Statin treatment may lower the risk of postradiation epilepsy in patients with nasopharyngeal carcinoma

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SUMMARY

Objective: This study aimed to clarify the effect of statins on preventing the risk of postradiation epilepsy.

Methods: We performed a retrospective analysis of neurological nasopharyngeal carcinoma patients with a history of radiotherapy. Patients with a history of epilepsy before radiation and those who received prophylactically antiepileptic treatment were excluded. The demographic and clinical data of these patients were collected through chart review. We used Kaplan–Meier analysis (log-rank test) to examine the effect of statins on epilepsy-free survival. Cox regression analysis was utilized to identify independent predictive variables.

Results: Our study included 532 patients (405 males and 127 females) with a mean follow-up of 28.1 months. During follow-up, 471 (88.5%) patients developed radiation-induced brain necrosis (RN). Within a mean latency of 24.1 months, 88 (16.5%) patients experienced epilepsy, of whom 27 (27 of 88, 30.7%) patients suffered from epilepsy before the diagnosis of RN. Thirty-six (36 of 88, 40.9%) cases of epilepsy occurred after RN onset, and in 22 cases (22 of 88, 25.0%) epilepsy was the first presentation of RN. Three patients suffered from epilepsy but did not have RN. Eighty-eight patients in our cohort were treated with statins because of hyperlipidemia or prevention of cardiocerebrovascular diseases, of whom six (6.8%) developed epilepsy, whereas in those without statin, the epileptic rate was 18.5%. Log-rank test found that there was a significant difference in epilepsy-free survival between patients who used statins and those who did not (p = 0.016). After adjusting for confounding variables, multivariate Cox regression analysis revealed that statin use could still significantly reduce the risk of epilepsy after radiation (hazard ratio = 0.36, 95% confidence interval = 0.15–0.82, p = 0.015). However, for the patients who already suffered from RN, statin treatment did not lower the risk of post-RN epilepsy.

Significance: Early statin use may reduce the risk of postradiotherapy epilepsy in patients with nasopharyngeal carcinoma.

KEY WORDS: Radiation, Epilepsy, Statin.
necrosis (RN) is one of the common and serious radiotherapy-related complications. Previous studies have suggested that RN could cause epilepsy. Moreover, radiation could also lead to the occurrence of seizure in healthy brain. Up until now, the treatment strategy of postradiation epilepsy is similar to other secondary epilepsy. Little study focuses on the prevention of postradiation epilepsy. Although there is no clinical evidence about prophylactic antiepilepsy for postradiation epilepsy, we wondered whether there is any drug that is good for both RN and epilepsy.

Because patients receiving radiotherapy have higher risk of vascular damage and atherosclerosis, we have sometimes treated these patients with statins to prevent the ischemic stroke. In recent years, statins have also been found to show neuroprotective effects and have been suggested to have anticonvulsant effects in epilepsy. Thus, we wondered whether statins could lower the risk of epilepsy secondary to radiotherapy or RN. We undertook this study to examine the long-term prognosis of patients receiving radiotherapy. Because different kinds of head and neck tumor require different radiation strategies, we only included patients with nasopharyngeal carcinoma (NPC), to correct for these confounding factors. By facilitating comprehensive coverage of patient characteristics, including demographic data, neurological symptoms, radiological findings, and treatments, we aimed to clarify the effect of statins on preventing the risk of postradiation epilepsy.

### METHODS

**Patients and data collection**

A total of 697 NPC patients with history of radiotherapy admitted to the Department of Neurology at Sun Yat-Sen Memorial Hospital between January 2005 and December 2015 were enrolled. We retrospectively collected the demographic and clinical data of these patients through chart review. Study exclusion criteria were as follows: (1) patients who have a history of epilepsy before radiation; (2) patients with intracranial lesions other than RN that may lead to epilepsy, such as stroke, metastatic intracranial tumors, and trauma; (3) patients who have received prophylactically antiepileptic drugs; and (4) patients without follow-up. After application of our exclusion criteria, 532 patients were included in our study.

