Intraoperative Real-time Near-infrared Image-guided Endoscopic Endonasal Surgery for Pituitary Tumors

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Method Article

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Abstract

Background: In endoscopic endonasal surgery of pituitary tumors, the intraoperative judgment and tissue identification depend largely on surgeons' surgical experience.

Objective: To assess whether the delayed-window indocyanine green (ICG) (DWIG) technique can visualize and distinguish the normal pituitary gland and tumor under the endoscope in real-time during surgery.

Methods: Eight patients with pituitary adenoma who received 12.5 mg ICG were observed by near-infrared (NIR) fluorescence during the surgery to identify the pituitary gland and tumors.

Results: The normal pituitary gland and pituitary adenoma were visualized by NIR fluorescence in all 8 patients. The relative ratio of the fluorescence emission of the normal gland to that of the tumor (signal-to-background ratio [SBR] normal gland/tumor) increased after 15 min, peaking at 5.8±4.9 at 90 min. It suggested that pituitary gland was more clearly visualized during that period. The tumor/blood (SBR tumor) and normal gland/ blood (SBR gland) NIR fluorescence was significantly positively correlated with each K^{trans} on dynamic contrast-enhanced MRI, indicating blood–brain barrier (BBB) permeability.

Conclusions: This study showed the utility of the DWIG technique for identifying a normal pituitary gland from a tumor in endoscopic endonasal surgery from 15 to 90 min following ICG administration, "negative tumor staining". Permeability can contribute to gadolinium enhancement on MRI and to ICG retention and NIR fluorescence in a normal pituitary gland and tumor.

Introduction

Intraoperative judgment and tissue identification depend on a surgeon's surgical experience in resecting a pituitary tumor. Although neuronavigation is commonly used during the surgery, only the preoperative location of the normal pituitary gland is used as a reference, and real-time intraoperative tissue location information is not available. As such, the simple and reliable method of tissue and structure identification, that can be used intraoperatively, does not interfere with observation or manipulation, and provides real-time information, is needed.

Recently, second-window ICG (SWIG) for tumor lesions was utilized, in which a high dose (5 mg/kg) of ICG was administered to a patient with brain tumor within 24 h before surgery, and then, near-infrared (NIR) fluorescence from the tumor itself could be observed during the surgery. The utility of SWIG has been shown in the context of meningiomas,[5] glioblastomas,[6] metastatic tumors,[3,4] and other brain tumors using the enhanced permeability and retention (EPR) effect to take advantage of ICG accumulation in tumors. EPR likely accentuates the difference in fluorescence intensity between the tumor and normal parenchyma. However, SWIG requires a high-dose administration of ICG corresponding to the maximum safe capacity for biological use, which may incur side effects, limit its application to patients, and require administration 1 day prior to observation. Zeh et al. reported that the NIR-SBR in mice with glioblastoma peaked at 1-h post-infusion, not at 24 h.[14] In light of these findings, we hypothesized that the administration of ICG at more than 1 h before surgery might be sufficient and feasible for the visualization of the tumor. We modified the dose and timing of ICG administration to normal dose during the surgery. NIR fluorescence could be observed after early period, at almost more than 1 h after administration.[11, 10] We defined this modified technique as "delayed-window ICG (DWIG)." Using the DWIG technique, fluorescence from the tumor can be detected following the early phase of blood flow after the intraoperative administration of ICG (5–25 mg). Considering these findings, DWIG, the ICG administration at the early phase during surgery, seems to be a useful adjuvant therapy for pituitary tumors as well to improve their resection rate and reduce their recurrence. However, its efficacy and mechanism remain unknown. Here, we intraoperatively administered 12.5 mg of ICG to patients with pituitary adenoma and observed its effect using the DWIG technique. The objectives of the present study were two folds: first, to determine whether DWIG can visualize and distinguish a pituitary tumor from the normal gland; second to analyze whether the mechanism of ICG fluorescence may implicate with vascular permeability.

Methods

Study design and ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards, of the institutional research committee of the hospital of Fujita Health University (CRB4180003) and Saiseikai Yokohamashi Tobu Hospital (202056) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients.

Surgery and DWIG technique

Twenty-five patients with pituitary adenoma were enrolled in this study, including twenty patients with non-function pituitary adenoma, three with somatotroph adenoma, and two with lactotroph adenoma. Only eight patients can undergo dynamic contrast-enhanced (DCE) perfusion magnetic resonance imaging (MRI) and Gadrinium (Gd) -enhanced dynamic MRI due to insurance system so that we analyzed these eight patients in detail in this study (Table 1). Each patient received intravenous administration of 12.5 mg of ICG (C43H47N2NaO6S2, Daiichi Sankyo, Tokyo, Japan) mixed with 10 mL of 0.9% saline during the surgery. NIR visualization was performed from 0 to 180 min following ICG administration.

After administration of ICG, ICA was first detected, after which the venous phase was detected; the cavernous sinus was shown and washed out gradually. NIR fluorescence was detected from the blood for a while. During the first 15 min following the ICG administration, NIR fluorescence could be detected from the normal pituitary gland and tumor at the same level. After almost 15 min, NIR fluorescence from the gland could be stronger than the tumor until 180 min using an illumination system. Fluorescence excitation and exposure were registered when the gland and the tumor were exposed for the first time. The distance from the endoscope to the tumor was set at the frontal wall of the sphenoid sinus during the observation. The tumor was dissected and resected under DWIG based on the fluorescence guidance. Operative videos were recorded and stored; subsequently, the pictures with NIR fluorescence were captured. Fluorescence was reflected as a relative score, and fluorescence intensities of the tumor and blood were quantified to calculate the signal-to-background ratio (SBR) tumor reflecting the fluorescence of the tumor/blood.

