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Feasibility of bevacizumab-IRDye800CW as a tracer for fluorescence-guided meningioma surgery

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OBJECTIVE Meningiomas are frequently occurring, often benign intracranial tumors. Molecular fluorescence can be used to intraoperatively identify residual meningioma tissue and optimize safe resection; however, currently no clinically approved agent is available for this specific tumor type. In meningiomas, vascular endothelial growth factor α (VEGFα) is upregulated, and this biomarker could be targeted with bevacizumab-IRDye800CW, a fluorescent agent that is already clinically applied for the resection of other tumors and neoplasms. Here, the authors investigated the feasibility of using bevacizumab-IRDye800CW to target VEGFα in a CH-157MN xenografted mouse model.

METHODS Five mice with CH-157MN xenografts with volumes of 500 mm^3 were administered intravenous bevacizumab-IRDye800CW. Mice were imaged in vivo at 24 hours, 48 hours, and 72 hours after injection with the FMT2500 fluorescence imaging system. Biodistribution was determined ex vivo using the Pearl fluorescent imager at 72 hours after injection. To mimic a clinical scenario, 2 animals underwent postmortem xenograft resection using both white-light and fluorescence guidance. Lastly, fresh and frozen human meningioma specimens were incubated ex vivo with bevacizumab-IRDye800CW, stained with anti-VEGFα, and microscopically examined.

RESULTS In vivo, tumors fluoresced at all time points after tracer administration and background fluorescence decreased with time. Ex vivo analyses of tracer biodistribution showed the highest fluorescence in resected tumor tissue. Brain, skull, and muscle tissue showed very low fluorescence. Microscopically, fluorescence was observed in the cytoplasm and was correlated with VEGFα expression patterns. During postmortem surgery, both the tumor bulk and a small tumor remnant were detected. Bevacizumab-IRDye800CW bound specifically to all tested human meningioma samples, as indicated by a high fluorescent signal in the tumor bulk compared with the surrounding healthy dura mater.

CONCLUSIONS Bevacizumab-IRDye800CW showed meningioma specificity, as illustrated by high VEGFα-mediated uptake in the meningioma xenograft mouse model. Small tumor lesions were detected using fluorescence guidance. Thus, the next step will be to assess the feasibility of using already available clinical grade bevacizumab-IRDye800CW to optimize meningioma resection in a human trial.

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KEYWORDS meningioma; molecular fluorescence guided surgery; bevacizumab-IRDye800CW; vascular endothelial growth factor α; tumor

Meningiomas comprise approximately one-third of intracranial tumors in adults. Surgical treatment is indicated when a meningioma becomes symptomatic or evidently grows over time.[1] In contrast to most tumors elsewhere in the body, extending surgical margins in a neurosurgical setting can be complicated. Treatment is curative in intent, for which complete resection is essential. This requires a clear delineation between tumor and healthy tissue. The extent of residual tumor tissue after resection can be graded using the Simpson grading scale.[2] A

ABBREVIATIONS DAPI = 4',6-diamidino-2-phenylindole; DMEM/F12 = Dulbecco's modified Eagle Medium/Nutrient Mixture F-12; H&E = hematoxylin and eosin; HRP = horseradish peroxidase; MFGS = molecular fluorescence-guided surgery; MFI = median fluorescence intensity; PBS = phosphate-buffered saline; TBR = tumor-to-background ratio; VEGFα = vascular endothelial growth factor α.

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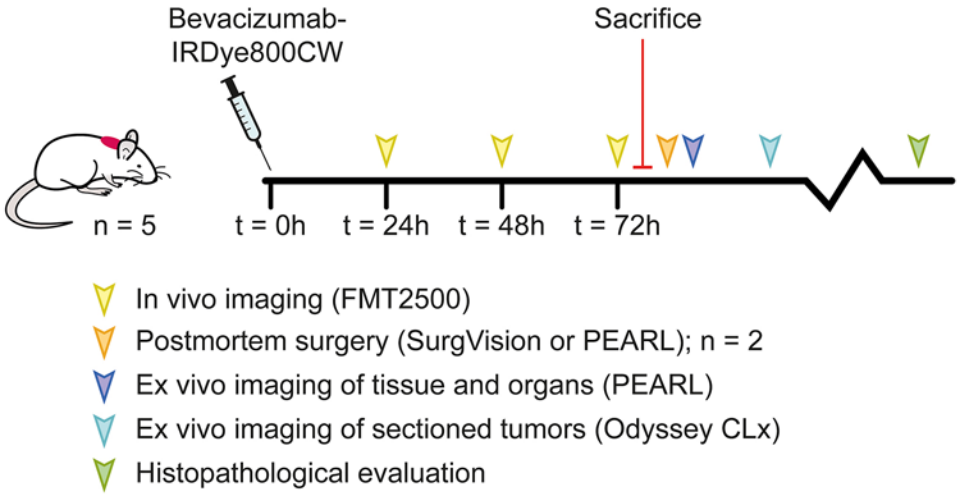

FIG. 1. Illustration of the in vivo and ex vivo study procedures in mice. Five CH-157MN xenografted mice were intravenously injected with 100 μg of bevacizumab-IRDye800CW. In vivo imaging with the FMT2500 system was performed at 24 hours, 48 hours, and 72 hours after injection. After the last imaging examination, all mice were sacrificed. Two mice underwent postmortem surgery with the SurgVision or Pearl system. The tissues and organs of all mice were imaged with the Pearl system immediately after sacrifice and subsequently fixated in formalin. Tumors were sectioned into slices and imaged with the Odyssey CLx. Lastly, selected tissues and organs were processed for histopathological analysis. Figure is available in color online only.

higher Simpson grade is associated with a higher incidence of recurrence.[3] Therefore, a method that safely increases extent of meningioma resection is needed. This would be particularly useful for not only the treatment of meningiomas at complex anatomical locations with intricate relationships with essential anatomical structures, but also for the treatment of recurrent meningiomas and the intraoperative detection of (un)intentional residual meningioma in (for example) the dural tail or bone (of the skull and skull base).