The following variables of interest were collected for each patient: age, gender, time of receiving brain radiation, radiation strategy (conventional radiation or intensity-modulated radiation therapy [IMRT]), complications of radiation, time of diagnosis of epilepsy and related presentation, electroencephalographic (EEG) results, lipid level at admission, time of receiving statin treatment, history of hypertension, history of diabetes mellitus, and history of coronary artery diseases.

**Statistical analysis**

Baseline characteristics were summarized and reported as number of cases and percentages or means (standard deviation). Chi-square test was used for comparison of categorical variables, and Student t-test was used for continuous variables between the two groups. Survival analysis was performed using Kaplan–Meier analysis, log-rank test, and Cox regression analysis. Cases were censored to the first occurrence of seizure event or to the date of last follow-up. Pearson correlation analysis was used to determine whether a significant correlation existed between analyzed variables. Variables without high correlation tested by Pearson correlation or of clinical interest were further evaluated in a multivariate Cox regression model. All p-values were reported as two-sided, with level of significance defined as $p < 0.05$.

Statistical analysis was performed using Stata 13.0 (StataCorp, College Station, TX, U.S.A.).

### RESULTS

**Summary of general characteristics**

A total of 532 patients (405 males and 127 females) with a mean follow-up of 28.1 months were included in our study. One hundred ninety-eight (37.2%) patients received IMRT. During follow-up, 471 (88.5%) patients had RN and 285 (53.6%) patients had radiation-induced cranial nerve injury. All baseline characteristics are summarized in detail in Table 1. Patients were treated with statins because of hyperlipidemia or prevention of cardiocerebrovascular diseases. A total of 88 patients were treated with statins, of whom 81 (92.0%) patients developed RN during follow-up. Seven patients began statin treatment before RN, seven
begun statin treatment at the time when RN was diagnosed, and 67 used a statin after RN onset. Table 2 shows statin use by RN grade. No significant difference in statin use was found among different RN grades ($p = 0.229$).

During a mean latency of 24.1 months, 88 (16.5%) patients experienced epilepsy, of whom 27 (27 of 88, 30.7%) patients suffered from epilepsy before the diagnosis of RN. Thirty-six (36 of 88, 40.9%) cases of epilepsy occurred after RN onset, and in 22 cases (22 of 88, 25.0%) epilepsy was the first presentation of RN. Three patients suffered from epilepsy but did not have RN. Among the 88 patients with epilepsy, 10 (11.4%) had a simple partial seizure, nine (10.2%) had a complex partial seizure, five (5.7%) had a secondary generalized attack, and 64 (72.7%) had a generalized seizure. Seventy-eight (88.6%) cases of epilepsy were controlled by antiepilepsy monotherapy. Fifty-three (60.2%) patients had at least one EEG record in the chart review, and 28 of them (28 of 53, 52.8%) showed abnormal EEG presentation.

Risk factors for epilepsy after radiation

Table 3 depicts the differences between patients who presented with and without epilepsy. Eighty-two of 444 (18.5%) nonepilepsy patients had received statins previously; in contrast, this rate was much lower in epilepsy patients (18.5% vs. 6.8%, $p = 0.007$, Table 3). More patients who developed epilepsy also suffered from RN in the follow-up when compared with those without epilepsy (96.6% vs. 86.9%, $p = 0.006$), although epilepsy may have occurred before or after RN. Patients with epilepsy showed lower low-density lipoprotein cholesterol on admission compared with those without epilepsy. There was no other significant difference between patients with or without epilepsy.

