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Nation-wide Brain Tumor Registry-based Study of Intracranial Meningioma in Japan: Analysis of Surgery-related Risks

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Abstract

Although surgical resection is the most preferred treatment for intracranial meningiomas, a detailed analysis of the surgery-related risks based on large population data has not been conducted to date. In this study, we analyzed the nation-wide brain tumor registry to assess the surgical risk factors for intracranial meningiomas to provide information for an optimal treatment strategy. Data of 4081 meningioma patients who underwent initial resection between 2001 and 2008 were extracted from the Brain Tumor Registry of Japan (BTRJ) database and reviewed for postoperative mortality, aggravation of Karnofsky Performance Score (KPS), and complications. The total in-hospital mortality rate was 0.59%. Male sex and tumor size ≥30 mm were independent risk factors for mortality. Among 4081 cases, 4.4% of patients had KPS that were lowered by 20 or more points at the time of discharge after surgery. Age ≥65 years, higher WHO grading, tumor location at the skull base, tumor size \geq 30 mm, and non-gross total resections were associated with lowering of KPS scores by 20 or more points. The overall incidence of surgical complications was 19.3%. The rate of occurrence of new postoperative seizure in patients with supratentorial meningioma was 10.9%. All complications except for vascular complications occurred with significantly lower frequencies in asymptomatic patients than in symptomatic patients. Our results provide useful information regarding the surgical risks when surgical intervention is being considered for intracranial meningiomas. Surgery is an important option for asymptomatic meningiomas as the mortality rate and complication rate in the current study were sufficiently low.

Keywords: brain tumor registry, complication, KPS, meningioma, mortality

Introduction

Meningioma is the most common benign intracranial tumor with the rate of incidence increasing with age.^{1,2)} Given the aging population and recent improvements in access to radiological evaluation, the reported rate of meningioma incidence could increase further. Surgical resection is the most common treatment for meningioma. However, a number of clinical issues regarding the optimal treatment strategy for meningioma persist. For example, the advantages of surgical resection for asymptomatic meningiomas over conservative

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management have not been demonstrated yet; it is unclear which group of patients are at risk for specific complications. Given the prevalence of meningioma, detailed analyses based on large sets of epidemiological data would be helpful in seeking answers to these questions.^{3,4)}

Since the establishment of the committee of Brain Tumor Registry of Japan (BTRJ) in 1973, data regarding the incidence, treatment methods and outcomes, and recurrence rate have been collected in the registry in cooperation with the members of the Japan Neurosurgical Society.⁵⁾ BTRJ is a nation-wide registry of patients of all ages with brain tumors of all types. The database has been in publication since 1977.⁶⁾ It maintains records for individual patients, including details such as age, sex, past medical history, tumor characterization and classification, treatment strategies, date of surgery, date of recurrence, and types of complications. Recent editions of the registry for data newly registered between 2001 and 2008 were published with follow-up data in 2014 and 2017, respectively.^{7,8)} With the collaboration of more than a hundred academic institutions and high-volume centers, more than 4000 cases of primary brain tumors and 700-800 cases of metastatic brain tumors have been recorded annually since 2001. We aimed to examine the outcomes of surgical treatments of meningioma made between 2001 and 2008 in Japan and evaluate the efficacy of current treatment strategies to enable improvements in the quality of treatment for this common disorder.

Materials and Methods

Data collection

We analyzed the data collected by BTRJ between 2001 and 2008 for recurrence rates based on longterm MRI-based follow-up data and surgery-associated complications. Data for each patient with intracranial meningioma were registered and updated in each participating institution. Although we aimed for a comprehensive analysis of the treatment outcomes for meningiomas in Japan, it is worth noting that the actual extent of data coverage by BTRJ for whole brain tumor surgeries is unknown. In a previous study, Yoshimoto et al. analyzed data gathered by the Japan Diagnosis Procedure Combination Database and reported that a total of 1758 meningioma cases were surgically treated in the 1-year period between April 2013 and March 2014.9 According to the BTRJ database, the average number of surgeries for meningioma treatment was 834 cases per year. Given that the data from most academic facilities and high-volume medical centers in Japan were included in both the clinical databases, we estimated that approximately 50% of the surgeries for meningioma were registered in BTRJ. This study was approved by the institutional review board (No. 1527-III) and by The Japan Neurosurgical Society (No. 2019007). The requirement of written informed consent from the patients was waived by the above-mentioned boards owing to the use of retrospective anonymized data.