One of the approaches for intraoperative identification of tumor tissue is molecular fluorescence-guided surgery (MFGS). MFGS is based on the "red flag" technique, in which a biomarker that is upregulated on meningioma cells is fluorescently labeled. We previously identified vascular endothelial growth factor α (VEGFα) as a potential biomarker[4] that is significantly upregulated in all meningioma grades and histopathological subtypes.[4] In tumors, VEGFα is mainly active on endothelial cells and mediates increased vascular permeability and angiogenesis. VEGFα can be effectively targeted with bevacizumab,[5] which has been fluorescently labeled with IRDye800CW to form the fluorescent tracer bevacizumab-IRDye800CW, as described previously.[6]

Thus far, this tracer has already been applied in multiple clinical trials in over 250 patients with breast, colorectal, and esophageal cancers.[7,8] In the current study, we evaluated whether bevacizumab-IRDye800CW could potentially be used for MFGS in intracranial meningioma patients. Our work focused on preclinical meningioma models consisting of both xenografted mice and human surgical specimens.

Methods

The experimental approach was similar to that of described previously work and is outlined below.[9] The ethical treatment of the animal and human research subjects was reviewed by the Institutional Review Board of the University of Groningen and University Medical Center Groningen. Animal care complied with the *Guide for the Care and Use of Laboratory Animals*. The Institutional Review Board approved the experimental protocol and patient materials for informed consent.

Xenograft Mice Models

Anesthesia was induced with 5% isoflurane and maintained at 2.5%. Xenografts were generated in five 6-to-8-week-old BALB/c-nu mice (Janvier Laboratories). For that purpose, 1.5 million CH-157MN cells[10] (courtesy of Prof. G. Yancey Gillespie, University of Alabama School of Medicine, Birmingham, Alabama) were cultured, suspended in serumless Dulbecco's modified Eagle Medium/Nutrient Mixture F-12 (DMEM/F12), and subcutaneously injected between the shoulder blades. Tumor growth was monitored twice per week using calipers.

Tracer Kinetics and Biodistribution

Mice were anesthetized when the xenograft volume reached 500 mm^3. Bevacizumab-IRDye800CW (100 μg, 50 μl, 0.67 nmol) was intravenously administered into the retro-orbital venous sinus in a single dose. Mice were imaged with the FMT2500 fluorescence imaging system (PerkinElmer) 24 hours, 48 hours, and 72 hours after tracer injection while under general anesthesia. After the final scan, the animals were terminated with heart puncture (exsanguination) and cervical dislocation. For further ex vivo analysis, the organs, tissues, and fluids of interest were scanned using the Pearl fluorescent imager (LI-COR Biosciences) to determine the biodistribution. After formalin fixation, the tumors were sectioned into

