Research Article

Identification of risk factors for poor language outcome in surgical resection of glioma involving the arcuate fasciculus: an observational study

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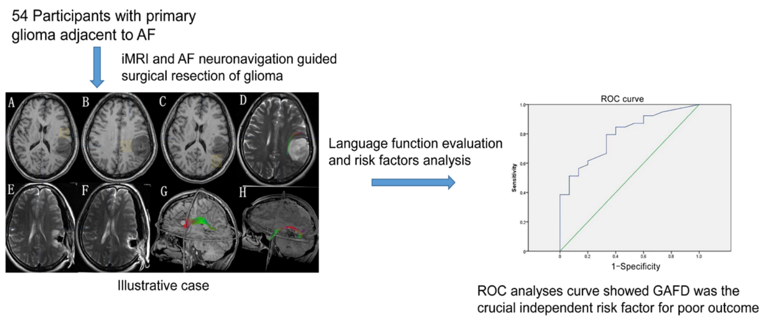
Graphical Abstract *Intraoperative MRI (iMRI) combined with diffusion tensor imaging can minimize the injury of patients' language function for glioma involving arcuate fasciculus and glioma-to-arcuate fasciculus (AF) distance is a crucial independent risk factor for postoperative language outcome*



Abstract

The arcuate fasciculus is a critical component of the neural substrate of human language function. Surgical resection of glioma adjacent to the arcuate fasciculus likely damages this region. In this study, we evaluated the outcome of surgical resection of glioma adjacent to the arcuate fasciculus under the guidance of magnetic resonance imaging and diffusion tensor imaging, and we aimed to identify the risk factors for postoperative linguistic deficit. In total, 54 patients with primary glioma adjacent to the arcuate fasciculus were included in this observational study. These patients comprised 38 men and 16 women (aged 43 ± 11 years). All patients underwent surgical resenction of glioma under the guidance of magnetic resonance imaging and diffusion tensor imaging. Intraoperative images were updated when necessary for further resection. The gross total resection rate of the 54 patients increased from 38.9% to 70.4% by intraoperative magnetic resonance imaging. Preoperative language function and glioma-to-arcuate fasciculus distance were associated with poor language outcome. Multivariable logistic regression analyses showed that glioma-to-arcuate fasciculus distance was the major independent risk factor for poor outcome. The cutoff point of glioma-to-arcuate fasciculus distance for poor outcome was 3.2 mm. These findings suggest that intraoperative magnetic resonance imaging combined with diffusion tensor imaging of the arcuate fasciculus can help optimize tumor resection and result in the least damage to the arcuate fasciculus. Notably, glioma-to-arcuate fasciculus distance is a key independent risk factor for poor postoperative language outcome. This study was approved by the Ethics Committee of the Chinese PLA General Hospital, China (approval No. S2014-096-01) on October 11, 2014.

Key Words: arcuate fasciculus; central nervous system; brain; diffusion tensor imaging; intraoperative magnetic resonance imaging; language function; risk factor; trial

Chinese Library Classification No. R445; R741; R739.4

Introduction

Language is a complex human-specific advanced cognitive function, and language deficits are associated with low quality of life and short overall survival (McGirt et al., 2009). The arcuate fasciculus (AF) is a critical component of the human language network (Rilling, 2014). The classical language pathway model is composed of Broca's area and Wernicke's area, which are connected by the AF (Geschwind, 1970;

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Kwon and Jang, 2011). The typical symptoms of injury to the AF in the dominant hemisphere are conduction aphasia and naming difficulties, although some patients may exhibit Broca's aphasia, Wernicke's aphasia or transcortical aphasia (Laubstein, 1993; Catani et al., 2005; Incekara et al., 2018). The surgical objective for glioma adjacent to the AF is maximum extent of resection (EOR) with minimum postoperative language deficit (Kuhnt et al., 2012). However, optimizing the balance between EOR and language function has remained challenging (Caverzasi et al., 2016; D'Andrea et al., 2016).