NIR imaging system

The ICG technique visualization was performed using the following light equipment system: CLV-S200IR (infrared light source) CH-S200-XZ-EA (3 CMOS camera head) (Olympus, Carl Zeiss Co., Ltd., Japan), which utilized an NIR excitation light source (805 nm) and a camera (820–860 nm). NIR images were captured and stored for further assessment. The straightforward telescope (0°; diameter, 4 mm) (Karl Storz GmbH & Co KG, Tuttlingen, Germany) was used.

Image and statistical analyses

In all patients, DCE perfusion MRI examination and postprocessing were obtained, and the protocol was followed by the literature.[13,12] The pharmacokinetic model introduced by Tofts et al. can also be used to calculate these parameters K^{trans} , K^{ep} (=K^{trans}/V^e), V^e, V^p as shown in Table3.[12,13] DCE perfusion-MRI, dynamic MRI, and ICG-NIR videos were stored to assess the feasibility and efficacy of real-time ICG-NIR imaging for pituitary adenomas and to analyze the correlation among DCE perfusion-MRI, dynamic MRI, and ICG-NIR. We obtained a background reading from the blood to generate SBR. As the intensity of fluorescence luminescence is a relative value, values from the normal gland and tumor relative to the fluorescence luminescence of the blood were used. In addition, region of interest (ROI) analysis was performed to quantify the amount of fluorescence from the tissues. We selected five ROIs corresponding to the tumor and normal tissue lesions on the images and assessed their average values. We drew five ROIs on Gd-enhanced dynamic T1 MR images to compare the enhanced tumor with the normal brain parenchyma and analyzed their average values, which we called the ratio of Gd-enhanced T1 normal pituitary gland signal to tumor (T1BR), using ImageJ software (NIH Image, Bethesda, MD, USA). Univariate analyses were performed using a chi-squared or Fisher's exact test to compare categorical variables and an unpaired t-test or Mann–Whitney rank-sum test and simple linear regression analysis for continuous variables. Statistical significance was set to $p<0.05$. Statistical analyses were performed using JMP version 14.1.0 (SAS Institute Inc., Cary, NC, USA).

Results

DWIG shows near-infrared fluorescence of the normal pituitary gland

In this study, we used the DWIG technique, and fluorescence-guided observation was performed for 180 min from the dye injection. Patient characteristics are summarized in Table 1. Three representative cases are shown in Fig. 1 (somatotroph adenoma), Fig. 2 (lactotroph adenoma), and Fig. 3 (non-function adenoma). All patients showed NIR fluorescence in the tumor and normal gland. NIR fluorescence could show the normal pituitary gland and tumor until 15 min from administration and thereafter in normal cases. The normal pituitary gland retained its fluorescence and became brighter than the tumor from 15 min and thereafter. The relative fluorescence ratio of a normal pituitary gland to blood (SBR gland) was 1.5±0.6 at 15 min and increased thereafter, peaking at 4.5±3.4 at 90 min (Sup Fig. 2). The SBR gland maintained higher value and was 3.5±0.5 at 180 min. The relative ratio of the pituitary tumor to blood (SBR tumor) showed the different phenomenon to the SBR gland: 1.3±0.4 at 15 min, 0.8±0.1 at 90 min, and 0.8±0.2 at 180 min (Sup Fig. 2). Thus, we confirmed that the relative ratio of the fluorescence emission of the normal gland to the tumor (SBR normal gland/tumor) increased until 90 min: 1.5±0.8 at 15, 3.1±0.9 at 30, 2.9±1.6 at 60, 5.8±4.9 at 90, and 5.0±2.1 at 180 min (Fig. 4). DWIG assessments showed that from 15 to 90 min, the normal pituitary gland showed stronger fluorescence than the tumor, we called "Negative tumor staining". No residual tumor was observed using NIR fluorescence following surgery except case 7. Moreover, postoperative MRI scans did not show any residual lesions except case 7.

Blood–brain barrier permeability in normal pituitary gland and tumor may underpin NIR fluorescence

The mechanism of Gd-MRI can only be influenced by vascular permeability.[9] Thus, we calculated the parameters K^{trans}, K^{ep}, V^e, and V^p using DCE perfusion-MRI to assess the relationship between permeability and NIR fluorescence. The SBR tumor (tumor/blood) had significantly positive correlation with tumor K^{trans} ($p<0.001$, $R^2=0.96$) (Fig. 5), but not with K^{ep} (p=0.23), V^e (p=0.002), and V^p (p=0.47) (Table 2). The SBR gland (normal gland/blood) had also significantly positive correlation with normal gland K^{trans} (p=0.0032, $R^2=0.79$) (Fig. 6), but not with normal gland K^{ep} (p=0.82), V^e (p=0.058), or V^p (p=0.076) (Table 2). The thinness of the normal pituitary gland did not influence the results. The tumor K^{trans}, K^{ep} V^e, and (V^e-V^p) had significant differences from the normal gland K^{trans} (p=0.019), K^{ep} (p=0.014), V^e (p=0.007), and (V^e-V^p) (p=0.007), and tumor V^p and tumor (K^{trans}-K^{ep}) were not different from normal gland V^p (p=0.79) and normal gland (K^{trans}-K^{ep}) (p=0.79) (Supplemental Figure 1A–D).

