

Prospective Molecular screening of relapsing inoperable skull base and frontal anterior meningiomas

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PLAN

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INTRODUCTION

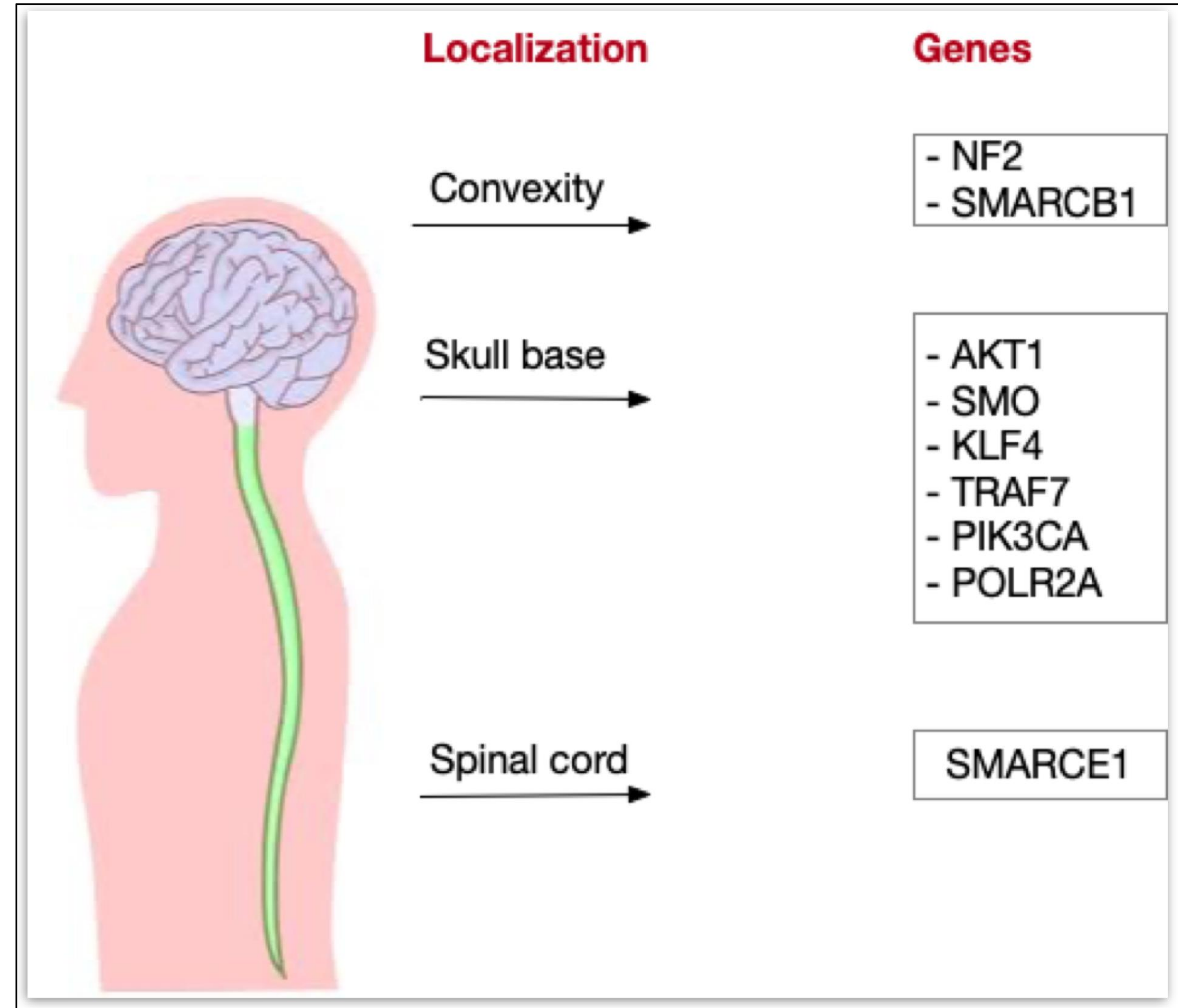
- Meningiomas are the most common primary CNS tumors in adults.
- Its about 37% of all intracranial tumors in USA
- 90% of theme are intracranial and 10% located in the spine.
- Meningiomas mostly occur in elderly population between 60 and 70 years old and are very rare in childhood <4% of all cerebral pediatric neoplasm.
- 80% of them can be cured surgically alone.
- Prognosis and relapsing of meningioma
 - Grade
 - location: simpson grade

