Tumor doubling time as preoperative predictor of malignancy and recurrence in newly diagnosed meningioma

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Abstract

Most meningiomas are benign, and the indications for surgery are determined by size and symptoms, but some are malignant and have a high recurrence rate. Currently, no preoperative prognostic factors have been established. The purpose of this study was to investigate whether tumor doubling time (Td) is useful in predicting tumor prognosis. Patients who underwent surgery for newly diagnosed meningioma at our hospital between 2007 and 2021 with preoperative magnetic resonance (MR) imaging evaluation over a period of 6 months were included in this study. We calculated the Td from the preoperative MR images and examined the correlation between Td and WHO grade, MIB-1 SI, and other conditions. A total of 269 newly diagnosed meningiomas were operated on during the study period, of which 62 met inclusion criteria. The median Td was 1082 days (54–8579 days), and MIB-1 SI was 2.45% (0.7–14.6%). Td and MIB-1 SI had a negative correlation (\( r = -0.319, p = 0.0122 \)). MIB-1 SI was higher in patients with \( Td < 3 \) years than in those with \( Td \geq 3 \) (\( p = 0.005 \)), and the incidence of high WHO grade (grade2) was higher in patients with \( Td < 1 \) year than in patients with \( Td \geq 1 \) (\( p = 0.014 \)). Meningiomas with \( Td < 3 \) years had significantly higher MIB-1 SI, and tumors with \( Td < 1 \) year had a higher likelihood of malignancy. Therefore, early treatment should be considered in patients with short Td meningioma even if asymptomatic, and further consideration could be given to radical resection at the time of surgery.

Keywords Meningioma · MIB-1 SI · Recurrence · Risk factor · Tumor doubling time

Introduction

Meningioma is a common intracranial tumor, accounting for approximately 24% of all primary brain tumors [1]. Currently, surgical treatment is determined by the tendency to increase in size and the appearance of neurological deficits. Although the MIB-1 staining index (MIB-1 SI) has been reported to correlate with recurrence rate [15], the MIB-1 SI is the information that can be obtained after surgery. If the tumor characteristics can be predicted on preoperative imaging, it will be useful in deciding the indication for surgery. We focused on tumor doubling time (Td) as one of the non-invasive prognostic factors. It has not been shown in the study for newly diagnosed meningiomas that the shorter the Td is (the faster tumor growth rate is), the higher the malignancy is (the higher proliferative potential is). In this study, we retrospectively examined the correlation between Td and MIB-1 SI and WHO grade.

Materials and methods

Data collection

We retrospectively collected data on WHO grade, MIB-1 SI, tumor localization (skull base or non-skull base), resection degree (Simpson grade), histological characteristics, and presence of recurrence in cases of newly diagnosed meningioma operated on at our hospital between January 2007 and January 2021.

WHO grade and MIB-1 SI, and histological characteristics were obtained from the pathology report. Tumor localization was classified as either skull base or non-skull base. Simpson grade was determined from surgical
records. The presence of recurrence was confirmed by the medical records.

Measurement of Td and tumor growth rate.

Tumor volumes were measured using FUJIFILM’s “SYNAPSE VINCENT version 6.3” 3D image analysis system volume analyzer in patients who had undergone magnetic resonance imaging (MRI) at least twice with an observation period of more than 6 months before surgery.

The images used for volume measurement were in the following priority: Gadolinium (Gd) enhanced T1 weighted images (WI) thin slice (thickness of less than 1.2 mm) > thin slice of other sequences (only if the boundary between tumor and brain is clear) > Gd enhanced T1WI thick slice (thickness of about 5 mm) > thick slice of other sequences.

In cases in which three or more MRI scans were performed preoperatively, priority was given to images from the imaging date with the largest period between the two MRI scans.

If Td (day) is defined as the time it takes for the tumor volume to double, and the previous imaging day is T1 (day) and the volume is V1 (ml), and the subsequent imaging day is T2 (day) and the volume is V2 (ml), then V2 = 2(T2−T1)/Td × V1. In other words, Td was calculated from the equation Td = (T2 − T1)log2/log(V2/V1) [10].

The absolute tumor growth rate was defined as the volume of tumor growth per year (cm³/year), and the relative tumor growth rate was defined as the ratio of the volume of tumor growth from the initial diagnosis (%/volume/year), assuming linear growth.

Statistical approach

Only cases with enlarged tumors were included in the statistical analysis. Statistical analysis was performed using the statistical software “EZR version 1.54” (Jichi Medical University Saitama Medical Center) [9].

For individual data analysis, Spearman’s correlation function test was used for bivariate correlations, and Mann–Whitney U test or Kruskal–Wallis test was used for comparison between groups. p value < 0.05 was considered statistically significant.

Results

Two hundred and sixty-nine newly diagnosed meningiomas were operated in our hospital during the period. Out of these 269 patients, 153 patients underwent MRI more than twice before surgery, and 71 patients had an MRI interval of more than 6 months (183 days). Eventually, Td was calculated in 62 patients with enlarged tumors.