For the past few years, diffusion tensor imaging (DTI)-based tractography has been the most common method for reconstruction of white matter fibers *in vivo* (Wu et al., 2007; Lerner et al., 2014), making it possible to non-invasively study important subcortical tracts in brain tissue. DTI-based AF tractography makes visualization of the AF possible, and the feasibility and accuracy of this approach have been confirmed by several studies (Andrade et al., 2015; Caverzasi et al., 2016; Incekara et al., 2018; Bernard et al., 2019; Keser et al., 2020). In addition, combined with intraoperative magnetic resonance imaging (iMRI), DTI-based AF tractography helps increase the EOR of the lesion while preserving AF fibers (Kuhnt et al., 2012). However, language outcome and risk factors, such as EOR, gross total resection rate, number of iMRI sessions, residual volume of tumor and glioma-to-AF distance (GAFD), for glioma near AF after iMRI and DTI-guided surgical resection have not yet been well addressed. For patients with a high risk of postoperative linguistic deficit, the surgical strategy might be more conservative.

In the present study, we evaluate the impact of iMRI and DTI-based tractography on surgical outcome of glioma adjacent to AF, and identify risk factors for postoperative linguistic deficit. We also investigate whether AF tractography can help preserve language function.

Subjects and Methods

Clinical information

In total, 54 patients with primary glioma adjacent to the AF admitted to the Department of Neurosurgery, First Medical Center of Chinese PLA General Hospital, China were recruited from January 2012 to January 2013 in this prospective observational study. Inclusion criteria were right-handed adults with glioma located in the vicinity of the AF in the dominant hemisphere (Kuhnt et al., 2012). Exclusion criteria were left-handed adults, being unable to finish language function tests, harboring general contraindications to undergo magnetic resonance imaging (MRI) such as claustrophobia, lesions involving the speech cortex, and recurrent glioma. The dominant hemisphere was confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971) and functional MRI. All patients underwent iMRI and DTI-based tractography-guided tumor resection (38 men, 16 women, mean age 43 ± 11 years, range 20–75 years). Pathologic diagnosis was glioma, identified by postoperative histologic examination. The study was approved by the Ethical Committee of the PLA general Hospital, Beijing, China (approval No. S2014-096-01) on October 11, 2014. Signed informed consent was obtained by all patients or their family members. The flow chart is shown in **Figure 1**.

Neuroimaging processing

Preoperative and iMRI scan were performed with 1.5T high field MRI (Espree, Siemens, Munich, Germany), with the same protocol previously reported (Sun et al., 2011; Chen et al., 2012). A T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence was measured with the following parameters: echo time (TE) = 3.02 ms, repetition time (TR) = 1650 ms, matrix = 256 × 256, field of view = 250 mm × 250 mm, slice thickness = 1 mm.

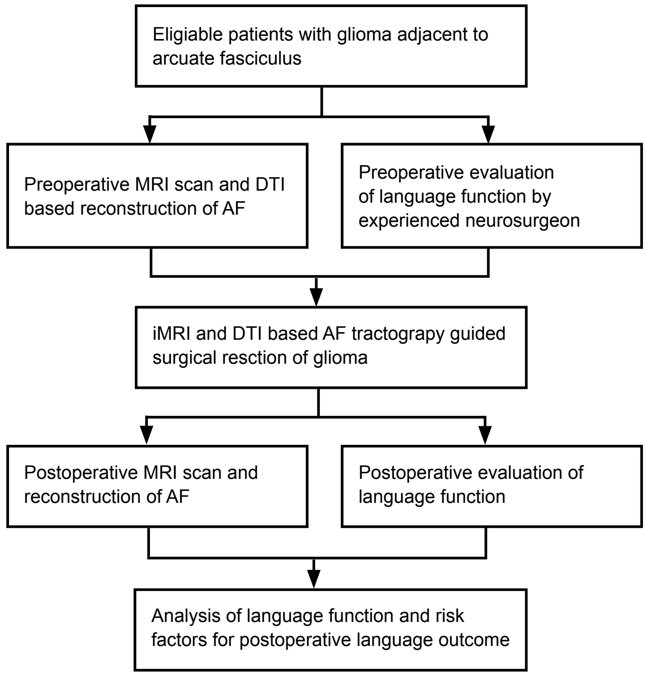

Figure 1 | Flow chart of iMRI and DTI-based AF tractography-guided surgical resection of glioma adjacent to the AF.
AF: Arcuate fasciculus; DTI: diffusion tensor imaging; iMRI: intraoperative magnetic resonance imaging.

