最終試験の結果の要旨

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　　　主査および副査の５名は、令和２年９月７日、学位申請者 Manisha Bohara 君に面接し、学位申請論文の内容について説明を求めると共に、関連事項について試問を行った。具体的には、以下のような質疑応答がなされ、いずれについても満足すべき回答を得ることができた。

Question 1) How do you define atypical and anaplastic meningioma?
Answer) Atypical meningioma is defined as tumor with increased mitotic activity (≥ 4 mitoses per 10 high-powered fields), brain invasion, or three or more of the following features: increased cellularity, small cells with a high nuclear-to-cytoplasmic ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, or foci of spontaneous or geographic necrosis. Anaplastic meningiomas have ≥ 20 mitoses per 10 high-powered fields and/or malignant characteristics resembling carcinoma, sarcoma, or melanoma.
Question 2. a) In the brain, how do the pathologists count the Ki-67?
Answer) It is done within the hot spot by counting the total number of positive-staining tumor cells divided by the total number of tumor cells.
Question 2. b) Do you know the antigen of this antibody that reacts?
Answer) Ki-67 monoclonal antibodies directed against Ki-67 recognizes a nonhistone nuclear protein expressed in proliferating cells during G1-, S-, G2-, and M-phases of the cell cycle, but it is not present in quiescent (G0) cells.
Question 3) Is there any difference in the value of ADC among the histological subtypes of low grade meningiomas (LGMs) like in between meningothelial and fibrous meningiomas?
Answer) We did not assess the difference among the histological subtypes of LGMs. However, previous studies have shown no significant difference in mean ADC values between fibrous and meningothelial meningiomas.
Question 4) In what kind of diseases practically IVIM imaging can be used?
Answer) It has been widely used in various diseases of different body organs such as brain, pancreas, liver, lungs, prostate, breast as IVIM MRI can measure both tissue perfusion and diffusion.
Question 5) Contrast-enhanced T1WI (conventional MRI) can show some heterogeneity in the high grade meningiomas (HGMs) in comparison with LGMs. So, can you say IVIM imaging has some distinct advantages than conventional imaging?
Answer) Although there are some atypical features that may suggest HGMs in contrast-enhanced T1WI (conventional MRI), differentiating HGMs and LGMs purely on the basis of conventional MRI is difficult. Whereas IVIM imaging allows separate and simultaneous estimation of diffusion and perfusion parameters reflecting tumor cellularity and vascularity respectively without using a contrast agent.
Question 6) Do you know how the treatment might be different in HGMs from LGMs?
Answer) In LGMs, most asymptomatic patient with small tumor (≤ 3cm) are best managed by observation; else, patient should undergo surgical resection whenever feasible. In WHO grade III meningioma, regardless of tumor size and symptom status, surgery is indicated with adjuvant radiotherapy. For patient with grade II meningioma, postoperative radiotherapy is recommended for incomplete resection and in case of complete resection, postoperative radiotherapy maybe considered based on the balance between potential benefits and risks of side effects of the radiotherapy.
Question 7) How much time did it take for one analysis?
Answer) We used IVIM analysis software to generate IVIM maps (D, D*, f) from DW imaging data and for each case, it took less than 10 seconds.
Question 8) Why is number of females more than males in LGMs than in HGMs in your study?
Answer) Meningiomas are more common in women, with a female-to-male ratio of approximately two or three to one. This female predominance is less pronounced or absent in those with atypical or anaplastic meningiomas.
Question 9) Is there any gene mutation in meningioma?
Answer) The best characterized genetic alteration is loss of 22q chromosome which is frequently associated with mutation in the neurofibromatosis type 2 (NF2) gene. Besides NF2 mutation, mutations in AKT1, SMO, TRAF7, KLF4 have also been detected. Mutations in the TERT promotor region in particular have been associated with

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an aggressive clinical course.

Question 10) How small can meningioma be identified using IVIM method?

Answer) IVIM imaging using a single shot echo-planar imaging pulse sequence suffers from susceptibility artifacts. So, it might be difficult to identify small meningioma using this method.

