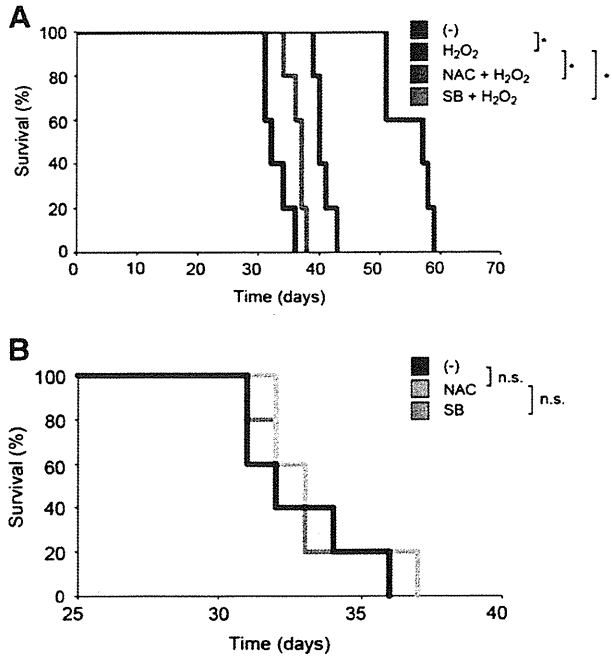

Figure 7 Pivotal role for ROS-dependent p38 MAPK activation in hydrogen peroxide-induced loss of tumor-initiating capacity of GICs. (A, B) GS-Y03 cells cultured in the absence or presence of NAC (10 mM) or SB203580 (SB, 10 μM) for 30 min were further treated with or without H_2O_2 (100 μM) as indicated in the figure for 6 days, and the cells (1×10^4) were then implanted intracranially into nude mice. Kaplan–Meier survival curves of the mice (5 mice per group) are shown separately in (A) and (B), to avoid overlap of neighboring curves. Note that the curves for the control group (indicated by (−)) in (A) and (B) are identical. $^*P < 0.05$. n.s., not significant.

the survival benefit of hydrogen peroxide treatment that would have been conferred if the GICs had been treated with hydrogen peroxide alone (Fig. 7A). Thus, the results suggest that, while the basal levels of intracellular ROS and p38 activity may not have a major impact on the tumor-initiating capacity of GICs, ROS-dependent activation of p38 is essential for the loss of tumor-initiating capacity caused by oxidative stress.

GICs have more potent antioxidant defense mechanism than their serum-differentiated counterparts

Our earlier observation that BSO induced p38-dependent differentiation of GICs suggested that the intracellular ROS level of GICs should be kept low by actively scavenging ROS produced by the cells themselves to prevent premature p38 activation and maintain the undifferentiated state for self-renewal. We therefore hypothesized that GICs may have a higher capacity to remove intracellular ROS, in other words, more potent antioxidant defense mechanism compared to differentiated tumor cells. To test this idea, we used in this study pairs of undifferentiated and serum-differentiated GICs (Matsuda et al., 2012) and compared their capacity to resist oxidative challenge. When GICs and their serum-differentiated counterparts were treated with different concentrations of hydrogen peroxide, the intracellular ROS levels were consistently lower in undifferentiated cells than in serum-differentiated cells in all three GICs examined (Figs. S12A and B). Thus, the results are in support of the idea that GICs may have a more potent antioxidant defense mechanism compared to their differentiated counterparts, which could be a reflection of the necessity of GICs to keep the intracellular ROS level in check to maintain their stem-like state.

Discussion

Despite the wealth of studies investigating the role of ROS in cancer cell biology (Pan et al., 2009), surprisingly little is known about its specific role in cancer stem cells (Kobayashi and Suda, 2012; Shi et al., 2012). In particular, control of the cellular fate of cancer stem cells, i.e., to remain in the stem cell state and continue self-renewal or to undergo differentiation into specific lineages, is one of the most important issues to be addressed and elucidated in the field of cancer stem cell biology. However, the role of ROS in the control of this critical cellular decision process remains largely unexplored (Kobayashi and Suda, 2012; Shi et al., 2012). With respect to normal stem cells such as hematopoietic stem cells and neural stem cells, there are a number of studies that examined the role of ROS in their biology. However, most of the studies are focused on the role of ROS in the control of their proliferation and self-renewal, and few address the role of ROS in the process of differentiation (Ito et al., 2004, 2006; Kim and Wong, 2009; Le Belle et al., 2011; Smith et al., 2000). Furthermore, the results of the studies indicate that the role of ROS in the control of stem cell self-renewal, for example, may be context-dependent, lending support to both ideas that ROS promote and inhibit self-renewal of stem cells (Ito et al., 2004, 2006; Kim and Wong, 2009; Le Belle et al., 2011; Smith et al., 2000; Yang et al., 2012). Thus, the role of ROS in the control of self-renewal and differentiation of cancer stem cells is not only unknown but is even unpredictable from current literature, warranting and underscoring the necessity of investigating their role in stem cells of each cancer type.

Here in this study, we examined the role of ROS in GICs and demonstrated that intracellular ROS promote both the loss of self-renewal and the differentiation of GICs, together with the molecular mechanism involved therein. Strikingly, our results suggested that "loss of self-renewal" and "differentiation" are separable phases governed by distinct molecules that are not necessarily coupled. We found, consistent with a previous report (Abdouh et al., 2009), that Bmi1 plays a key role in the maintenance of self-renewal capacity of GICs by showing that knockdown of Bmi1 impairs sphere formation and stem cell marker expression by GICs, but that Bmi1 knockdown alone is not sufficient to induce their differentiation. On the other hand, we have previously demonstrated that FoxO3 activation is sufficient to drive GICs into differentiation (Sunayama et al., 2011), and found in this study that FoxO3 knockdown does prevent differentiation of GICs promoted by ROS. Nevertheless, even in the absence of FoxO3 activation, GICs still underwent ROS-dependent loss of self-renewal capacity (i.e., reduced sphere formation and stem cell marker expression) yet without differentiation marker expression. These findings bring to light an "intermediate" cellular state (neither stem-like nor differentiated) that stands in the middle of the process of

differentiation and also suggest that differentiation is not a "default consequence" of loss of self-renewal. Importantly, we successfully identified p38 as a key player that orchestrates these two disparate phases. We have shown that p38 is required for both ROS-induced Bmi1 degradation and FoxO3 activation, and consistent with its role as a master regulator of Bmi1 and FoxO3, oxidative stress failed to promote loss of self-renewal and differentiation of GICs when the activity of p38 was blocked. The detailed mechanisms by which p38 promotes Bmi1 degradation and FoxO3 activation remain to be determined and speculative, but Bmi1 phosphorylation by p38-activated MAPKAP kinase 3 may play a role in Bmi1 degradation (Kim et al., 2011; Voncken et al., 2005), and p38 itself has been shown to directly phosphorylate and activate FoxO3 (Ho et al., 2012).

The pivotal role of the ROS–p38 axis in the control of the tumor-initiating capacity of GICs was also demonstrated in this study. We have previously shown that treatment with hydrogen peroxide inhibits the tumor-initiating capacity of GICs, suggesting that ROS may be involved in the control of their tumor-initiating capacity (Sunayama et al., 2011). Here, the results of this study indicate that the inhibitory effect of hydrogen peroxide on the tumor-initiating capacity of GICs is effectively canceled by concomitant treatment with an antioxidant NAC or a p38 inhibitor SB203580, demonstrating that increase in intracellular ROS and p38 activation are responsible for the loss of tumor-initiating capacity of GICs. Regarding how the ROS–p38 axis controls the tumor-initiating capacity of GICs, one might assume that p38-dependent FoxO3 activation plays a key role, given our previous data indicating that FoxO3 activation is sufficient to deprive GICs of their tumor-initiating capacity (Sunayama et al., 2011). However, a previous study demonstrated that Bmi1 knockdown is sufficient to inhibit the tumor-initiating capacity of GICs (Abdouh et al., 2009), which we also confirmed in our study (Fig. S14). If we take both these observations into consideration, we could safely speculate that the activation of the ROS–p38 axis would ensure loss of tumor-initiating capacity of GICs in a "redundant" manner, i.e., through both Bmi1 downregulation and FoxO3 upregulation. Here, it may deserve noting that Bmi1 knockdown, which did not induce differentiation of GICs in vitro at least in our experimental condition, was sufficient to inhibit their tumor-initiating capacity. The role of differentiation per se in the control of tumor-initiating capacity of GICs remains unknown, but it is imaginable that cells not committed to differentiation may have a higher chance of reverting to the stem-like condition, i.e., to tumor-initiating cells. Whether differentiation plays a role in "stably maintaining" the cellular state characterized by loss of tumor-initiating capacity, therefore, may be among the issues to be addressed in future studies.

We have demonstrated also in this study that inhibition of the cellular antioxidant mechanism could promote differentiation of GICs. We also observed that GICs have an enhanced antioxidant mechanism compared to their serum-differentiated counterparts. Based on these findings, we speculate that GICs may need to actively maintain their intracellular ROS levels below a threshold to prevent loss of self-renewal and premature differentiation. Indeed, cancer stem cells have been associated with lower levels of intracellular ROS than non-stem cancer cells in human breast cancers and in head and neck cancers (Diehn et al., 2009). Thus, it would also be interesting to speculate that the ROS^{low} phenotype is a common property of cancer stem cells required for the maintenance of their self-renewal capacity. However, even if it is actually the case, we need to be reminded that this does not necessarily imply that an increase in the intracellular ROS level is the "physiological cue" for the loss of the stem-like properties and tumor-initiating capacity of GICs. Indeed, our data indicated that inhibition of the ROS–p38 axis alone failed to have a discernible effect on and therefore was not required for normal tumor growth. In contrast, our data at the same time indicated that the activation of the ROS–p38 axis has a significant inhibitory effect on tumor growth. Since the intracellular ROS level is elaborately maintained low through a network of antioxidant enzymes and nuclear factors that control them (Zhang et al., 2010), interventions to perturb either each enzyme or this network system as a whole would therefore be of therapeutic benefit.

In conclusion, we have shown that ROS have a role in the control of the stem-like state and differentiation of GICs. An increase in intracellular ROS caused loss of self-renewal and differentiation of GICs via p38-mediated degradation of Bmi1 and activation of FoxO3, respectively. Our results also suggest that the ROS–p38 axis may be a novel therapeutic target to curb the tumor-initiating capacity of GICs. Interventions modulating the intracellular ROS level could therefore be a potential therapeutic approach to prevent recurrence and realize better clinical management of glioblastoma.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scr.2013.09.012.

References

Abdouh, M., Facchino, S., Chatoo, W., Balasingam, V., Ferreira, J., Bernier, G., 2009. BMI1 sustains human glioblastoma multiforme stem cell renewal. J. Neurosci. 29 (28), 8884–8896.

Bailey, H.H., 1998. L-S, R-buthionine sulfoximine: historical development and clinical issues. Chem. Biol. Interact. 111–112, 239–254.

