Karnofsky Performance Score; LMGPG, lung-molGPA prognostic groups (A2: AD 2nd group GPA score 1.5–2; A3: AD 3th group GPA score 2.5–3; N2: non- AD 2nd group GPA score 1.5–2; N3: non-AD 3th group GPA score 2.5–3); PST, prior systemic therapy; y/o, year old.

or Fisher's exact test (when appropriate) were used for comparing categorical variables. Due to the small number of cases (see results), we did not perform additional subgroup or sensitivity analyses. Statistical analysis was performed using software R package "survival" & "cmprsk".

Results

Study population and treatment (Table 1)

We identified 23 patients eligible for analyses (*Figure 1*). Most of them were male, adenocarcinoma, and had received prior or concurrent systemic therapy. The LMGPG distribution was not statistically different for FCFRT *vs.* GKS (P value 0.74). For those treated with FCFRT, the median radiotherapy dose and fraction were 36 Gy (range, 30–50 Gy) and 10 fractions (range, 5–22 months). A few of them used CTV (n=6) or IGRT (n=3). For those treated with GKS, the median marginal dose was 20 Gy [range, 15–22 Gy).

Subsequent treatment and overall clinical outcomes

All patients had received subsequent systemic therapy after FCFRT or GKS, whereas six patients had received additional local treatment during follow-up. At the time of analysis after a median follow-up of 8 months (range, 1–38 months), eight patients were dead. One patient treated with FCFRT was identified to have potential radiotherapy-related complication in need of inpatient care.

OS

The 1- and 2-year OS rate was not statistically different for FCFRT *vs.* GKS in UVA (56% and 56% (FCFRT) *vs.* 65% and 65% (GKS), P value 0.9). The OS curve was shown in *Figure 2*. There was also no statistical difference in MVA with hazard ratio (HR) of death 0.96 when FCFRT was compared to GKS (95% CI, 0.21–5.22).

LP and DBM

The cumulative incidence of LP at 1 and 2 years were 31% and 31% for FCFRT (*vs.* 0 and 50% for GKS) without statistical significance (P value 0.79) as shown in *Figure 3*. The cumulative incidence of DBM at 1 and 2 years were 14% and 14% for FCFRT (*vs.* 17% and 17% for GKS) without statistical significance (P value 0.88) as shown in *Figure 4*.

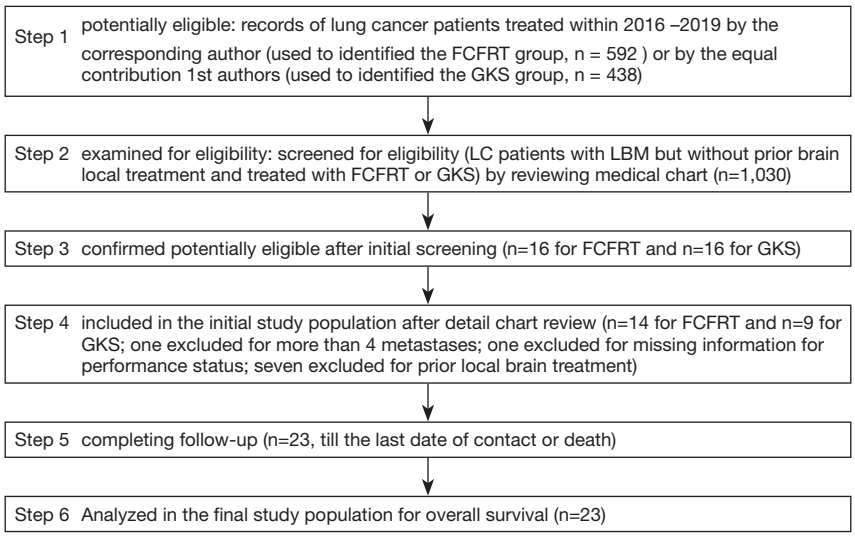

Figure 1 Study flow chart (STROBE format). FCFRT, Focal conformal fractionated radiotherapy; GKS, gamma knife surgery; LBM, limited brain metastasis; LC, lung cancer.

