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Lateral ventricule invasion and radiation dose to subventricular zone: Their impact to the treatment outcomes of glioblastoma

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► ***Original article***

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ABSTRACT

Background: This study was conducted to evaluate the recurrence patterns of GBM in regard to its contact with LVs, the relation between radiation doses to subventrivular zone (SVZ). ***Materials and Methods***: Between 2012 and 2014, 80 adult patients with GBM were included this trial. Median follow-up period was 15 months. Median tumor size was 4.5 cm (1.3-8 cm), where 58% of the patients had a tumor larger than 4 cm. All of the lesions were located supratentorial part of brain. Tumors were classified based on whether the mass involved the SVZ and/or LVs. Reccurrence patterns and treatment outcomes were compared. ***Results:*** Tumor progression occurred in 60 (75%) of the patients. Of those 31 (51.6%) were in-field. Median progression-free survival (PFS) and median overall survival (OS) times were 11 and 15 months, respectively. On multivariate analysis, the negative prognostic factors were maximal surgical resection (p=0.027), LV-invading tumor (p=0.001) and p53 positivity (p=0.034) for PFS. It was found that the patients receiving >50 Gy to iSVZ dose (p=0.024) or >40 Gy to cSVZ dose (p=0.002) or >40 Gy to bSVZ dose (p=0.028) or >50 Gy to bSVZ dose (p=0.008) tended to have more recurrences. Both in-field and out-field recurrences were not affected by higher radiation doses. ***Conclusion:*** LVs invading and/or location close to the SVZs can be considered as an important prognostic factor in terms of decreased PFS and OS rates. Additionally both SVZs sparing and dose escalation to SVZs approaches are required to be evaluated in further researches.

Keywords: *Glioblastoma, subventricular zone, lateral ventricule invasion, progression-free survival.*

INTRODUCTION

Glioblastoma (GBM) is the most common and most malignant adult primary brain tumor [1, 2]. Standard treatment approach is maximal safe resection followed by external beam radiation therapy (EBRT) concomitant and adjuvant chemotherapy. Despite the applied aggressive treatments, GBM frequently recurs within 2 cm of the original treated tumor [3]. On the other hand, distant recurrences have been shown to detect, particularly when the original tumor has an invasion of subventricular zone (SVZ) [4].

Differences in recurrence patterns and patient survival have been shown between the patients grouped according to the lesion location with respect to the cortex and the SVZ. There are several reports showing association between tumor infiltration of SVZ and worse survival outcomes [5-7]. Addition to worse survival results, it is concluded that tumors contacting the SVZ are more likely to be multifocal and occur in distant sites from primary lesion [4]. The SVZ is considered as the origin of neural stem cells (NSCs) and it is hypothesized that the largest area of neurogenesis is located at the SVZ in adult human brain [8]. Multipotent NSCs line the lateral walls of the lateral ventricles (LVs). NSCs originating from SVZ migrate to other parts of the brain to serve as mature neural cells.

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Increasing the radiation dose to SVZ might be an option to reduce the tendency for progression and poor survival of the tumors contacting LV and SVZ [9]. Several papers detect better progression free survival (PFS) with the help of higher radiation doses to SVZ [10-14]. A dose escalation trial could not show any overall survival (OS) benefit with the radiation doses up to 70 Gy [11]. But subgroup analysis of that trial showed that the patients receiving higher doses to the ipsilateral SVZ had better results. Other studies regarding this issue have completely different results of abovementioned ones and they could not find any additional benefit when the SVZ is exposed to higher doses [15]. Due to the conflicting results of current literature, dose to SVZ remains controversial.

The aim of this study was to evaluate the recurrence patterns of GBM in regard to its contact with LVs, the relation between radiation doses to the ipsilateral SVZ (iSVZ), contralateral SVZ (cSVZ), bilateral SVZ (bSVZ) and outcomes of these patients who were treated in a single institution with current treatment approach.