Discussion

ICG dose and NIR fluorescence intensity

We referred to a prior SWIG protocol.[7] and developed a technique called DWIG, which is sufficient for differentiation in meningiomas[10] and spinal schwannoma[11] as we previously reported. For pituitary lesions, a previous study showed that ICG endoscope could observe differences in early blood flow between the normal pituitary gland and tumors.[1] Another study reported the feasibility and usefulness of NIR fluorescence using SWIG on pituitary adenomas.[2] The current study revealed that NIR fluorescence of 12.5 mg ICG (DWIG) remained in both the normal pituitary gland and tumor within the first 15 min without any differences, but fluorescence of tumor decreased at 15 min and thereafter. Thus, the difference in the fluorescence emission between the tumor and pituitary gland seems to be useful to confirm the location of the normal pituitary gland and facilitate to resect tumor from 15 to 90 min following administration. Subsequently, the intensity of fluorescence from the normal pituitary gland weakened at 180 min. Although the difference in the fluorescence emission was detected, it was not appropriate to delineate the tumor and gland. Amano et al. reported that the pituitary gland and tumor were contrasted in maximum at 7 and 15 min.[11] In other words, after 15 min, the normal pituitary gland can be clearly differentiated from the tumor. Their conclusions seem to be consistent with our results, although they did not show the ratio of SBR normal gland/tumor.[1] Inoue et al. noted that the time to contrast might depend on the size of the pituitary gland with significant difference. The normal pituitary gland is contrasted in restricted period (23–27 s), but faster than that in pituitary tumors (50–56 s).[4] Our data have no difference in fluorescence emission between pituitary tumors and glands at early stages. Perfusion of ICG in pituitary lesions might be too fast to be detected in our current protocol and system.

Our technique, DWIG, can provide the evident differences in fluorescence between the normal gland and tumor during endoscopic surgery 15–90 min after ICG administration. The higher score of K^{trans} and K^{ep} implied higher permeability, resulting in higher volume of ICG transportation from intravascular to extravascular spaces. It may result in the differences of ICG retention period between the pituitary tumor and normal gland. Our results suggest that this phenomenon has a correlation with the following factors: tumor K^{trans}, K^{ep}, and V^e were significantly different from the normal gland K^{trans}, K^{ep}, and V^e. (Sup Fig. 1)

Mechanisms of ICG fluorescence

We hypothesized that ICG retention is caused by the EPR effect, which in turn disturbs the lymphatic drainage system and increases vessel permeability through defective endothelial cells with wide fenestrations caused by an increase in the accumulation of agents from tumor cells.[7] ICG administration and fluorescein may be feasible for the optical monitoring of blood–brain barrier (BBB) disruption.[3] DCE perfusion-MRI can be used to assess BBB permeability and fluid and molecular exchange between the interstitial extracellular and intracellular fluid matrices.[12] However, the BBB does not exist in the pituitary gland. As such, the mechanism of Gd and ICG retention in the pituitary lesion seems to be different from that in other brain tumors. Thus, we analyzed K^{trans}, K^{ep}, V^e, V^p, and cerebral blood volume in both the tumor and normal pituitary gland on DCE perfusion-MRI scans. Only tumor K^{trans}, normal gland K^{trans}, and tumor V^e showed a significant difference with the SBR tumor and SBR gland, but K^{ep}, normal gland V^e, and V^p were not significantly different (Fig. 5 and 6). Thus, only BBB permeability seems to be correlated with Gd retention[9] and ICG retention in the pituitary lesion. An improved DCE perfusion-MRI method using Gd-based contrast agents with an individual arterial input function curve has been created to measure the BBB permeability constant K^{trans} in the healthy brain, as K^{trans} values in a healthy brain are typically 10 to 100 times lower than those in patients with brain tumors, stroke, or infections. [9] It implies that K^{trans} value might be a predictive factor for DWIG in a pituitary tumor. This supports our hypothesis that the ICG retention occurs in areas of enhanced vascular permeability through EPR effect.[8,3] Accumulating data suggest that vascular permeability may correlate with the fluorescence intensity in DWIG.

Limitations

Our current study has some limitations. The first is the sample size: The sensitivity and specificity are largely affected by the sample size, however, sample size was small because this was a pilot study. Thus, accurate calculations were limited in this study although we previously reported the sensitivity and specificity of DWIG in meningiomas[10]. The second is the equipment problem: the endoscope system has an automatic exposure feature that can average the pixel intensity to normalize the background and assign it a neutral gray color. The camera tries to balance the exposure when set to the automatic exposure mode. To address these issues, we used the score related to fluorescence of the blood and fixed the gain and illumination manually, resulting in the avoidance of false-positive tumor margins. Furthermore, those parameters can be used throughout the surgery, however, the scores are relative and not absolute values.

Conclusions

We show for the first time the utility of the DWIG technique for identifying a normal pituitary gland from a pituitary adenoma in real-time endoscopic endonasal surgery from 15 to 90 min following ICG administration by ”negative tumor staining”. NIR fluorescence of ICG can provide about 6 times stronger fluorescence at 90 min in a normal pituitary gland than that of a tumor. The permeability, as shown by K^{trans} on DCE perfusion-MRI, can contribute to Gd enhancement on MRI and to ICG retention and tumor NIR fluorescence. The difference of values on K^{trans}, K^{ep}, and V^{e} between the normal pituitary gland and tumor may also correlate with ICG retention. Further assessments are required to address its clinical benefits and limitations, and to advance its clinical implementation.