Variables and study population

Data obtained from the BTRJ database documented demographic details including the date of birth, sex, and race and clinical characteristics such as the classification and characterization of meningiomas, symptoms, treatment strategies (surgical resection, other types of surgical interventions, radiation, and others), date of surgical resection, extent of resection (EOR), pathological diagnosis, WHO grading of the tumors, timing of postoperative radiation (adjuvant or after recurrence), Karnofsky Performance Score (KPS) score before and after treatment, date of recurrence, date of last visit, mortality, and surgery-associated complications (vascular/medical/new postoperative seizure/others). The EOR was evaluated based on postoperative MRI and classified into four groups as gross total resection (GTR) with 100% resection, near total resection (NTR) with 95-99% resection, subtotal resection (STR) with 75-94% resection, and partial resection (PR) with 74% or less resection. WHO grading was determined at the pathology department of each institution. Postoperative KPS was evaluated at the time of discharge. Recurrence was defined as radiological recurrence after GTR or regrowth of a residual mass on MR images obtained during the follow-up period. Mortality was defined as death during admission for surgery. Vascular complications included any type of stroke while medical complications included pneumonia and deep venous thrombosis. Other complications such as cranial nerve deficits, infections, cerebrospinal leakage, and fracture were categorized as "others."

The total number of registered primary brain tumors were 13,431 between 2001 and 2004⁷⁾ and 16,722 between 2005 and 2008.⁸⁾ Among these, data for a total of 7341 patients (24.3%) with intracranial meningiomas were extracted. Patients with multiple meningiomas were excluded because information regarding which tumors among the multiple ones in each case were surgically treated was lacking. We applied additional exclusion criteria as shown in Fig. 1. Patients of other races (non-Japanese), patients previously treated for meningioma, and patients whose initial treatment was not surgical resection were excluded. Among the remaining 6254



Fig. 1 A flowchart of the cohort selection in this study. First, 453 patients were excluded to focus on the Japanese patients with single meningiomas, with no previous treatment. Patients who underwent surgery other than resection were then eliminated. Lastly, 2173 patients were excluded because some data essential for analysis were missing. A total of 4081 patients were enrolled in this study.

Japanese patients with single meningiomas undergoing resection as primary treatment, 2173 patients were excluded because data regarding their KPS, recurrence, tumor size, and age were missing. Consequently, data for 4081 patients were included in this study. Owing to the lack of data, 227 patients were further excluded from the analysis of complications, other than mortality.

Statistical analysis

The Fisher exact test was used for univariate analysis. Multiple logistic regression tests were used for multivariate analysis to identify the risk factors for perioperative mortality and aggravation of KPS. Two-tailed p values <0.05 were considered as statistically significant. All analyses were performed with JMP 14 software (SAS Institute, Cary, NC, USA).

Results

The demographic details of patients included in the study are shown in Table 1. Median age of patients was 59 years (interquartile range: 50–67 years). Among the registered patients, 70.5% were women. The percentage of patients classified as WHO grade I, II, and III were 92.4%, 6.3%, and 1.3%, respectively. Based on our classification, as indicated in Supplementary Table 1, 43.6% of the tumors originated in the skull base. GTR was achieved in 58.9% of the patients, whereas NTR, STR, and PR were achieved in 23.1%, 11.2%, and 6.6%, respectively.

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Table 1Patient demographics (n = 4081)