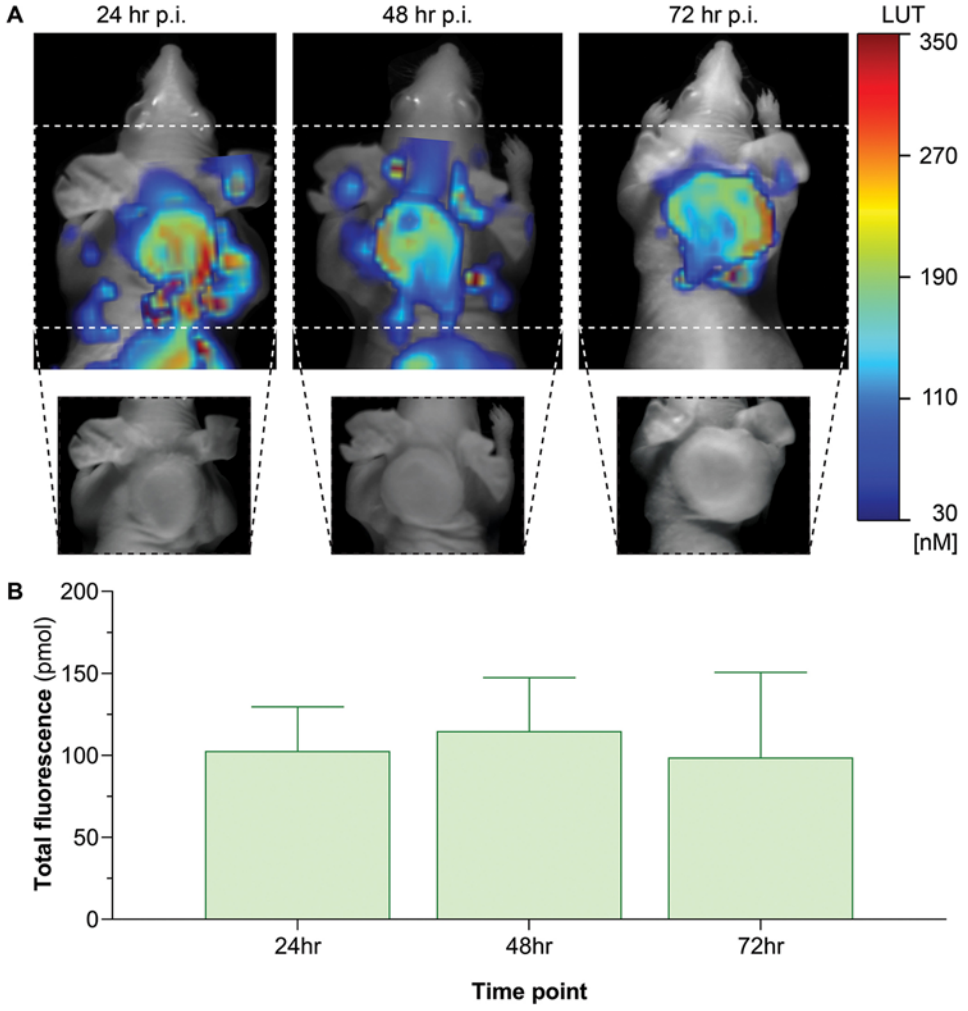

FIG. 2. In vivo fluorescence of bevacizumab-IRDye800CW over time. CH-157MN xenografted mice were injected with bevacizumab-IRDye800CW and imaged 24 hours, 48 hours and 72 hours after injection with the FMT2500 in vivo fluorescence imaging system. Fluorescence was located to the tumor at all time points, whereas background fluorescence decreased (**A**). Tumor fluorescence quantification showed stable uptake over time (**B**). Mean (*bars*) and SD (*error bars*) values are shown. LUT = look up table; p.i. = post injection. Figure is available in color online only.

3-mm-thick slices, which were macroscopically imaged using a flatbed scanner (Odyssey CLx, LI-COR Biosciences).

Postmortem Surgery Using MFGS

To mimic a clinical scenario, 1 animal underwent postmortem xenograft resection 72 hours after tracer injection using the fluorescence guidance of the SurgVision fluorescence intraoperative camera system. After the bulk of the tumor was resected under white-light fluorescence, the camera was switched to fluorescence to check extent of resection. The same procedure was followed in a second animal, but this time the Pearl imaging system was used to determine the presence of fluorescent lesions. Further ex vivo analysis was performed as described above. Histopathology was used to investigate the tissue type of the macroscopically identified tumor or muscle tissue, as described below.

Histopathological Evaluation

Tissue was processed into paraffin blocks and consecutive 4-μm-thick slices were microscopically imaged with a 4′,6-diamidino-2-phenylindole (DAPI) counterstain (ProLong Diamond Antifade Mountant with DAPI, Thermo Fisher), hematoxylin and eosin (H&E), or anti-VEGFα. For VEGFα staining, the antigens were retrieved with Tris/HCl on deparaffinized sections followed by an endogenous peroxidase block. Sections were washed and incubated with the primary antibody RB-9031-PO (1:100, Thermo Fisher) for 1 hour at room temperature. Sections were subsequently incubated with secondary goat–anti-rabbit horseradish peroxidase (HRP) antibody (1:100, DAKO) and tertiary rabbit–anti-goat HRP antibody (1:100, DAKO) for 1 hour at room temperature. Lastly, sections were incubated with 3,3-diaminobenzidine solution (Sigma-Aldrich) for 10 minutes and finally counterstained with hematoxylin for 2 minutes. An inverted