Declarations

Conflict of interest statement

J.Y.K.L owns stock options in Visionsense.

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All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jun MUTO, Yutaka MINE, Motoharu HAYAKAWA. The first draft of the manuscript was written by Jun MUTO, Yutaka MINE, Kazuhiro MURAYAMA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

The authors affirm that human research participants provided informed consent for publication of the images in Figures 1,2,3

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Tables

Table 1. Characteristics of patients with pituitary adenoma (1)

	Age	Gender	Pathology	SBR(Normal Gland/Tumor)	T1BR	Resection
1	47	F	Non function adenoma	5.1	2	GTR
2	41	F	Non function adenoma	5.3	2.2	GTR
3	65	M	Non function adenoma	9.8	4.9	GTR
4	62	M	Somatotroph adenoma	9.3	3.6	GTR
5	25	F	Non function adenoma	6.2	2	GTR
6	43	M	Non function adenoma	9.5	3.5	GTR
7	63	M	Lactotroph adenoma	2.3	1.8	STR
8	78	M	Non function adenoma	3.2	0.2	GTR

The clinical data of eight patients with pituitary adenoma in this study are shown. These data include age, SBR,T1BR, and resection rate.

ICG, indocyanine green; M, male; F, female; GTR, gross tumor resection; PR, partial resection,: SBR,Signal Background Ratio: T1BR, ratio of gadolinium-enhanced T1 tumor signal to the brain

Table 2. Characteristics of patients with pituitary adenoma (2)

	Fluorescence	Normal gland Thickness	K*trans* (Normal Gland)	K^{ep} (Normal Gland)	V_P(Normal Gland)	V^e (Nornal Gland)	K*trans* (Tumor)	K^{ep} (Tumor)	V^P (Tumor)	V^e (Tumor)
1	Positive	Thick	1.48	1.48	0.01	1	0.36	1.15	0.37	0.1
2	Positive	Thin	0.47	0.74	0.08	0.67	0.12	1.5	0.003	0.03
3	Positive	Thin	1.3	2	0.01	0.68	0.11	0.6	0.02	0.19
4	Positive	Thick	1.21	1.84	0.03	0.96	0.02	1.02	0.01	0.04
5	Positive	Thin	1.68	3.03	0.01	0.67	0.46	1.03	0.05	0.46
6	Positive	Thick	0.49	1.59	0.04	0.34	0.2	1.27	0.01	0.09
7	Positive	Thin	1.01	3.98	0.05	0.26	0.6	1.39	0.18	0.43
8	Positive	Thin	1.39	2.33	0.09	0.71	0.81	1.42	0.02	0.6

The clinical data of eight patients with pituitary adenoma in this study are also shown. These data include fluorescence, NIR tumor SBR, ratio of Gd-enhanced T1 tumor to normal brain tissue, signal intensity of NIR fluorescence, and the scores of K^{trans}, K^{ep}, V^e, and V^p on MRI scans.

Table 3: Parameters calculated by DCE perfusion-MRI.

Parameters	Unit	Clarification/description
Ktrans	/min	constant transfer volume from the intravascular to the extravascular space
K^{ep} (=K^{trans}/V^e)	/min	constant transfer volume from the extravascular to the intravascular space
V^e	mL/100 mL of tissue	volume of the extravascular extracellular space
V^p	mL/100 mL of tissue	fractional plasma volume

Figures

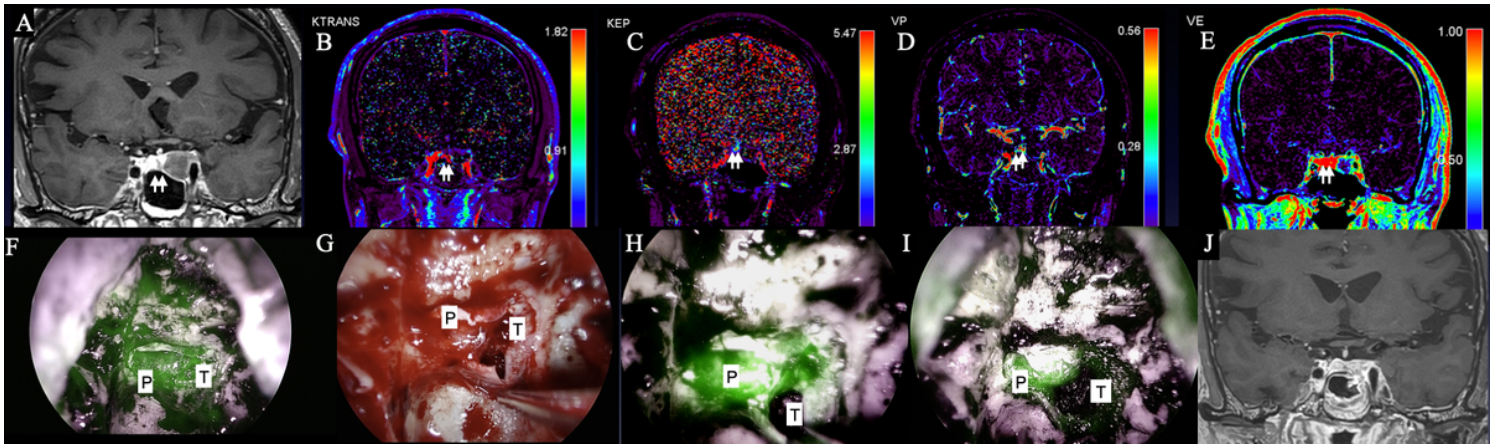

Figure 1

(Case 1) (Patient No. 4)