Factor	Value
No. of patients	4081
Age (median [IQR], years)	59 (50, 67)
<19	34 (0.8%)
20–29	76 (1.9%)
30–39	248 (6.1%)
40-49	597 (14.6%)
50–59	1175 (28.8%)
60–69	1171 (28.7%)
70–79	669 (16.4%)
<80	111 (2.7%)
Sex	
Male	1205 (29.5%)
Female	2876 (70.5%)
WHO grade	
Grade I	3771 (92.4%)
Grade II	256 (6.3%)
Grade III	54 (1.3%)
Location	
Skull base	1778 (43.6%)
Non-skull base	2303 (56.4%)
Tumor size (median [IQR], mm)	35 (27, 50)
<20	247 (6.1%)
20–29	871 (21.3%)
30–39	1118 (27.4%)
40-49	822 (20.1%)
50-59	539 (13.2%)
>60	484 (11.9%)
Extent of resection	
GTR	2404 (58.9%)
NTR	942 (23.1%)
STR	459 (11.2%)
PR	268 (6.6%)
Preoperative symptom	
Symptomatic	3180 (77.9%)
Asymptomatic	901 (22.1%)
Complication	
None	3517 (86.2%)
Vascular complications	129 (3.2%)
Medical complications	72 (1.8%)
Others	328 (8.0%)
Unknown	59 (1.4%)
KPS (Preop, Postop)	

Factor	Value
100	1578 (38.7%), 1995 (48.9%)
90	1417 (34.7%), 1243 (30.5%)
80	577 (14.1%), 435 (10/7%)
70	212 (5.2%), 161 (3.9%)
60	148 (3.6%), 108 (2.6%)
50	80 (2.0%), 59 (1.4%)
40	42 (1.0%), 28 (0.7%)
30	13 (0.3%), 14 (0.3%)
20	14 (0.3%), 10 (0.2%)
10	0 (0.0%), 5 (0.1%)
0	0 (0.0%), 24 (0.6%)

GTR: gross total resection, IQR: interquartile range, NTR: near total resection, PR: partial resection, STR: subtotal resection.

Median KPS score was 90 both before and after surgery. While 86.2% of the patients had no complications, vascular complications such as hemorrhage or infarction occurred in 3.2% of them. Medical complications, mostly pneumonia and deep venous thrombosis, were seen in 1.8% of the patients.

Analyses of post-surgery complications and quality of life

We first investigated the association between clinical factors and postoperative death from any cause (Table 2). Total mortality rate was 0.59%. Univariate analyses revealed that age of 65 years or more (p = 0.047), male sex (p = 0.012), WHO grade II/III tumors (p = 0.031), tumor size ≥ 30 mm (p = 0.049), and presence of preoperative symptoms (p = 0.044) were risk factors for mortality. However, for asymptomatic meningiomas, the in-hospital mortality rate was as low as 0.11% (1/901 cases). Multivariate analysis demonstrated that mortality was higher after surgery among male patients (p = 0.049) and those with a large tumor (≥ 30 mm, p = 0.019), as shown in Supplementary Table 2.

We next explored the predictive factors for postoperative lowering of KPS scores by 20 points or more. Among the 4081 cases examined, 180 (4.4%) of the patients had KPS scores that were lowered by 20 points or more at the time of discharge after surgery. Lowering of KPS score was more frequently observed in patients aged 65 years or more (p = 0.04), those with tumors of WHO grade II/III (p = 0.01),

	Mortality	P value
All	0.59% (24/4081)	
Age		
<65	0.40% (11/2724)	
≥65	0.97% (13/1346)	0.047
Sex		
Male	1.08% (13/1205)	
Female	0.38% (11/2876)	0.012
WHO grade		
Grade I	0.50% (19/3771)	
Grade II/III	1.61% (5/310)	0.031
Location		
Skull base	0.62% (11/1778)	
Non-skull base	0.56% (13/2303)	0.84
Tumor size		
<30	0.09% (1/1118)	
≥30	0.78% (23/2963)	0.009
Extent of resection		
GTR	0.41% (10/2412)	
NTR or less	0.84% (14/1669)	0.10
Preoperative symptom		
Symptomatic	0.72% (23/3180)	
Asymptomatic	0.11% (1/901)	0.044

 Table 2
 Univariate analysis of factors associated with mortality

GTR: gross total resection, NTR: near total resection.

those with tumors located at the skull base (p <0.001), those with a tumor size \geq 30 mm (p = 0.005), those for whom EOR was NTR or less (p <0.0001), and those with preoperative symptoms (p = 0.02) (Table 3). Among 901 patients with asymptomatic meningiomas, 27 (3%) had significantly lowered KPS scores after the surgery. Multivariate analysis showed that an age of 65 years or more (p = 0.04), tumors with WHO grading of II/III (p = 0.03), tumor location at the skull base (p = 0.01), tumor size \geq 30 mm (p = 0.02), and EOR at NTR or less (p <0.001) were associated with significant lowering of KPS scores after surgery (Supplementary Table 3).