Survival analysis

Eighty-eight patients in our cohort received statin treatment, of whom six (6.8%) developed epilepsy during follow-up, whereas in those without statin the epileptic rate was 18.5% (82 of 444). Log-rank test found that there was a significant difference in epilepsy-free survival between patients who used statins and those who did not ($p = 0.016$, Fig. 1). After adjusting for age, gender, chemotherapy, and necrosis size, multivariate Cox regression analysis revealed that statin use could still significantly reduce the risk of epilepsy after radiation (hazard ratio [HR] = 0.36, 95% confidence interval = 0.15–0.82, $p = 0.015$, Table 4). Table 4 also depicts the association between statin use in different periods and risk of epilepsy. For the 415 patients who already suffered from RN, statin treatment did not lower the risk of post-RN epilepsy. In addition, larger necrosis did not lead to higher post-RN risk.

**Discussion**

In our cohort, 16.5% of patients with radiotherapy history experienced postradiation epilepsy. After adjusting for confounding factors, our results revealed that statin use could significantly reduce the risk of epilepsy after radiation.
Epilepsy is a common symptom in patients receiving radiotherapy, especially in those with RN. In this study, by following up 532 NPC patients who had ever receiving radiotherapy, we found an epilepsy rate similar to those reported in patients undergoing stereotactic radiosurgery for brain metastases. Our previous study with a smaller cohort also reported a 15.8% epilepsy rate in 101 RN cases. There are several reasons that radiation could lead to epilepsy. First, radiation causes endothelial cell damage, induces blood–brain barrier (BBB) damage, and aggravates brain edema. In addition, growing evidence suggests that inflammatory cytokines produced by radiation may also be involved in the pathophysiology of epilepsy. Frequent seizure onset, conversely, would aggravate inflammatory processes. Furthermore, free radical damage and autoimmune response related to radiation necrosis may also be closely tied up with epilepsy. In our cohort, among the 88 patients with epilepsy, most cases mainly manifested as temporal lobe epilepsy, which may be related to the specific radiation field for nasopharyngeal carcinoma. We also found that 30.7% patients suffered from epilepsy before the diagnosis of RN, and in 25.0% epilepsy acted as the first presentation of RN, which indicated that radiotherapy could induce epilepsy and this risk may further increase when patients suffer from RN. However, whether larger RN leads to higher epileptic risk has not yet been fully addressed. Although the Cox regression analysis showed a higher HR in grade I RN as compared with that in non-RN patients, we did not find a significantly higher HR in grade II and grade III patients. There are some confounding factors that affect the presence of epilepsy. Besides RN location, the relatively large difference of sample size between different RN grades may also lead to a deviation of epileptic rate among the groups.

Statins, widely used in the treatment of hyperlipidemia, provide primary and secondary prevention against cardiovascular disease and stroke. In addition to lowering lipids, statins have pleiotropic neuroprotective effects. Numerous clinical studies have sought to determine statins’ therapeutic potential in various central nervous system disorders, including dementia, multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, depression, and epilepsy. The effect of statins particularly on epilepsy has received increasing attention in recent years. Laboratory and clinical data have demonstrated the inhibition and antiepileptic effect of statins. In the vast majority of experimental seizure models, statins exhibited anticonvulsant action. Guo et al.’s study provided initial evidence that statins may reduce the risk of poststroke early onset seizures, particularly if used in the acute phase. In addition, in patients who present with poststroke early onset seizures, statin treatment may prevent the progression of seizure-induced neurodegeneration. There are some possible explanations for the mechanism underlying the antiepileptic effects of statins. Statins have been shown to have anti-inflammatory effects.

**Figure 1.** Survival analysis of epilepsy in patients with or without statins. 

| Statin use | Survival Rate | Hazard Ratio (95% CI) | p |
|---|---|---|---|
| Yes | 0.99 (0.95–1.02) | 0.393 |
| No | 0.74 (0.60–1.02) | 0.055 |