A 62-year-old man, with changed facial and tongue appearances, presented with diplopia and consulted to our department. Neurological findings revealed a partial left oculomotor nerve palsy. Gd-MRI (coronal view, A) revealed a normal pituitary gland (white arrows) and pituitary adenoma suggesting somatotroph adenoma. The patient's growth hormone and somatomedin C levels on admission were 9.2 (0–2.7 ng/mL) and 627 (76–228 ng/mL), respectively. The patient was admitted to the hospital and received a steroid. Subsequently, his nerve palsy was completely recovered in a few days. Thus, he was diagnosed with acromegaly. His normal pituitary gland (double arrows) showed higher

intensity on Ktrans (B), Kep (C), Vp (D), and Ve (E) by DCE perfusion-MRI, as compared to the tumor. He received 12.5 mg ICG during surgery, and the DWIG technique was applied. After opening the dura matter during surgery, NIR fluorescence could be detected from the tumor and normal gland at 10 min (F). In Fig. 1F, T indicated tumor, and P indicated the normal pituitary gland. After the confirmation of the pituitary tumor, the tumor was dissected from the normal gland in the bright light (G). The tumor decreased and lost NIR fluorescence, although the normal gland kept its fluorescence at 30 (H) and 90 (I) min. NIR fluorescence in the pituitary gland then decreased in 180 min (Sup Fig. 3). NIR fluorescence might help surgeons locate the lesion of the pituitary gland in the case that the pituitary gland was difficult to identify under a bright light. Postoperative Gd-MRI revealed gross total resection (J). Pathological examination revealed a pituitary adenoma. No recurrence was observed for 8 months. The hormonal concentrations were normalized after surgery, and the growth hormone and somatomedin C levels were 1.4 and 218 at 8 months, respectively.

NIR, near-infrared; Gd, gadolinium; MRI, magnetic resonance imaging; Ktrans, volume transfer constant; Kep, rate constant; P, the location of the normal pituitary gland; T, the location of tumor; Ve, volume of the extravascular extracellular space; Vp, vascular plasma volume

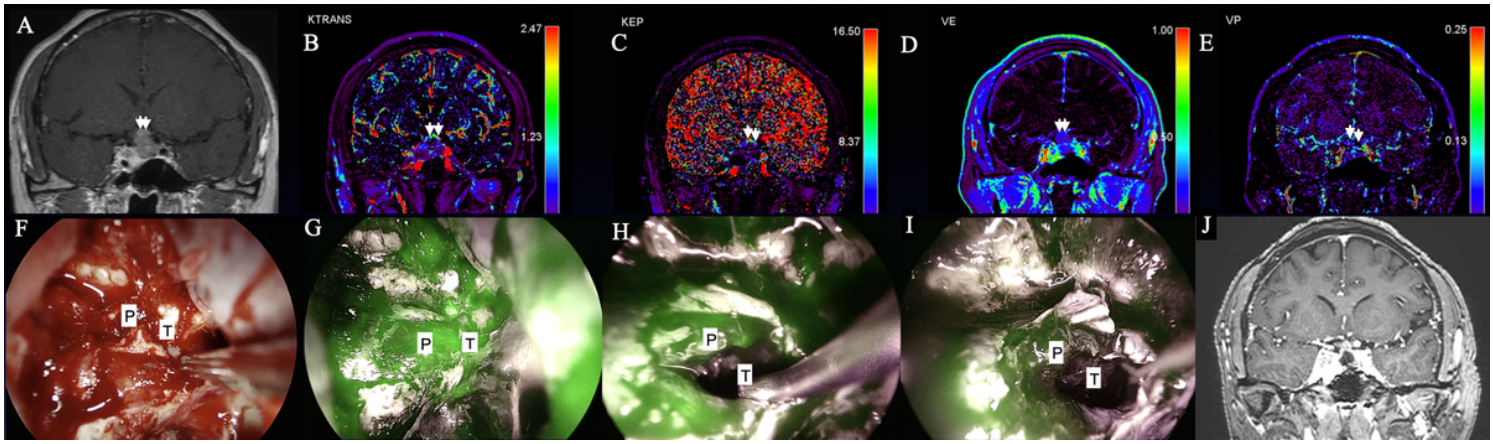

Figure 2

(Case 2). (Patient No. 7)

A 54-year-old man presented with impotence and was in the nearby hospital by carbergolin for 3 years in the nearby hospital. Gradually his prolactin score was increased to 1402 (3.46–19.40), and Gd-MRI revealed an growing enhanced mass (35 mm in maximum diameter) in the sellar region extending into the right cavernous sinus (coronal view, A), suggesting lactotroph adenoma. The patient was referred to our hospital. MRI revealed that the normal pituitary gland was located on the front and top of the tumor (A, white arrows). The normal gland had a higher intensity on Ktrans (B), almost the same intensity on Kep (C), and a lower intensity on Vp (D) and Ve (E) than the tumor in the sellar region on DCE perfusion-MRI. The pituitary adenoma was surgically resected and NIR in the same manner as in Case 1. After dural incision, the normal gland and tumor were exposed on the surface under the bright light (G), and both the normal gland and tumor were positive for NIR fluorescence 10 min following 12.5mg ICG injection (F). During tumor resection, the NIR fluorescence intensity of the tumor decreased when assessed at 30 min (H). The surgeons confirm the exact location of the normal gland via NIR fluorescence during resection (H). After tumor resection, there was no residual tumor inside the sellar region via NIR fluorescence, and the intensity of NIR fluorescence was decreased at 60 min (I). Postoperative Gd-MRI scan revealed no enhanced mass in the sellar region (J). Pathological examination showed a pituitary adenoma. The patient's prolactin score decreased after surgery and was 280 on discharge.