Binda, E., Visioli, A., Reynolds, B., Vescovi, A.L., 2012. Heterogeneity of cancer-initiating cells within glioblastoma. Front. Biosci. (Schol. Ed.) 4, 1235–1248.

Binello, E., Germano, I.M., 2011. Targeting glioma stem cells: a novel framework for brain tumors. Cancer Sci. 102 (11), 1958–1966.

Boivin, A., Hanot, M., Malesys, C., Maalouf, M., Rousson, R., Rodriguez-Lafrasse, C., et al., 2011. Transient alteration of cellular redox buffering before irradiation triggers apoptosis in head and neck carcinoma stem and non-stem cells. PLoS One 6 (1), e14558.

Cheng, L., Bao, S., Rich, J.N., 2010. Potential therapeutic implications of cancer stem cells in glioblastoma. Biochem. Pharmacol. 80 (5), 654–665.

Diehn, M., Cho, R.W., Lobo, N.A., Kalisky, T., Dorie, M.J., Kulp, A.N., et al., 2009. Association of reactive oxygen species levels and radioresistance in cancer stem cells. Nature 458 (7239), 780–783.

Ho, K.K., McGuire, V.A., Koo, C.Y., Muir, K.W., de Olano, N., Maifoshie, E., et al., 2012. Phosphorylation of FOXO3a on Ser-7 by p38 promotes its nuclear localization in response to doxorubicin. J. Biol. Chem. 287 (2), 1545–1555.

Ikushima, H., Todo, T., Ino, Y., Takahashi, M., Miyazawa, K., Miyazono, K., 2009. Autocrine TGF-beta signaling maintains tumorigenicity of glioma-initiating cells through Sry-related HMG-box factors. Cell Stem Cell 5 (5), 504–514.

Ito, K., Hirao, A., Arai, F., Matsuoka, S., Takubo, K., Hamaguchi, I., et al., 2004. Regulation of oxidative stress by ATM is required for self-renewal of haematopoietic stem cells. Nature 431 (7011), 997–1002.

Ito, K., Hirao, A., Arai, F., Takubo, K., Matsuoka, S., Miyamoto, K., et al., 2006. Reactive oxygen species act through p38 MAPK to limit the lifespan of hematopoietic stem cells. Nat. Med. 12 (4), 446–451.

Kelly, G.S., 1998. Clinical applications of N-acetylcysteine. Altern. Med. Rev. 3 (2), 114–127.

Kim, J., Wong, P.K., 2009. Loss of ATM impairs proliferation of neural stem cells through oxidative stress-mediated p38 MAPK signaling. Stem Cells 27 (8), 1987–1998.

Kim, J., Hwangbo, J., Wong, P.K., 2011. p38 MAPK-Mediated Bmi-1 down-regulation and defective proliferation in ATM-deficient neural stem cells can be restored by Akt activation. PLoS One 6 (1), e16615.

Kobayashi, C.I., Suda, T., 2012. Regulation of reactive oxygen species in stem cells and cancer stem cells. J. Cell. Physiol. 227 (2), 421–430.

Le Belle, J.E., Orozco, N.M., Paucar, A.A., Saxe, J.P., Mottahedeh, J., Pyle, A.D., et al., 2011. Proliferative neural stem cells have high endogenous ROS levels that regulate self-renewal and neurogenesis in a PI3K/Akt-dependant manner. Cell Stem Cell 8 (1), 59–71.

Matsuda, K., Sato, A., Okada, M., Shibuya, K., Seino, S., Suzuki, K., et al., 2012. Targeting JNK for therapeutic depletion of stem-like glioblastoma cells. Sci. Rep. 2, 516.

Naka, K., Hoshii, T., Muraguchi, T., Tadokoro, Y., Ooshio, T., Kondo, Y., et al., 2010. TGF-beta-FOXO signalling maintains leukaemia-initiating cells in chronic myeloid leukaemia. Nature 463 (7281), 676–680.

Neman, J., Jandial, R., 2010. Decreasing glioma recurrence through adjuvant cancer stem cell inhibition. Biologics 4, 157–162.

Pan, J.S., Hong, M.Z., Ren, J.L., 2009. Reactive oxygen species: a double-edged sword in oncogenesis. World J. Gastroenterol. 15 (14), 1702–1707.

Phillips, T.M., McBride, W.H., Pajonk, F., 2006. The response of CD24(−/low)/CD44+ breast cancer-initiating cells to radiation. J. Natl. Cancer Inst. 98 (24), 1777–1785.

Sato, A., Sunayama, J., Matsuda, K., Seino, S., Suzuki, K., Watanabe, E., et al., 2011. MEK-ERK signaling dictates DNA-repair gene MGMT expression and temozolomide resistance of stem-like glioblastoma cells via the MDM2-p53 axis. Stem Cells 29 (12), 1942–1951.

Sato, A., Sunayama, J., Okada, M., Watanabe, E., Seino, S., Shibuya, K., et al., 2012. Glioma-initiating cell elimination by metformin activation of FOXO3 via AMPK. Stem Cells Transl. Med. 1 (11), 811–824.

Shi, X., Zhang, Y., Zheng, J., Pan, J., 2012. Reactive oxygen species in cancer stem cells. Antioxid. Redox Signal. 16 (11), 1215–1228.

Smith, J., Ladi, E., Mayer-Proschel, M., Noble, M., 2000. Redox state is a central modulator of the balance between self-renewal and differentiation in a dividing glial precursor cell. Proc. Natl. Acad. Sci. U. S. A. 97 (18), 10032–10037.

Stupp, R., Mason, W.P., van den Bent, M.J., Weller, M., Fisher, B., Taphoorn, M.J., et al., 2005. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N. Engl. J. Med. 352 (10), 987–996.

Sunayama, J., Matsuda, K., Sato, A., Tachibana, K., Suzuki, K., Narita, Y., et al., 2010a. Crosstalk between the PI3K/mTOR and MEK/ERK pathways involved in the maintenance of self-renewal and tumorigenicity of glioblastoma stem-like cells. Stem Cells 28 (11), 1930–1939.

Sunayama, J., Sato, A., Matsuda, K., Tachibana, K., Suzuki, K., Narita, Y., et al., 2010b. Dual blocking of mTor and PI3K elicits a prodifferentiation effect on glioblastoma stem-like cells. Neuro Oncol. 12 (12), 1205–1219.

Sunayama, J., Sato, A., Matsuda, K., Tachibana, K., Watanabe, E., Seino, S., et al., 2011. FoxO3a functions as a key integrator of cellular signals that control glioblastoma stem-like cell differentiation and tumorigenicity. Stem Cells 29 (9), 1327–1337.

Tabatabai, G., Weller, M., 2011. Glioblastoma stem cells. Cell Tissue Res. 343 (3), 459–465.

Voncken, J.W., Niessen, H., Neufeld, B., Rennefahrt, U., Dahlmans, V., Kubben, N., et al., 2005. MAPKAP kinase 3pK phosphorylates and regulates chromatin association of the polycomb group protein Bmi1. J. Biol. Chem. 280 (7), 5178–5187.

Yang, S.R., Rahman, I., Trosko, J.E., Kang, K.S., 2012. Oxidative stress-induced biomarkers for stem cell-based chemical screening. Prev. Med. 54, S42–S49 (Suppl.).

Zhang, Q., Pi, J., Woods, C.G., Andersen, M.E., 2010. A systems biology perspective on Nrf2-mediated antioxidant response. Toxicol. Appl. Pharmacol. 244 (1), 84–97.

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The 70th Annual Meeting Special Topics — Part II: Multidisciplinary Treatment for High Grade Gliomas

Usefulness of Multimodal Examination and Intraoperative Magnetic Resonance Imaging System in Glioma Surgery

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Abstract

Extensive surgical removal of tumor tissue can contribute to longer survival for patients with gliomas. Intraoperative magnetic resonance (iMR) imaging is important for safe and maximal resection of brain tumors. A new operating room equipped with a 1.5-T MR imaging system and neuronavigation opened at Yamagata University Hospital in 2008. Using this new suite, we have safely treated over 200 cases. Use of iMR imaging improved glioma resection rates in 25 (34%) of 73 cases, and gross total resection was achieved in 48 patients (66%). Motor evoked potential (MEP) monitoring was performed in combination with iMR imaging for 32 gliomas. MEP monitoring was successful in 30 cases (94%). Transient decreases in MEP amplitude were seen in two patients. One patient showed transient motor weakness and another showed improvement of motor function. The iMR imaging system provides useful information for tumor resection that allows intraoperative modification of surgical strategies. Combining MEP monitoring with iMR imaging appears to offer the most effective method for safe glioma surgery near eloquent areas.

Key words: intraoperative magnetic resonance imaging, glioma, intraoperative monitoring

Introduction

Intraoperative magnetic resonance (iMR) imaging and neuronavigation have substantially changed the principles of surgery for brain tumors. iMR imaging can provide updated information on anatomical structures and unanticipated brain events, thereby allowing safer and more accurate surgery.[1-4] Our institution installed a fully integrated neurosurgical suite including neuronavigation and an intraoperative 1.5-T high-field MR imaging system (Surgical Suite®) in 2008. This system provides high-quality images with short scan times. The Surgical Suite® has separate components in the operating room and the MR imaging room, so can be used not only for intraoperative scanning, but also for pre- and postoperative scans and brain checks for inpatients at Yamagata University Hospital. Using this new suite, we have safely treated over 200 cases of brain tumors, including gliomas, metastatic brain tumors, meningiomas, and pituitary adenomas. This study reviews our initial experiences, to evaluate the advantages and limitations of this suite in glioma surgery.

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Material and Methods

Figure 1 shows the appearance of the operating system, Surgical Suite® (GE Healthcare, Milwaukee, Wisconsin, USA). The high-field (1.5-T) MR imaging system (Signa HDx; GE Healthcare) is located in a separate room, which allows us to use standard surgical instruments irrespective of their magnetic properties. Intraoperative MR imaging includes T_1-weighted, T_2-weighted, T_2^*-weighted, fluid-attenuated inversion recovery, diffusion-weighted, and T_1-weighted with gadolinium imaging. If necessary, diffusion tensor imaging can be performed. About 1 hour is needed for iMR imaging, including patient transfer time.

A total of 202 consecutive patients were treated in the Surgical Suite® at Yamagata University Hospital between July 2008 and September 2011. The histological diagnoses were glioma (n = 73, 36.1%), pituitary adenoma (n = 35, 17.3%), meningioma (n = 18, 8.9%), metastatic tumor (n = 19, 9.4%), and others (n = 57, 28.2%).

Surgical planning was based on multiple sequences of MR imaging performed 1 or 2 days before surgery. Using a navigation planning workstation (iPLAN 2.6; Brainlab AG, Feldkirchen, Germany), target lesions and important anatomical structures were coded as colored objects. Diffusion tensor imaging and functional MR imaging were performed to visualize important tract and functional areas (pyramidal tract, motor cortex, and speech area). If the tumor was located in or around the pyramidal tract and or motor cortex, electrophysiological monitoring such as motor evoked potential (MEP) monitoring was performed by transcortical stimulation using reduction to <50% amplitude compared to before tumor resection as the warning level. If the surgeon considered that the goals of surgery had been met or the risk of injury to a functional area or tract was high, iMR imaging was performed. If iMR imaging indicated incomplete resection, the surgical planning was revised according to the newly obtained images, and the surgical procedure was resumed based on the updated navigation information.