Question 11) What are the causes of recurrence of meningiomas?

Answer) Tumor size and localization, higher histological grade (II, III), higher proliferative index (ki-67), incomplete resection higher (Simpson grade III-V) are some of the factors associated with the recurrence of meningiomas.

Question 12) Are there any other histochemical markers besides ki-67?

Answer) The other histochemical markers to identify meningiomas are epithelial membrane antigen, progesterone receptor, somatostatin receptor 2A.

Question 13) Can meningiomas become cancerous by repeated recurrence?

Answer) Benign meningiomas occasionally recur and histological malignant transformation is rare. Atypical meningiomas are neither malignant (cancerous) nor benign, but they may become malignant.

Question 14) In this study, you concluded heterogeneity histogram parameters of ADC, D, and f can be helpful to differentiate tumor grade. Which one is the most useful parameter of all?

Answer) In our study, standard deviation (SD) of ADC, SD of D and coefficient of variation of f showed the highest area under the ROC curve (AUC), although the AUC values between them didn't differ significantly. So, further studies are required.

Question 15) Is histogram analysis routinely used in the clinical practice?

Answer) Although whole-lesion histogram analysis has been increasingly used for the differentiation of histological grades in different tumors, it has not been routinely used in clinical practice as an emergent promising imaging tool.

Question 16) In the future, can radiological parameters be applied to the research of radiogenomics or AI?

Answer) The radiomics features extracted from conventional MR images was reported to be useful in predicting the grades of meningiomas. In the future, the quantitative parameters obtained from IVIM imaging can be applied to the research of radiogenomics or AI.

Question 17) IVIM method measures both diffusion and microperfusion. Is there any correlation between MRI IVIM and MR perfusion imaging?

Answer) Previously, some studies have shown significant correlation between f by IVIM and CBV by DSC perfusion-weighted imaging.

Question 18) In slide 5, you presented three IVIM parameters. Can you explain what does these parameters mean?

Answer) With IVIM MRI, we can estimate three quantitative parameters: f (perfusion fraction), the fraction of diffusion related to microperfusion reflecting the microvascular blood volume; D* (pseudo-diffusion coefficient), proportional to capillary blood velocity due to microperfusion; D (true diffusion coefficient), pure diffusion of a water molecule reflecting tissue cellularity.

Question 19) You chose 45 LGMs and 14 HGMs. Does it include the recurrent tumors?

Answer) No, it does not. We only included the newly diagnosed cases.

Question 20) The histopathological features of meningothelial meningioma is different from the other subtypes of LGMs. If you excluded other subtypes, would your results be different?

Answer) Since in our study, there are more cases of meningothelial meningiomas in LGMs, there might not be significant difference in our result even if we excluded other subtypes.

Question 21) You manually drew region of interest (ROIs) and obtained the voxels in the ROIs. The parameters might be related to the tumor volume as the large tumor will have more number of voxels. The large tumor might be more heterogeneous than the small tumor. Did you analyze the heterogeneity of parameters within LGMs depending on the tumor size?

Answer) We evaluated the heterogeneity of parameters in LGMs, however, we did not compare the parameters among groups with different sizes.

Question 22) LGMs and HGMs are both hypervascular. What is pathological difference between the groups?

Answer) Homogenous hyperperfusion pattern is associated with LGMs whereas heterogeneous hyperperfusion pattern associated with HGMs.

Question 23) Can you detect the tumor using this method when it is invaded in the bone, cavernous sinus?

Answer) It can sometimes be difficult due to MR artifacts.

Question 24) IVIM imaging measures tumor cellularity and vascularity. In the histological sections, did you measure or ask pathologist to measure the cellularity and vascularity?

Answer) We did not. We just collected data on histopathological diagnosis and ki-67 labeling index.

　以上の結果から、5名の審査委員は申請者が大学院博士課程修了者としての学力・識見を有し

ているものと認め、博士（医学）の学位を与えるに足る資格を有するものと認定した。