Notably, information regarding complications is available in the BTRJ database. Table 4 shows the associations between clinical factors and complication rates. After excluding 227 patients whose data regarding complications were not complete, the overall incidence of complications was found to be 19.3% (754/3854 cases). Although age had no influence on the overall rate of complications, the risk of medical complication in patients aged 65 years

	KPS aggravated by 20 or more	p Value
All	4.4% (180/4081)	
Age		
<65	3.95% (108/2735)	
≥65	5.35% (72/1346)	0.04
Sex		
Male	4.90% (59/1205)	
Female	4.21% (121/2876)	0.36
WHO grade		
Grade I	4.16% (157/3771)	
Grade II/III	7.42% (23/310)	0.01
Location		
Skull base	5.68% (101/1778)	
Non-skull base	3.43% (79/2303)	< 0.001
Tumor size		
<30	2.95% (33/1118)	
≥30	4.96% (147/2963)	0.005
Extent of resection		
GTR	2.74% (66/2412)	
NTR or less	6.83% (114/1669)	< 0.001
Preoperative symptom		
Symptomatic	4.81% (153/3180)	
Asymptomatic	3.00% (27/901)	0.02

Table 3Univariate analysis of factors associated withKPS aggravation by 20 or more

GTR: gross total resection, NTR: near total resection.

or more was three times as high as that in patients younger than 65 years of age (1.0% vs 3.4%, p < 0.001). Men had a higher overall rate of surgery-related complications than women (p <0.001). Additionally, the risk of new postoperative seizure was 1.5 times higher in men than in women (p = 0.001). Higher WHO grading for tumor was associated with increased overall rate of complications (p = 0.001), medical complications (p = 0.002), and new postoperative seizure (p <0.001). Tumor location had a significant impact on the rate of seizure and other complications. New postoperative seizure was seen twice as frequently in non-skull base meningiomas than in skull base ones, while other complications occurred at twice the rate of non-skull base cases (p <0.001). When the tumor size was \geq 30 mm, the overall rate of complications was significantly higher (p <0.001). In particular, the rate of new postoperative seizure significantly increased (p <0.001). EOR had a strong influence on the complication rate, too. However, incomplete resection was not associated with an

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Factor	Complication			p Value
	Any	19.3% (754/3854)		
	New seizure*	10.9%	(289/2644)	
Age		Age <65 $(n = 2586)$	Age ≥65 (n = 1268)	
	Any	19.4% (501)	19.2% (244)	0.92
	Vascular	3.3% (83)	3.2% (41)	1.00
	Medical	1.0% (27)	3.4% (43)	< 0.001
	New seizure*	11.3% (194)	10.2% (95)	0.40
	Others	8.9% (229)	7.1% (90)	0.07
Sex		Male n = 1136	Female n = 2718	
	Any	22.9% (260)	17.8% (485)	< 0.001
	Vascular	3.4% (38)	3.2% (87)	0.84
	Medical	2.5% (28)	1.6% (42)	0.06
	New seizure*	14.0% (113)	9.6% (176)	0.001
	Others	9.4% (107)	7.8% (211)	0.11
WHO grade		WHO grade I (n = 3559)	WHO grade II/III (n = 295)	
	Any	18.7% (666)	26.8% (79)	0.001
	Vascular	3.2% (113)	4.1% (12)	0.39
	Medical	1.6% (57)	4.4% (13)	0.002
	New seizure*	10.2% (247)	19.7% (42)	< 0.001
	Others	8.2% (292)	9.2% (27)	0.58
Location		Skull base (n = 1662)	Non-skull base (n = 2192)	
	Any	20.4% (333)	18.8% (412)	0.34
	Vascular	3.5% (58)	3.1% (67)	0.46
	Medical	2.2% (37)	1.5% (33)	0.11
	New seizure*	6.8% (67)	13.4% (1653)	< 0.001
	Others	11.4% (190)	5.9% (129)	< 0.001
Tumor size		<30 mm (n = 1059)	≥ 30 mm (n = 2795)	
	Any	14.3% (151)	21.3% (594)	< 0.001
	Vascular	2.7% (29)	3.4% (100)	0.31
	Medical	1.0% (11)	2.1% (59)	0.03
	New seizure*	5.9% (43)	12.9% (246)	< 0.001
	Others	7.5% (79)	8.6% (240)	0.27
Extent of resection		GTR (n = 2302)	NTR or less $(n = 1552)$	
	Any	17.9% (411)	21.5% (334)	0.005
	Vascular	2.4% (56)	4.5% (69)	0.008
	Medical	1.3% (30)	2.6% (40)	0.005
	New seizure*	11.4% (193)	10.0% (96)	0.30
	Others	7.3% (168)	9.7% (151)	0.009

