Bevacizumab is more effective in nasopharyngeal carcinoma patients with lower maximum radiation dose to the temporal lobe

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Nasopharyngeal carcinoma (NPC), due to its location and routes of spread, requires radiation therapy to the skull base and may include a portion of the temporal lobes of the brain in the high dose volume by virtue of its anatomic location. Radiation-induced brain necrosis (RN) usually develops months to years after radiation therapy. It is histologically characterized by fibrinoid changes to the blood vessels and ischemia leading to coagulative necrosis of the brain parenchyma and demyelination (1,2). On imaging, radiation treatment-related changes in the temporal lobes can sometimes be difficult to differentiate from intracranial tumor recurrence. After radiation therapy, magnetic resonance imaging (MRI) may commonly show mild cerebral edema or white matter changes (3). RN is a severe form of late radiation toxicity to the central nervous system. It causes necrotizing leukoencephalopathy, which appears as confluent regions of T2/FLAIR hyperintensity on MRI, often associated with edema and heterogenous enhancement. Additional imaging techniques and sequences including MR perfusion, MR spectroscopy, susceptibility-weighted imaging (SWI), diffusion-weighted imaging (DWI) and positron emission tomography (PET) can be useful to establish the diagnosis (4,5).

Radiation treatment-related changes noted on imaging may be asymptomatic or symptomatic. If changes are asymptomatic and mild, conservative follow-up is appropriate, as these radiographic changes will often improve or stabilize with time (3). Symptoms of RN may include cognitive dysfunction, memory impairment, dizziness, seizures, headaches, personality changes or confusion (6). Management options for symptomatic RN may include corticosteroids, bevacizumab or surgery.

In this article, Li *et al.* performed a retrospective review of 50 patients who were treated with bevacizumab for RN that developed after receiving radiation therapy for nasopharyngeal cancer (7). All patients were followed for 6 months, and clinical data as well as brain edema volume based on MRI findings were analyzed. Patients were included if they completed radiation therapy at least 6 months prior, had no prior treatment of RN with corticosteroids, and no evidence of tumor recurrence or metastases. They were treated with bevacizumab 5 mg/kg intravenously once every 2 weeks for up to 4 courses.

Seventy-six percent of patients had an effective response, defined as a ≥25% reduction in brain edema volume, with a median decrease in RN volume seen on T2/FLAIR of 73%. The maximum dose to the temporal lobe (D_{max}) and total radiation dose of the neck were the only two factors that were significantly different between patients with and without an effective response. A random forest model analysis identified D_{max} of the temporal lobe as the main predictor of effective response with a threshold of 75.5 Gy, with an accuracy rate of 94.7% for predicting effectiveness of bevacizumab. These results suggest that bevacizumab is more effective in reducing brain edema in patients with temporal lobe D_{max} less than 75.5 Gy.

Fifteen out of 38 patients had recurrence of RN, and shorter duration between radiation therapy and either RN

diagnosis or bevacizumab treatment were found to be the top two predictors of RN recurrence. The authors also analyzed baseline serum VEGF levels which were only available in 15 patients, but found no significant difference between patients with and without an effective response. Limitations of the study include lack of details about how patients were diagnosed with RN, whether they had to be symptomatic to be included, and whether patients received any additional treatment with corticosteroids, and had longer follow-up.

Nevertheless, this article by Li *et al.* contributes significantly to the literature on treatment of RN with bevacizumab (7). In general, asymptomatic RN can be managed conservatively without intervention, and in patients who are symptomatic from cerebral edema, corticosteroids can be used as a first-line therapy. The data for bevacizumab appears promising but is based on small retrospective studies and two prospective randomized trials. A double-blind clinical trial from MD Anderson randomized patients with RN (with progressive neurologic signs or symptoms) from treatment for various head and neck and central nervous system tumors, to receive either bevacizumab (7.5 mg/kg once every 3 weeks, up to 4 times) or placebo (8). Patients were allowed to receive dexamethasone. All bevacizumab treated patients (5/5 of the randomized patients and 7/7 patients who crossed over) responded, while no placebo patients (0/7) did. The median decrease in edema and in contrast enhancement was 59% and 63%, respectively, in those treated with bevacizumab. Another open label trial was published last year by the same group as the current study by Li *et al.*, which randomized 112 patients with RN from radiation therapy for NPC to receive either bevacizumab (5 mg/kg every 2 weeks, for up to 4 courses) or steroids (methylprednisolone 500 mg IV daily for 3 days, followed by oral prednisone for 2 months) (9). A greater percentage of patients randomly assigned to the bevacizumab arm had a radiographic response compared to patients randomly assigned to the steroid arm (65.5% versus 31.5%, P<0.001), with a corresponding decrease in edema volume of 52% versus 19%, and reduction in enhancement of 25% versus 5%. Bevacizumab remained significant on multivariate analysis for treatment outcome. The bevacizumab group also had greater proportional benefit in terms of improvement in neurological signs/symptoms and cognitive function. There was no difference in the rate of RN recurrence, with 12 and 11 patients developing RN recurrence in the bevacizumab and steroid arms, respectively.

In addition to these prospective trials, there have been a few retrospective series, including the current study which to our knowledge represents the largest retrospective experience reported in the literature. In a recent meta-analysis of bevacizumab for the treatment of RN by Delishaj *et al.*, approximately 91% of patients had a clinical benefit after bevacizumab, 98% had radiographic improvement, and of the studies that analyzed pre- and post-treatment imaging, there was a median decrease in T1 contrast enhancement and T2/FLAIR signal abnormality of 64% and 60%, respectively (10).

The risk of developing RN after radiation for NPC is dependent on several treatment-related factors. In a large retrospective review of 849 patients with NPC treated with radiotherapy alone, Yeh *et al.* reported a higher incidence of RN with doses above 72 Gy (11%) versus less than 72 Gy (4%) (11). Lee *et al.* reviewed 1,032 patients with early-stage NPC and found that higher dose per fraction and B.I.D. fractionation were independent risk factors for symptomatic necrosis (12).

Intensity-modulated radiation therapy (IMRT) can reduce the radiation dose and volume to the temporal lobes compared with 2D or 3D conformal techniques (13). In a prospective, randomized trial comparing IMRT with 2D conventional radiation, the rate of temporal lobe necrosis was significantly lower in the IMRT group (13% *vs.* 21%) (14). The use of induction chemotherapy or adaptive radiation planning may allow for additional dose reduction to the temporal lobes in patients with locally advanced disease (15).

Treatment with bevacizumab carries significant cost and a risk of adverse events, so there is a need to identify factors associated with a favorable response. In the present study by Li *et al.*, the inclusion criteria required radiographic evidence of RN but did not require patients to be symptomatic. It is unclear how many asymptomatic patients were included in this study, but we believe that asymptomatic patients can be observed. Patients with D_{max} to the temporal lobes of >75.5 Gy had lower rates of response to bevacizumab, and a short interval between radiation therapy and RN was associated with a higher risk of RN recurrence. It is unclear if these factors correlate with a more irreversible RN process that is refractory to medical management, or if bevacizumab in particular is less effective in these settings.

This study by Li *et al.* raises other interesting questions: what is the optimal bevacizumab dosing and number of cycles to be given for RN? Several different bevacizumab

dosages have been reported in the literature, but it is unclear which one is optimum. Is there an additional benefit with concurrent or sequential corticosteroid treatment? Bevacizumab remains a promising treatment for RN, with high overall rates of radiographic and clinical response. It is our hope that future studies will help further refine management of brain RN in the setting of follow-up care after definitive treatment of NPC.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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