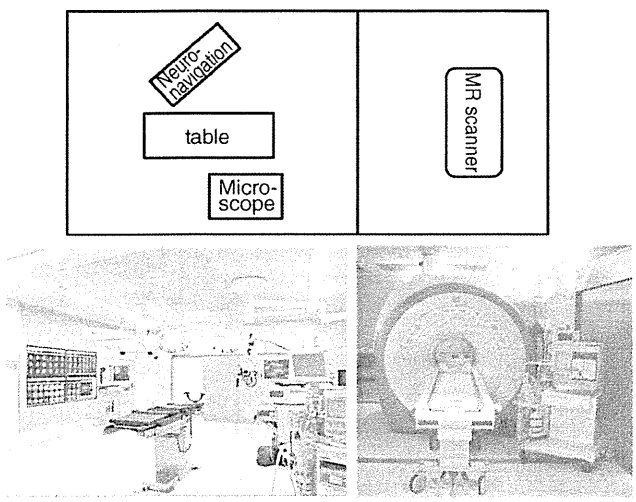

Fig. 1 Layout and photographs of the Surgical Suite®. A magnetically shielded sliding door separates the magnetic resonance (MR) imaging room (*right*) from the operation room (*left*).

The extent of resection (EOR) was determined by comparing the MR images obtained before surgery with those obtained within 72 hours after surgery. EOR was calculated based on manual segmentation of the tumor outline in the planning software. Glioma volume was defined as the volume of increased intensity on T_1-weighted imaging with gadolinium. Tumor volume for non-enhanced tumors was defined as the area of increased intensity on T_2-weighted imaging. Subtotal or greater resection was defined as a postoperative finding of a >95% reduction in tumor volume.

Results

iMR imaging was performed 225 times during the 202 procedures. The period of interruption for each intraoperative MR imaging session was about 1 hour. The results of iMR imaging affected the surgical strategy in 33 of these 202 cases, including strategies for 25 of 73 gliomas (34%), 3 of 35 pituitary adenomas (8.6%), and 5 of 57 others. Additional removal after iMR imaging was performed in over 50% of cases of non-enhanced tumors and recurrent lesions. Gross total resection was achieved in 66% of 73 glioma cases (n = 48).

Volumetric analysis of primary supratentorial gliomas (n = 40) found that mean initial tumor volumes were 54.9 cm^3 (range 1.2–160.0 cm^3) in

Table 1 Summary of volumetric analysis in primary supratentorial gliomas

	LGG	HGG	All	HGG by Sanai et al.[9]
Number of patients	7	33	40	500
Gd enhancement (+/−)	2/5	29/4	31/9	—
Tumor volume (cm^3)*	18.3 (1.0–49.0)	54.9 (1.2–160.0)	48.4 (1.0–160.0)	65.8 (0.3–476.1)
Additional removal (+)	2 (33%)	9 (27%)	11 (32%)	—
Additional removal volume (cm^3)*	3.9 (0.4–7.3)	2.4 (0.3–8.0)	2.6 (0.3–8.0)	—
Residual tumor volume (cm^3)*	4.6 (6.5–12.7)	2.3 (0.8–25.5)	2.6 (0.8–25.5)	2.3 (0–80)
Intraoperative resection rate*	80.5% (40.7–100)	93.5% (34.5–100)	91.7% (34.5–100)	—
Resection rate*	83.2% (40.7–100)	95.1% (34.5–100)	93.5% (34.5–100)	96% (10–100)

*Values are mean (range). Gd: gadolinium, HGG: high-grade glioma, LGG: low-grade glioma.

high-grade glioma (HGG) and 18.3 cm^3 (range 1.0–49.0 cm^3) in low-grade glioma (LGG). The volume of additional removal after iMR imaging was 2.4 cm^3 (range 0.3–8.0 cm^3) in HGG and 3.9 cm^3 (range 0.4–7.3 cm^3) in LGG. Residual tumor volume was 2.3 cm^3 (range 0.8–25.5 cm^3) in HGG and 4.6 cm^3 (range 6.5–12.7 cm^3) in LGG. The EOR was 95.1% in HGG and 83.2% in LGG (Table 1). In addition, iMR imaging revealed an unexpected brain event in 1 patient (acute subdural hematoma). To evaluate the impact of iMR imaging, we analyzed the relationship between supratentorial glioma surgical staging (Table 2) and the incidence of additional removal after iMR imaging. This surgical staging was proposed by Nomura and Kayama and the Japanese Brain Tumor group in 2004.[5] We analyzed 44 cases of primary supratentorial glioma (4 cases were added following the volumetric analysis): stage 1, n = 0; stage 2, n = 5; stage 3, n = 21; stage 4, n = 12; stage 5, n = 6. No additional removal was performed for cases in stages 1, 2, or 5. Additional removal after iMR imaging achieved subtotal resection in 3 cases (14%) in stage 3 and 3 cases (25%) in stage 4 (Fig. 2).

MEP monitoring was combined with iMR imaging in 32 gliomas. MEP monitoring was successful in 30 cases (94%), and was only unsuccessful in 2 patients with preoperative severe motor weakness. Table 3 shows the results of MEP monitoring and postoperative motor function. Preoperative motor deficits were improved in 4 patients and remained unchanged in 19 patients. Permanent motor deficits were identified in 5 patients, 2 patients with decreased amplitude of MEP and 3 patients with no changes in MEP amplitude. Transient decreases in MEP amplitude were seen in 2 patients. One of these two patients had left temporal glioblastoma and showed transient decreases in MEP amplitude caused by middle cerebral artery compression (Fig. 3). iMR imaging showed no ischemic changes, but diffusion-weighted imaging after surgery clearly showed an ischemic lesion around the left internal capsule.

Table 2 Surgical staging for glioma

Stage	Definition
1	tumor size ≤1 cm or within one gyrus
2	Stage 1 (+1) or tumor size >1 cm to <3 cm
3	Stage 2 (+1) or tumor size >3 cm
4	Stage 3 (+1) or stage 2 (+1+1)
5	Stage 3 (+1+1) or stage 2 (+1+1+1) or multiple lesions, disseminated lesions, extra-CNS lesions

+1: Eloquent area (motor, speech, visual); thalamus, basal ganglia, bilateral lesions; sylvian fissure (insular cortex). CNS: central nervous system. Reproduced with permission from Kayama et al.: [A proposed staging system for glioma surgery]. *No Shinkei Geka Journal* 13: 448–453, 2004 (Japanese),[5] ©2004, The Japanese Congress of Neurological Surgeons.

Discussion

The present study suggests that the best use for iMR imaging and integrated navigation seems to be for glioma surgery. In our series, 34% of glioma cases

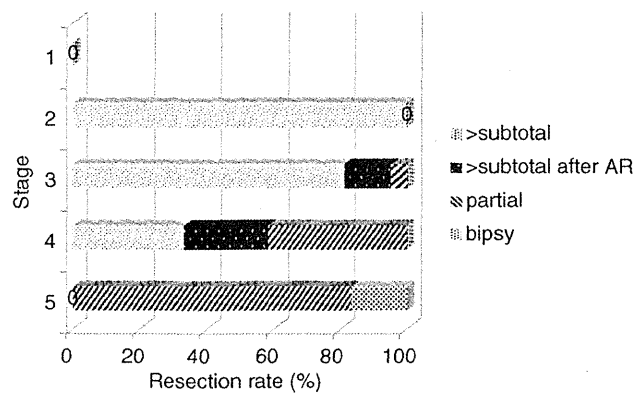

Fig. 2 Surgical staging and resection rate. Tumors in stages 1, 2, and 5 underwent no additional removal (AR) after intraoperative magnetic resonance imaging. AR was performed for 14% of stage 3 cases and 25% of stage 4 cases.

Table 3 Results of intraoperative motor evoked potential (MEP) monitoring and postoperative motor function

MEP	Postoperative motor function				Total
	Improve	No change	Transient aggravation	Permanent aggravation	
No change	3	19	1	3	26
Transient decrease in amplitude	1	0	1	0	2
Permanent decrease in amplitude (<50%)	0	0	0	2	2
Total	4	19	2	5	30

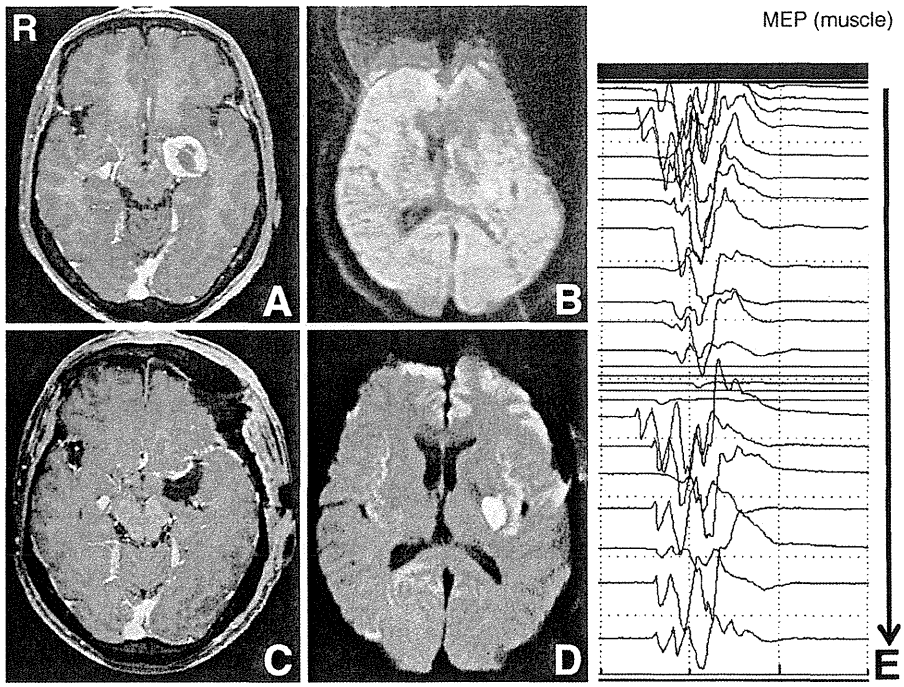

Fig. 3 Representative case of left temporal glioblastoma showing transient decrease in motor evoked potential (MEP) amplitude. A: Preoperative T_1-weighted magnetic resonance (MR) image with gadolinium. B: Intraoperative diffusion-weighted MR image. C: Postoperative T_1-weighted MR image with gadolinium. D: Postoperative diffusion-weighted MR image. E: Temporal changes in response of the thenar muscles. Transient decrease in amplitude occurred during middle cerebral artery compression, but recovered after releasing the compression.

were improved and the EOR was increased following iMR imaging. This modality offers particularly important contributions to modification of surgery in non-enhanced and recurrent tumors. In addition, iMR imaging is a good method to overcome technical problems encountered during surgery, such as unclear margins of microscopic and pathological findings and brain shift. In patients with newly diagnosed glioblastomas, increased EOR parallels improvements in overall survival, even at the highest levels of resection, and subtotal resections as low as 78% confer survival benefits.[9] Our results are similar to these findings (Table 1). In our series, the resection rate of LGG was lower than that of HGG. Three of 7 LGGs were located in eloquent areas, so we intentionally performed partial resection. The resection rates of these cases ranged from 40.7% to 71.9%. Safer resection could be performed for LGG than for HGG considering the long natural history of LGG. Randomized controlled trials of iMR imaging-guided glioma surgery did not demonstrate survival benefits.[10] However, iMR imaging guidance in glioma surgery did help surgeons achieve the optimum EOR.