Other sequences included T2-weighted images (TE = 93 ms, TR = 5500 ms, matrix = 512 × 512, field of view = 230 mm × 230 mm, thickness = 3 mm), T2 fluid-attenuated inversion recovery (T2 flair) images (TE = 84 ms, TR = 9000 ms, matrix = 256 × 256, field of view = 230 mm × 230 mm, thickness = 3 mm) and postcontrast 3D MPRAGE. For DTI, we applied a single-shot, spin-echo diffusion-weighted echo planar imaging sequence with the following parameters: TE = 147 ms, TR = 9400 ms, matrix = 128 × 128, field of view = 251 mm × 251 mm, thickness = 3 mm, bandwidth = 1502 Hz/Px, diffusion-encoding gradients in 12 directions using *b*-values of 0 and 1000 s/mm^2, voxel = 1.9 mm × 1.9 mm × 3 mm, 40 slices without intersection gap, repeated 5 times.

After rigid registration of b0 and anatomical images, the AF was reconstructed with a tracking algorithm based on the tensor deflection algorithm (Kuhnt et al., 2012). Fiber tracking was performed by the first author who was blinded to patients' language function. We utilized the "Fibre tracking" module in iPlan 3.0 (BrainLAB, Feldkirchen, Germany) for AF reconstruction with a fractional anisotropy (FA) threshold of 0.15 and fiber length of 50 mm. AF tractography was performed with three regions of interest (ROI), either in the coregistered T1 images or FA maps. The first ROI was placed on the left inferior frontal gyrus, the second ROI was placed on the lateral part of the corona radiata, and the third ROI was placed on the posterior part of the left superior temporal gyrus. The fibers passing through these ROIs were the final tracts of interest. After selecting appropriate fibers, a 3D object was automatically generated with a hull, and then transferred to the neuronavigation system. In addition, tumor segmentation of high-grade glioma was performed on the basis of postcontrast T1 3D MPRAGE images, and that of low-grade glioma on T2 flair images.

Surgery

All 54 patients underwent iMRI and DTI-based AF tractography guided surgical resection of glioma. Neuronavigation was used for location of glioma and the nearby AF. iMRI scan was performed when the surgeon believed glioma was totally removed or when surgical judgement was hampered by intraoperative brain shift. iMRI scan helped evaluate the EOR of glioma and update intraoperative images. AF could also be updated by intraoperative DTI. Further resection was continued until the surgeon believed that satisfactory tumor resection was achieved.

Evaluation of language function

Evaluation of language function was performed using the Western Aphasia Battery (Shewan and Kertesz, 1980) preoperatively and postoperatively by an independent experienced neurosurgeon who was blinded to neuroimaging findings and surgical procedure. To avoid the influence of "plasticity of language network" (Zheng et al., 2013; Jiao et al., 2020; Keser et al., 2020), all evaluations of language function were done within 2 weeks after surgery. Aphasia quotients (AQ) reflect the severity of language dysfunction, and an AQ < 93.8 was defined as aphasia (Shewan and Kertesz, 1980). Compared with preoperative language status, stable or improved postoperative language function was considered as a good outcome, and deteriorated language function was considered a poor outcome.

Statistical analysis

All statistical analyses were performed using SPSS 19.0 (IBM Corporation, Armonk, NY, USA). Pearson chi-squared test (or Fisher's exact test) and independent samples *t*-test were used to assess risk factors for postoperative language outcome. Multivariate logistic regression analyses were used to identify the independent risk factors. The receiver operating characteristic curves (area under curve, AUC) was performed to analyze the predictive accuracy of the factors. $P < 0.05$ was considered statistically significant.