MATERIALS AND METHODS

Patients

Between 2012 and 2014, 80 adult patients with a histologic diagnosis of GBM whom were referred for radiotherapy at Ege University were included in this research after institutional review board approval. The Research Ethics Board approval was obtained from Ege University Ethic Committee with the decision number 15-5.1/7. Following tumor surgery with an aim of maximal resection all patients received standard adjuvant treatment of 60 Gy irradiation (with Lineer Accelator, Electa, Synergy Model, England) in 6 weeks and concomitant 75 mg/m^2 Temozolomid capsule (TMZ) daily. After chemoradiotherapy additional at least 6 cycles TMZ (150-200 mg/m^2, 5 days at every month) was prescribed. The patients' demographic data, disease characteristics and treatment data were recorded.

The median age of patients in this trial was 57 years (range, 19-75 years). 71% were male and 29% were female. The KPS score was 90-100 in 50 (61.7%) patients, and lower than 90 in 30 (38.3%) patients and was 90 or higher in 50 (61.7%) patients. Of the patients, 80.2% underwent maximal surgical resection and 38.3% had biopsy or subtotal resection. There was single lesion was detected in 68 (84%) patients and multiple lesions in 12 (16%) patients. Median tumor size was 4.5 cm (range, 1.3-8 cm), where 58% of the patients had a tumor larger than 4 cm. All of the lesions were located supratentorial part of brain. Karnofsky Performance Status were ≥90% in 61,7% of the patients.

Imaging

The brain MRI prior to therapy and follow-up imaging were performed following clinical guidelines. Imaging was performed at 1.5 or 3 T and included axial and coronal diffusion-weighted imaging, three-dimensional FLAIR, axial T1WI, axial T2WI, and axial and coronal postcontrast T1WI after intravenous administration of gadolinum. A neuroradiologist evaluated the pretreatment imaging on each patient to determine the originate of the tumor, the dimensions of the contrast-enhancing tumor, and for the presence of multifocal disease, which was defined as a site of abnormal contrast enhancement or nonenhancing FLAIR hyperintense lesions that were discrete from the primary tumor site, not typical of nonspecific white matter disease, and had other features suspicious for tumor such as mass effect or hyperperfusion [6]. Tumors were classified based on whether the mass involved the SVZ, which was defined as the contrast-enhancing lesion touching the lining of the lateral ventricle, and cortex, which was defined as the contrast enhancing lesion contacting the cortex [7]. The median ipsilateral, contralateral, bilateral SVZ doses were 51.1 Gy (range, 1.43-61.6 Gy), 41.6 Gy (range, 1.33-61.4 Gy), and 46.2 Gy (range, 1.39-61.5 Gy), respectively. At initial diagnosis 49/80 (60.5%) GBMs were LV-contacting whereas 31/80 (39.5%) were non-LV-contacting. Patient characteristics are listed in table 1.

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Radiation therapy planning and recurrence definition

Treatment volumes were determined by preoperative MRI co-registration with planning CT. T1-weighted post-contrast enhancement and also T2-Flair MRI axial sequences were used. Contrast enhancement area at T1 was defined as Gross Tumor Volume (GTV), Clinical target volume (CTV) included a 1.5-2 cm additional margin around GTV and 3 mm margin was added to define Planning Target Volume (PTV) (figures 1 and 2). We included the patients completing the treatment which was accepted as standard approach for GBMs and also we wanted to be used at least 3 dimensional conformal RT planning with homogenous RT dosage and distributions. The SVZ volume was defined as a 5-mm margin along the lateral wall of the LVs as suggested by the atlas for RTOG 0933 [13, 16, 17]. Dose-volume histograms were calculated, and organs at-risk, treatment volume doses were planned by using the RTOG adequacy criteria. The mean doses of iSVZ, cSVZ and bSVZ were evaluated with the total 40, 50, and 60 Gy threshold doses. The definition of recurrence types was done according to recommendations of Chen where in-field recurrence was defined as the tumor having >80% of enhancement volume within the 95% isodose line and out-field recurrence was defined as any tumor outside the 95% isodose line with respect to the treatment volume [18].