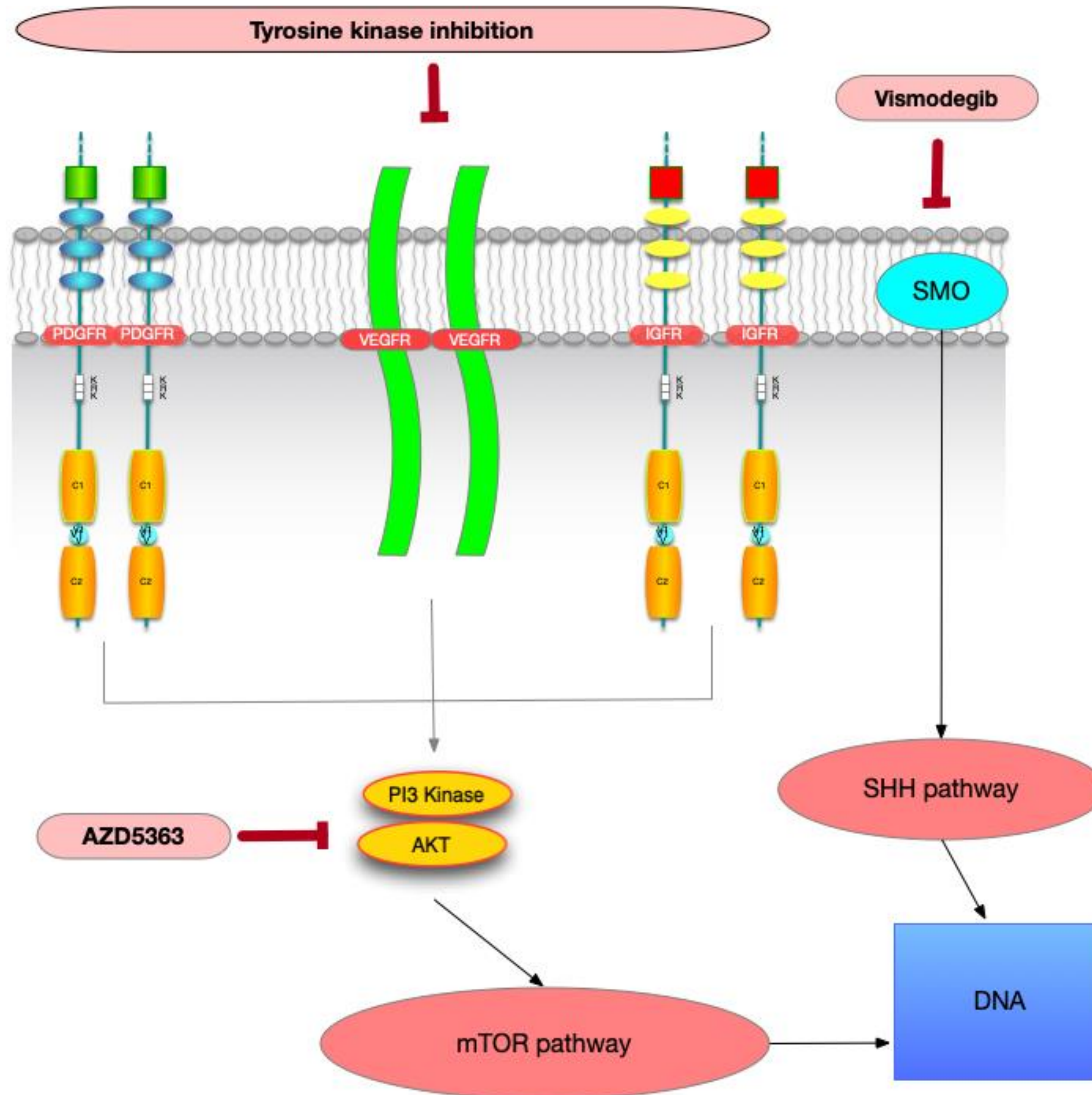
EMBRYOLOGY

- Meningiomas arise from meningotheelial arachnoid cells.
- Interestingly, the meninges of the brain convexity and skull base are derived from the neural crest and mesodermal structure, respectively,
- This may affect their histological feature and somatic mutations.

LOCALISATION AND MOLECULAR ALTERATION

- Tumour localisation defines molecular alterations
- Drivers for key mitogenic pathways
 - PIK3-AKT / mTOR
 - ERK
 - SHH
- Over-expression of tyrosine kinase receptors
 - VEGFR
 - IGFR
 - PDGFRA
- Drugs available for targets





GOAL

Our experience in screening for targetable molecular alterations of untreatable meningiomas led us to hypothesise that these mutations were less frequent than expected considering available studies.

- Goal : To evaluate screening strategies for patients with
 - recurrent and inoperable skull base and frontal meningiomas
 - prospectively reviewed in Neuro oncology / Neurosurgery in the service meetings.

METHODS

- Prospective study from 2018 to 2022
- Molecular status in the first biopsy of relapsing patients after surgery with
 - pathologically diagnosed meningioma
 - located at SB or in frontal areas,
 - When radiotherapy was prescribed in our center's multidisciplinary meeting.
- NGS to determine the molecular status of mTOR and SHH pathways.
- Further evaluation of IHC prescreening using filamine, GAB1 and OTX2 was also conducted.

RESULTS

- Patient selections:
 - 61 patients were included:
 - 59% (N=36) in SB with median age 53 while 77% (N=47) were female.
 - 61% (N=37) were grade 1,
 - 33% (N=20) were grade 2
 - and 6% (N=4) grade 3.

RESULTS

- **Molecular alterations**
 - **SMO mutation** : 2 (3.3%) meningiomas,
 - grade 1 : 2/2 meningothelial meningiomas
 - **SHH mutation** : 1 (1.6%)
 - **PIK3CA mutation** : 5 (8.2%) meningiomas
 - grade 1 : 4/5 , transitional meningiomas
 - grade 2 : 1/5
 - **AKT1 mutation** : 9 (14.8%) meningiomas
 - grade 1 : 6/9, transitional meningiomas
 - grade 2 : 3/9