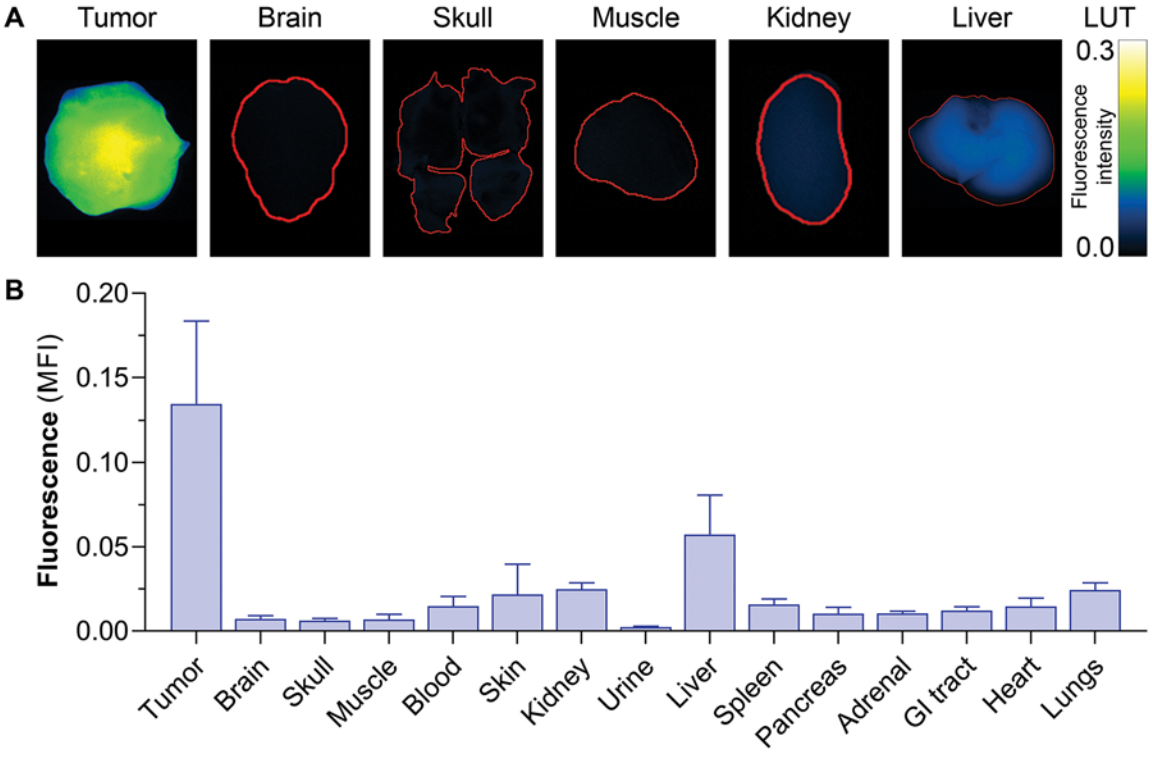

FIG. 3. Ex vivo fluorescence uptake of bevacizumab-IRDye800CW. Animals were sacrificed 72 hours after injection, and organs and tissues were individually imaged ex vivo with the Pearl system. Fluorescence was high in tumor tissue but low in relevant background tissues such as the brain, skull, and muscle. Slight uptake was visible in the liver and kidneys due to the excretion and metabolism of the tracer (**A**). This resulted in the biodistribution as indicated (**B**). Mean (*bars*) and SD (*error bars*) values are shown. GI = gastrointestinal. Figure is available in color online only.

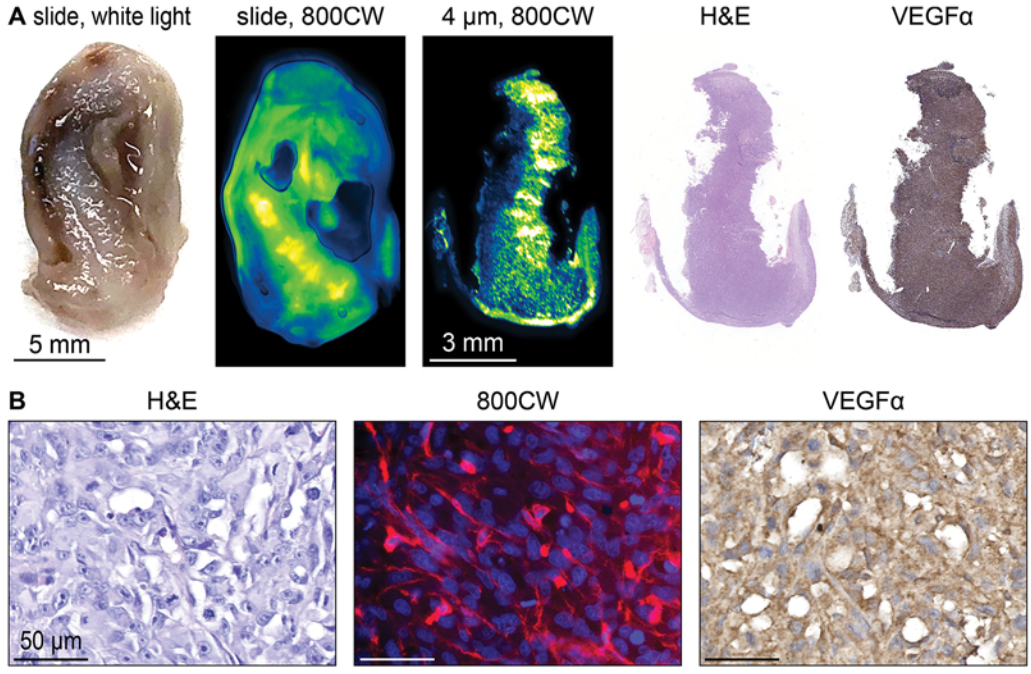

FIG. 4. Correlation of fluorescence uptake to VEGFα expression in CH-157MN xenografts. CH-157MN xenografts were sliced into 3-mm-thick sections. Tumor slices were scanned with the Pearl and Odyssey CLx systems and subsequently stained for both H&E and VEGFα. Fluorescence was correlated with tumor tissue expressing VEGFα (**A**). Tumor slices were processed into 4-µm-thick sections and stained with an anti-VEGFα antibody and H&E. Microscopically, both the VEGFα and bevacizumab-IRDye800CW subcellular signals were in the cytoplasm (**B**). Figure is available in color online only.

microscope (DMI6000B, Leica Biosystems), with adjustments as described previously,[11] was used for fluorescence microscopy. Slices stained with H&E or anti-VEGFα were scanned with the NanoZoomer 2.0 HT multislide scanner (Hamamatsu). Figure 1 gives an overview of the study procedures.

Statistical Analysis

Data were analyzed using ImageJ and GraphPad Prism 8.0. The tumor-to-background ratio (TBR) was calculated by dividing the median fluorescence intensity (MFI) of the tumor by that of the brain.