This study analyzed surgical staging and additional (modified) removal after iMR imaging. For tumors classified in stages 1, 2, or 5, no modification was required after iMR imaging. Stage 5 tumors are not resectable to ensure preservation of brain function. In contrast, tumors in stages 3 and 4 underwent the modification after iMR imaging in 15–25% of cases. Moreover, over 50% of recurrent or non-enhanced tumors underwent modification after iMR imaging. iMR imaging is mainly useful for safety management in patients with stage 1, 2, or 5 lesions. Safety management is one of the important purposes of iMR imaging. In our series, we were able to detect left acute subdural hemorrhage during right temporal glioblastoma removal,[7] and could remove the hematoma immediately after tumor resection. The postoperative course was uneventful and the patient remained alive as of 26 months postoperatively.

Review of iMR imaging-guided resection of glioblastoma pointed out the limitations in the available literature,[6] and also suggested cost as an important outcome parameter. Our Surgical Suite® has separate components in the operating room and MR imaging room. Consequently, the system can be used not only for intraoperative imaging, but also for pre- and postoperative imaging and brain checks for inpatients. We have also tried to use iMR imaging in various neurosurgical operations. T_1-weight-

ed imaging with gadolinium clearly shows residual tumor in the pituitary region, and intraoperative time-resolved contrast-kinetics imaging can reveal complete resection of arteriovenous malformation without the need for conventional catheter angiography.[8]

The present study examined the associations between MEP monitoring and postoperative motor function in 32 patients. MEP monitoring was successful in 30 patients (94%), excluding 2 patients with severe preoperative motor weakness. Preoperative motor deficits recovered in 4 patients, whereas 19 patients showed no changes in motor function. Permanent deficits occurred in 5 patients. We were able to detect decreases in amplitude for 2 patients, but the remaining 3 patients did not show any change in MEP amplitude during surgery. One patient with precentral gyrus glioblastoma suffered motor weakness of the upper limb, and one patient had frontal gliosarcoma. We temporarily clipped the feeding arteries, and checked MEP responses within 20–30 minutes during gliosarcoma removal. We confirmed that MEP responses were unchanged, and then cut the feeder vessels. Postoperative MR imaging revealed an ischemic lesion, including the pyramidal tract. We speculate that the blood supply to the pyramidal tract during surgery was sufficient, but was altered by leptomeningeal anastomosis after surgery. Figure 3 shows the usefulness of MEP monitoring. Compression of the middle cerebral artery caused decrease in MEP amplitude. We were able to prevent permanent deficits based on the warnings provided by MEP monitoring. MEP monitoring is an essential tool for preserving motor function in patients with glioma near the motor cortex or pyramidal tract. We have safely performed 6 awake craniotomies with the use of this iMR imaging system. Combining MEP monitoring with awake craniotomy and iMR imaging appears to offer the most effective method for safe glioma surgery near eloquent areas. Further study of the impact of an iMR imaging system on surgical success and patient survival within the context of a large, prospective, population-based project is needed to confirm the present findings.

The present study shows that iMR imaging provides useful information that allows intraoperative modification of the surgical strategy, and MEP monitoring provides useful information for preserving motor function in patients with gliomas near the primary motor cortex and pyramidal tract. Combined use of iMR imaging, neuronavigation, and MEP monitoring offers the optimal tool for treating brain tumors around the motor cortex or pyramidal tract. This approach could be very helpful for maximizing resection and minimizing morbidity.

References

1) Black PM, Alexander E 3rd, Martin C, Moriarty T, Nabavi A, Wong TZ, Schwartz RB, Jolesz F: Craniotomy for tumor treatment in an intraoperative magnetic resonance imaging unit. *Neurosurgery* 45: 423–430, 1999
2) Black PM, Moriarty T, Alexander E 3rd, Stieg P, Woodard EJ, Gleason PL, Martin CH, Kikinis R, Schwarz RB, Jolesz F: Development and implementation of intraoperative magnetic resonance imaging and its neurosurgical applications. *Neurosurgery* 41: 831–845, 1997
3) Claus EB, Horlacher A, Hsu L, Schwartz RB, Dellolacono D, Talos F, Jolesz F, Black PM: Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guide. *Cancer* 103: 1227–1233, 2005
4) Fahlbusch R, Ganslandt O, Buchfelder M, Schott W, Nimsky C: Intraoperative magnetic resonance imaging during transsphenoidal surgery. *J Neurosurg* 95: 381–390, 2001
5) Kayama T, Sonoda Y, Sato S, Fujimaki T, Shibui S, Nomura K: [A proposed staging system for glioma surgery]. *No Shinkei Geka Journal* 13: 448–453, 2004 (Japanese)
6) Kubben PL, ter Meulen KJ, Schijins OE, ter Laak-Poort MP, Van Overbeekr JJ, van Santbrik H: Intraoperative MRI-guided resection of glioblastoma multiforme: a systematic review. *Lancet Oncol* 12: 1062–1070, 2011
7) Sakurada K, Kikuchi Z, Kuge A, Takemura S, Kokubo Y, Sato S, Kayama T: [Detection of acute subdural hemorrhage using intraoperative MR imaging during glioma surgery: case report]. *No Shinkei Geka* 38: 1115–1120, 2010 (Japanese)
8) Sakurada K, Kuge A, Takemura S, Huniu H, Kokubo Y, Kondo R, Sato S, Kayama T: Intraoperative magnetic resonance imaging in the successful surgical treatment of an arteriovenous malformation: case report. *Neurol Med Chir (Tokyo)* 51: 512–514, 2011
9) Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS: An extent of resection threshold for newly diagnosed glioblastoma. *J Neurosurg* 115: 3–8, 2011
10) Senft C, Bink A, Vatter H, Gasser T, Seifert V: Intraoperative MRI-guidance and extent of resection in glioma surgery: a randomized, controlled trial. *Lancet Oncol* 12: 997–1003, 2011

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CLINICAL STUDY

Treatment outcomes in glioblastoma patients aged 76 years or older: a multicenter retrospective cohort study

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Abstract Age is one of the most important prognostic factors in glioblastoma patients, but no standard treatment has been established for elderly patients with this condition. We therefore conducted a retrospective cohort study to evaluate treatment regimens and outcomes in elderly glioblastoma patients. The study population consisted of 79 glioblastoma patients aged ≥76 years (median age 78.0 years; 34 men and 45 women). The median preoperative Karnofsky performance status (KPS) score was 60. Surgical procedures were classified as biopsy (31 patients, 39.2 %), <95 % resection of the tumor (21 patients, 26.9 %), and ≥95 % resection of the tumor (26 patients, 33.3 %). Sixty-seven patients (81.0 %) received radiotherapy and 45 patients (57.0 %) received chemotherapy. The median overall progression-free survival time was 6.8 months, and the median overall survival time was 9.8 months. Patients aged ≥78 years were significantly less likely to receive radiotherapy ($p = 0.004$). Patients with a postoperative KPS score of ≥60 were significantly more likely to receive maintenance chemotherapy ($p = 0.008$). Multivariate analyses identified two independent prognostic factors: postoperative KPS score ≥60 (hazard ratio [HR] = 0.531, 95 % confidence interval [CI] 0.315–0.894, $p = 0.017$) and temozolomide therapy (HR = 0.442, 95 % CI 0.25–0.784, $p < 0.001$).The findings of this study suggest that postoperative KPS score is an important prognostic factor for glioblastoma patients aged ≥76 years, and that these patients may benefit from temozolomide therapy.

Keywords Glioblastoma · Karnofsky performance status score · Elderly patients · Temozolomide

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Introduction

Previous studies have reported several prognostic factors for glioblastoma including age, performance status (PS), the extent of tumor resection, and biological markers, with age being one of the most important factors [1].

Stupp et al. [2] conducted a phase III randomized clinical trial of 573 glioblastoma patients aged 18–70 years with World Health Organization PS 0–2, and reported a median overall survival (mOS) of 12.1 months in the group who received radiotherapy alone and 14.6 months in the group who received both radiotherapy and temozolomide (TMZ). On the basis of these results, the standard treatment for glioblastoma is a combination of surgical resection, radiotherapy, and chemotherapy with TMZ. However, the trial by Stupp et al. [2] included only patients aged ≤70 years. Several other important clinical trials also excluded elderly patients, and no standard treatment has been established for this group.

Some prospective studies have reported the use of TMZ in older patients with glioblastoma. Brandes et al. [3] conducted a prospective trial in elderly glioblastoma patients that included three treatment arms: (1) standard radiotherapy, (2) standard radiotherapy plus adjuvant procarbazine, lomustine, and vincristine (PCV), and (3) standard radiotherapy plus adjuvant TMZ. Patients in the TMZ group showed significantly increased OS compared with those treated with radiotherapy alone (14.9 vs. 11.2 months). In multivariate analysis, only the Karnofsky performance status (KPS) score was a significant factor associated with OS, and the association of TMZ was not significant. Pérez-Larraya el al. [4] reported a nonrandomized, phase II trial for patients ≥70 years old with a postoperative KPS score of <70. These patients were treated with TMZ without radiotherapy, and benefits were seen for TMZ alone in comparison with historical controls.

There is no clear definition of 'elderly' in this patient group, although many studies have defined elderly as ≥60 years or ≥65 years. The mean age of onset of glioblastoma is in the 60 s. Because of the aging population, the proportion of glioblastoma patients who are in the elderly age group is increasing. One report stated that the number of glioblastoma patients aged ≥65 years is expected to double from 2,000 to 2,030 [5].

One approach to developing treatment standards for elderly patients is to investigate glioblastoma in a group of more advanced age. A population-based study of 2,882 glioblastoma patients in Norway found that 15.9 % were aged ≥75 years [6]. Data from the Brain Tumor Registry of Japan (1984–2000) showed that 10.0 % of glioblastoma patients were aged ≥75 years [7]. This group is referred to as "late-stage elderly" in Japan. Only one previous study by Piccirilli et al. [8] has reported treatment outcomes in elderly late-stage glioblastoma patients.