Patient characteristics of 62 meningiomas are shown in Table 1, the median age was 61 years old (25–86 years old), and the woman accounted for 77.4% of all patients. The median Td was 1082 days (54–8579 days). One patient did not have MIB-1 SI in the pathology report, and 61 patients had the median MIB-1 SI of 2.5% (0.7–14.6%). Td and MIB-1 SI had a negative correlation (r = −0.319, p = 0.0122) (Fig. 1). Td was significantly shorter in WHO grade 2 compared to WHO grade 1 (median: 290.7 vs. 1090.8 days, p = 0.034). There was no significant difference in Td between Simpson grades (p = 0.569). Also, there was no significant association of Td with tumor localization (p = 0.41) (Table 2). There was only one case of recurrence during the observation period, and statistical analysis of Td and recurrence was impossible. The cases were divided into three equal groups by initial volume—under 2.5 cm² (n = 21), 2.5–5 cm² (n = 21), and over 5 cm² (n = 20)—the median was 824, 922, and 1904 days, respectively (p = 0.001).

MIB-1 SI was significantly higher in patients with Td < 3 years than in those with Td ≥3 years (median: 3.35 vs. 2.00%, p = 0.005) (Fig. 2), and the incidence of WHO grade 2 was significantly higher in patients with Td < 1 year than in those with Td ≥1 year (37.5 vs. 3.8%, p = 0.014) (Table 3). All of the five patients with WHO grade 2 had Td of less than 3.5 years.

Absolute tumor growth rate had a median value of 1.25 cm³/year (range, 0.17–15.44 cm³/year), and relative tumor growth rate had a median value of 34.1%/year (range, 3–3657%/year). Comparing WHO grades 1 and 2, absolute tumor growth was not significantly different between the

### Table 1 Characteristics of the 62 meningiomas (N=62)

| Characteristics    | Value          |
|--------------------|----------------|
| Age median (yr)    | 61.0 (25–86)   |
| Sex n (%)          |                |
| Male               | 14 (22.6)      |
| Female             | 48 (77.4)      |
| Location n (%)     |                |
| Skull base         | 23 (37.1)      |
| Non skull base     | 39 (62.9)      |
| Median Td (days)   | 1082 (54–8679) |
| Median MIB-1 SI (%)| 2.5 (0.7–14.6) |
| WHO grade n (%)    |                |
| Grade1             | 57 (91.9)      |
| Grade2             | 5 (8.1)        |
| Grade3             | 0 (0)          |
| Simpson grade n (%)|               |
| Grade1             | 23 (37.1)      |
| Grade2             | 20 (32.3)      |
| Grade3             | 10 (16.1)      |
| Grade4             | 9 (14.5)       |

Td tumor doubling time, MIB-1 SI MIB-1 stunning index

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WHO grades (median 1.2 vs. 2.4 cm³, \( p = 0.121 \)), while relative tumor growth was significantly greater in WHO grade 2 (median 29.8 vs 247.9%, \( p = 0.0245 \)).

**Discussion**

Recently, the incidence of meningiomas has increased due to the easy availability of imaging studies, and the tumor size at the time of detection tends to be small [2]. The efficacy of early resection for such meningiomas has not been proven.

**Table 2** Comparison of tumor doubling time

| Td (days) | \( p \) value |
|-----------|-------------|
| WHO grade (median) | 0.034 |
| 1 | 1090.8 |
| 2 | 290.7 |
| Simpson grade (median) | 0.569 |
| 1 | 1090.8 |
| 2 | 1071.3 |
| 3 | 1477.6 |
| 4 | 824.0 |
| Localization (mean) | 0.41 |
| Skull base | 721.5 |
| Non skull base | 1138.0 |

**Td** tumor doubling time

WHO grades (median 1.2 vs. 2.4 cm³, \( p = 0.121 \)), while relative tumor growth was significantly greater in WHO grade 2 (median 29.8 vs 247.9%, \( p = 0.0245 \)).

Although Chamoun et al. stated that in most incidental meningiomas, observation is the primary treatment because of the lack of growth or slow growth rate, resection is desirable in cases of symptomatic large tumors, tendency to increase in size, or strong suspicion of malignancy on imaging [4], but no specific figures were given. In our report, we showed that the incidence of WHO grade 2 is significantly higher in rapidly growing meningiomas with a Td of less than 1 year, and this rapid growth could be a basis for surgery even in asymptomatic patients.

Although there have been reports on the relationship between MIB-1 SI of first operation and Td in recurrent meningioma [8, 11], our report is the first to show the relationship between preoperative Td and MIB-1 SI in newly diagnosed meningioma. Oya et al. reported a high recurrence rate when the MIB-1 SI was more than 3% [15], and based on our results, tumors with Td of less than 3 years have a significantly higher MIB-1 SI, suggesting a higher recurrence rate after removal. This indicates that preoperative Td may be useful in considering the treatment
strategy such as radical resection for short Td meningiomas prior to surgical histopathological diagnosis.

