JBUON 2019; 24(3): 1252-1258
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Efficacy of chemoradiotherapy combined with bevacizumab in patients with nasopharyngeal carcinoma: A comparative study

Fangxiang Zhang, Tiejun Yuan, Min Gao

Department of Otolaryngology, Weifang People's Hospital, Weifang, China.

Summary

Purpose: *To investigate the efficacy of chemoradiotherapy combined with bevacizumab in patients with nasopharyngeal carcinoma and its clinical value in the cognitive function and radiation-induced brain injury.*

Methods: *A total of 80 patients with nasopharyngeal carcinoma treated in our hospital from March 2013 to October 2015 were selected and randomly divided into the control group (n=40) and the observation group (n=40). Patients in the control group were treated with three-dimensional conformal radiotherapy and regular chemotherapy, while patients in the observation group were treated with bevacizumab. Progression-free survival (PFS) and median survival (MS), the therapeutic effect, the levels of vascular endothelium-related indexes, S-100B protein and neuron-specific enolase (NSE), the changes in subjective evaluation criteria for cognitive function, the changes in auditory event-related potential P300 amplitude and latency, and the changes in neurological score during treatments were compared.*

Results: *In the observation group, both PFS and MS were longer than those in the control group ($p<0.05$); meanwhile, the overall effective rate of treatment was significantly higher ($p<0.05$). In addition, S-100B protein and NSE levels in the observation group 6 months after treatments were obviously lower than those in control group. At 3 and 6 months after treatments, the cognitive function score in the observation group was obviously higher compared to the control group. The auditory event-related potential P300 amplitude in observation group was lower than that in control group, while the latency was longer compared to the control group. At 3 and 6 months after treatments, the neurological score in observation group was remarkably higher than that in control group ($p<0.05$).*

Conclusions: *The combined application of bevacizumab for patients with nasopharyngeal carcinoma after chemoradiotherapy can significantly prolong the survival time of patients, improve the clinical therapeutic effect and the cognitive function of patients, and reduce the incidence rate of radiation-induced brain injury.*

Key words: *nasopharyngeal carcinoma, radiotherapy, radiation-induced brain injury, bevacizumab, cognitive function, chemotherapy*

Introduction

Nasopharyngeal carcinoma is a frequently-occurring tumor in the southern provinces in China. Previous studies have proved that the pathogenesis of nasopharyngeal carcinoma is related to factors such as environment and genetics, and Epstein-Barr virus infection is considered as an independent risk factor for the occurrence and development of this disease [1]. Nasopharyngeal carcinoma is a malignant tumor with moderate and higher sensitivity to radiotherapy, and it seriously threatens

Corresponding author: Min Gao, BM. Department of Otolaryngology, Weifang People's Hospital, 151 Guangwen Street, Quwen District, Weifang, 261041 Shandong, China.
Tel: +86 013884819999, Email: gjcr94@163.com
Received: 12/11/2018; Accepted: 15/12/2018

the physical and mental health of people [2], while its treatment is dominated by radiotherapy, especially for patients with locally middle-advanced nasopharyngeal carcinoma [3]. Chemotherapy can be combined when necessary to improve the clinical therapeutic effect, but large-dose chemoradiotherapy, in addition to treating the disease and killing the malignant tumor cells, will inevitably kill normal cells [4,5].

Radiation-induced brain injury is a major complication after radiotherapy for nasopharyngeal carcinoma. It is a severe condition and difficult to treat and its prognosis is poor [6]. Therefore, radiotherapy will lead to an even devastating situation on the prognosis of patients once radiation-induced brain injury occurs. Bevacizumab is a currently commonly used monoclonal antibody and widely recognized as a biological agent inhibiting the vascular endothelial growth factor receptor [7]. Previous studies have demonstrated that bevacizumab has shown good clinical in the treatment of radiation-induced brain injury. However, whether bevacizumab has value in the treatment of cognitive dysfunction caused by radiation-induced brain injury deserves further clinical investigation. In this study, radiation-induced brain injury in nasopharyngeal carcinoma patients was treated with bevacizumab and the results are cited below.

Methods

General data

A total of 80 patients with nasopharyngeal carcinoma treated in our hospital from March 2013 to October 2015 were selected. All patients were preliminarily diagnosed via preoperative imaging examination and definitely diagnosed via pathological biopsy. All of them signed informed consent before enrollment. This study was approved by the Ethics Committee of Weifang People's hospital. The longest follow-up period in this study was 5 years, and survival time more than 5 years indicated clinical cure.