Results

Role of iMRI in surgical resection

All 54 glioma patients underwent iMRI and neuronavigation-guided surgical resection successfully. Postoperative histological examination confirmed the initial diagnosis. This group comprised 21 patients with World Health Organization (WHO) low-grade glioma (1 with grade I, 20 with grade II) and 33 patients with high-grade glioma (16 with grade III, 17 with grade IV). The average volume of glioma was 58.7 cm^3 (5.2–192.1 cm^3). The first iMRI scan confirmed that 21 of the 54 patients had achieved total resection, and 33 patients had residual tumor. In 8 of the 33 patients with residual lesions, the GAFD was too small. The operator thought further resection may cause postoperative aphasia or aggravation of symptoms. Therefore, the resections for these 8 patients were completed after the first intraoperative scans. Update of intraoperative images and further resection were performed in the remaining 25 cases (10 with grade II, 8 with grade III, 7 with grade IV). In the last iMRI scan, 17 of the 25 patients achieved total resection, while 8 patients did not. The gross total resection rate of the 54 patients with glioma increased from 38.9% to 70.4% by iMRI. The total resection of 17 patients (31.5%) benefited from iMRI and neuronavigation. In the 25 patients who continued to undergo resection after the first iMRI scan, the average extent of resection increased from 87.3% to 97.4%, and the average volume of residual tumor decreased from 8.8 to 2.2 cm^3 (P = 0.004). In total, the average extent of resection in the 54 glioma patients increased from 92.1% to 96.8% in the last scan (P = 0.000).

Language function outcome of glioma patients with surgical resection under iMRI

After surgery, language function in 15 cases (27.8%) worsened compared with the preoperative state, with the mean AQ score decreasing from 90.6 to 66, which was defined as poor outcome. Among these, further resection was continued in 7 patients after the first iMRI, while no further resection was performed after the first iMRI in 8 patients (χ^2 = 0.001, P = 0.973). The other 39 patients showed no change or improvement in language function, which was defined as a good outcome.

Risk factors of poor outcome for glioma resection under iMRI

All demographic and clinical characteristics of patients with good and poor surgical outcomes are shown in **Table 1**. Preoperative function status (P = 0.010) and a shorter GAFD (P = 0.001) were identified as significant risk factors for postoperative poor outcome. No significant difference was found in sex (P = 0.530), age (P = 1.000), WHO grade (P = 0.436), number of iMRI sessions (P = 0.325), glioma volume (P = 0.778), residual volume after first iMRI (P = 0.635), residual volume after final iMRI (P = 0.399), final EOR (0.360), or gross total resection (0.604). Multivariable logistic regression analysis showed that shorter GAFD was the only independent risk factor for postoperative poor outcome (P = 0.009; **Table 2**). In 54 glioma patients, the mean GAFD was 4.6 mm (range 0–14.3 mm). Among the 15 patients with poor outcome, 14 had GAFD ≤ 5 mm, and 1 had 5 mm < GAFD ≤ 10 mm. The AUC was 0.792. The cutoff point of the GAFD for poor outcome was 3.2 mm (**Figure 2**).

Table 1 | Demographic and clinical characteristics of primary glioma patients with good and poor surgical outcomes

	Good outcome	Poor outcome	*P*-value
*n**	39(72.2)	15(27.8)	
Sex*			0.530
Male	26(66.7)	12(80)	
Female	13(33.3)	3(20)	
Age (yr)#	43.0±11.2	43.0±11.0	1
World Health Organization grade*			0.436
I	0	1(6.7)	
II	15(38.4)	5(33.3)	
III	12(30.8)	4(26.7)	
IV	12(30.8)	5(33.3)	
iMRI times*			0.325
1	21(53.8)	8(53.3)	
2	17(43.6)	5(33.3)	
3	1(2.6)	2(13.4)	
Glioma volume (mL)#	57.8±35.1	60.9±40.8	0.778
RV after first iMRI (mL)#	5.4±8.4	6.7±9.2	0.635
RV after final iMRI (mL)#	2.3±5.5	3.7±5.0	0.399
Final extent of resection (%)#	97.2±5.1	95.8±5.0	0.36
Gross total resection†			0.604
Yes	16	5	
No	23	10	
Preoperative function*			0.010
Aphasia	9(23.1)	9(60)	
Non-aphasia	30(76.9)	6(40)	
GAFD (mm)#	5.5±3.4	2.3±2.0	0.001

*Data were expressed as number (%), and analyzed by chi-squared test. #Data were expressed as the mean ± SD, and analyzed by independent samples *t*-test. †Data were expressed as number, and analyzed by chi-squared test. GAFD: Glioma-to-arcuate fasciculus distance; iMRI: intraoperative magnetic resonance imaging; RV: residual volume.