Human Specimens

Meningioma specimens resected at the neurosurgical department of the University Medical Center Groningen between 2006 and 2012 were available, as reported previously.[4,9] Ten frozen 4-μm-thick sections were retrospectively analyzed. They were incubated with bevacizumab-IRDye800CW (10^{-6} M, 15 μg, 100 μl, 0.1 nmol) for 1 hour, washed, mounted with Prolong Antifade containing DAPI (Thermo Fisher), and microscopically imaged, as described above. Consecutive sections were stained with H&E and anti-VEGFα. Anti-VEGFα staining was performed with the primary antibody sc-152 (1:100, Santa Cruz) for 1 hour at room temperature. Sections were washed with phosphate-buffered saline (PBS) and subsequently incubated with secondary goat–anti-rabbit Alexa Fluor 647 antibody (1:75, DAKO). We imaged 800CW and DAPI using an inverted microscope, as described above. Anti-VEGFα was imaged using a confocal microscope (Leica SP8 confocal laser scan microscope, Leica Biosystems), and H&E sections were scanned with the NanoZoomer system.

Additionally, 6 fresh surgical specimens of convexity meningioma containing both dura mater and tumor bulk were prospectively collected. These were washed 3 times with PBS at 4°C and incubated ex vivo with bevacizumab-IRDye800CW (5×10^{-8} M, 30 μg, 4 ml, 0.2 nmol) in DMEM/F12 for 4 hours at 37°C. Tissue was washed 5 times with PBS at 37°C, fixated overnight in formalin, and processed into paraffin blocks. Consecutive 4-μm-thick sections were stained with DAPI, H&E, and anti-VEGFα. VEGFα staining was performed as described above, with the primary antibody RB-9031-PA-O (1:100, Thermo Fisher) and appropriate secondary and tertiary antibodies.

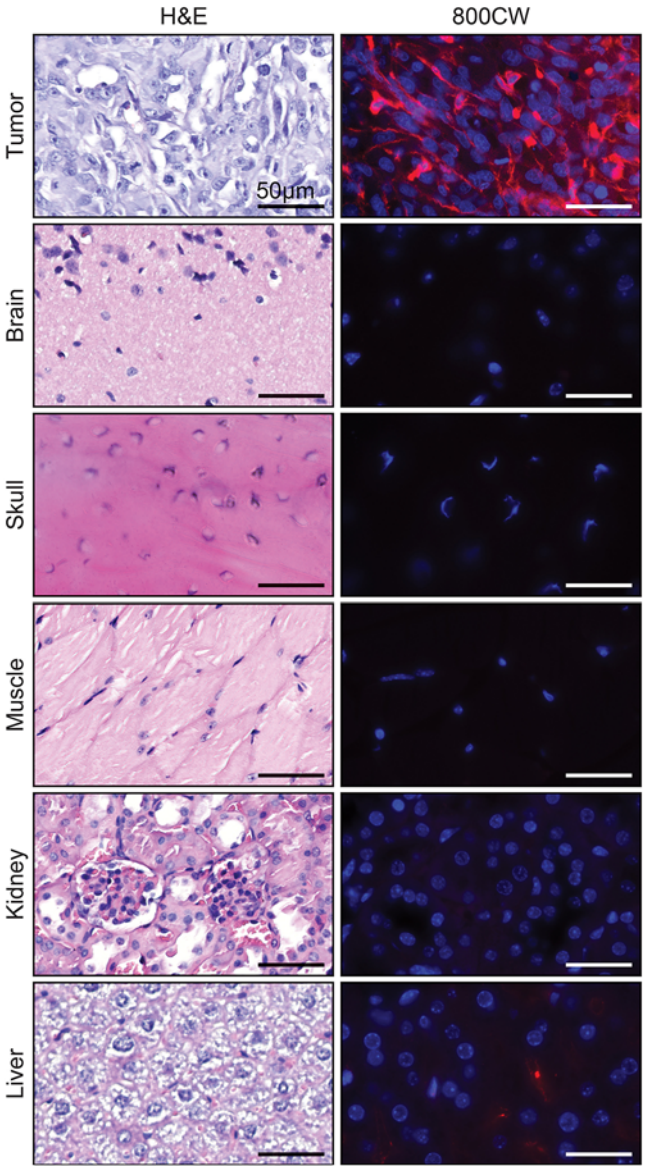

FIG. 5. H&E and bevacizumab-IRDye800CW micrographs of the tissues of interest. Tissues were harvested from mice injected with bevacizumab-IRDye800CW. The tumor showed high fluorescence uptake, whereas the brain, skull, muscle, kidney, and liver showed (almost) no fluorescence. Figure is available in color online only.

Results

Kinetics and Biodistribution of Bevacizumab-IRDye800CW in Xenografted Mice

Xenografted mice were longitudinally imaged in vivo to study tracer kinetics. Tracer fluorescence was detected at all 3 time points (Fig. 2A). Tumor fluorescence remained stable over time, whereas background fluorescence decreased with time, resulting in higher qualitative TBR at later time points (Fig. 2A–B).

The bevacizumab-IRDye800CW biodistribution was determined ex vivo in the individual organs, tissues, and fluids after the last imaging time point. The highest fluorescence was detected in the tumor, with a mean ± SD MFI of 0.135 ± 0.049. Neurosurgical background tissue, such as brain, skull, and muscle tissue, showed very low fluorescence with MFIs ranging from 0.004 to 0.011 (Fig. 3). Therefore, the tracer provided a high TBR of 18.7 ± 4.5 in this xenograft model. The kidneys and liver showed slightly higher fluorescence with MFI values ranging from 0.018 to 0.096, indicating their role in the metabolization and excretion of bevacizumab-IRDye800CW. As discussed in more detail below, we previously determined that bevacizumab-IRDye800CW uptake was VEGF mediated because the fluorescence signals in the IgG-IRDye800CW and carboxylated IRDye800CW control groups were significantly lower.

