Editorial

Clues to improve the cost-effectiveness of radiotherapy for brain metastases from non-small cell lung cancer: cost reduction, patient selection, and better understanding of neurocognitive deterioration

Hirotake Saito[1], Toshimichi Nakano[2], Hidefumi Aoyama[2]

[1]Division of Radiation Oncology, Niigata University Medical and Dental Hospital, Niigata, Japan; [2]Department of Radiology and Radiation Oncology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Correspondence to: Dr. Hirotake Saito. Division of Radiation Oncology, Niigata University Medical and Dental Hospital, 1-754 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan. Email: 1rtkcyte@med.niigata-u.ac.jp.

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In September 2018, Girard *et al.* published the article 'Extra cost of brain metastases (BM) in patients with non-squamous non-small cell lung cancer (NSCLC): A French national hospital database analysis' (1). They extracted the data of 2,500 metastatic NSCLC patients from the national medical information database and divided the patients into two groups: those with metastases other than brain (n=1,529), and those with BMs (n=971). The study's analyses revealed that the presence of BM at diagnosis contributed to the excessive medical cost of €553 per patient-month, and Girard *et al.* stated that radiotherapy (RT) and palliative care are the principal components of the increased cost.

Their study is of great clinical importance because it provided detailed information on the healthcare costs due to the management of BM from NSCLC. However, we feel that the economic burden of the treatment for BM is emphasized too much, and we are concerned that NSCLC patients with BM might miss the opportunity to receive appropriate treatment. In this editorial, we discuss the cost-effectiveness of cranial RT for BM and we consider several perspectives on the selection of individualized treatment strategies.

The goals of treatment for BM include the relief of neurologic symptoms, the prevention of tumor regrowth, and the maintenance of functional independence. Cranial RT plays an integral role in this context. In the Radiation Therapy Oncology Group (RTOG) 9508 trial by Andrews *et al.*, patients with 1–3 BMs were randomly assigned to either whole-brain RT (WBRT) alone or WBRT followed by a stereotactic radiosurgery (SRS) boost (2). For patients with a single BM, WBRT + SRS significantly improved overall survival (OS) compared to WBRT alone [median survival time (MST) 6.5 *vs.* 4.9 months, P=0.039]. Patients in the WBRT + SRS group were more likely to have a stable or improved Karnofsky Performance Status (KPS) score at 6 months' follow-up compared to the patients assigned to WBRT alone (43% *vs.* 27%, P=0.03).

Aoyama *et al.* evaluated the significance of adding WBRT to SRS in the Japanese Radiation Oncology Study Group (JROSG) 99-1 trial, in which patients with 1–4 BMs were randomly assigned to either SRS alone or SRS + WBRT (3). The 12-month brain tumor recurrence rate was significantly lower in the SRS + WBRT group compared to the SRS-alone group (46.8% *vs.* 76.4%, P<0.001), whereas the OS was not significantly improved with WBRT (MST, 7.5 *vs.* 8.0 months, P=0.42).

In addition, improved intracranial tumor control is associated with stabilized neurocognitive function (NCF). The average duration until the deterioration of patient's Mini-Mental State Examination (MMSE) score was longer in the SRS+WBRT group compared to the SRS-alone group (16.5 *vs.* 7.6 months, P=0.05) (4). However, towards

the 24th month post-RT, the SRS + WBRT patients exhibited clinically meaningful declines in their MMSE scores, which could be a manifestation of RT-induced late neurotoxicity.

The impact of WBRT had long been undetermined in BM patients who are not candidates for SRS, until the results of the QUARTZ trial were published (5). The QUARTZ investigators recruited NSCLC patients with BMs that were unsuitable for surgical resection or SRS and randomly assigned them to either WBRT plus supportive care (SC) including dexamethasone, or SC alone. There was no improvement in OS (MST, 9.2 *vs.* 8.5 weeks, P=0.80) between the two arms. However, it should be highlighted that the subgroup analyses of the QUARTZ study posed a clinically relevant hypothesis; i.e., that the efficacy of WBRT differs based on various clinical factors (6). WBRT significantly improved the OS in younger patients in that study [those <60 years old; hazard ratio (HR) 1.48; 95% confidence interval (CI), 1.01–2.16], and in those with ≥5 BMs (HR 1.37; 95% CI, 1.01–1.86), and in those with high Graded Prognostic Assessment (GPA) scores (2.5–3.0; HR 1.65; 95% CI, 1.04–2.60). The GPA score is calculated based on the patient's age, KPS, the presence/absence of extracranial metastasis (ECM), and the number of BMs (7). These findings suggest that in patients with controlled systemic cancer, a good general condition and a large intracranial tumor volume, successful treatment for BM leads directly to improved survival.

In 1997, Mehta *et al.* published the first cost-effectiveness study of various treatment modalities for the management of BM, and their results demonstrated that the cost-effectiveness of SRS was superior to that of surgical resection (8). There are several strategies to further improve the cost-effectiveness of cranial RT, i.e., a reduction of healthcare costs, the identification of the subgroup of patients who will benefit from RT, and the early detection of adverse events.

Gamma knife radiosurgery requires invasive skull fixation with local anesthesia, and the use of less-invasive methods would help decrease the healthcare costs. For this reason, hypofractionated stereotactic radiotherapy (SRT) provided by a linear accelerator using noninvasive thermoplastic shell fixation has become one of the treatment options (9). It is also important to shorten the overall treatment time. When treating multiple BMs with conventional SRT, the isocenters are placed inside each tumor, and it takes time to move the isocenter from one tumor to another. With the use of single-isocentric rotational volumetric modulated arc therapy (VMAT), multiple BMs can be treated at one time, and the treatment time is shortened compared to traditional multi-isocentric RT plans (10).