We conducted a retrospective cohort study of glioblastoma patients aged ≥76 years who were treated at seven institutions in the Tohoku Brain Tumor Study Group, to evaluate treatment regimens and outcomes. We also aimed to elucidate problems specific to glioblastoma patients in this age group, and factors affecting the prognosis of these patients.

Methods

This study included patients aged ≥76 years with primary glioblastoma who were treated at seven institutions participating in the Tohoku Brain Tumor Study Group between January 1995 and January 2010. The diagnosis of glioblastoma was confirmed by histopathological examination in all patients.

Questionnaire survey forms were sent to each institution. Information collected in the survey was based on medical and surgical records, and head computed tomography (CT) or magnetic resonance imaging (MRI) findings. Factors surveyed included the number, location, and maximum diameter of tumors; preoperative and postoperative KPS scores; the extent of tumor resection; radiotherapy; chemotherapy (nimustine [ACNU] and ranimustine [MCNU]/TMZ); adverse reactions to chemotherapy; additional treatments; and preoperative and postoperative complications. Extent of resection was classified as biopsy if <50 % was resected, <95 % resection if 50–94 % of the tumor was resected, and ≥95 % resection if 95–100 % of the tumor was resected according to the assessment of the surgeon. Nine of the authors (T.U., K.A., T.S., K.S., T.K., T.B., M.I., C.K., and H.A.) then reviewed radiological images from all patients to determine the accuracy of tumor resection classification. Adverse reactions to chemotherapy were classified according to the Common Toxicity Criteria for Adverse Events (CTCAE) Version 3.0 of the National Cancer Institute.

Patients who did not undergo contrast-enhanced CT or MRI before surgery were excluded. If several contrast-enhanced lesions were detected but T2-weighted or fluid-attenuated inversion recovery MRI indicated continuity between these lesions, the tumor was considered to be solitary. The preoperative KPS score was defined as the lowest KPS score recorded between admission and initial surgery, and the postoperative KPS score was defined as the highest KPS score recorded between surgery and discharge. We chose to use the lowest KPS score for preoperative assessment in order to eliminate the effects of corticosteroid or osmotic diuretic drugs. For the postoperative KPS score, the highest records were considered to eliminate the effects of transient, postoperative neurological worsening.

The first day of treatment was defined as the day of surgery. Progression-free survival (PFS) was defined as the time to detection of tumor growth or death. Overall survival (OS) was defined as the time to the last confirmed survival date or death. Tumor growth was assessed using Macdonald's Criteria [9]. Age, maximum tumor diameter, and preoperative and postoperative KPS scores were compared between patients with values lower than the median and patients with values equal to or higher than the median.

Univariate analyses were performed using the Chi squared test and Mann–Whitney U-test. Survival curves were calculated using the Kaplan–Meier method and were compared using the log-rank test. Statistical significance was defined as a p value <0.05. Multivariate analyses of risk factors were performed using the Cox proportional hazards model. All analyses were performed using IBM SPSS statistics software, version 19.0 (IBM SPPS, Chicago, IL).

Results

Baseline characteristics of patients

Data from 80 patients were recorded, and 1 patient with inadequate preoperative images was excluded. Table 1 shows the baseline characteristics of the 79 patients included in the study. There were 34 men and 45 women, with a median age of 78.0 years (range 76–86 years). The preoperative KPS score ranged from 10 to 90 (median 60). The follow-up period ranged from 1.3 to 51.4 months (median 9.3 months). Seventy-five patients (94.9 %) died before the survey date. No patients died within 30 days after surgery.

The initial surgical procedure was biopsy in 31 patients (39.2 %) and tumor resection in 48 patients (60.8 %). One patient who underwent tumor resection did not undergo postoperative contrast-enhanced imaging and was excluded from the analysis of tumor resection. Twenty patients (25.3 %) underwent <95 % resection and 28 patients (35.4 %) underwent ≥95 % resection. Sixty-four patients (81.0 %) received radiotherapy, and 43 patients (54.4 %) received chemotherapy (12 patients received ACNU/MCNU and 25 patients received TMZ, and 6 patients received both ACNU and TMZ). All of the ACNU/MCNU-treated patients in this study were treated prior to the approval of TMZ in Japan in 2006. ACNU was administered as adjuvant chemotherapy followed by radiation for 2–4 (median 3) cycles to 2 patients. TMZ was also administered as adjuvant chemotherapy for 1–32 (median 6.5) cycles (150–200 mg/m^2 day, 5 days/4 weeks) to 27 patients.

Tumor recurrence was observed in 51 patients (64.6 %). Additional treatments for recurrence included stereotactic radiotherapy in five patients (6.3 %) and salvage surgery in three patients (3.8 %).

Treatment regimens according to age and KPS scores

Table 2 shows treatment regimens according to age and pre- and postoperative KPS scores. Patients aged ≥78 years were significantly less likely to receive radiotherapy ($p = 0.004$). Patients with a postoperative KPS score of ≥60 were significantly more likely to receive maintenance chemotherapy than patients with a postoperative KPS score of <60 ($p = 0.008$). Biopsy versus tumor resection was not significantly associated with age or preoperative KPS score.

Perioperative complications

Table 3 shows perioperative complications. The complications that occurred in five or more patients were analyzed using the log-rank test. Complications directly associated with surgery (worsening of hemiparesis, worsening of cognitive dysfunction, postoperative bleeding, and worsening of aphasia) were observed in 18 of the 79 patients (22.8 %). Patients with a previous stroke had a significantly shorter survival time ($p = 0.048$).

Univariate analyses of relationships between patient characteristics and survival

The median PFS (mPFS) was 6.8 months, and the median OS was 9.8 months (Fig. 1).

Tables 1 and 3 show the results of univariate analyses of the relationships between patient characteristics and mOS. The factors that were significantly associated with mOS were a postoperative KPS score of <60 or ≥60 (7.4 vs. 14.3 months, $p < 0.001$), previous stroke present or absent (5.9 vs. 10.2 months, $p = 0.048$), radiotherapy received or not received (11.8 vs. 5.3 months, $p = 0.001$), and TMZ received or not received (16.3 vs. 7.1 months, $p < 0.001$). There was no significant difference in mOS between patients with a preoperative KPS score of ≥60 or <60 (10.2 vs. 9.5 months, $p = 0.736$). Figure 1 shows Kaplan–Meier curves of estimated survival. Patients who underwent <95 % resection tended to have a shorter mOS than patients who underwent ≥95 % resection, but this difference was not significant (8.8 vs. 15.8 months, $p = 0.052$). Patients who underwent ≥95 % resection tended to have a longer mOS than those who underwent biopsy only, but this difference was also not significant (9.1 vs. 13.0 months, $p = 0.103$).

The median PFS was 4.6, 5.8, 10.0, and 17.9 months in the no-chemotherapy ($n = 36$), ACNU/MCNU-treated ($n = 12$), TMZ-treated ($n = 25$), and ACNU/MCNU plus TMZ-treated ($n = 6$) groups, respectively. There was no statistically significant difference between the ACNU/MCNU-treated and TMZ-treated groups ($p = 0.812$).

Table 1 Baseline patient characteristics and patient treatments, and the results of univariate analyses of the relationships between these factors and overall survival

Characteristic	No. of patients (%)	*p* value (log-rank test)
Gender		0.822
Male	34 (43.0)	
Female	45 (57.0)	
Age (years)		
Median	78	
Range	76–86	
≥78	55	0.504
<78	24	
Preoperative KPS score		
Median	60	
Range	10–90	
≥60	40	0.736
<60	39	
Postoperative KPS score		
Median	60	
Range	10–100	
≥60	44	<0.001*
<60	35	
Multicentric disease		0.87
No	71 (89.9)	
Yes	8 (10.1)	
Disease distribution		
Right	31 (39.2)	
Left	39 (49.4)	
Midline	2 (2.5)	
Bilateral	7 (8.9)	
Tumor location		
Frontal	33 (41.8)	
Temporal	11 (13.9)	
Parietal	22 (27.8)	
Occipital	3 (3.8)	
Basal ganglia	3 (3.8)	
Thalamus	2 (2.5)	
Corpus callosum	2 (2.5)	
Lateral ventricle	1 (1.3)	
Other	2 (2.5)	
Maximum tumor diameter (cm)		
Median	4.5	
Range	1.4–8.0	
≥4.5	40	0.107
<4.5	35	
Extent of surgery		0.052
Biopsy	31 (39.2)	
<95 % resection	21 (26.9)	
≥95 % resection	26 (33.3)	
Radiotherapy		0.001*
Yes	64 (81.0)	
59.4–61.6 Gy (30–35 fr)	42 (65.6)	
30–39 Gy (10–13 fr)	14 (21.9)	
52–54 Gy (26–27 fr)	3 (4.7)	
84 Gy (44 fr)	2 (3.1)	
15 Gy (brachytherapy)	2 (3.1)	
60 Gy (40 fr)	1 (1.6)	
Chemotherapy		
Yes	43 (54.4)	
TMZ therapy		<0.001*
Total	31	
Concomitant	19	
Adjuvant	27	
ACNU/MCNU therapy		0.84
Total	18	
Concomitant	16	
Adjuvant	3	
Myelosuppression (CTCAE grade ≥ 3)		
Concomitant ACNU/MCNU	5/16 (31.3)	
Concomitant TMZ	4/19 (3.7)	
Adjuvant ACNU/MCNU	1/3 (33.3)	
Adjuvant TMZ	1/27 (3.7)	
Adjuvant SRT/SRS	5 (6.3)	0.078
Second look surgery	3 (3.8)	
Recurrence		
Yes	51 (64.6)	
No	19 (24.1)	
Unknown	9 (11.4)	
Outcome		
Alive	4 (5.1)	
Dead	75 (94.9)	

* $p < 0.05$

Multivariate analyses using the Cox proportional hazards model

Table 4 shows the results of multivariate analyses of the relationships between mOS and postoperative KPS score (<60 or ≥60), radiotherapy (received or not received), TMZ (received or not received), and previous stroke (present or absent). Postoperative KPS score (hazard ratio [HR] = 0.531, 95 % confidence interval [CI] 0.315–0.894, $p = 0.017$) and TMZ therapy (HR = 0.442, 95 % CI 0.25–0.784, $p < 0.001$) were identified as independent prognostic factors.