Table 4 Association between the clinical factors and the complication rates (n = 3854, there may be more than one complication per patient)

Factor	Complication			p Value
Preoperative symptoms		Symptomatic (n = 3007)	Asymptomatic (n = 847)	
	Any	20.5% (615)	15.4% (130)	< 0.001
	Vascular	3.3% (100)	3.0% (25)	0.66
	Medical	2.1% (64)	0.7% (6)	0.005
	New seizure*	12.1% (237)	7.7% (52)	0.002
	Others	8.9% (267)	6.1% (52)	0.01

Table 4 Association between the clinical factors and the complication rates (n = 3854, there may be more than onecomplication per patient) (Continued)

*The incidences of new seizure were calculated from the data of 2644 patients with supratentorial meningioma who had no preoperative seizure.

increased risk of new postoperative seizures. Presence of preoperative symptoms was also associated with an overall increase in the risk of complications (p < 0.001).

Discussion

Surgery should be judiciously considered in the treatment of meningioma.^{10,11)} After surgical intervention has been determined, maximal safe resection as a surgical intervention is considered to be the best option.¹²⁻¹⁴⁾ In both scenarios, it is imperative to understand the incidence as well as the propensity of surgery-related risks. Given that meningiomas are the most common brain tumors, a large-scale population-based study regarding surgical complications will guide surgeons, neurologists, and patients in selecting the optimal treatment plan. As previous large population-based studies only analyzed treatment modality or the survival period,^{15–18)} there were no current data on the surgical complications available within nationwide brain tumor registries. For this reason, we investigated the risk factors for surgical complications and postoperative deterioration of daily living activities based on the large-scale data from a nationwide brain tumor registry.

Mortality rate associated with meningioma resection has previously been reported to be between 0.7% and 1.5%.^{4,19} The overall in-hospital mortality rate in this study was low despite considering that the mortality rate from the original data was 0.75%(55/7341 cases), before applying the exclusion criteria. Although detailed information regarding the cause of death was not available, male sex and tumor size ≥ 30 mm were risk factors for in-hospital mortality. In our study, male patients tended to develop medical complications more frequently than female patients. Given that mortality after meningioma resection occurs mostly owing to medical complications such as respiratory failure and cardiac arrest,²⁰⁾ close attention must be paid to medical comorbidities for male patients. Our data also showed a trend toward statistical significance (p = 0.057) for a higher risk of death in elderly patients. Similarly, a previous study reported that the mortality rate 3 months after the surgery was higher in patients aged 65 years or more compared to that in patients under 65 years of age, but this was comparable to an age-matched general population.²¹⁾ Another study showed that both 1-year and 5-year mortality rates were comparable with those for unselected cohorts and emphasized the importance of assessment of preoperative performance status and comorbidities, especially for elderly patients.²²⁾ Combined with our results, we believe that mortality in elderly patients would be similar to that in younger patients or in at least age-matched controls if the indications for surgery are adequately considered.