To improve the efficacy of RT, the selective use of cranial RT is essential (11). Several factors determine the necessity of RT, including the patient's general condition, ECMs, and epidermal growth factor receptor (EGFR) gene mutations.

In 2012, Sperduto *et al.* proposed a novel prognostic index, the diagnosis-specific GPA (DS-GPA) (12). It is calculated using different clinical factors such as patient age, KPS, number of BMs, presence of ECM, and molecular subtype, by the primary site. A DS-GPA score of 4.0 correlates with the best prognosis, and a DS-GPA score of 0.0 corresponds to the worst prognosis. For selected BM patients with a good general condition and a limited number of ECMs, the combination of SRS and WBRT has the potential to improve intracranial tumor control and OS.

In the secondary analysis of the RTOG 9508 trial comparing WBRT + SRS with WBRT alone in patients with 1–3 BMs, patients were post-stratified by their DS-GPA scores and NSCLC was the dominant primary tumor (13). The patients with high DS-GPA scores (3.5–4.0) showed improved survival when treated with WBRT + SRS compared to those treated with WBRT alone (P=0.05). In the secondary analysis of the JROSG 99-1 trial, Aoyama *et al.* post-stratified NSCLC patients according to their DS-GPA scores and reported that the patients with DS-GPA scores of 2.5–4.0 had longer survival when treated with SRS + WBRT compared to those treated with SRS alone (P=0.04) (14). The survival benefit of adding WBRT was not observed in the patients with low DS-GPA scores (0.5–2.0, P=0.86). The positive impact of WBRT on OS could be explained by improved intracranial tumor control. The addition of WBRT significantly ameliorated the BM-recurrence-free rate in the DS-GPA 2.5–4.0 group (P<0.001).

In patients with metastatic NSCLC harboring activating EGFR mutation, BMs as well as systemic metastases are often treated with first-line EGFR-tyrosine kinase inhibitors (TKIs). Magnuson *et al.* conducted a multi-institutional retrospective analysis and reported that in a multivariate analysis, both first-line SRS (HR 0.39; 95% CI, 0.26–0.58, P<0.001) and first-line WBRT (HR 0.70; 95% CI, 0.50–0.98, P=0.039) significantly improved OS compared to first-line TKI with RT being considered at intracranial progression (15). RT is thus indispensable in the management of EGFR-mutant NSCLC, a distinct biological entity which seems radiosensitive in nature (16).

One of the most clinically relevant late adverse events of WBRT is the deterioration in NCF (4). Among the neurocognitive test batteries used in clinical settings, the MMSE is the most widely used due in part to its convenience. However, the MMSE has several weak points, i.e., a ceiling effect (17) and inadequate sensitivity. In the secondary analysis of the RTOG 0214 trial evaluating prophylactic WBRT for advanced NSCLC, there were greater 12-month declines in the immediate recall (P=0.03) and delayed recall (P=0.008) domains of the Hopkins Verbal Learning Test (HVLT) in the prophylactic WBRT arm compared to the control arm (18). However, there were no significant differences in MMSE scores (P=0.60) between the two arms. The HVLT is superior to the MMSE in detecting subtle changes in NCF. The Response Assessment in Neuro-Oncology (RANO) Working Group has proposed that the revised version of HVLT (HVLT-R) be used in combination with other test batteries to evaluate executive function and processing speed in clinical trials dealing with BMs (19).

Neurocognitive deterioration after WBRT is thought to be caused not only by the toxic effect of irradiation but also by worsening of the patient's general condition. According to the results of a recent randomized trial, the omission of WBRT appears to lead to the preservation of NCF. Brown *et al.* reported that there was significantly less cognitive deterioration at 3 months after SRS alone than after SRS + WBRT (63.5% *vs.* 91.7%, P<0.001) (20). These results should be interpreted with caution. It is of note that the Brown *et al.* study recruited 213 patients (SRS alone, n=111, SRS + WBRT, n=102), but only 57% (63/111) of the patients in the SRS-alone group and 47% (48/102) of the patients in the SRS + WBRT group underwent HVLT-R at 3 months. The NCF was measured at 3 months post-WBRT, a time point at which RT-induced late neurotoxicity is scarcely observed. The selection of the study endpoint might thus be inappropriate.

The deterioration in NCF at a few months post-WBRT is frequently observed in BM patients with worsened general condition. Saito *et al.* analyzed the HVLT-R scores after WBRT and reported that a significant deterioration in the HVLT-R scores at 4 months post-WBRT was observed in the patients who dropped out thereafter (21). The most frequent cause of dropping out was a worsened general condition due to systemic cancer. In contrast, the patients who continued their regular visits until the 8-month examination did not exhibit significant NCF deterioration at 4 months post-WBRT. Therefore, NCF deterioration at a few months post-WBRT might be due to worsening of the patient's general condition and should be distinguished from true RT-induced late neurotoxicity.

In conclusion, RT plays an integral role in the management of BMs from NSCLC. Further efforts should be made to (I) reduce the costs of the use of RT, (II) appropriately select good candidates for RT, and (III) minimize treatment-related toxicities of RT.

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Footnote

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