Table 2 Treatment regimens according to age and KPS scores

	Age <78	Age ≥78	*p* value	Preoperative KPS <60	Preoperative KPS ≥60	*p* value	Postoperative KPS <60	Postoperative KPS ≥60	*p* value
Biopsy	7	24	0.317	14	17	0.647			
Resection	17	31		25	23				
Radiotherapy (+)	24	40	0.004*	31	33	0.781	26	38	0.249
Radiotherapy (–)	0	15		8	7		9	6	
Concomitant chemotherapy (+)	13	21	0.648	20	14	0.129	15	19	1.000
Concomitant chemotherapy (–)	9	34		18	25		20	23	
Adjuvant chemotherapy (+)	11	21	0.44	15	17	0.813	8	24	0.008*
Adjuvant chemotherapy (–)	10	30		21	19		23	17	

* $p < 0.05$

Table 3 Perioperative complications, and the results of univariate analyses of the relationships between these factors and overall survival

Complication	*n*	*p* value (log-rank test)
Preoperative complications		
Hypertension	28	0.778
Malignant tumor	10	0.417
Cognitive dysfunction	5	0.639
Chronic respiratory failure	5	0.271
Stroke	5	0.048*
Ischemic heart disease	4	
Arrhythmia	4	
Diabetes mellitus	2	
Chronic renal failure	2	
Liver dysfunction	2	
Postoperative complications		
Hemiparesis	13	0.096
Cognitive dysfunction	6	
Postoperative hemorrhage	2	
Aphasia	3	
Respiratory dysfunction	2	
Deep vein thrombosis	1	

* $p < 0.05$

Discussion

Among all 79 patients, mPFS was 6.8 months and mOS was 9.8 months. Even though the study included glioblastoma patients aged ≥76 years with a low PS, the outcomes were relatively favorable.

Age is one of the most important prognostic factors in glioblastoma patients [1]. The lack of standard treatment regimens for elderly glioblastoma patients may be one of the reasons why this group has a poor prognosis. These patients may be less likely to receive surgery, radiotherapy, and chemotherapy. Kita et al. [10] reported that the proportion of glioblastoma patients receiving only best supportive care increased with age, and that 75 % of patients aged ≥75 years received only best supportive care. Barnholtz-Sloan et al. [11] analyzed the treatment of 1,753 malignant glioma patients aged ≥66 years, and found that multidisciplinary treatment was significantly less common in patients aged ≥75 years.

Of the 79 patients in the present study, 48 (60.8 %) underwent surgical resection, 64 (81.0 %) received radiotherapy, and 45 (57.0 %) received chemotherapy. Data from the Brain Tumor Registry of Japan between 1984 and 2000 show that 3,695 of 5,328 patients (69.4 %) underwent tumor resection, 4,649 of 5,395 patients (86.2 %) received radiotherapy, and 3,403 of 4,985 patients (68.3 %) received chemotherapy [7]. All these treatment regimens were administered at a lower rate in our study group. Our findings show that more elderly patients were significantly less likely to receive radiotherapy, and that elderly patients with low a postoperative KPS score were significantly less likely to receive maintenance chemotherapy. Although biopsy versus surgical resection was not significantly associated with age or preoperative KPS score, we observed that radiological findings reflecting tumor location and extent of invasion might influence the choice of biopsy versus surgical resection. Scott et al. [12] conducted a retrospective study of 206 glioblastoma patients aged ≥70 years, and reported that 45 % of patients underwent surgical resection, 60 % received radiotherapy, and 20 % received chemotherapy, with a mOS of 4.5 months. In comparison, the patients in our study were more likely to receive radiotherapy and chemotherapy, which may have contributed to the longer survival times.

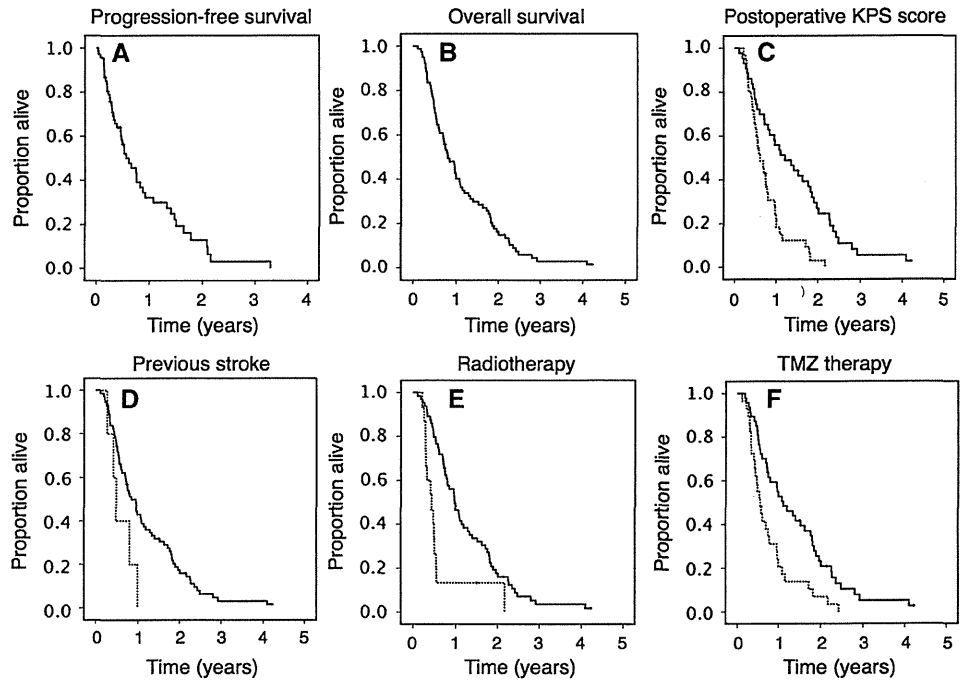

Fig. 1 Kaplan–Meier survival curves. **a** Progression-free survival. **b** Overall survival (OS). **c** OS in patients with a postoperative KPS score of ≥60 (*solid line*) and <60 (*dotted line*) ($p < 0.001$). **d** OS in patients without a previous stroke (*solid line*) and with a previous stroke (*dotted line*) ($p = 0.048$). **e** OS in patients who received radiotherapy (*solid line*) and who did not receive radiotherapy (*dotted line*) ($p = 0.001$). **f** OS in patients who received TMZ (*solid line*) and who did not receive TMZ (*dotted line*) ($p < 0.001$). All these factors were significantly associated with OS according to the log-rank test

Table 4 Multivariate analyses of factors associated with overall survival

	p value	Odds ratio	95 % CI
Postoperative KPS	0.017*	0.531	0.315–0.894
Radiotherapy	0.142	0.615	0.321–1.178
TMZ therapy	0.005*	0.442	0.25–0.784
Stroke	0.213	1.822	0.709–4.679

* $p < 0.05$

Some reports have indicated that elderly patients should be treated as aggressively as younger patients [13–20], especially patients with a favorable PS [13, 16, 17]. Minniti et al. [21] conducted a prospective trial of 32 primary glioblastoma patients aged ≥70 years. These patients received a combination of surgery, radiotherapy (total of 60 Gy), and chemotherapy with TMZ, and the mOS was 10.6 months. Multivariate analysis identified only preoperative KPS score as an independent prognostic factor. They concluded that elderly patients with a favorable preoperative KPS score should receive multidisciplinary treatment.

The previously reported prognostic factors for elderly glioblastoma patients are preoperative KPS score, extent of tumor resection, radiotherapy, chemotherapy, and O^6-methylguanine-deoxyribonucleic acid methyltransferase (MGMT) activity [1, 2, 8, 12, 15–17, 19–24]. In our study of patients of a more advanced age, multivariate analyses identified postoperative KPS score and TMZ therapy as independent prognostic factors. It is interesting that prognosis was correlated with postoperative but not preoperative KPS score, suggesting that selection of treatment strategies based on preoperative KPS score may be less suitable in glioblastoma patients aged ≥76 years.

In the current study, the prognosis tended to be more favorable in patients who underwent ≥95 % resection than patients who underwent <95 % resection, but this difference was not significant ($p = 0.052$). However, a larger extent of tumor resection has been reported to contribute to improved outcomes in elderly glioblastoma patients [15, 17]. Chaichana et al. [23] examined risk factors to identify patients who would benefit from surgical resection. They suggested that surgery would be less beneficial in patients with one or more of the following factors: a low preoperative KPS score, chronic obstructive pulmonary disease, neurological symptoms, or a large tumor. As these factors are common in elderly patients, the benefits of aggressive surgery should be considered carefully.

Chemotherapy with TMZ is reported to be relatively safe and effective for the treatment of elderly glioblastoma patients [4, 8, 12, 14, 17, 21–30]. In our study, 31 patients received TMZ. Of the 19 patients (21.1 %) with CTCAE grade 3 myelosuppression, 4 received TMZ concomitantly with radiotherapy. Of the 27 patients (3.7 %) who received maintenance chemotherapy, one received TMZ as maintenance chemotherapy. The adverse reactions to TMZ are generally tolerable, and using TMZ as aggressively as possible may contribute to improved outcomes. Gállego Pérez-Larraya et al. [4] administered TMZ alone to

glioblastoma patients aged ≥70 years with postoperative KPS scores of ≤70, and reported that the adverse reactions were tolerable and patient outcomes were improved.

Some studies have reported low efficacy of radio-chemotherapy using TMZ and severe adverse reactions among elderly patients. In the European Organization for the Research and Treatment of Cancer (EORTC)–National Cancer Institute of Canada (NCIC) study, the HRs for death in patients receiving TMZ were 0.5 in patients aged <50 years ($p = 0.001$), 0.63 in patients aged 50–60 years ($p < 0.05$), 0.64 in patients aged 61–65 years ($p = 0.096$), and 0.78 in patients aged 66–70 years ($p = 0.34$), indicating that improvement of outcomes due to TMZ therapy decreased as patient age increased [2, 31]. Minniti et al. [21] conducted a prospective study of primary glioblastoma patients aged ≥70 years who received a combination of surgery, radiotherapy, and TMZ, and found grade 3–4 hematologic toxicity in 28 % of patients. Although the results of our study suggest that TMZ should be used aggressively, it is also necessary to be aware that TMZ may cause more severe adverse reactions in elderly patients than in younger patients. The Neuro-Oncology Working Group (NOA) 08 trial reported that postoperative monotherapy with TMZ is not inferior to radiotherapy in elderly patients, but the effects of TMZ are greatly affected by the methylation status of the MGMT promoter [30]. In the future, different treatment strategies may be employed according to the methylation status of the MGMT promoter.

A randomized phase III trial (NCT00482677) conducted by the NCIC Clinical Trials Group is currently ongoing. This study compares TMZ and short-course radiation with short-course radiation alone for the treatment of newly diagnosed glioblastoma in elderly (≥65 years) patients. The results of this study may strongly influence the treatment strategy for elderly glioblastoma patients.

This study has several limitations, including its retrospective design, reliance on questionnaire surveys for data, variation in radiotherapy regimens, and imprecise assessment of the extent of tumor resection. However, our results elucidate the present status and treatment outcomes of glioblastoma patients aged ≥76 years, which is an age group that has rarely been studied to date. Our findings may provide important information for the planning of future prospective clinical studies, which will be needed to establish a standard of treatment for elderly glioblastoma patients.

Conclusions

This study found that glioblastoma patients aged ≥76 years had an mPFS of 6.8 months and mOS of 9.8 months. Our findings suggest that the postoperative KPS score is an important prognostic factor in glioblastoma patients aged ≥76 years, and that these patients may benefit from TMZ therapy.

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Conflict of interest There are no conflicts of interest to declare.