NIR, near-infrared; Gd, gadolinium; MRI, magnetic resonance imaging; Ktrans, volume transfer constant; Kep, rate constant; P, the location of the normal pituitary gland; T, the location of tumor; Ve, volume of the extravascular extracellular space; Vp, vascular plasma volume

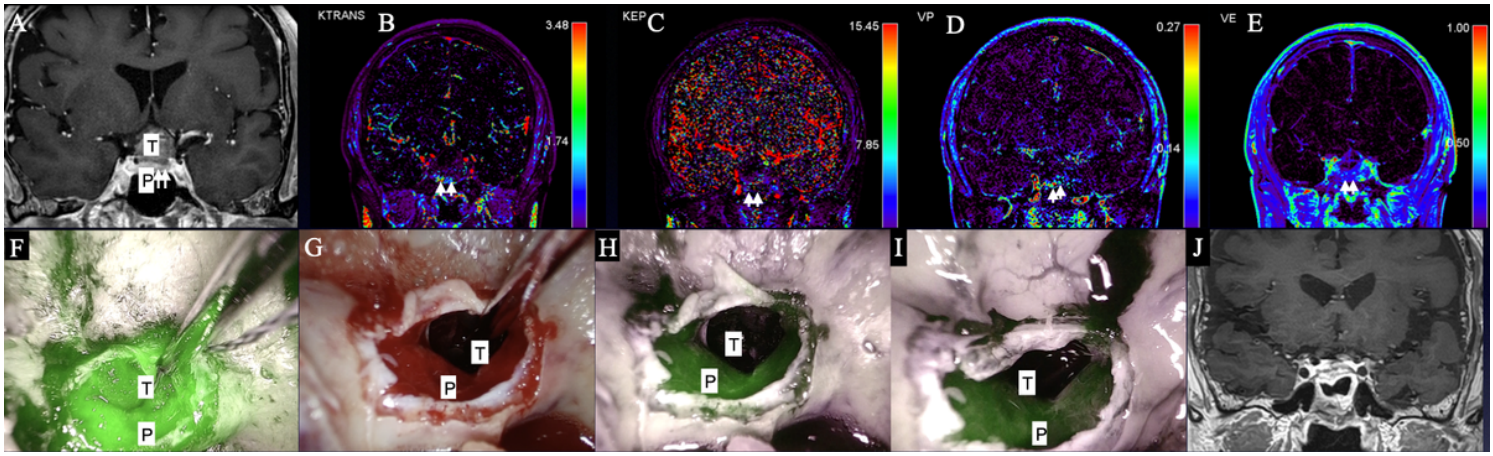

Figure 3

(Case 3). (Patient No. 6)

A 70-year-old man with bitemporal hemianopsia was referred to our hospital. His Gd-MRI revealed an enhanced mass (35 mm in maximum diameter) in the sellar lesion. The normal pituitary gland was mainly located in front of the tumor, indicated with white arrows (A). His hormone levels were normal, suggesting the presence of non-function pituitary adenoma. The values of all the parameters (K^{trans} [B], K^{ep} [C], V^{p} [D], and V^{e} [E]) in normal glands are higher than pituitary tumors on DCE perfusion-MRI (B–E). The sizes of non-functional pituitary adenomas are usually larger than the hormone-secreting adenomas. Hence, its pituitary gland tends to be thinner and is hard to be identified. After dural incision, the tumor and pituitary glands were observed in the bright light (G). The pituitary gland was located in front of the tumor. NIR fluorescence could be observed both in the tumor and gland 10 min after 12.5mg ICG administration (F). However, NIR fluorescence of the tumor decreased with time, and the pituitary gland could be identified from the tumor 60 min during tumor resection (H). It seems to be beneficial in the identification of tumor and confirmation of the exact gland location for surgeons. After tumor resection inside the sellar lesion, no residual tumor was observed via NIR fluorescence, and the intensity of NIR fluorescence decreased at 180 min (I). The tumor was totally resected using NIR fluorescence, and a postoperative Gd-MRI scan revealed gross total resection (J). Pathological examination revealed a pituitary adenoma. There was also no recurrence of symptoms for 8 months.

NIR, near-infrared; Gd, gadolinium; MRI, magnetic resonance imaging; K^{trans}, volume transfer constant; K^{ep}, rate constant; P, the location of the normal pituitary gland; T, the location of tumor; V^{e}, volume of the extravascular extracellular space; V^{p}, vascular plasma volume