Postoperative preservation of neurological function is an important goal of meningioma treatment. In general, elderly patients are likely to have more comorbidities and are less tolerant to surgical stress. Prolonged bed rest after surgery frequently impairs the ambulatory ability of aged patients, resulting in lowering of KPS scores, as shown in our study. Consistent with a previous report,²³⁾ male sex was associated with an increased risk of new postoperative seizure in the present study. While the reasons for this are not fully understood, it is known that the WHO grade II and III meningiomas are more common in men.^{24–26)} Higher grade meningiomas are more likely to cause peritumoral brain edema and brain invasion that are reported as risk factors for poor seizure outcomes.^{23,27} Higher WHO grades and larger size of tumors were also associated with increased risk of medical complications in this study, probably because more extensive and complicated surgical strategies requiring longer operation time were adopted to achieve a higher EOR in such cases. The location of the tumor showed a significant relation to the type of complication. While new postoperative seizures occurred more frequently in non-skull base meningiomas, non-vascular and non-medical complications occurred more frequently in skull base meningiomas than in non-skull base ones. A possible explanation is that operating on a skull base meningioma often involves aggressive drilling, opening of the paranasal sinus, and complicated dural closure. This increases the risk of postoperative cerebrospinal fluid leak and infection. Therefore, the tumor location at the skull base was more likely to result in lowering of KPS at discharge. With regard to EOR, our results clearly demonstrate that non-GTR procedures were associated with an increased risk of lowering KPS and other complications. However, we believe that this should not be interpreted as GTR being superior. As tumor consistency or vascular encasement is a critical factor that lowers the EOR, aggressive resection of high-risk tumors increases the risk of surgical complications and lowering of KPS. Our results seem to reflect the generally accepted idea regarding surgical treatment of meningioma in that tumor characteristics are more important than the EOR. It is important to fine-tune the goal of surgical treatment according to the intraoperative observations on tumor characteristics such as consistency or severity of adherence to critical structures to preserve postoperative neurological functions.

The rationale to determine the need for surgery for asymptomatic meningiomas is another unsolved clinical issue. Current evidence for the treatment of asymptomatic meningiomas is Level IV or V and the grade of recommendation remains at Grade C.^{10,11,28,29)} Therefore, the treatment strategy for asymptomatic meningiomas must be formulated by integrating data on the natural history and surgical risks.¹⁰⁾ Although diverse classifications of complications exist in the literature, the overall incidence of surgical complications of asymptomatic meningiomas ranges from 9.4 to 35.6%.^{11,28,29} Considering the low mortality and morbidity rate shown in this study, surgery is an important treatment option for asymptomatic meningiomas. Based on these results, we would like to emphasize that it is difficult to completely avoid vascular complications, even for asymptomatic meningiomas. Our results provide detailed information regarding the surgery-related risks when surgical intervention is being considered for asymptomatic meningiomas.

There are a few limitations to this study. First, although most academic facilities and high-volume medical centers in Japan contributed to the BTRJ, it should be noted that not all surgeries for meningioma conducted in Japan were registered. Second, data on comorbidities were not registered, which could change the interpretations of surgical risks. Third, we had to exclude 2173 (2173/6254, 34.7%) patients undergoing resection as the primary treatment owing to incomplete data. We investigated the possible bias of this exclusion criteria within the 6254 patient population. Specifically, there was no statistical difference in age (mean age, 58.4 in analyzed group vs 58.3 in excluded group, p = 0.80) and tumor location (skull base, 43.6% in analyzed group vs 45.5% in excluded group, p = 0.15). The mortality rate was significantly lower in the excluded group than in the analyzed group (0.17% [3/1778] vs 0.59% [23/4081], p = 0.03), with the overall rate of complication also significantly lower in the excluded group relative to the analyzed group (11.4% [224/1,969] vs 19.3% [754/3,854], p <0.001). While these data imply that the patients excluded, owing to incomplete data, may have a better outcome, we believe that the surgical risk should not be underestimated.

Conclusions

The nation-wide brain tumor registry, BTRJ, provided the largest dataset for the analysis of factors related to surgical complications in meningioma. Male sex and tumor size ≥30 mm were independent risk factors for mortality. KPS in 4.4% of patients were lowered by 20 points or more. It also suggests that surgical resection for asymptomatic meningiomas is a safe and important treatment option with a low rate of surgery-related complication. Considering that meningiomas are the most common brain tumors, this large-scale population-based study regarding the surgical complications will guide surgeons, neurologists, and patients in selecting the optimal treatment plan.

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Conflicts of Interest Disclosure

The authors did not receive financial support for this work. All authors have registered online Selfreported COI Disclosure Statement Forms through the website for the Japan Neurosurgical Society members.

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