Statistical analysis

SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) version 21.0 was used for statistical analysis. Patients were stratified according to age (>60 vs <60), KPS at diagnosis (90-100 vs <90), surgery (maximal surgical resection vs biopsy/subtotal resection), SVZ invasion (invading vs non-invading). The Student *t-test* was used to check differences among these parameters. Chi-squared test was used to analyze the differences among groups in terms of tumor contact and recurrence patterns. PFS and OS were calculated from the first day of treatment until the time of any event or the last day of follow-up. Univariate analysis was performed by the Kaplan–Meier method to analyze prognostic factors for the specific end points, with comparison using a log-rank test. Subsequent multivariate analysis was performed using the Cox regression to identify independent prognostic factors. All p-values are two-sided and <0.05 is accepted as significant.

Table 1. The characteristics of patients

Characteristic	n=80	LV-invading n=49 (%60)	non-LV-invading n=31(%40)	p value
Age (median)	57 (range, 19-75)	57 (range, 21-75)	53 (range, 19-73)	
Sex				
Female	23 (28,4%)	9 (18,4%)	14 (45,2%)	***0.010***
Male	57 (70,6%)	40 (81,6%)	17 (54,8%)	
Resection type				
Maximal resection	65 (80,2%)	42 (85,7%)	23 (74,2%)	0.222
Biopsy/Subtotal	15 (19,8%)	7 (14,3%)	8 (25,8%)	
KPS				
≥90	50 (61,7%)	28 (57,1%)	22 (71%)	0.213
<90	30 (38,3%)	21 (42,9%)	9 (29%)	
Number of lesion				
Single	68 (84%)	40 (81,6%)	28 (90,3%)	0.289
Multiple	12 (16%)	9 (18,4%)	3 (9,7%)	
Tumor size	4,8 cm	5,9 cm	3,3 cm	
>4 cm	47 (58%)	42 (85,7%)	5 (16,1%)	***<0.001***
≤4 cm	33 (42%)	7 (14,3%)	26 (83,9%)	
IDH Status				
(-)	58 (72,5%)	30 (61,2%)	28 (90,3%)	0.215
(+)	5 (6,25%)	4 (8,16%)	1 (3,2%)	
Uknown	17 (21,25%)	15 (30,6%)	2 (6,4%)	

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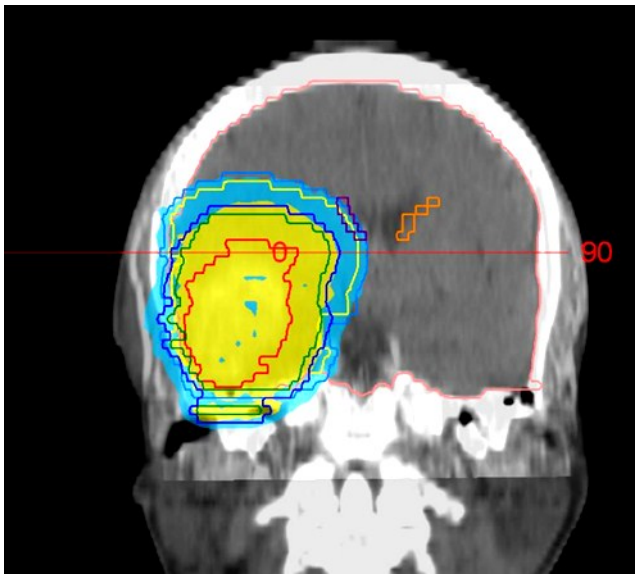

Figure 1. The relation between the dose level of 60-50 Gy and SVZs

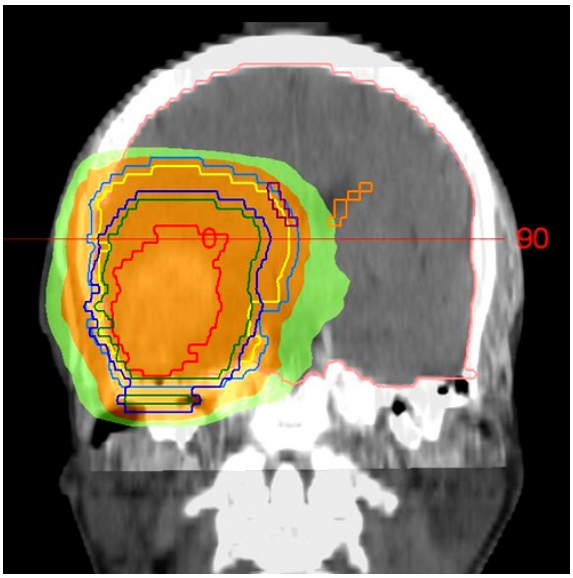

Figure 2. The relation between the dose level of 30-40 Gy and SVZs.