RESULTS

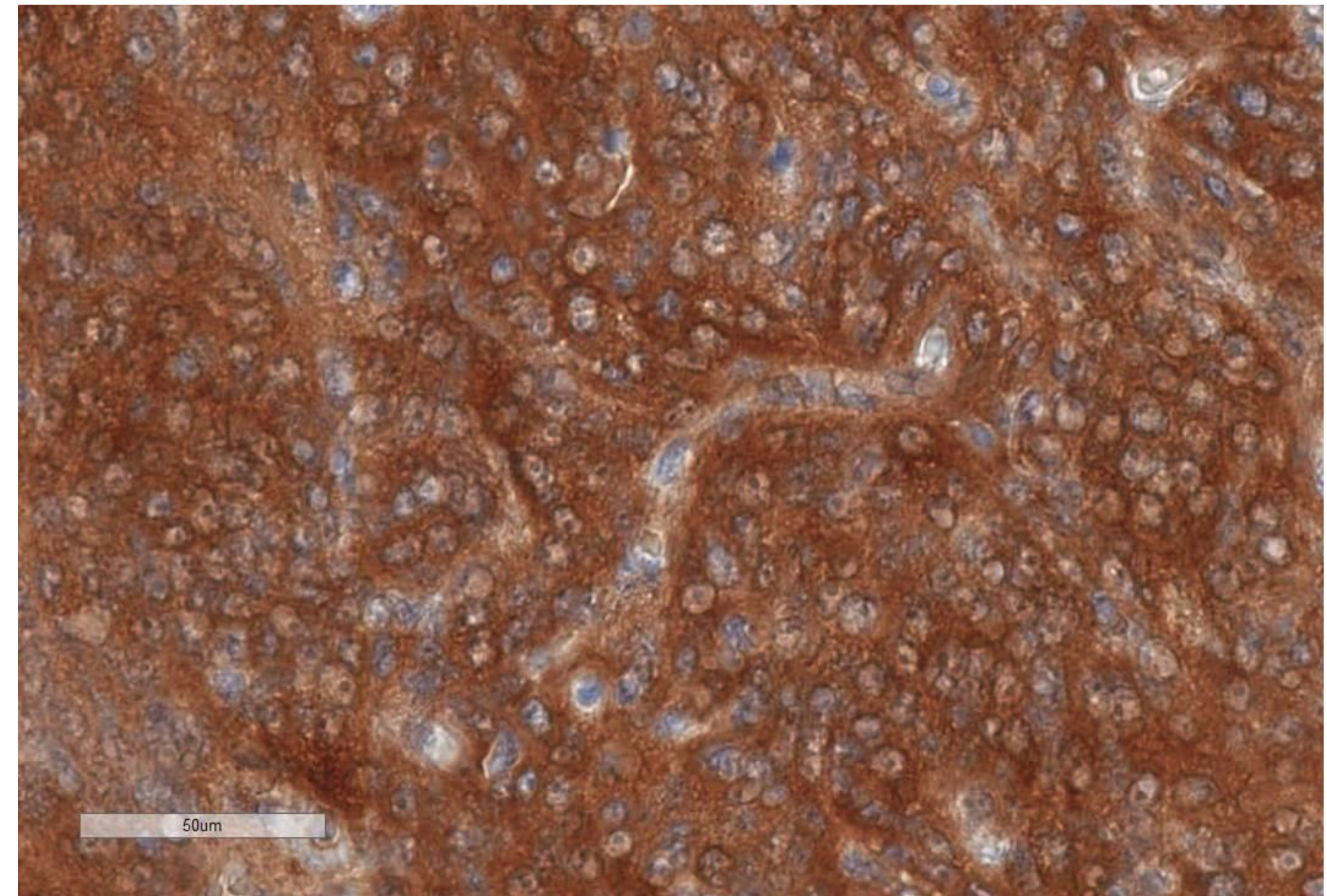
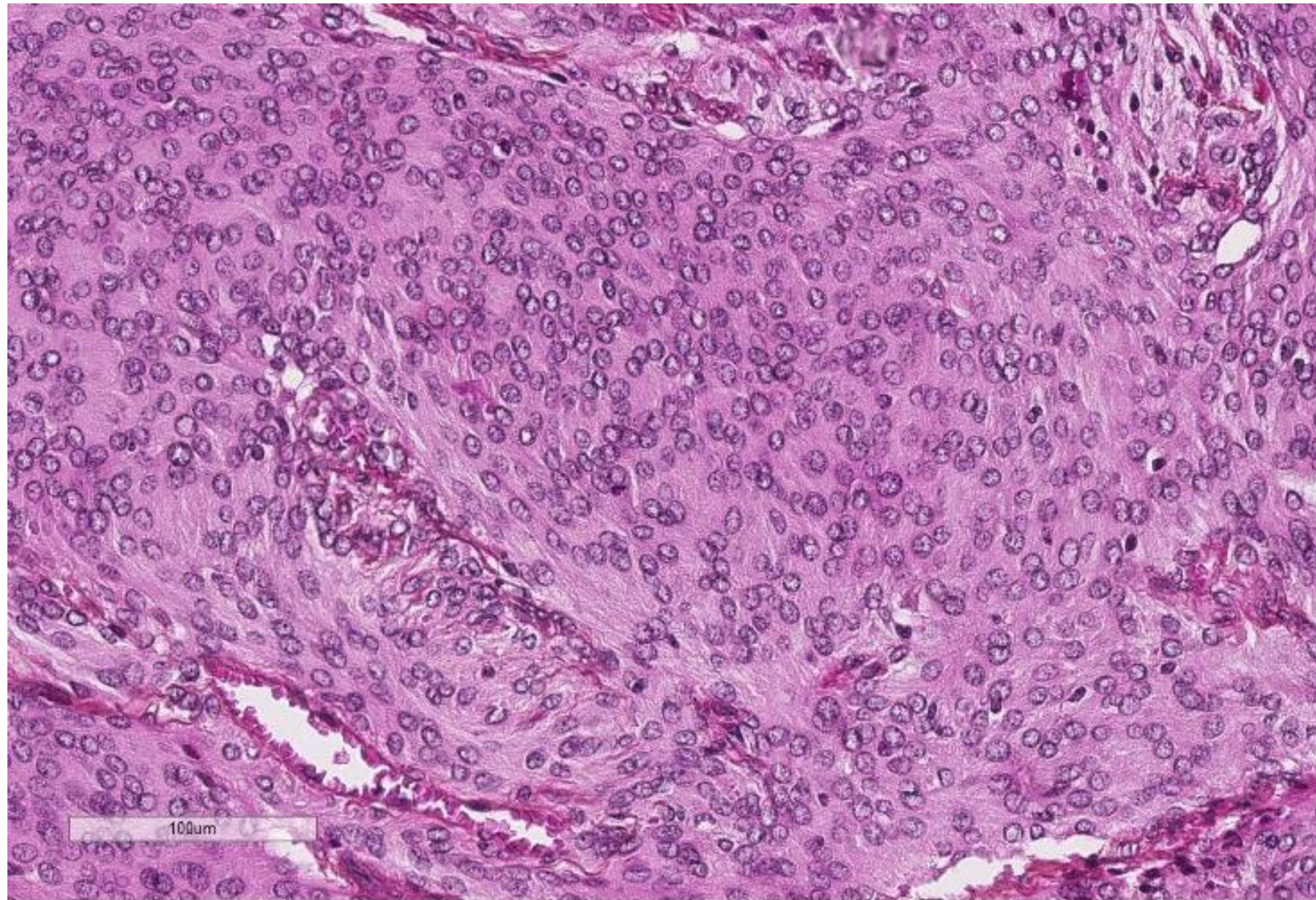
- Tumor's Location, Bone Infiltration and molecular alteration:
 - SMO mutation :
 - 2/2 skull base location
 - no bone infiltration
 - PIK3CA mutation :
 - 5/5 in skull base location
 - 1/5 with bone infiltration
 - AKT1 mutation :
 - 5/9 in skull base location
 - 4/9 with bone infiltration