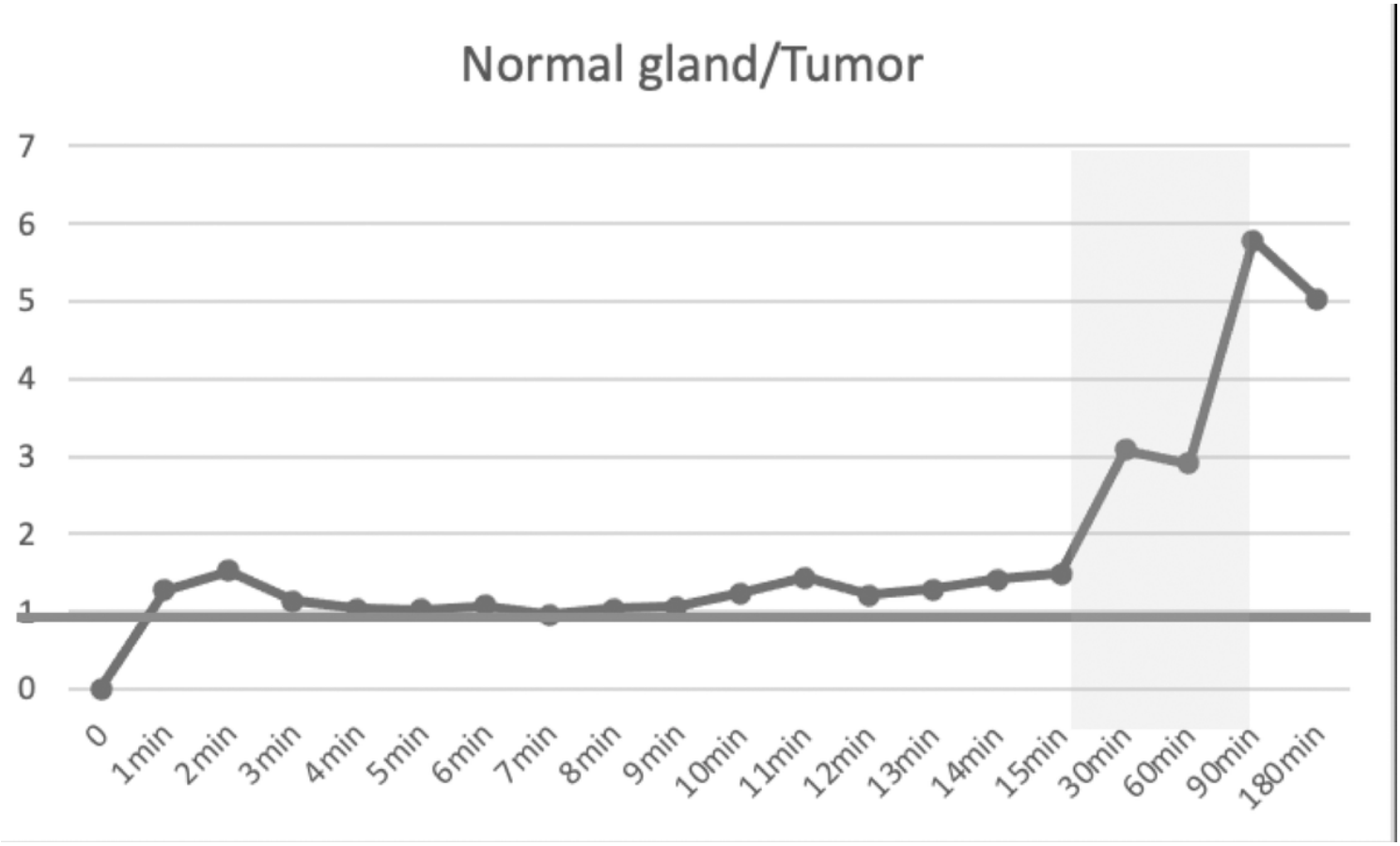

Figure 4

The change in the relative ratio of fluorescence emission of the pituitary gland to tumor (SBR pituitary gland/tumor)

From 15 to 90 min following ICG administration, SBR pituitary gland/tumor increased and peaked at 90 min.