Patients with malignant tumors in other sites, cardiopulmonary or hepatic-renal insufficiency, allergic to the drug to be used, systemic immune dysfunction complicated with endocrine-related diseases, distant metastasis of nasopharyngeal carcinoma, hearing impairment, mental disorders, language impairment or tumor cachexia before enrollment, or complicated with nervous system ischemic or hemorrhagic stroke in the past were excluded.

The patients enrolled were divided into the control group (n=40) and the observation group (n=40) using a random number table. In the observation group, there were 26 males and 14 females aged 18-55 years with an average of 40.5±1.1 years. There were 18 cases in stage II, 19 cases in stage III and 3 cases in stage IV according to the American Joint Committee on Cancer (AJCC). At enrollment, the plasma S-100B protein level was 0.3±0.1 ng/mL, the neuron-specific enolase (NSE) level was 8.1±0.5 ng/mL, the auditory event-related potential P300 amplitude was 9.0±0.5 μV, and the latency was 398.6±13.7 ms.

In the control group, there were 25 males and 15 females aged 18-55 years with an average of 40.6±1.1 years. There were 19 cases in stage II, 19 cases in stage III and 2 cases in stage IV according to AJCC. At enrollment, the plasma S-100B protein level was 0.3±0.1 ng/mL, the NSE level was 8.0±0.5 ng/mL, the auditory event-related potential P300 amplitude was 9.1±0.5 μV, and the latency was 398.7±13.8 ms. There were no statistically significant differences in the gender, age, duration of nasopharyngeal carcinoma, AJCC tumor stage, plasma S-100B protein, NSE, auditory event-related potential P300 amplitude and latency between the two groups ($p>0.05$).

Methods

The patients in the control group were treated with three-dimensional conformal radiotherapy. The patients were fixed with thermoplastic body model made according to the condition of lesion, followed by multi-slice spiral CT scanning and positioning. The target region was delineated in the lesion using the three-dimensional conformal radiotherapy system. The total dose of radiotherapy was 50 Gy in 95% planning target volume (PTV) (2 Gy/time) for 5 times a week. Gemcitabine-cisplatin (GP) chemotherapy was administered: Gemcitabine (1000 mg/m^2, NMPN H20030105, Jiangsu Hanson Pharmaceutical Co., Ltd., Nanjing, China) was intravenously administered on days 1 and 8, and cisplatin (25 mg/m^2, NMPN H22022966, Tonghua Maoxiang Pharmaceutical Co., Ltd., Tonghua, China) was intravenously administered on days 1 and 3. Chemotherapy was repeated once every 4 weeks, and 3 courses of treatment were considered as 1 treatment cycle. Nutritional support was given to all patients during treatment, and the patients with neurological dysfunction were treated with neurotrophic drugs, hormones, hyperbaric oxygen and functional exercise.

The patients in the observation group were treated with bevacizumab (5 mg/kg, approval No. registration No.: S20120068, Roche, Basel, Switzerland) via intravenous injection once every 14 days till disease progression.

Observation indexes

The survival-related indexes after treatments including progression-free survival (PFS) and overall survival (OS), the levels of vascular endothelium-related indexes before and after treatments, the cognitive function-related biochemical indexes at 6 months after treatments including S-100B protein and NSE, the changes in subjective evaluation criteria for cognitive function before treatments and at 3 and 6 months after treatments, the changes in auditory event-related potential P300 amplitude and latency at 6 months after treatments and the changes in neurological score during treatments were compared between the two groups.