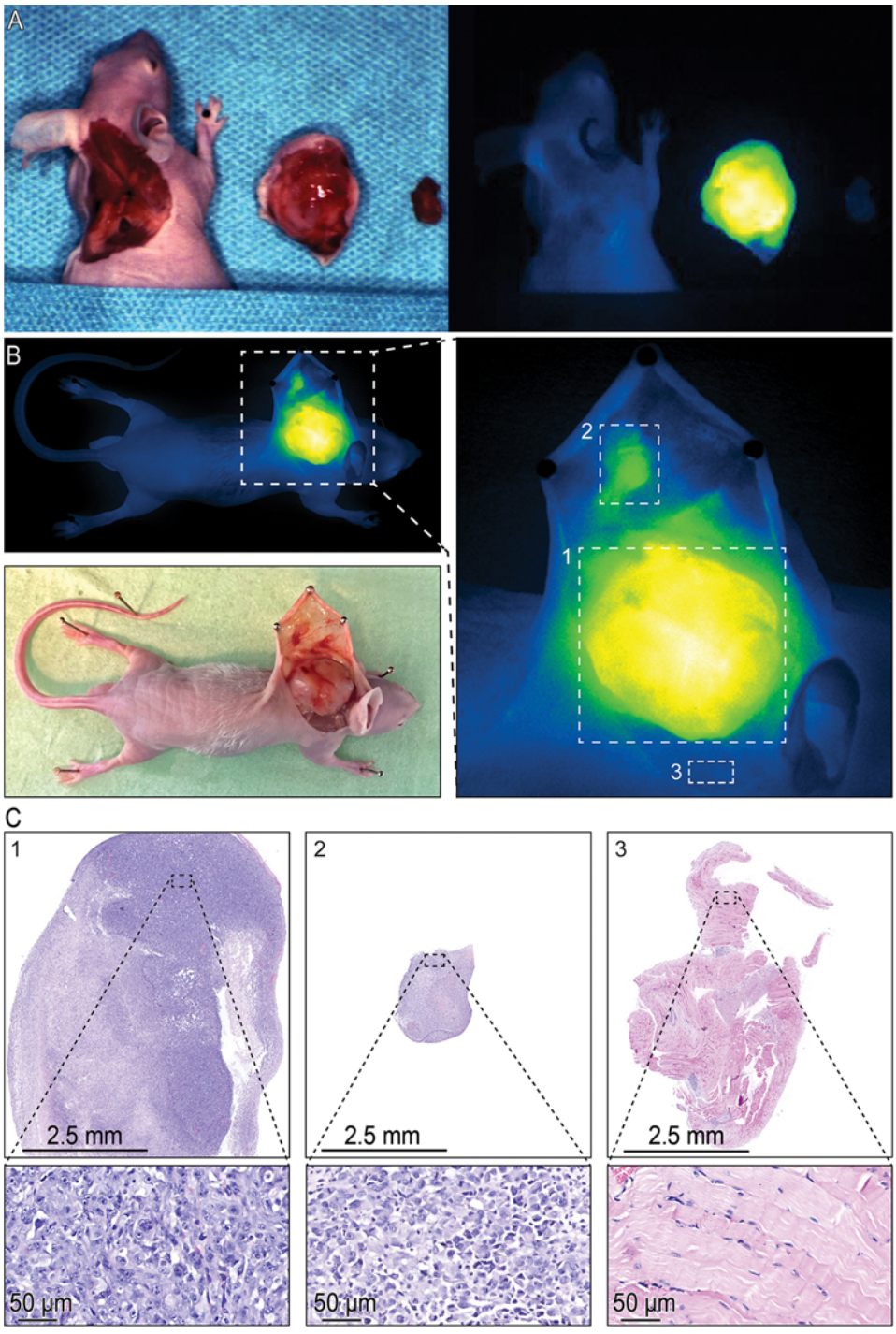

FIG. 6. Postmortem MFGS on xenograft-bearing mice. Two animals were injected with bevacizumab-IRDye800CW 72 hours prior to imaging with the SurgVision (**A**) or Pearl (**B**) system during tumor resection. The *numbered rectangles* in the magnifications of panel B correspond to the histological images in panel C. SurgVision imaging showed excellent tumor delineation using both white light (A, *left panel*) and fluorescence (A, *right panel*), illustrating the proof-of-principle of this intraoperative camera system. Pearl imaging with fluorescence and white light (B, *left side*) showed that the tumor bulk and a small piece of fluorescent tissue were attached to the skin (B, *right side*). Histopathological examination showed that both the fluorescing bulk and small tissue piece consisted of tumor material. Tumor cells had large open nuclei with a central nucleolus, varying amounts of light-blue, blurry cytoplasm, and high mitotic counts. In contrast, nonfluorescent background tissue contained only muscle tissue (**C**). Figure is available in color online only.

Subsequently, the (subcellular) localization of the fluorescent signal was examined. Tumor slices that were 3-mm-thick showed macroscopic fluorescence, mainly in the vital parts of the tumor as determined with pathological macroscopy. Fluorescence may have been correlated with VEGFα expression in the tumor (Fig. 4A). Microscopically, fluorescence was mainly observed in the cytoplasm. Similar VEGFα expression was observed in the xenografts (Fig. 4B). Additionally, microscopical analysis showed low fluorescence in the brain, skull, muscle, kidney, and liver tissues (Fig. 5). Lastly, no tracer toxicity was observed in any animals.