SBR, signal-to-background ratio; ICG, indocyanine green

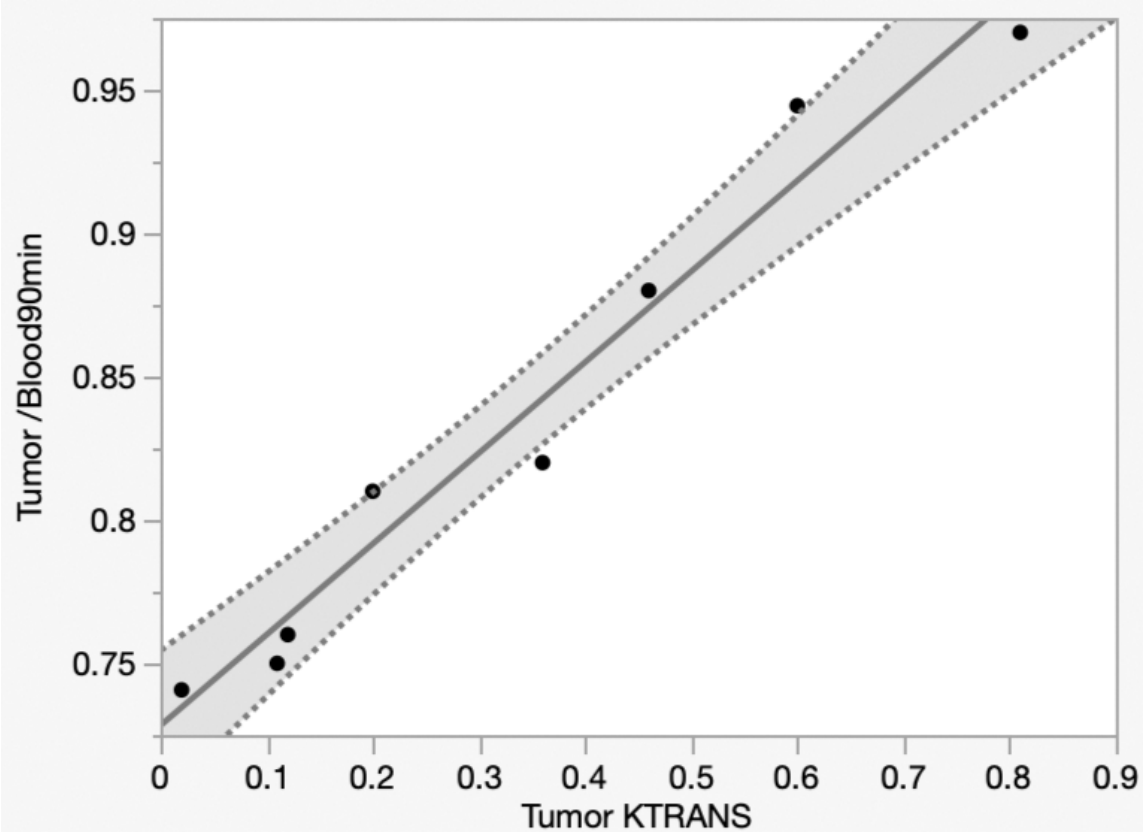

Figure 5

Linear regression plot of NIR

SBR tumor and K^{trans}

SBR tumor at 90 min versus K^{trans} of the tumor. The SBR tumor increased with K^{trans} on DCE perfusion-MRI ($p<0.001$, $R^2=0.96$), suggesting that the mechanism of NIR fluorescence in pituitary tumor by ICG mimics Gd enhancement on MRI.

NIR, near-infrared; SBR, signal-background ratio; K^{trans}, volume transfer constant; ICG, indocyanine green; MRI, magnetic resonance imaging; DCE perfusion-MRI, dynamic contrast-enhanced perfusion magnetic resonance imaging

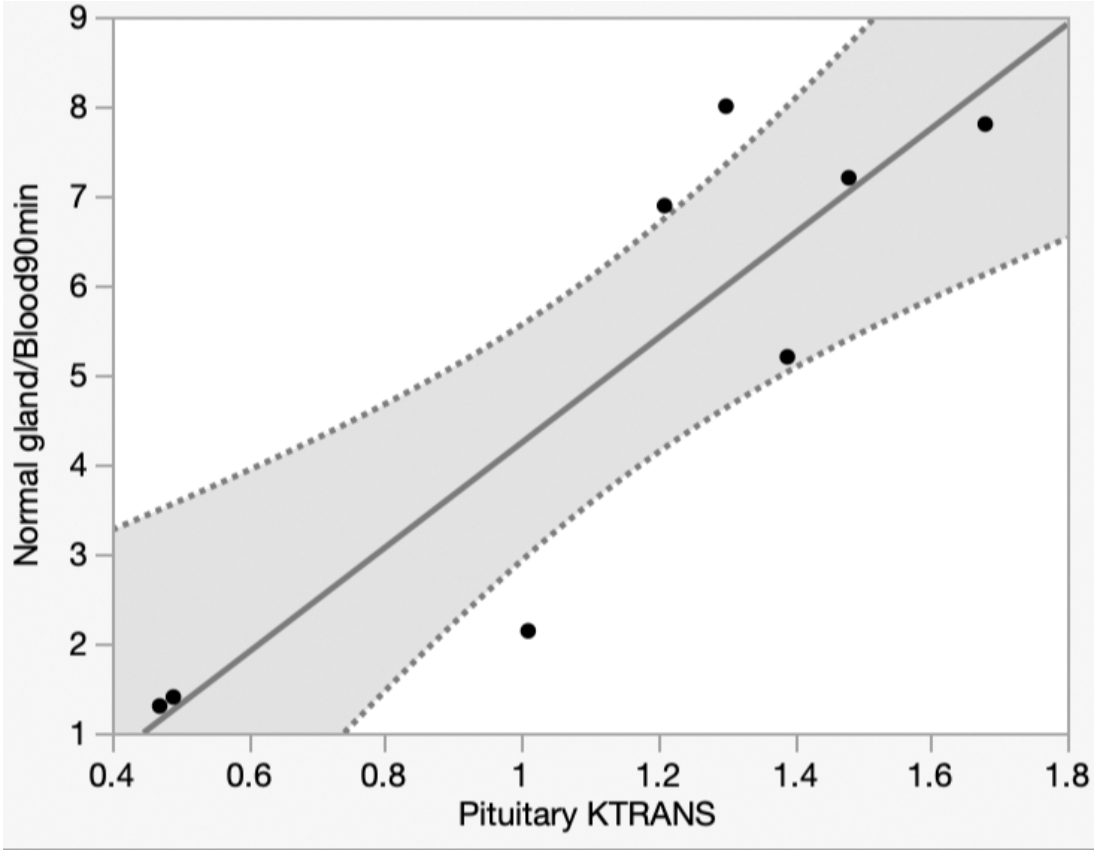

Figure 6

Linear regression plot of NIR

SBR gland and K^{trans}

SBR gland at 90 min versus K^{trans} of the normal pituitary gland on MRI. SBR gland had a positive correlation with K^{trans} ($p=0.003$, $R^2=0.79$), suggesting that the mechanism of NIR fluorescence in the pituitary gland by ICG also mimics Gd enhancement on MRI.

NIR, near-infrared; MRI, magnetic resonance imaging; SBR, signal-to-background ratio; K^{trans}, volume transfer constant; T1BR, ratio of gadolinium-enhanced T1 tumor signal to the brain; ICG, indocyanine green; Gd, gadolinium

Supplementary Files

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