Evaluation criteria

The evaluation criteria for the clinical therapeutic effect were as follows: complete remission (CR): The lesion completely disappeared in the imaging studies after treatment for 28 days and above. Partial remission (PR): The maximum diameter of the lesion was reduced by more than 50% in the imaging studies after treatment for 28 days and above. Stable disease (SD): The maximum diameter of lesion was reduced by 25-50% in the imaging studies after treatment, and there were no new lesions in the reexamination within 28 days. Progression: The maximum diameter of the lesion was increased by more than 25% in the imaging studies after treatment, or there were new lesions. Effective rate (%) = (cases of CR +cases of PR + cases of SD)/total cases×100%. The vascular endothelium-related indexes included mainly endothelin-1 (ET-1, detected via radioimmunoassay, normal value: 43.50-58.38 ng/L) and nitric oxide [NO, detected via enzyme-linked immunosorbent assay (ELISA), normal value: 13.8-34.6 μmol/L]. The cognitive function-related biochemical indexes included plasma S-100B protein (detected via ELISA, normal value: <0.5 μg/L) and NSE (detected via ELISA, normal value: <12.5 μg/L). The subjective evaluation of cognitive function was based on the mini-mental state examination (MMSE): 30 questions in 7 items with a total score 0-30 points. Score below 27 points indicated cognitive dysfunction, and the score was positively proportional to the cognitive function of patients. The objective evaluation of cognitive function was performed via the auditory event-related potential using the UK OXPORD evoked potential machine: The ''auditory target/non-target stimulus'' was given, and the stimulus intensity was set as 110 DB, filter bandwidth as 1-50 Hz, and multiplicity of target stimulus as 30 times. The P300 amplitude and latency in target stimulus were recorded in detail. The neurological function was evaluated using the European Stroke Scale (ESS), a total of 14 items with a total score of 0-100 points. The score was positively proportional to the neurological function of objects.

Table 1. Comparison of survival time-related indexes between the two groups after treatments (months, x±s)

	PFS	*MS*
Observation group	11.2±1.8	24.7±3.5
Control group	9.7±1.4	19.1±3.1
t	4.160	7.575
p	0.000	0.000

PFS: progression-free survival, MS: median overall survival

Statistics

SPSS 20.0 software (IBM, Armonk, NY, USA) was used for statistical processing. Measurement data were expressed as mean±standard deviation (x±s). T-test was used for the comparison of means between two groups, and chi-square test was used for the comparison of rates between two groups. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of survival time-related indexes between the two groups after intervention

In the observation group, both PFS and MS were longer than those in the control group (p<0.05) (Table 1).

Comparison of the therapeutic effect between the two groups

The overall effective rate of treatment in the observation group was significantly higher than that in the control group (p<0.05) (Table 2).

Comparison of vascular endothelium-related indexes between the two groups before and after intervention

There were no statistically significant differences in the levels of vascular endothelium-related indexes (ET-1 and NO) between the two groups before intervention (p>0.05). After intervention in both groups, the ET-1 level was lower than that before intervention (p<0.05), while the NO level was higher than that before intervention (p<0.05). In the observation group, the ET-1 level after intervention was lower than that in the control group after intervention (p<0.05), while the NO level was higher than that in the control group after intervention (p<0.05) (Table 3).

Comparison of cognitive function-related biochemical indexes between the two groups at 6 months after intervention

In terms of the cognitive function-related biochemical indexes, the S-100B protein and NSE levels in the observation group at 6 months after intervention were obviously lower than those in the control group (p<0.05) (Table 4).

Table 2. Comparison of the therapeutic effect on solid tumors between the two groups

	CR	*PR*	*SD*	*Ineffective*	*Effective rate (%)*
Observation group (n)	11	12	16	1	2.5
Control group (n)	8	9	10	13	32.5
x^2			-		34.341
p			-		0.000

Changes in subjective evaluation criteria for cognitive function in both groups during treatments

Before treatments and at 3 and 6 months after treatments, the cognitive function score was 21.1±0.7, 27.8±0.4 and 28.5±0.2 points, respectively, in the observation group, and 21.2±0.7, 24.6±0.3 and 24.7±0.3 points, respectively, in the control group. There was no statistically significant difference in the cognitive function score between the two groups before treatments (t=0.639, p=0.525), and the cognitive function score in the observation group was obviously higher compared to the control group at 3 and 6 months after treatments (t=66.656 and 40.477, p<0.05) (Figure 1).

Changes in objective evaluation criteria for cognitive function in both groups

The comparison of auditory event-related potential P300 amplitude and latency at 6 months after treatments revealed that the auditory event-related potential P300 amplitude in the

Table 3. Comparison of vascular endothelium-related indexes between the two groups before and after treatments (mean±SD)

	ET-1 (ng/L)	*NO (μmol/L)*
Observation group		
Before treatments	243.9±37.7	8.1±1.1
After treatments	78.9±11.3	15.9±1.6
Control group		
Before treatments	244.1±37.8	8.2±1.1
After treatments	109.3±14.9	11.2±1.4
t1	26.515	25.407
p1	0.000	0.000
t2	20.983	13.981
p2	0.000	0.000
t3	0.024	0.407
p3	0.981	0.685
t4	10.281	10.657
p4	0.000	0.000

t1 & p1: in the comparison in observation group before and after treatments; t2 & p2: in the comparison in control group before and after treatments; t3 & p3: in the comparison between the two groups before treatments; t4 & p4: in the comparison between the two groups after treatments