GAB1 EXPRESSION

- **Strong expression (H-score >120) :**
 - **SMO mutation :**
 - 1/2 strongly positive (H-score : 120/300)
 - 1 négative - AFA fixative solution
 - **SHH mutation :**
 - 1/1 Grade III (H-score : 180/300)
 - **PIK3CA mutation:**
 - 1/5 Grade II (H-score : 195/300)

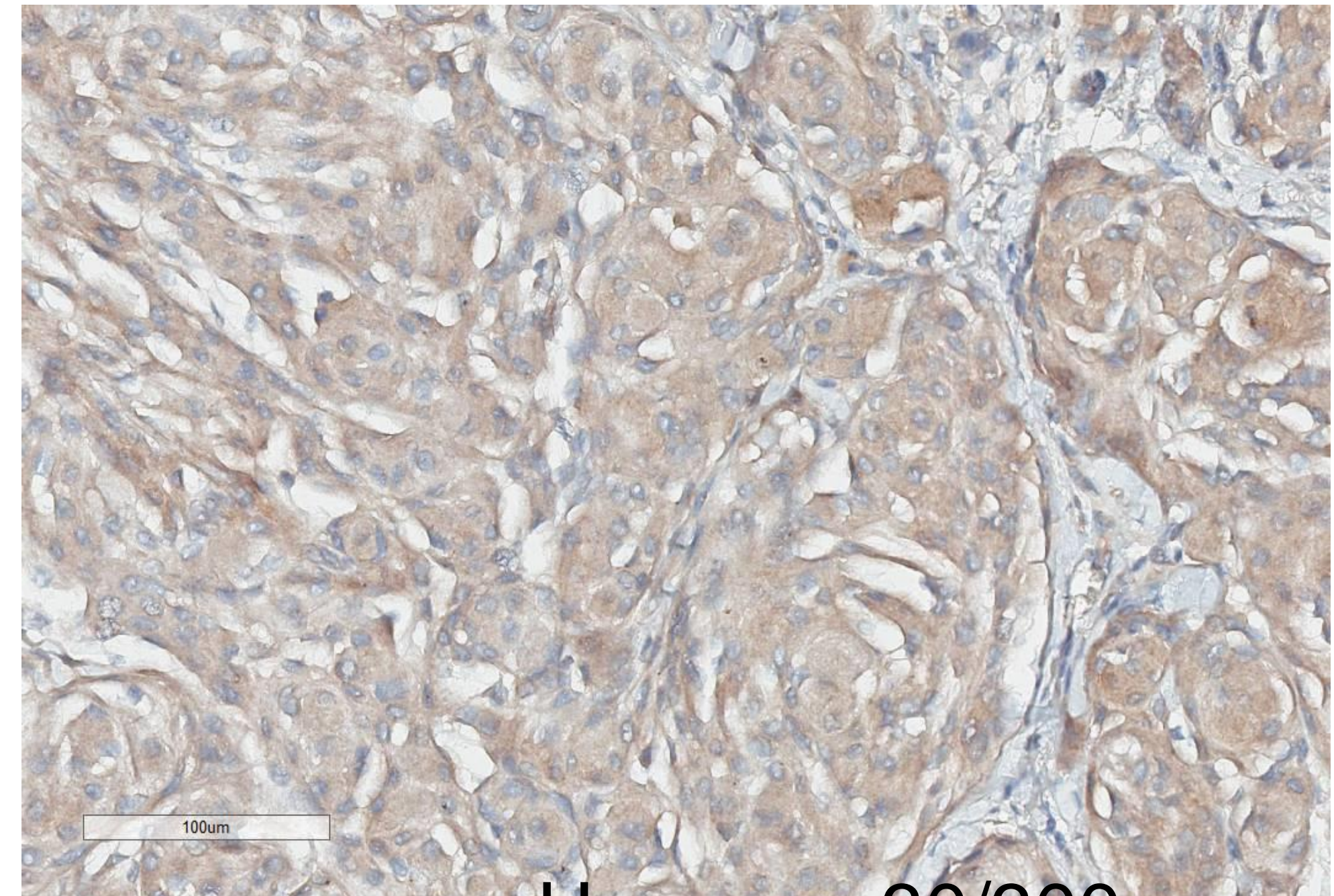
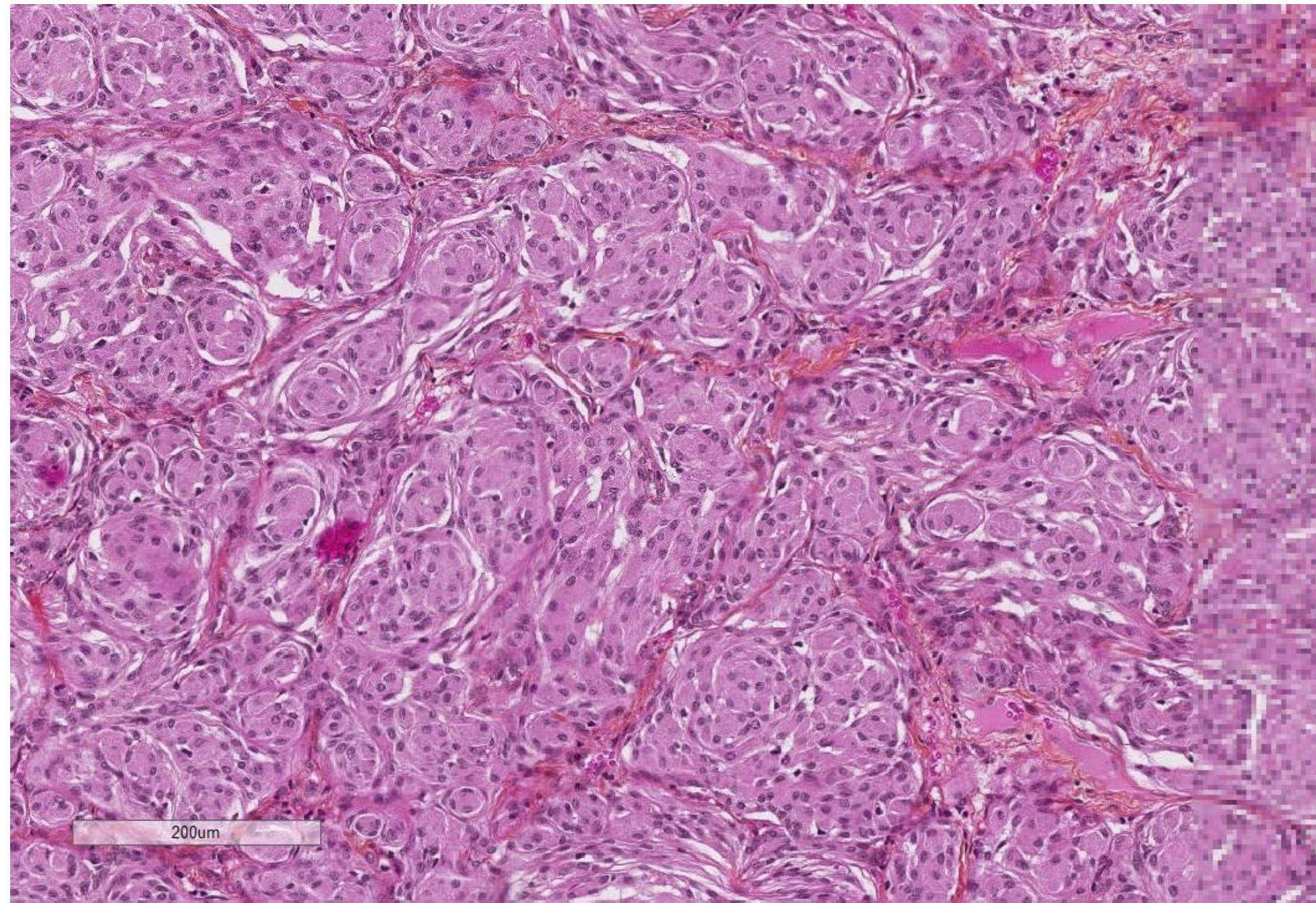
 - **5 wild type meningioma (H-score : 130-175/300)**
- **Low expression (H-score < 120) :**
 - **AKT1 mutation:**
 - 9/9 Grade I/II (H-score : 0-80/300)
 - **PIK3CA mutation:**
 - 4/5 Grade I (H-score : 0-60/300)

GAB1 EXPRESSION : SMO



H-score= 120/300

GAB1 EXPRESSION : AKT1



H-score= 30/300

CONCLUSION

- In intention to treat we showed that SHH targetable activating mutations are rarer than previously described in systematic retrospective studies of skull base meningiomas.
 - SMO mutation : 3,28% vs 11% (Strickland M et al 2017) or vs 28% (Boetto J et al 2017)
 - AKT1 mutation : 14.75% vs 19% (Strickland M et al 2017) or 15% (Boetto J et al 2017)
 - PIK3CA mutation : 8.2% in other studies < 4-7%
 - These new data should be taken in account for future therapeutic trial designs.
- GAB1 could be a useful marker for immunohistochemical pre-screening of cases amenable to sequencing for
 - Sonic hedgehog pathway (but not all targetable by vismodegib : 1 SHH gene mutation)
 - mTOR pathway genes.

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Thank you for your attention !