RESULTS

Median follow-up period was 15 months (range, 7-50 months). Tumor progression/ reurrence occurred in 60 (75%) of the patients. Of those 31 (51.6%) were in-field and 29 (48.4%) were out-field.

Univariate analysis results both for PFS and OS

Median PFS was 11 months (7-38 months) for whole group. PFS was 15 months (7-38 months) among the patients with non-SVZ invading tumor and 9 months (7-27 months) in the patients with SVZ-invading tumor. The difference between invading and non-invading group was significant on univariate analysis (p<0.001). There was no significant difference for age, number of lesion, extent of surgery, IDH-1 status. But, having lower KPS score (p=0.018), subependymal involvement (p=0.001), *p19* positivity (p=0.050) and >4cm tumor size (p<0.001) were negative prognostic factors. On univariate analysis, we could not find any statistically difference in terms of recurrence sites between SVZ involving and non -SVZ involving tumors (p=0.186). The rates of in -field and out-field recurrences were similar between two groups.

Median OS was 15 months (7-50 months) for whole group, median OS was 18 months (7-50 months) among the patients with non-SVZ invading tumor and 12 months (7-39 months) in the patients with SVZ invading. The difference was significant on univariate analysis (p<0.001). Being 60 years or younger (p=0.003), having single lesion (p=0.027), maximal surgical resection (p=0.045) were favorable prognostic factor for OS. Univariate analyze results were shown in table 2. Survival curves were shown in figures 3 and 4.

Multivariate analysis results both for PFS and OS

On multivariate analysis, it was found that having maximal surgical resection (p=0.027), SVZ-invading tumor (p=0.001) and *p19* positivity (p=0.034) were negative prognostic factors for PFS. The prognostic factors affecting OS were patients age at diagnosis (p=0.001), the number of lesions (p=0.002) and the relation with LV (p=0.045) on multivariate analysis (table 2). It was seen that SVZ invasion was unfavorable factor for PFS but this did not have any negative effect over OS.

The radiation dose of SVZs

The SVZ doses were evaluated by using 3

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cut-off values (40, 50 and 60 Gy). Progression patterns were analyzed in regard to mean iSVZ, cSVZ and bSVZ threshold doses. It was found that the patients receiving >50 Gy to iSVZ dose (p=0.024) or >40 Gy to cSVZ dose (p=0.002) or >40 Gy to bSVZ dose (p=0.028) or >50 Gy to bSVZ dose (p=0.008) tended to have more recurrences. We could not find any statistically significant relation between radiation doses over 60 Gy and progression. Multivariate analysis failed to show any factor having impact on the relation between survival and dose to SVZ.

The recurrence patterns was compared according to the applied radiation dose level to SVZs. For this comparison, all the non-recurrent patients were excluded from our evaluation data. We could not find any significant change in the recurrence patterns according to radiation dose level (all p values >0.05). Both in-field and out-field recurrences were not affected by higher radiation doses. We also compared PFS and OS times for the recurrent patients. In our analysis, the radiation dose level to SVZs did not have any negative effect both over PFS and OS times of patients with in-field recurrences (all p values >0.05).

Table 2. The results of univariate statistical analysis for Progression-Free Survival (PFS) and Overall Survival (OS)

Prognostic Factor ***(Log-rank)***	**PFS** **(*p* value)**	**OS** **(*p* value)**
LVs invasion or SVZ involvement	<0.001	<0.001
Subtotal surgery	NS	0.045
>60 years	NS	0.003
Having multiple lesions	NS	0.027
>4 cm tumor	<0.001	NS
<90% KPS	0.018	NS
Subependymal involvement	0.001	NS
p53 positivity	0.050	NS