Table 4. Comparison of cognitive function-related biochemical indexes between the two groups at 6 months after treatments (ng/mL, mean±SD)

	S-100B protein	*NSE*
Observation group	2.8±0.2	0.7±0.1
Control group	5.1±1.1	1.8±0.3
t	13.011	22.000
p	0.000	0.000

Table 5. Comparison of auditory event-related potential P300 amplitude and latency at 6 months after treatments between the two groups (mean±SD)

	Amplitude (μV)	*Latency (ms)*
Observation group	6.9±0.3	466.7±32.5
Control group	9.1±0.5	398.7±13.8
t	23.862	12.180
p	0.000	0.000

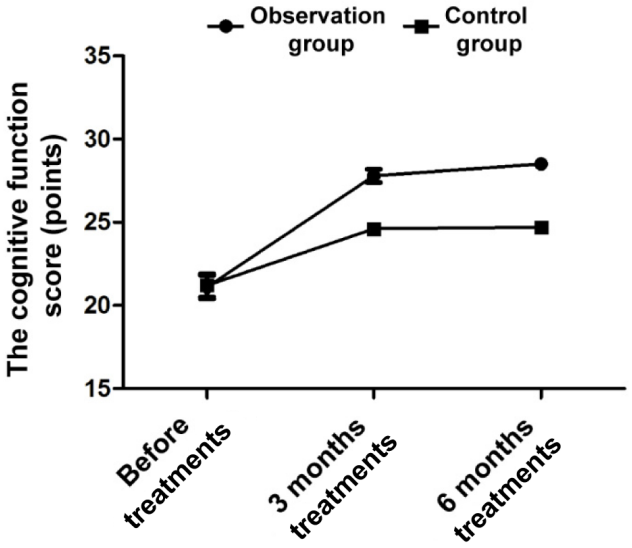

Figure 1. Changes in cognitive function in both groups during treatments. The cognitive function score in the observation group is obviously higher than that in the control group at 3 and 6 months after treatments (p<0.05).

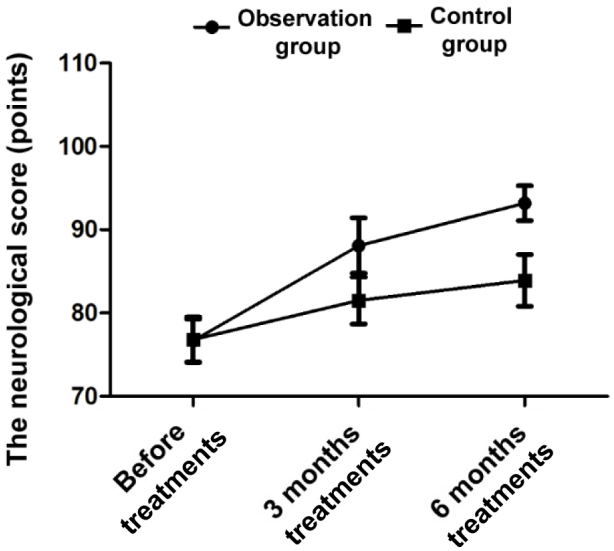

Figure 2. Changes in the neurological score in both groups during treatments. The neurological score in the observation group is remarkably higher than that in the control group at 3 and 6 months after treatments (p<0.05).

observation group was lower compared to the control group ($p<0.05$), while the latency was longer than that in control group ($p<0.05$) (Table 5).

Changes in the neurological score in both groups during treatments

Before treatments and at 3 and 6 months after treatments, the neurological score was 76.7±2.6, 88.1±3.3 and 93.2±2.1 points, respectively, in the observation group, and 76.8±2.7, 81.5±2.8 and 83.9±3.1 points, respectively, in the control group. No statistically significant difference in the neurological score between the two groups before treatments ($t=0.168$, $p=0.866$) was noted, but the neurological score in the observation group was remarkably higher than that in the control group at 3 and 6 months after treatments ($t=9.645$ and 15.8709, $p<0.05$) (Figure 2).