Regarding another histological feature, Chiba et al. reported that sheet-like growth is associated with recurrence rate in WHO grade 1 meningiomas [5], but there was no significant difference in Td between patients with and without sheet-like growth in our study ($p = 0.65$). We need to examine the association of Td with other quantitative histological markers other than MIB1 or molecular anomaly.

The natural history of meningioma should be taken into consideration when using Td to determine a treatment strategy. Hashiba et al. found that incidentally discovered meningiomas did not always follow an exponential growth pattern [6]. Recently, the growth patterns of meningiomas have been reported to be exponential, linear, and decelerating [14]. Nakasu et al. reported exponential growth in 14.8%, linear growth in 37.7% (including some deceleration cases), and deceleration in 47.5% [13], while Bebbahani et al. reported exponential growth in 25.9%, linear growth in 16.7%, and deceleration in 35.2% [3], suggesting that the exponential growth pattern is generally less than one quarter. Observational studies of benign meningiomas with a long follow-up period have reported a Gompertz curve-like growth pattern, with exponential growth in the early stages, linear growth in the middle stages, and a deceleration curve that gradually approaches a plateau [12]. Td is an indicator of growth rate assuming exponential growth of the tumor and may not be applicable to all stages of meningioma. We also examined relative tumor growth rate as an index of linear tumor growth rate, and indicated that WHO grade 2 tumors grow faster than WHO grade 1 tumors, assuming linear growth. A previous report suggested that WHO grade 1 meningiomas have a Gompertz curve-like growth curve, whereas WHO grade 2 meningiomas have an exponential growth curve, and in comparing the rate of growth when the WHO grade is unknown before surgery, it is appropriate to compare tumor growth by Td, assuming exponential growth. But, if Td is calculated exponentially for linearly or slowly growing tumors, the shorter the observation period, the more likely that the growth rate will be underestimated. In fact, in our data, observation period and Td were positively correlated ($r = 0.397$, $p = 0.0014$), and the shorter the observation period, the shorter the Td tended to be. One reason may be that tumors with a fast growth rate are operated earlier and the observation period is shorter; however, considering that Td varies depending on the observation period, it would be necessary to examine the accuracy of Td by measuring in two or more periods with more than three imaging evaluations in actual clinical practice. But it is difficult to accurately examine because meningiomas that have been followed for a long period grow very slowly and errors in volume measurement have a greater impact on Td. Instead of examining Td by period, we examined Td by volume at the time of initial diagnosis. We indicated that the larger the initial volume of tumor, the longer the Td, and thus, slower the growth rate. This suggests that the large initial volume may have already exceeded the inflection point in the Gompertz curve and entered the deceleration phase. Tumors that are initially large and have a long Td may not require surgery as long as they are asymptomatic. On the contrary, tumors that are small in size and have a short Td at initial presentation include those that are highly malignant, suggesting that frequent imaging follow-up and early surgical intervention may be necessary.

In our report, there was no significant difference in Td between skull base and non-skull base tumor localizations. Hashimoto et al. reported that skull base meningiomas have significantly lower MIB-1 SI and slower growth rate [7], and the biological characteristics of meningiomas may differ depending on the site. When we examined the association between Td and MIB-1 SI separately for skull base meningioma and non-skull base meningioma, we found a negative correlation in non-skull base meningioma ($r = -0.316$, $p = 0.0499$), but no correlation in skull base meningioma ($r = -0.259$, $p = 0.245$). The use of preoperative Td in determining the treatment strategy for skull base meningioma should be carefully considered.

There are various limitations in this report. Tumors with observation periods of 6 months or less were excluded from the study; there is concern that Td may have been over- or underestimated. In addition, there was only one case of recurrence during the observation period of the included patients, and we were not able to directly examine the correlation between Td and recurrence rate.

Prospective studies with multiple cases of asymptomatic meningioma are needed.

Conclusion

Preoperative Td and MIB-1 SI were shown to have a negative correlation, and meningiomas with preoperative Td of less than 1 year have a significantly higher incidence of WHO grade 2. Therefore, early treatment should be considered for the patients with short Td meningioma even if asymptomatic.

Meningiomas with a preoperative Td of less than 3 years may have a high postoperative recurrence rate, and further consideration could be given to radical resection at the time of surgery.

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Author contribution All authors contributed to the study conception and design. Data collection and analysis were performed by YM, TS, DK. The first draft of the manuscript was written by YM, and all
authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Declarations**

**Ethics approval** The study was approved by the institutional review board of Tokyo Medical and Dental University. All patients in this study provided their informed consent for the inclusion of their clinical data in this manuscript.

**Consent to participate** Informed consent was obtained from all individual participants included in the study.

**Consent for publication** Informed consent was obtained from all individual participants included in the study.

**Competing interests** The authors declare no competing interests.

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