Table 2 | Multivariate logistic regression analysis of risk factors for postoperative poor language outcome in primary glioma patients

Variables	*B*	*S.E.*	*Wald* value	*P*-value	*OR*	95%*CI*
Pre-LF	1.185	0.718	2.722	0.099	3.27	0.800–13.357
GAFD	–0.433	0.167	6.742	0.009	0.649	0.468–0.899

CI: Confidence interval; GAFD: glioma-to-arcuate fasciculus distance; OR: odds ratio; Pre-LF: preoperative language function.

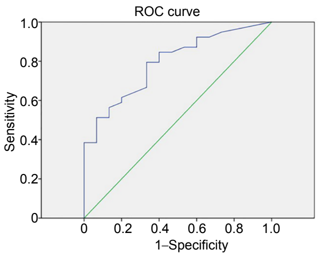

Figure 2 | Receiver operating characteristic curve for glioma-to-arcuate fasciculus distance.
The area under the curve is 0.792, and the cutoff point is 3.2 mm.

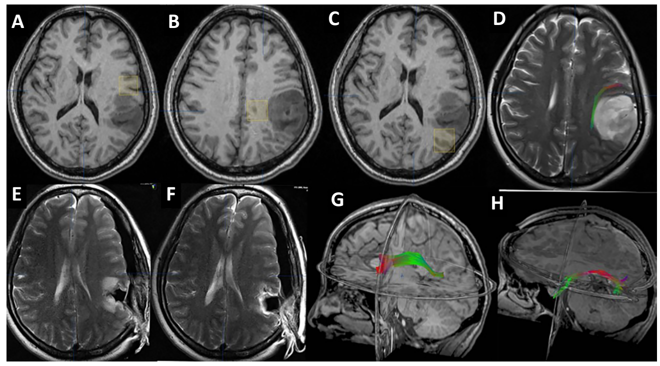

Figure 3 | A typical patient with glioma involving the AF after iMRI-guided surgical resection.
A female patient with left parietal lobe glioma. (A–C) The AF was reconstructed based on T1 anatomical datasets. The first ROI was placed on the left inferior frontal gyrus (A), the second ROI was placed on the lateral part of the corona radiata (B), and the third ROI was placed on the posterior part of the left superior temporal gyrus (C). (D) Some of the AF fibers were involved in the tumor, with GAFD = 0 mm. (E) First iMRI revealed residual tumor. (F) After further resection, final iMRI confirmed gross total resection. (G) Preoperative reconstruction of AF fibers. (H) After rigid registration of pre- and intraoperative images, intraoperative diffusion tensor tractography showed part of the AF was diminished, with the mean FA value having decreased from 96.8 to 60.1. AF: Arcuate fasciculus; GAFD: glioma-to-arcuate fasciculus distance; iMRI: intraoperative magnetic resonance imaging; ROI: region of interest.

Illustrative case

The patient (a 42-year-old woman) presented with intermittent dizziness for 1 year. Preoperative physical examination showed no language dysfunction, with an AQ score of 94. Preoperative MRI revealed a left parietal lobe lesion without enhancement. Tumor segmentation was delineated according to T2 flair images. The AF was reconstructed based on T1 anatomical datasets, which revealed that some AF fibers were involved in the tumor, with a GAFD = 0 mm. The first iMRI revealed residual tumor, and further resection was continued with update of neuronavigation. Gross total resection was achieved, which was confirmed by final iMRI. After rigid registration of pre- and intraoperative images, intraoperative diffusion tensor tractography showed that part of the AF was diminished, with the mean FA value decreasing from 0.47 to 0.32. Postoperative language function test showed that AQ deceased from 96.8 to 60.1. Pathologic result was astrocytoma, WHO grade II–III (**Figure 3**).