Postmortem Surgery Using Bevacizumab-IRDye800CW

To mimic a clinical setting for MFGS, 2 mice were injected with the tracer and underwent postmortem fluorescence-guided surgery using the SurgVision or Pearl system. The tumor was clearly distinguished using both white-light and fluorescence guidance (Fig. 6A–B, Video 1).

VIDEO 1. Postmortem resection in a xenografted mouse using MFGS. A xenografted animal was injected with bevacizumab-IRDye800CW and imaged 72 hours later with the SurgVision intraoperative fluorescence camera system. This video shows the white-light resection on the left side and the fluorescence guidance on the right side. Throughout resection, the tumor can be distinguished using both white-light and fluorescence imaging. © University Medical Center Groningen, published with permission. Click here to view.

Both the tumor and small tumor remnant were detected with repeated imaging with the Pearl system during tumor resection, demonstrating the benefit of MFGS (Fig. 6B–C). In addition to the tumor bulk, a small tumor lesion was visualized and low background fluorescence was detected in muscle tissue (Fig. 6B–C). With muscle as the background tissue, this resulted in a TBR of 3.0.

Bevacizumab-IRDye800CW and VEGFα Expression in Human Meningioma Specimens

To study the applicability of bevacizumab-IRDye800CW in patients with all 3 meningioma grades (Table 1), 4-μm-thick slices of frozen sections were incubated with bevacizumab-IRDye800CW. Additionally, consecutive slices were stained with anti-VEGFα and H&E. All samples showed fluorescence in both bevacizumab-IRDye800CW and anti-VEGFα sections. In both stained sections, fluorescence was mainly detected in the cytoplasm and fluorescence intensity was correlated with the level of VEGFα expression (Fig. 7A).

In freshly resected specimens, a radiological dural tail sign was observed in some patients, although no tumor cells invading the dura mater were identified on histopathological analysis in those few cases. Furthermore, hyperostosis was observed intraoperatively in a few patients. However, we had only bone dust after resecting hyperostosis with a high-speed drill, which did not allow for decalcification and histopathological analysis. Moreover, the analysis of the bony structures involved in the meningioma was not a part of the experimental ex vivo protocol. Analysis of bony structures is the subject of the investigation of a currently running clinical trial (LUMINA trial, EU Clinical Trials Register no. EUCTR2020-006141-19-NL), which is explained in more detail in the *Discussion*. Bevacizumab-IRDye800CW detected in the freshly resected specimen (Table 1, Fig. 7B–C) showed microscopically higher fluorescence in the tumor bulk and low levels in the healthy dura mater. Similarly, VEGFα was expressed abundantly in the tumor bulk but not the dura mater.

TABLE 1. Baseline characteristics of the tested meningioma specimens

Sex/ Age (yrs)	WHO Grade/Subtype	Specimen Type	VEGFα Score*	
			Tumor Bulk	Dura Mater
F/77	I/Meningothelial	Frozen	3	ND
F/38	I/Meningothelial	Frozen	1	ND
F/75	I/Transitional	Frozen	2	ND
F/64	I/Fibromatous	Frozen	3	ND
F/61	II/Atypical	Frozen	3	ND
M/63	II/Atypical	Frozen	2	ND
F/82	II/Atypical	Frozen	3	ND
M/43	III/Anaplastic	Frozen	3	ND
F/72	III/Anaplastic	Frozen	1	ND
F/64	III/Anaplastic	Frozen	1	ND
F/84	I/Meningothelial	Fresh	2	0
F/70	I/Transitional	Fresh	3	1
F/43	I/Microcystic & meningothelial	Fresh	2	0
F/75	I/Fibromatous	Fresh	3	0
F/60	I/Secretory	Fresh	2	0
F/37	I/Meningothelial	Fresh	3	1

ND = not determined.

* The VEGFα score ranged from 1 to 3 on the basis of the following stain scoring system: negative, 0; weak/focal staining, 1; moderate/diffuse staining, 2; and strong/diffuse staining (3).[4]

Discussion

In the preclinical models of this study, we showed that bevacizumab-IRDye800CW can be used as a tumor-targeting tracer for meningiomas. This concept was tested in vivo and ex vivo in a subcutaneous xenograft model originating from a human meningioma cell line, as well as ex vivo using frozen and fresh surgical specimens. Bevacizumab-IRDye800CW was able to bind to the meningioma cells but not the surrounding dura mater.