References

1. Li J, Wang M, Won M, Shaw EG, Coughlin C, Curran WJ Jr, Mehta MP (2011) Validation and simplification of the radiation therapy oncology group recursive partitioning analysis classification for glioblastoma. Int J Radiat Oncol Biol Phys 81:623–630
2. Stupp R, Mason WP, Van den Bent MJ, European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups, National Cancer Institute of Canada Clinical Trials Group et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996
3. Brandes AA, Vastola F, Basso U, Berti F, Pinna G, Rotilio A, Gardiman M, Scienza R, Monfardini S, Silvio M, Ermani M (2003) A prospective study on glioblastoma in the elderly. Cancer 97:657–662
4. Gállego Pérez-Larraya J, Ducray F, Chinot O et al (2011) Temozolomide in elderly patients with newly diagnosed glioblastoma and poor performance status: an ANOCEF phase II trial. J Clin Oncol 29:3050–3055
5. Laperriere N, Weller M, Stupp R, Perry JR, Brandes AA, Wick W, van den Bent MJ (2012) Optimal management of elderly patients with glioblastoma. Cancer Treat Rev 39(4):350–357
6. Gulati S, Jakola AS, Johannesen TB, Solheim O (2012) Survival and treatment patterns of glioblastoma in the elderly: a population-based study. World Neurosurg 78:518–526
7. Committee of Brain Tumor Registry of Japan (2009) Report of brain tumor registry of Japan (1984–2000), 12th edition. Neurol Med Chir (Tokyo) 49(Suppl):S1–S96
8. Piccirilli M, Bistazzoni S, Gagliardi FM, Landi A, Santoro A, Giangaspero F, Salvati M (2006) Treatment of glioblastoma multiforme in elderly patients. Clinico-therapeutic remarks in 22 patients older than 80 years. Tumori 92:98–103
9. Macdonald DR, Cascino TL, Schold SC, Cairncross JG (1990) Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277–1280
10. Kita D, Ciernik IF, Vaccarella S, Franceschi S, Kleihues P, Lütolf UM, Ohgaki H (2009) Age as a predictive factor in glioblastomas: population-based study. Neuroepidemiology 33:17–22
11. Barnholtz-Sloan JS, Williams VL, Maldonado JL, Shahani D, Stockwell HG, Chamberlain M, Sloan AE (2008) Patterns of care and outcomes among elderly individuals with primary malignant astrocytoma. J Neurosurg 108:642–648
12. Scott JG, Suh JH, Elson P et al (2011) Aggressive treatment is appropriate for glioblastoma multiforme patients 70 years old or older: a retrospective review of 206 cases. Neuro Oncol 13:428–436
13. Balducci M, Fiorentino A, De Bonis P et al (2012) Impact of age and co-morbidities in patients with newly diagnosed glioblastoma: a pooled data analysis of three prospective mono-institutional phase II studies. Med Oncol 29:3478–3483

14. Combs SE, Wagner J, Bischof M, Welzel T, Wagner F, Debus J, Schulz-Ertner D (2008) Postoperative treatment of primary glioblastoma multiforme with radiation and concomitant temozolomide in elderly patients. Int J Radiat Oncol Biol Phys 70:987–992
15. Ewelt C, Goeppert M, Rapp M, Steiger HJ, Stummer W, Sabel M (2011) Glioblastoma multiforme of the elderly: the prognostic effect of resection on survival. J Neurooncol 103:611–618
16. Fiorica F, Berretta M, Colosimo C et al (2010) Glioblastoma in elderly patients: safety and efficacy of adjuvant radiotherapy with concomitant temozolomide. Arch Gerontol Geriatr 51:31–35
17. Gerstein J, Franz K, Steinbach JP, Seifert V, Fraunholz I, Weiss C, Rödel C (2010) Postoperative radiotherapy and concomitant temozolomide for elderly patients with glioblastoma. Radiother Oncol 97:382–386
18. Kushnir I, Tzuk-Shina T (2011) Efficacy of treatment for glioblastoma multiforme in elderly patients (65+): a retrospective analysis. Isr Med Assoc J 13:290–294
19. Oszvald A, Güresir E, Setzer M, Vatter H, Senft C, Seifert V, Franz K (2012) Glioblastoma therapy in the elderly and the importance of the extent of resection regardless of age. J Neurosurg 116:357–364
20. Stummer W, Nestler U, Stockhammer F et al (2011) Favorable outcome in the elderly cohort treated by concomitant temozolomide radiochemotherapy in a multicentric phase II safety study of 5-ALA. J Neurooncol 103:361–370
21. Minniti G, De Sanctis V, Muni R et al (2008) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma in elderly patients. J Neurooncol 88:97–103
22. Barker CA, Chang M, Chou JF, Zhang Z, Beal K, Gutin PH, Iwamoto FM (2012) Radiotherapy and concomitant temozolomide may improve survival of elderly patients with glioblastoma. J Neurooncol 109:391–397
23. Chaichana KL, Chaichana KK, Olivi A, Weingart JD, Bennett R, Brem H, Quinones-Hinojosa A (2011) Surgical outcomes for older patients with glioblastoma multiforme: preoperative factors associated with decreased survival. Clinical article. J Neurosurg 114:587–594
24. Mohan DS, Suh JH, Phan JL, Kupelian PA, Cohen BH, Barnett GH (1998) Outcome in elderly patients undergoing definitive surgery and radiation therapy for supratentorial glioblastoma multiforme at a tertiary care institution. Int J Radiat Oncol Biol Phys 42:981–987
25. Chaichana KL, Garzon-Muvdi T, Parker S, Weingart JD, Olivi A, Bennett R, Brem H, Quiñones-Hinojosa A (2011) Supratentorial glioblastoma multiforme: the role of surgical resection versus biopsy among older patients. Ann Surg Oncol 18:239–245
26. Chinot OL, Barrie M, Frauger E et al (2004) Phase II study of temozolomide without radiotherapy in newly diagnosed glioblastoma multiforme in an elderly populations. Cancer 100:2208–2214
27. Fiorica F, Berretta M, Colosimo C et al (2010) Glioblastoma in elderly patients: safety and efficacy of adjuvant radiotherapy with concomitant temozolomide. Arch Gerontol Geriatr 51:31–35
28. Gállego Pérez-Larraya J, Ducray F, Chinot O et al (2011) Temozolomide in elderly patients with newly diagnosed glioblastoma and poor performance status: an ANOCEF phase II trial. J Clin Oncol 29:3050–3055
29. Hashem SA, Salem A, Al-Rashdan A et al (2012) Radiotherapy with concurrent or sequential temozolomide in elderly patients with glioblastoma multiforme. J Med Imaging Radiat Oncol 56:204–210
30. Malmström A, Grønberg BH, Marosi C, Nordic Clinical Brain Tumour Study Group (NCBTSG) et al (2012) Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol 13:916–926
31. Wick W, Platten M, Meisner C, NOA-08 Study Group of the Neuro-oncology Working Group (NOA) of the German Cancer Society et al (2012) Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 13:707–715

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Special Theme Topic:
Treatment of Malignant Brain Tumor

Treatment Results of Glioblastoma during the Last 30 Years in a Single Institute

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Abstract

Treatment results of glioblastoma (GB) during the last 30 years in Tohoku University were analyzed to identify any improvements in patient outcome in all 332 histologically proven cases of newly diagnosed GB treated consecutively in our department between 1982 and 2011. These 30 years was divided into 5 treatment eras, Group 1 (1982–1988, without preoperative evaluation by magnetic resonance [MR] imaging, n = 46), Group 2 (1989–1996, with preoperative MR imaging, n = 41), Group 3 (1997–1999, additionally underwent intraoperative functional brain mapping and neuronavigation system, n = 38), Group 4 (2000–August 2006, underwent 30 Gy of whole brain radiation followed by 30 Gy of extended local accelerated hyperfractionated radiation therapy, n = 96), and Group 5 (September 2006–2011, adjuvant usage of temozolomide [TMZ], n = 111). Overall survival (OS) was calculated from the date of surgery to the death from any cause. The median survival time/2-year OS/5-year OS of Groups 1 to 5 were 10.7 months/10.9%/0%, 17.3 months/26.2%/6.9%, 15.9 months/23.7%/5.3%, 20.1 months/34.8%/15.5%, and 20.9 months/45.5%/19.7%. The prognosis for patients with GB improved significantly after the introduction of MR imaging. Younger GB, defined as patients aged below 60 years, or total tumor resection with all ages in Group 5 had 5-year OS of 31.0% and 30.1%, respectively. The prognosis of GB was improved significantly after the introduction of TMZ for elderly GB, recursive partitioning analysis class 5, or totally resected GB. Introduction of MR imaging and TMZ, and total resection of the tumor were important in the improvement of outcome for patients with GB.

Key words: glioblastoma, magnetic resonance imaging, surgery, survival, temozolomide

Introduction

Glioblastoma (GB) is the most common primary brain tumor and also has the poorest outcome, often with median survival time (MST) of only around a year. Analysis of 625 patients who underwent surgery for histologically confirmed GB between 1993 and 2004 in Atkinson Morley's Unit concluded that the survival of patients with GB had not changed.[12] Overall MST was 189 days (6.3 months). Assessment of patterns

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of diagnosis and relative survival rates across time with respect to the histological type of tumor using the population-based data from the Surveillance, Epidemiology, and End Results (SEER) Program of the US National Cancer Institute (1973–1999) revealed that patients with GB continued to have the poorest survival times.[1] Therefore, the survival times of patients with GB had not changed for more than two or three decades, despite neurosurgical advances, before the introduction of temozolomide (TMZ).[1,4,12]

Further analysis using the SEER database of 34,664 patients aged 20 years or older treated under a diagnosis of GB during the years 1973 to 2008 found that patients diagnosed with GB during the years 2000 to 2008 had a superior survival rate compared with earlier decades ($p \leq 0.001$).[13] A randomized clinical trial (European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) 22981/26981) in 2005 showed that TMZ administered with radiation therapy (RT) followed by adjuvant TMZ was effective.[11] MST could be prolonged to 14.6 months compared to 12.1 months in the control arm receiving only RT. Furthermore, almost 20% of the patients receiving TMZ with RT survived for over 2 years. The estimated adjusted hazard ratio from the SEER database showed that patients diagnosed in 2005–2006 (treated after the EORTC/NCIC 22981/26981 trial in 2004) had significantly improved survival rates compared to patients diagnosed in 2000–2001.[5] The MST and 2-year overall survival (OS) of 15 months and 26% in 2005–2006 (n = 2094) was similar to the MST and 2-year OS seen in the EORTC/NCIC phase III study. These results are encouraging and suggest that the current treatment of GB in the United States is now associated with improved survival compared to previous time cohorts. The SEER research database does not specify whether chemotherapy was administered, but the majority of patients diagnosed in 2005–2006 were presumably treated with TMZ plus RT, which led to the survival benefit when compared to earlier time periods. Widespread adoption of TMZ represents the most likely explanation for this survival improvement, although other treatment advances, such as increased extent of surgical resection, may also be important.[2] Analysis of 1,157 GB patients to investigate the effect of TMZ added to RT at population level, using the Cancer Registry of Norway, concluded that TMZ provided a 7.6-month OS benefit in the matched group analysis.[7]

Tohoku University Hospital is a flagship hospital in Sendai City, Miyagi Prefecture, in the middle of the Tohoku district. Patients are admitted from regional referring hospitals to our hospital. More than 90% of patients with GB in Miyagi Prefecture, with a population of about 2 million, are treated in our hospital. In addition, complicated cases including deep-seated or insulo-opercular tumors and tumors near/within eloquent areas are referred to our hospital from all parts of Tohoku district. The present study analyzed consecutive patients with newly diagnosed GB admitted since 1982 to assess trends in clinical characteristics over a 30-year period.