**Table 4. Multivariate Cox regression for epilepsy after radiation**

| Variable         | HR (95% CI) | p   | HR (95% CI) | p   |
|------------------|-------------|-----|-------------|-----|
| Age              | 1.00 (0.98–1.02) | 0.969 | 0.99 (0.95–1.02) | 0.393 |
| Gender, female vs. male | 0.58 (0.33–1.02) | 0.060 | 0.40 (0.15–1.05) | 0.062 |
| Chemotherapy     |             |     |             |     |
| No               | Ref         |     |             |     |
| Yes              | 1.24 (0.17–9.20) | 0.831 |             |     |
| Unknown          | 1.07 (0.15–7.90) | 0.946 |             |     |
| Statin, yes vs. no | 0.36 (0.15–0.82) | 0.015 | 0.65 (0.23–1.87) | 0.426 |
| Necrosis size    |             |     |             |     |
| 0                | Ref         |     |             |     |
| I                | 4.52 (1.41–14.51) | 0.011 |             |     |
| II               | 2.88 (0.75–10.98) | 0.122 | 0.64 (0.20–2.11) | 0.470 |
| III              | 2.23 (0.23–21.56) | 0.490 | 1.10 (0.15–8.22) | 0.925 |

CI, confidence interval; HR, hazard ratio; Ref, reference; RN, radiation-induced brain necrosis.

*Statistically significant.*
which might be an explanation for the treatment of epilepsy.19–22 It has been suggested that a compromised BBB could contribute to seizure development and progression of epilepsy.23 Statins have been shown to reduce BBB permeability and inflammation in neurological diseases. It may be related to the effect of statins in preventing brain injury caused by glutamatergic toxicity or activated N-methyl-D-aspartate receptors and the damage caused by intracellular calcium.24,25 In addition, demyelination, consecutive axonal loss, and gliosis are common in radiation injury. A study showed that 2-week administration of simvastatin immediately after seizure led to reduced astrocytosis, attenuated neuronal loss, decreased abnormal mossy fiber sprouting, and reduced seizure activity in the brain.26 Our study provides initial evidence that there was a significant difference in epilepsy-free survival between patients who used statins and those who did not. Surprisingly, when we focus on the patients who already suffered from RN, we did not find a significant difference of risk of epilepsy between patients with statins and those without statins. This finding indicates that the risk of epilepsy increases as early as the end of radiotherapy. The abnormal electrical activity may occur before the presence of visible radiological lesions. Because statin use may lower the risk of postradiotherapy epilepsy, we are considering whether it can also prevent the occurrence of RN. A future prospective cohort study is needed to validate this hypothesis.

This study has several limitations that need to be addressed for accurate interpretation of the results. First, given the retrospective nature of this study, our data suffered attrition bias due to missing documentation and loss to follow-up. Considering that patients without radiation-related complications may not come to follow-up, our cohort did not represent the real population of patients receiving radiotherapy. Second, some clinical information such as dose of radiotherapy was not obtainable in part of our patients; thus, we did not include these confounders in the regression analysis. To minimize this bias, we only included patients with NPC who shared similar radiation strategy. In addition, we compared the percentage of IMRT and conventional radiotherapy between patients with and without epilepsy but did not find a significant difference. We speculated that larger radiation dose could cause earlier presence of brain necrosis and radiation-related epilepsy. Furthermore, patients with RN in temporal lobe suffered from higher risk of epilepsy as compared with other locations.3 Because we only included NPC patients in our study, whether our results could be generalized to other cohorts needs further study. Finally, the category and dose of statins were not specified in relation to the risk of postradiation seizure. Studies have suggested that the neuroprotective effects of various statins may be a result of differing abilities to cross the BBB.27,28 In addition, experimental studies have suggested that the dose of statins can affect neuroprotective effects. A study found that increasing the pravastatin daily dose to 30 mg/kg/day resulted in a significant reduction in number of seizures.29 However, the number of patients with simvastatin and rosuvastatin treatment was small in our sample, so there was insufficient data to conduct appropriate subgroup analyses. Further prospective investigations with a larger cohort and sufficient information are needed to confirm the results.

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**Disclosure**

The authors declare no conflicts of interest. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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