Discussion

Nasopharyngeal carcinoma occurs frequently in the southern provinces in China. The effectiveness of radiotherapy has been widely recognized, and radiotherapy combined with chemotherapy has been the preferred therapeutic approach for nasopharyngeal carcinoma, especially in locally advanced disease [8]. With the development of medical technology, intensity modulated radiotherapy has been successfully applied in the treatment of nasopharyngeal carcinoma, significantly prolonging the survival of patients [9]. With the prolongation of survival, the mid- and long-term complications, such as radiation-induced brain injury, have also been significant, seriously affecting the quality of life of patients after radiotherapy. According to a study [10], manifestations of neurological impairment generally develop at 3-6 months after treatment in radiation-induced brain injury of nasopharyngeal carcinoma, which mainly include the decline in S-100B protein and NSE and changes in auditory event-related potential.

To better reduce the influence of radiation-induced brain injury after radiotherapy for nasopharyngeal carcinoma and improve the patient quality of life, the patients in the observation group were treated with bevacizumab. The survival-related indexes were compared between the two groups after treatments and the therapeutic effect in both groups was also assessed. The results revealed that both PFS and MS in the observation group were longer than those in the control group, and the overall effective rate of treatment in the observation group was higher compared to the control group, indicating that the application of bevacizumab in nasopharyngeal carcinoma patients receiving chemoradiotherapy had positive impact in the prolongation of survival and improved the overall clinical therapeutic effect. Moreover, the vascular endothelium-related indexes were compared between the two groups before and after treatments, and it was found that in the observation group the ET-1 level after treatments was lower than that in the control group after treatments, while the NO level was higher than that in the control group after treatments, indicating that the combined application of bevacizumab in nasopharyngeal carcinoma patients receiving chemoradiotherapy has a certain value in improving the vascular endothelial function. At the same time, the changes in the cognitive function-related biochemical indexes (S-100B protein and NSE) in both groups at 6 months after treatments were studied and it was found that the cognitive function score in the observation group was obviously higher than that in the control group at 3 and 6 months after treatments, suggesting that the treatment with bevacizumab in nasopharyngeal carcinoma patients receiving chemoradiotherapy is valuable in improving the cognitive function of patients. Besides, the changes in subjective and objective evaluation criteria for cognitive function in both groups were also studied, and the results showed that the MMSE score in the observation group was higher compared to the control group at 3 and 6 months after treatments. The comparison of auditory event-related potential P300 amplitude and latency at 6 months after treatments revealed that this potential was lower in the observation group, further suggesting that the combined application of bevacizumab in nasopharyngeal carcinoma patients receiving chemoradiotherapy has positive impact in improving the patients' cognitive function and reducing the severity and incidence rate of radiation-induced brain injury.

Finally, the changes in the neurological score in both groups during treatments were compared, and it was noted that the neurological score in the observation group was remarkably higher compared to the control group at 3 and 6 months after treatments, indicating that the combined application of bevacizumab in nasopharyngeal carcinoma patients receiving chemoradiotherapy has important value in improving the neurological function of patients with this disease after radiotherapy.

Bevacizumab is the most commonly used biological agent inhibiting the vascular endothelial growth factor [11], which can obviously improve the vascular endothelial function of cancer patients [12], inhibit neoangiogenesis in the tumor site, suppress the aseptic inflammatory response

in the body [13] and increase the body's immunity [14]. Moreover, it can also enhance the apoptosis and necrosis of malignant tumor cells [15], reduce the drug resistance of these cells and increase the therapeutic effect of chemotherapeutic drugs [16]. In radiation-induced brain injury, bevacizumab can effectively decrease the levels of vascular endothelial growth factor, reduce the tissue edema [17], especially the brain edema [18], promote the reduction of edema of brain cells after radiotherapy, and reduce the water molecule content in brain tissues [19], thus lowering the intracranial pressure, relieving the clinical symptoms and improving the neurological function [20].

Conclusion

The combined application of bevacizumab for patients with nasopharyngeal carcinoma after chemoradiotherapy can significantly prolong their survival and improve the clinical therapeutic effect, and it is also of great significance in improving their cognitive function and reducing the incidence rate of radiation-induced brain injury.

Conflict of interests

The authors declare no conflict of interests.