Materials and Methods

I. Data collection

Data was collected for the period 1982–2011 from the patient records and the electronic neurosurgical database. Only patients with histopathologically confirmed GB were included. Patient age, sex, performance status, date and type of surgery, adjuvant treatment, and length of survival were recorded. Recursive partitioning analysis (RPA) classification, proposed by the Radiation Therapy Oncology Group in 2011,[6] was utilized to evaluate the treatment results.

II. Historical changes of patient management and patient population

A total of 332 patients with newly diagnosed GB were treated consecutively in our department between 1982 and December 2011. All patients fundamentally underwent surgery to achieve the most extensive tumor resection possible. Two hundred and seventy patients underwent radical resection, and residual 62 underwent biopsy. RT was started within 2 weeks of surgery. Forty-six patients treated from 1982 to 1988 did not have preoperative evaluation by magnetic resonance (MR) imaging but by computed tomography (CT) (Group 1, pre MR era), 41 patients treated from 1989 to 1996 had preoperative MR imaging evaluation (Group 2, post MR era), and 38 patients treated from 1997 to 1999 underwent preoperative MR imaging with functional brain mapping and intraoperative navigation system monitoring (Group 3, post mapping era). Patients in these three groups received only extended local RT. The treatment volume for extended local RT was determined by the volume of the contrast-enhanced tumor on preoperative CT or MR imaging plus a 2-cm margin beyond the edema surrounding the tumor. In contrast, 96 patients aged below 70 years treated after 2000 underwent 30 Gy of whole brain RT followed by 30 Gy of extended local accelerated hyperfractionated (AHF) RT (Group 4, post whole brain radiation era). Patients aged 70 years and over were treated only with 60 Gy of extended

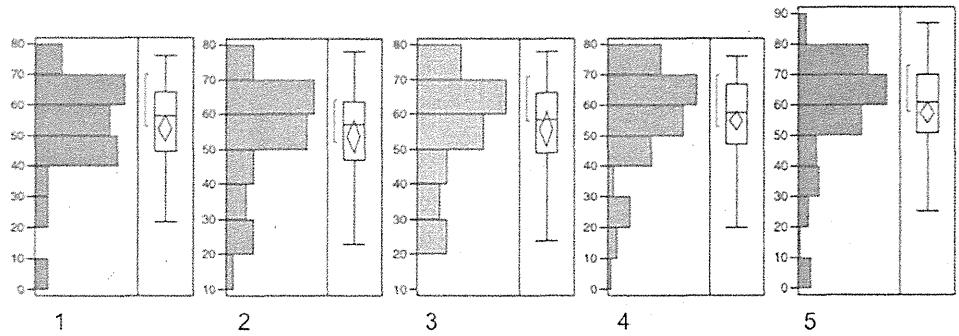

Fig. 1 Historical change of age distribution of patients with histologically proven glioblastoma in Tohoku University between 1982 and 2011. Numbers 1 through 5 correspond to Group 1 (1982–1988, pre magnetic resonance [MR] era), Group 2 (1989–1996, post MR era), Group 3 (1997–1999, post mapping era), Group 4 (2000–August 2006, post whole brain radiation era), and Group 5 (September 2006–2011, temozolomide era), respectively. Vertical axis indicates age.

local AHF RT to reduce the treatment period and damage to the whole brain.

Until 1996, nimustine hydrochloride, 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU), was administered to all patients, but ACNU treatment was stopped for patients aged 60 years and over (elderly GB) after 1997, because of the relatively high complication rate. TMZ became available in Japan after September 2006. All newly diagnosed patients aged 60 years and over and all recurrent cases received TMZ (Group 5, TMZ era, n = 111). All patients with newly diagnosed GB including those aged below 60 years (younger GB) were treated by TMZ after April 2009.

III. Surgical resection rate

Volumetric extent of resection was calculated based on the difference in preoperative and postoperative contrast-enhanced tumor volumes (expressed as a percentage) and the extent of resection for each patient was classified as gross total resection (disappearance of enhanced lesion on postoperative imaging), subtotal resection (over 75% resection), and partial resection (under 75% resection).

IV. Statistical analysis

The primary end point used for this study was OS, calculated as the time from the surgery to death from any cause. Statistical analysis was performed on July 31, 2012. At the time of the data analysis, 47 patients (14.2%) were known to be alive at recent clinical follow-up examination and were appropriately censored in the survival analysis. Another 13 patients (3.9%) were lost to follow up without available records of death. The Kaplan-Meier method was used to estimate OS for each group, and the logrank test was performed to determine statistically significant differences between groups. Factors with prognostic significance on univariate analysis were assessed by the Cox proportional hazards model for multivariate analysis. Significance was accepted at $p < 0.05$. All statistical tests were performed using JMP pro 9.0.2 (SAS Institute, Cary, North Carolina, USA).

Results

I. Treatment eras and age distribution

The historical change in age distribution during these 30 years is summarized in Fig. 1. Aging of the population was obvious, and both median and average ages increased by around 5 years. Median/average ages in Groups 1 to 5 were 56.5/52.3, 57.0/53.7, 58.5/55.5, 57.5/54.9, and 61.0/57.4 years.

II. Treatment eras and OS

The MST/2-year OS/5-year OS of Groups 1 to 5 were 322 days (10.7 months)/10.9%/0%, 520 days (17.3 months)/26.2%/6.9%, 476 days (15.9 months) /23.7%/5.3%, 603 days (20.1 months) /34.8%/15.5%, and 628 days (20.9 months) / 45.5%/19.7% (Fig. 2, Table 1). The prognosis for patients with GB was improved significantly only after the introduction of MR imaging ($p = 0.0004$). The survival curves demonstrated a trend toward improving, but the changes were modest and not statistically significant. However, the 2-year OS of all 111 patients in Group 5, treated since the introduction of TMZ, exceeded 45% and 5-year OS almost reached 20%.

III. Age, treatment eras, and OS

The OS of younger GB (n = 173) was significantly better than that of elderly GB (n = 159) ($p < 0.0001$) (Fig. 3A, Table 2). As mentioned above, the population of elderly GB was increasing, as more than half of the

patients were aged 60 years and over in Group 5 (Fig. 3B). Analysis of the OS according to age showed that introduction of MR imaging significantly improved the outcome in both groups (younger GB, p = 0.0065; elderly GB, p = 0.0014) (Fig. 3C, D, Tables 3 and 4). The OS of elderly GB was worse than that of younger GB, but the introduction of TMZ was significantly associated with improved OS (p = 0.0005) (Table 4). In younger GB, there was no significant difference between Groups 4 and 5. However, the 5-year OS of 49 patients aged below 60 years in Group 5 was 31.0% (Table 3).

IV. Surgical resection rate, treatment eras, and OS

Total resection of the tumor (n = 175) was significantly associated with better prognosis (Fig. 4A, Table 5). Two-year, 5-year, and 10-year OS of the patients with total resection were 42.9%, 17.4%, and 7.3%, respectively. Around half of the enhanced lesions on CT/MR imaging could be resected totally. There were no significant differences in resection rate between the 5 groups (Fig. 4B). In the biopsy group, there was no significant difference during the 30 years of the study (Fig. 4C, Table 6). In contrast, in the total resection group, the introduction of MR imaging (p = 0.0002) and TMZ (p = 0.0194) were significantly correlated with better OS (Fig. 4D, Table 7). Five-year OS of patients of all ages with total resection in the TMZ era was 30.1%.

V. RPA classification, treatment eras, and OS

There were significant differences between the three RPA classes (Fig. 5A, Table 8). MST of PRA classes 3, 4, and 5 were 37.9, 20.5, and 15.8 months, respectively. Most patients were classified into PRA class 5. There were no significant differences in distribution of RPA classification during the treatment eras (Fig. 5B). Introduction of MR imaging was significantly associated with better prognosis in both classes 4 and 5 (class 4, p = 0.0026; class 5, p = 0.0217) (Fig. 5C–E, Tables 9–11). In class 5, adoption of TMZ was significantly correlated with improvement of OS (p = 0.0085) (Table 11). This outcome might be highly influenced by our treatment protocols for elderly patients.

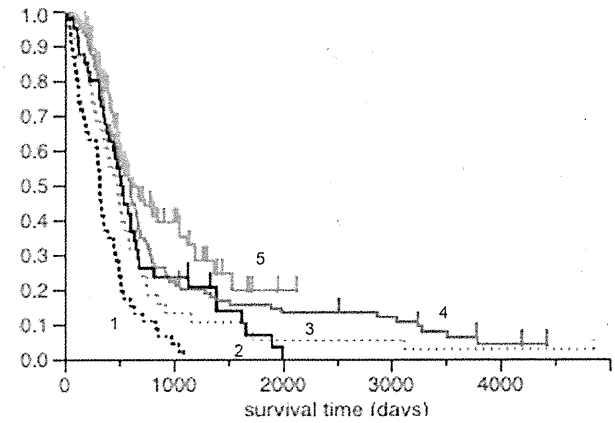

Fig. 2 Kaplan-Meier analysis of overall survival (OS) for histologically proven glioblastoma in Tohoku University between 1982 and 2011, stratified by the treatment eras. Numbers 1 through 5 correspond to Groups 1 (*black, dashed line*), 2 (*black, solid line*), 3 (*gray, dashed line*), 4 (*dark gray, solid line*), and 5 (*light gray, solid line*), respectively. Significantly increased OS was demonstrated between Groups 1 and 2 (p = 0.0004, logrank test).

VI. Prognostic factors

Multivariate analysis showed that all of the survival factors, introduction of MR imaging and TMZ, total resection of the tumor, age, and RPA classes previously identified by univariate analysis, were independent (Table 12). Introduction of MR imaging and total resection of the tumor were highly significant (p < 0.0001), followed by introduction of TMZ (p = 0.0004).

Table 1 Survival of patients with glioblastoma stratified by treatment era

Group (treatment era)	No. of patients	Median survival time (day)	Overall survival rate (%)			Probability			
			2-Year	5-Year	10-Year				
1	46	322	10.9	0.0	0.0	] p = 0.0004			
2	41	520	26.2	6.9	0.0		] NS		
3	38	476	23.7	5.3	2.6			] NS	
4	96	603	34.8	15.5	6.2				] NS
5	111	638	45.5	19.7	NR				

NR: not reached, NS: not significant.