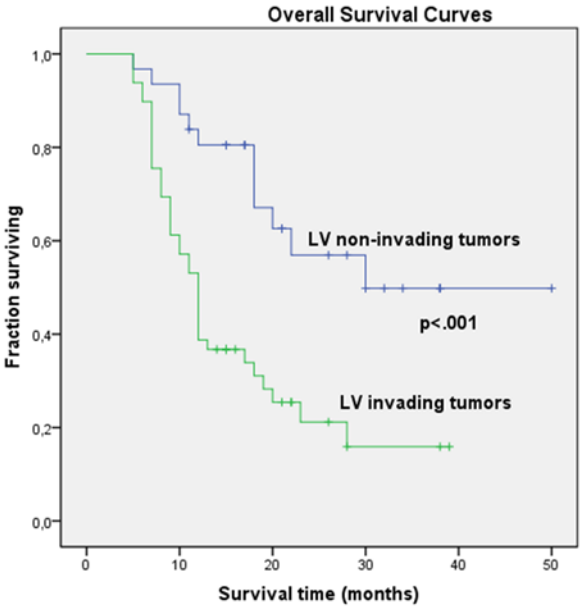

Figure 3. Overall survival curves of the patients according to the invasion status of LVs.

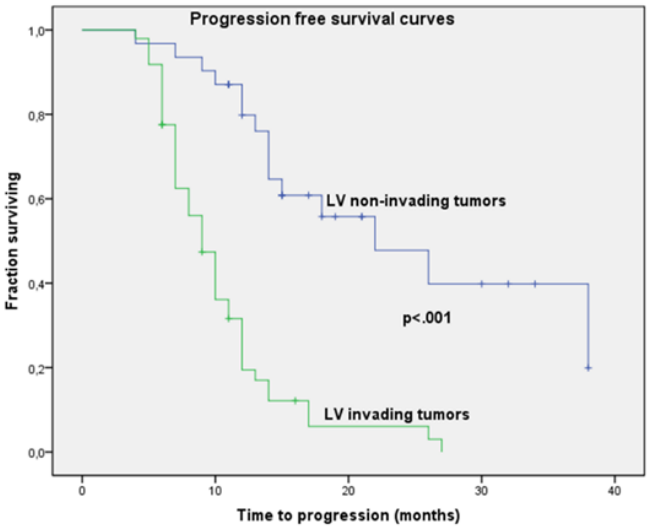

Figure 4. Progression free survival curves of the patients according to the invasion status of LVs.

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Table 3. The results of multivariate statistical analysis for Progression-Free Survival (PFS) and Overall Survival (OS)

Prognostic Factor *(Cox regression)*	**PFS** **(*p* value)**	**OS** **(*p* value)**
LVs invasion or SVZ involvement	0.001	0.045
Subtotal surgery	0.027	NS
>60 years	NS	0.001
Having multiple lesions	NS	0.002
p53 positivity	0.034	NS

DISCUSSION

At present, the role of neural stem cells in the development of GBMs and their role in tumor response to RT are widely discussed. Since it was considered that the tumor cells originating from SVZs have ability to migrate to other part of brain, those tumors supposed to have worse prognosis than the others [5]. When planning the postoperative radiotherapy tumors invading SVZ are usually covered within the high radiation doses; thus theoretically we can expect a better outcome. However current literature summarized below is inconclusive.

It has been accepted that SVZ-invading GBMs differ from those not-invading ones with respect to genetic profiles and patient prognosis [5-7]. In this trial, SVZ-invading tumors had less PFS and OS rates. After log-rank and cox regression analysis, we found that SVZ-invading GBMs had worse PFS rates. On the other hand, we could not show any negative effect over OS rates in cox -regression analysis although it was significant in log-rank tests. Our results are in concordance with prior results showing higher rates of regional, distant, and multifocal progression when tumors invading-SVZ [19]. Some studies have shown worse outcomes in SVZ-invading tumors (7), while others have shown worse results could be obtained when there was involvement of both the SVZ and corpus callosum [19].

