Objectives/Purpose

- The optimal adjuvant management for patients with atypical meningioma remains controversial, particularly after a gross total resection (GTR).
- The goal of this study was to review long-term outcomes in such patients aiming at identifying potential factors that associate with disease progression.
- In a parallel manner we investigated the following issues:
  - The minimal volume of residual disease that represent a cut-off at which radiotherapy should not be delayed beyond.
  - The growth pattern of atypical meningiomas with or without radiotherapy.
  - The time of disease progression between volumetric and planimetric measurement.

Patients and methods

- From August 1992 to August 2013, we found 70 patients with atypical meningioma treated at our institution (Table 1).
- Pathology review was performed based on WHO-2007 criteria, presence of brain invasion or a mitotic index of 4 or more per 10 high power field (HPF), either alone or combined. The diagnosis was also confirmed on the basis of the additive criteria of three or more of the 5 atypical histological features: area of geographic necrosis, nuclear pleomorphism, loss of architecture (cheating), high cellularity and the presence of focal small hypercellular clone.
- Patients with history of neurofibromatosis type 2, previous cranial radiotherapy, multiple lesions, previously resected grade I lesion that had transformed to a grade II at time of recurrence or inadequate imaging follow-up were excluded from this study.
- We performed pre- and post-operative measurements of tumor volume from magnetic resonance imaging. We assessed age, gender, tumor location, bone involvement, brain invasion, mitotic figure, pre-operative disease volume, extent of resection, use of adjuvant post-operative radiation therapy (PORT), and residual tumor volume at time of radiation therapy (RT) by uni- and multivariate analysis to determine their potential impact on disease recurrence (Table 1).
- Tumor growth rates were calculated directly from changes in volume over time based on real residual disease delineation at each MRI from the baseline throughout the follow-up for each patient.
- Statistical methods used to calculate recurrence-free survival (RFS), uni- and multivariate analysis and estimation of cut-off residual disease volume were Kaplan-Meier, Log rank test, Cox proportional model and Youden’s Index statistic, respectively.
- 40 patients (57%) underwent a gross total resection (GTR) and 30 (43%) underwent a subtotal resection (STR).
- PORT was delivered to 12 patients (30%) with a GTR and to only four (13%) with a subtotal resection (STR).
- With a median follow up time of 68.9 months, the 5-year progression-free survival (PFS) for GTR patients with or without PORT was 100% and 54.1%, respectively, (p=0.0058, 95%CI 66.4 - 123.3).
- Whereas, PFS for STR patients with or without PORT was 75% and 0%, respectively, (p=0.00026, 95%CI 7.7 - 16.53).

Results

- On multivariate analysis, STR and PORT were found to be the only independent significant prognostic factors that associated with disease progression, with corresponding hazard ratios of 5.4873 (95%CI 2.19 - 13.72, p=0.0003) and 0.0464 (95%CI 0.0059 - 0.364, p=0.0035), respectively.
- Based on Youden’s index statistic, a cut-off value that correspond to a residual volume of more than 8.76 cm³ at time of RT was associated with worse PFS (9% vs 56%, p=0.0079, 95%CI 16.37 - 123.3).
- In patients before receiving RT, the median relative and absolute growth rates, and tumor doubling time were 124.2%/year, 4.8 cm²/year and 1.67 year, respectively.
- These indices changed after RT to be 0.245%/year for relative growth rate, minus 0.09 cm²/year for absolute growth rate and minus 0.005 year for the doubling time, respectively, p > 0.05 for all comparisons, “negative values represent tumor shrinkage.”
- An earlier detection of failure was documented by measuring changes in residual tumor volumetrically rather than planimetrically (with median time lag of 18 months), Fig. 4.
- At time of disease progression detection, the median tumor volume was 4.89 cm³ on volumetric measurement compared to a median volume of 12.3 cm³ for planimetric measurement,
- The tumor volume will be already at least 50% larger by the time of planimetric detection, p = 0.0003.

Conclusion

- Atypical meningioma can behave aggressively and the disease progression rate, even after a GTR, remains high.
- The routine use of PORT remains a controversial issue particularly after GTR.
- Our data suggest that PORT reduces the disease progression rate and should be considered in most patients.
- Our study provides new information on the importance of using volume measurement to determine disease progression.
- This study identified variables of prognostic impact and parameters on tumor growth rates that may aid physicians in selecting patients that may benefit from an earlier adjuvant PORT
- The potential benefit of PORT post-GTR in patients with atypical meningioma needs to be confirmed on a randomized trial.

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Table 1. Patient characteristics, Univariate analysis (UVA) and Multivariate analysis (MVA)

<table>
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<th>Age Group</th>
<th>Gender</th>
<th>Tumor Location</th>
<th>Baseline</th>
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References

2. Youden’s index: A statistic that can be used to determine a cut-off value that corresponds to a residual volume of more than 8.76 cm³ at time of RT was associated with worse PFS (9% vs 56%, p=0.0079, 95%CI 16.37 - 123.3).
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Background

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