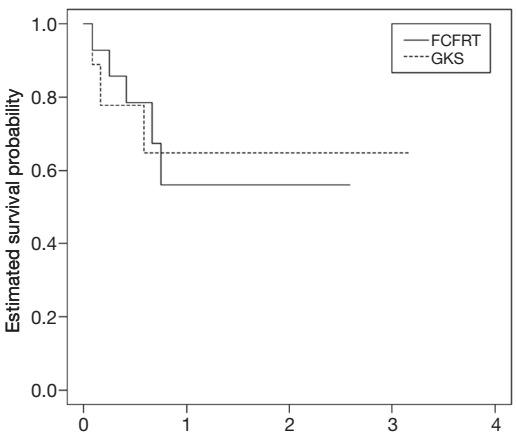

Figure 2 Kaplan-Meier overall survival curve (in years).

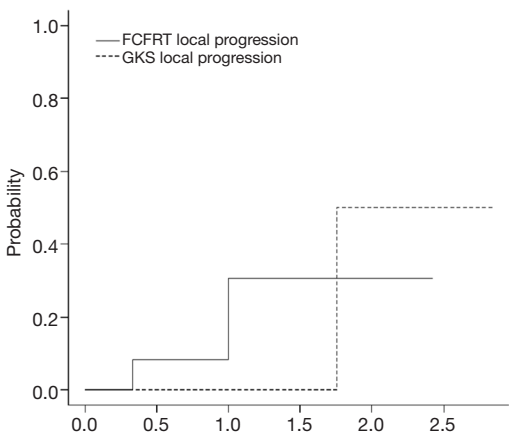

Figure 3 The cumulative incidence of local progression (in years).

Discussion

For LC patients with LBM, we found that the OS was not statistically different for definitive FCFRT or RS using GKS. There was also no statistical difference in LP or DBM. This was the 1st study to compare FCFRT *vs.* RS for LC patients with LBM to our knowledge.

Our results regarding FCFRT were slightly better to the literatures in which 1 year OS around 50% and 2 year OS around 30% were reported (6,7). Our results regarding RS were also slightly better to the literatures in which median OS around seven to nine months was reported (4,5). Therefore, it is likely due to the advancement in the systemic therapy and overall care, which highlights the importance of studying contemporary patients with adjustment for modern prognostic score (8) as did in our study.

There were several limitations of our study. Obviously our sample size was relatively small, and the treatment selection [FCFRT *vs.* RS] was not randomized. Furthermore, cognitive or quality-of-life outcomes were not measured in our study. Therefore, the interpretation of our finding should be cautious, and studies of larger scale with additional outcomes, especially RCTs, should be considered to compare FCFRT *vs.* RS to clarify the indication of FCFRT for LC patients with LBM. However,

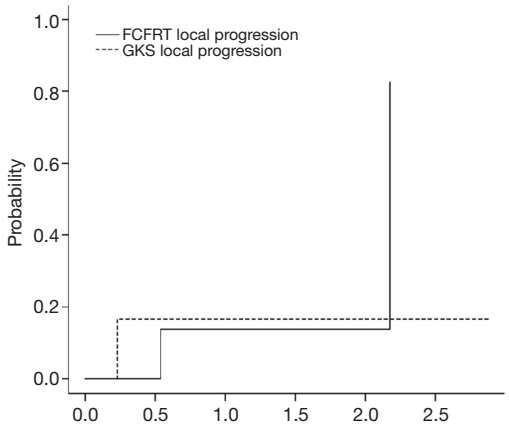

Figure 4 The cumulative incidence of distal brain metastases (in years).

when we searched clinical trial registry [https://clinicaltrials.gov/] in Dec 2019 using keywords (brain metastases | Lung Cancer Stage IV | radiosurgery | Phase 2, 3), we did not identify relevant studies. Therefore, our results provided a tentative evidence to consider FCFRT as an alternative for LC patients with LBM if RS was not favored.

Conclusions

For LC patients with LBM, the OS was not statistically different for definitive FCFRT or RS using GKS. There was also no statistical difference in LP or DBM. Further studies should be considered to clarify the indication of FCFRT.

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Footnote

Reporting Checklist: The authors have completed the STROBE Reporting Checklist. Available at http://dx.doi.org/10.21037/apm-19-574

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-19-574

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-19-574). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Our study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of our institute [CMUH106-REC3-119 (CR2)]. All participants gave informed consent before their treatments. We declared the patient's personal data have been secured.

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