Discussion

Maximizing tumor resection while minimizing injury to the AF remains a challenging task for glioma adjacent to AF. iMRI is mainly used for compensation for brain shift, measurement of the extent of tumor resection, and intraoperative visualization of the AF (Kuhnt et al., 2012). McGirt et al. (2009) reviewed 306 patients with glioblastoma in a single center for 10 years. For patients with postoperative motor or language dysfunction, the median survival time was about 3 months less than that of patients without neurological dysfunction. The 2-year survival rate of patients with language dysfunction was 0, while that of patients without new neurological dysfunction was 23%, suggesting that good postoperative linguistic function is associated with high quality of life and longer survival time (Jakola et al., 2011). DTI-based fiber tracking helps visualize the AF and the three-dimensional relationship with the glioma, which can help the surgeon select the appropriate surgical approach and remove the lesion without damaging the AF.

In this study, we used iMRI combined with AF navigation to resect glioma proximal to the AF in the dominant hemisphere. Consistent with the findings of D'Andrea et al. (2016) and Bohinski et al. (2001), gross total resection rate of glioma increased from 38.9% to 70.4%, and the extent of resection increased from 92.1% to 96.8% with assistance of intraoperative imaging update. Postoperatively, the language function in 15 patients (27.8%) was worse than before, while language function in the other patients was stable or improved. The results of language function are similar to those reported by Sanai et al. (2008), who summarized the experience of awake craniotomy in 250 glioma patients with intraoperative mapping, which was then considered the gold standard for location of functional area. Compared with preoperative language function, 22.4% of the patients had new aphasia or aggravation of the original symptoms 1 week after operation. iMRI and AF navigation helped improve the rate of gross total resection, producing functional outcome similar to that of awake craniotomy. This approach also had a lower risk than awake craniotomy, with reduced intraoperative epilepsy, airway management risk, and anxiety.

No statistical difference was found in sex, age, WHO grade, number of iMRI sessions, glioma volume, RV after first iMRI, RV after final iMRI, final EOR or gross total resection. Compared with high-grade glioma, the boundary of low-grade glioma is not clear, and postoperative neurological dysfunction is more likely to occur (Sun et al., 2011; D'Andrea et al., 2016). However, in our study, we did not observe an effect of WHO classification of glioma on the prognosis of language function. In contrast to arteriovenous malformation (Mascitelli et al., 2018), the volume of the lesion is not associated with postoperative linguistic function. iMRI helps increase the rate of gross total resection and EOR without increasing the incidence of new postoperative linguistic dysfunction or worsening of function. Multivariate logistic regression analysis showed that GAFD was an independent risk factor for the prognosis of language function. The AUC value was 0.79, and the cutoff value was 3.2 mm, which is longer than the 2 mm "safe distance" described by D'Andrea et al. (2016). Therefore, for glioma with GAFD less than 3.2 mm, consideration should be given to the risk associated with radical resection, and repeated iMRI scan may be safer.

Our research also has some limitations. For example, our system used 1.5T iMRI and DTI with 12 gradient directions. In a future study, we will implement 3.0T iMRI and DTI with 30 gradient directions to obtain a more reliable estimation of fibers. In addition to the AF, other white matter fiber tracts, such as the superior longitudinal fasciculus, inferior occipitofrontal fasciculus, uncinate fasciculus and inferior longitudinal fasciculus, participate in language processing (Incekara et al., 2018; Sydnor et al., 2018; Hill et al., 2019). Furthermore, we limited our current study to AF function in the dominant hemisphere. To further understand language function and subcortical language tracts, diffusion tensor tractography should be used to investigate the role of other brain white matter structures in language function in future studies.

In summary, iMRI combined with AF navigation can help maximize tumor resection while minimizing damage to the AF. GAFD is a major independent risk factor for postoperative new or worsening of linguistic dysfunction.

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HYL, JZ, XLC, BNX; literature search, data acquisition and analysis: FYL, HYL, JZ, ZHS, JSZ, GCS, XGY; manuscript preparation and editing: FYL, HYL, JZ. All authors performed experiment and approved the final version of the manuscript.

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Institutional review board statement: *The study was approved by the Ethical Committee of the PLA general Hospital, Beijing, China (approval No. S2014-096-01) on October 11, 2014.*

Declaration of patient consent: *The authors certify that they have obtained the consent forms from patients. In the form, patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published.*

Reporting statement: *The writing and editing of the article were performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.*

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