References

1. Xu Y, Rong X, Hu W et al. Bevacizumab Monotherapy Reduces Radiation-induced Brain Necrosis in Nasopharyngeal Carcinoma Patients: A Randomized Controlled Trial. Int J Radiat Oncol Biol Phys 2018;101:1087-95.
2. Zhang HJ, Yuan GL, Liang QL, Peng XX, Cheng SA, Jiang L. Addition of bevacizumab to systemic therapy for locally advanced and metastatic nasopharyngeal carcinoma. Oncol Lett 2018;15:7799-805.
3. Li Y, Huang X, Jiang J et al. Clinical Variables for Prediction of the Therapeutic Effects of Bevacizumab Monotherapy in Nasopharyngeal Carcinoma Patients With Radiation-Induced Brain Necrosis. Int J Radiat Oncol Biol Phys 2018;100:621-9.
4. He W, Zou C, Tian Z et al. Nasopharyngeal carcinoma treated with bevacizumab combined with paclitaxel liposome plus cisplatin: a case report and literature review. Onco Targets Ther 2017;10:67-72.
5. Yuan C, Xu XH, Xu L et al. Cetuximab versus nimotuzumab for the treatment of advanced nasopharyngeal carcinoma: A network meta-analysis. JBUON 2017;22:1004-10.
6. Li J, Zhao Z, Wu X et al. Bevacizumab plus cisplatin and helical tomotherapy in treatment of locally advanced nasopharyngeal carcinoma. Onco Targets Ther 2015;8:1315-9.
7. Chen Z, Xu XH. Combining antiangiogenic therapy and radiation in nasopharyngeal carcinoma. Saudi Med J 2015;36:659-64.
8. Subrayan V, Khaw KW, Peyman M, Koay AC, Tajunisah I. Intravitreal bevacizumab for radiation-induced cystoid macular oedema in patients with nasopharyngeal carcinoma: a clinical series. Ophthalmologica 2013;229:208-11.
9. Yudistiro R, Hanaoka H, Katsumata N, Yamaguchi A, Tsushima Y. Bevacizumab Radioimmunotherapy (RIT) with Accelerated Blood Clearance Using the Avidin Chase. Mol Pharm 2018;15:2165-73.
10. Christoforidis JB, Briley K, Binzel K et al. Systemic Biodistribution and Intravitreal Pharmacokinetic Properties of Bevacizumab, Ranibizumab, and Aflibercept in a Nonhuman Primate Model. Invest Ophthalmol Vis Sci 2017;58:5636-45.
11. Pathan A, Barash A, Tena LB, Finger PT. Palladium-103 plaque radiation therapy for ciliary body melanoma through a functioning glaucoma filtering bleb. Eur J Ophthalmol 2018;28:119-22.
12. Xiao J, Xu X, Li X et al. Re-188 Enhances the Inhibitory Effect of Bevacizumab in Non-Small-Cell Lung Cancer. Molecules 2016;21:1308.
13. Ter Weele EJ, Terwisscha VSA, Linssen MD et al. Development, preclinical safety, formulation, and stability of clinical grade bevacizumab-800CW, a new near infrared fluorescent imaging agent for first in human use. Eur J Pharm Biopharm 2016;104:226-34.
14. Radchenko V, Bouziotis P, Tsotakos T et al. Labeling and preliminary in vivo assessment of niobium-labeled radioactive species: A proof-of-concept study. Nucl Med Biol 2016;43:280-7.
15. Shechtman DL, Gold AS, McIntosh S, Steen J, Murray TG. Atypical Exophytic Retinal Capillary Hemangioma and Diagnostic Modalities. Optom Vis Sci 2016;93:107-12.
16. Martinez J, Besa S, Arab JP et al. Gastrointestinal neuroendocrine tumor with unresectable liver metastases: an example of multimodal therapeutic approach. Ann Hepatol 2015;14:752-5.
17. Oosting SF, Brouwers AH, van Es SC et al. 89Zr-bevacizumab PET visualizes heterogeneous tracer accumulation in tumor lesions of renal cell carcinoma patients and differential effects of antiangiogenic treatment. J Nucl Med 2015;56:63-9.

18. van Asselt SJ, Oosting SF, Brouwers AH et al. Everolimus Reduces (89)Zr-Bevacizumab Tumor Uptake in Patients with Neuroendocrine Tumors. J Nucl Med 2014;55:1087-92.
19. Christoforidis JB, Williams MM, Wang J et al. Anatomic and pharmacokinetic properties of intravitreal bevacizumab and ranibizumab after vitrectomy and lensectomy. Retina 2013;33:946 52.
20. Li S, Goins B, Hrycushko BA, Phillips WT, Bao A. Feasibility of eradication of breast cancer cells remaining in postlumpectomy cavity and draining lymph nodes following intracavitary injection of radioactive immunoliposomes. Mol Pharm 2012;9:2513-22.