Chen *et al.* reported 116 patients where they treated with 60 Gy and TMZ. They contoured iSVZ, cSVZ, bSVZ as we did. Their results showed that the outcomes were better for those received at least 40 Gy mean dose to iSVZ [13]. However other reports were not confirming their results. Adeberg *et al.* from evaluated the survival outcomes of GBM patients, who were treated with same procedure with Chen *et al.*, in 2014 [4]. They included 607 primary GBM patients and showed that SVZ-invading tumors had decreased both PFS and OS rates. According to these results, they concluded that having SVZ-invading status could be classified as a negative prognostic factor both for PFS and OS in addition to other well-known prognostic factors. Elicin *et al*. showed similar results with Adeberg *et al*. [15]. They included 60 GBM patients who were previously treated with RT and TMZ. They found that high iSVZ doses were associated with poor PFS rates. They emphasized that current literature was not mature enough for changing daily practice in terms of dose modulation to SVZs. Similar to these two trials, our study is not supporting a better outcome for SVZ-invading GBMs. Instead PFS and OS were worse in SVZ-invading GBMs though SVZs irradiated higher doses in our trial (PFS, 15 months vs 9 months, $p<0.001$; OS, 18 months vs 12 months, $p<0.001$).

In the current literature, some reports showed that SVZ-invading GBMs tend to recur outside the radiation volume (out-field recurrences). Adeberg *et al.* investigated the recurrence patterns in regard to SVZ invasion [4]. They showed that SVZ-invasion and LVs contact caused a higher risk of multifocal or distant recurrence than others. In 2015, Chen *et al*. evaluated the GBM recurrence patterns [13]. They treated 102 GBM patients with RT and TMZ. They defined the neurogenic regions as both SVZ and subgranular zone (SGZ). They evaluated the relation between tumors and neurogenic zone. They found that neurogenic zone contacting GBMs (both SVZ and SGZ) were more likely to recur outside the radiation volumes [13]. Liang *et al*. evaluated the adverse and distinct progression patters for GBMs with synchronous SVZ and

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corpus callosum (CC) invasion [19]. They included 108 patients and divided into two groups as SVZ and CC invaded group and non-invaded ones. They concluded that SVZ and CC invasion status determined the worse prognosis and progressions outside the radiation volume [19]. In this study, recurrence patterns of SVZ-invading and non-invading tumors were similar. Most recently, a meta-analysis was published for giving an exact message to this issue [20]. They included 2311 patients categorized as either LV invasion+ GBM or LV invasion- GBM from 15 studies. The log-rank and reported multivariate hazard ratios were analyzed separately. They concluded that patients with GBM contacting the LV have lower survival [20]. We saw similar worse treatment outcomes for SVZ-invading tumors in this present trial.

There is not any certain explanation which can make these treatment results understandable. The first hypothesis can be speculated that SVZ-invading tumors may spill to cerebrospinal fluid (CSF) and the tumor cells may be seeded to distant parts of brain by CSF. Additionally these subclinical diseases could not be abnormal enough to be detected by MRI at the time of diagnosis. Recurrence may then occur at areas of disease which was undertreated at the time of initial therapy. Secondly, alternative theories were developed to explain recurrence patterns of GBMs [6, 21]. These reports proposed that GBM is an invasive disease and tumor cells may penetrate diffusely to brain parenchyma at the time of diagnosis. Further studies are needed to evaluate the relatively contributions of these factors.

There are some limitations in our study. First, we had relatively small number of patients due to retrospective nature of our trial. Second, MRI evaluation for enhancing tumor progression is confounded by enhancing radiation necrosis and this makes difficult to diagnose real in-field recurrences. Lastly, genetic factors which are known to contribute to radiation sensitivity of GBMs need to be evaluated more detailed techniques. While cox regression was performed to show their role, we could not find any significant results. The reasons of this may be low number of IDH mutant tumors that our treatment cohort includes. Additionally we could not have a chance to evaluate methylation status of *MGMT* gene.

Treatment outcomes of GBM patients are heterogeneous and affected by multiple factors. Our results showed that SVZ-infiltrating or LV-contacting GBMs have worse results for both PFS and OS rates. The behavior of LV-contacting GBMs may be affected from the neural stem cells which are located around the SVZs. It may be speculated that SVZs infiltration gives tumor an aggressive character.

CONCLUSION

The clear message of this study is that LVs invading and/or location close to the SVZs can be considered as an important prognostic factor in terms of decreased PFS and OS rates. The current literature is not clear, on the other hand both SVZs sparing and dose escalation to SVZs approaches are required to be evaluated in further researches.

***Conflicts of interest*:** *Declared none.*

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