Although one may argue that tumor tracer uptake is partially due to the enhanced permeability and retention effect, we showed in a previous work that bevacizumab-IRDye800CW binding is mediated by VEGFα.[6] The monoclonal antibody bevacizumab binds to all bioactive isoforms and spliced variants of VEGFα, including the most prevalent cell membrane–bound and extracellular matrix–bound variant $VEGF_{165}$ and freely diffusible variant $VEGF_{121}$. This makes the antibody very suitable for visualization of all VEGFα variants.[5] Furthermore, an IRDye800CW-labeled IgG control group showed a significant reduction in fluorescence tumor uptake.[12,13] Moreover, bevacizumab treatment significantly reduced ^{89}Zr-beva-

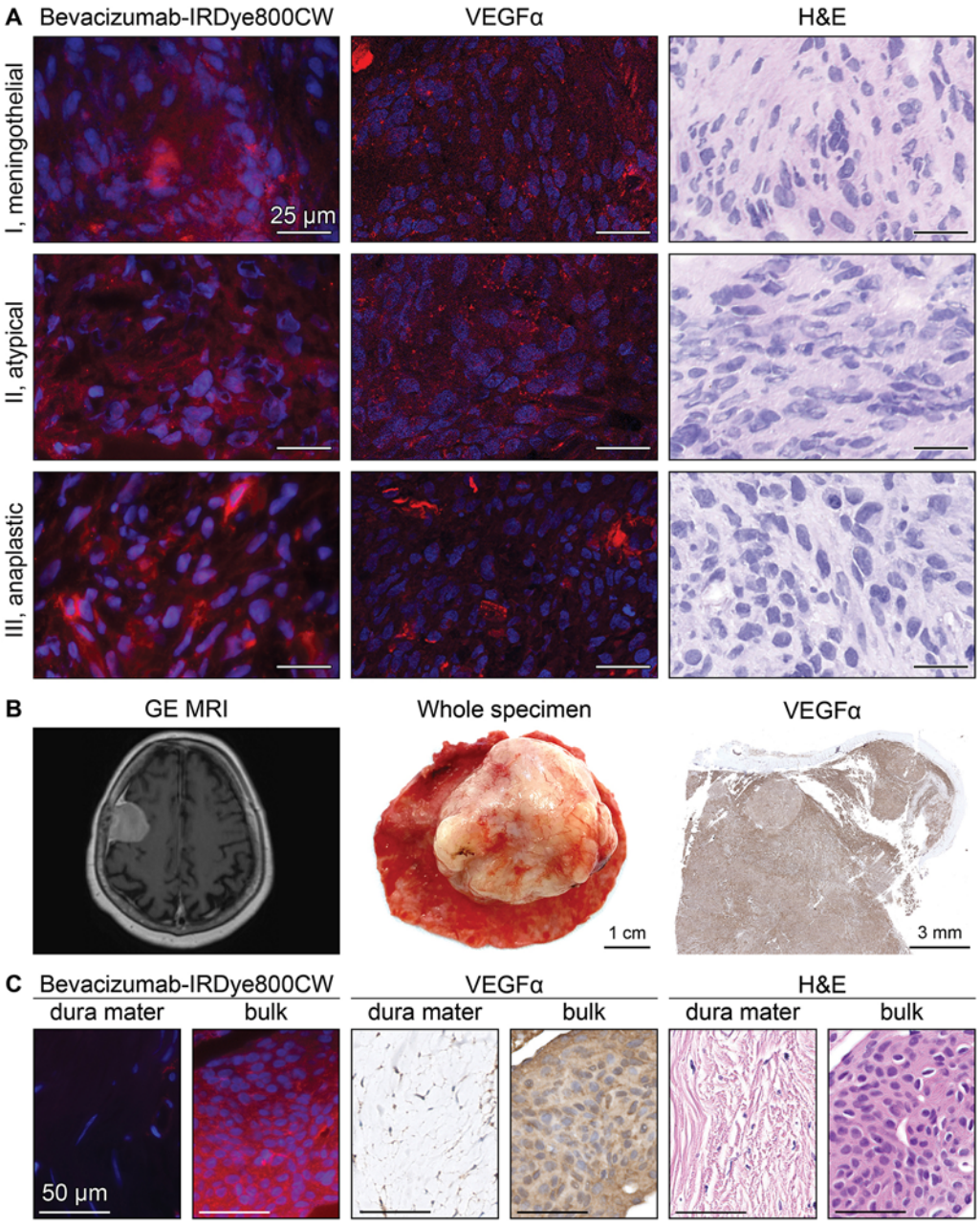

FIG. 7. Fluorescence uptake of bevacizumab-IRDye800CW in clinical specimens. **A:** Consecutive frozen sections representing all 3 WHO grades were incubated with bevacizumab-IRDye800CW or stained with an anti-VEGFα antibody or H&E. Tracer fluorescence (*left panel*) was subcellularly located in the cytoplasm, similar to the localization pattern of the anti-VEGFα staining (*middle panel*). **B:** Convexity meningiomas were used to determine tracer uptake in freshly resected specimen. **C:** These specimens were microscopically analyzed and bevacizumab-IRDye800CW fluorescence was located mainly in the cytoplasm, correlating with the VEGFα expression pattern. *Roman numerals* indicate WHO grade. Figure is available in color online only.

cizumab tumor uptake in several tumor models.[14] Additionally, we and others previously found that carboxylated IRDye800CW alone does not accumulate in tumor tissue, further illustrating the tumor-selective targeting of the currently investigated bevacizumab-IRDye800CW.[9,15,16]

Moreover, TBR increased with time in the xenograft mouse model. Background fluorescence decreased 48 hours after injection, whereas tumor fluorescence uptake remained stable; these findings are in line with those of previous studies.[12] Indeed, in a clinical setting, tracer administration at least 48 hours prior to surgery provides a higher TBR. In the current study, a high TBR was also detected and quantified ex vivo, with an average TBR of 18.7. This is comparable to another novel tracer, 800CW-TATE, that we recently evaluated and determined had a TBR of 21.1.[9] Although the TBR of patients in a clinical setting

may be lower due to (for example) currently available intraoperative imaging systems, we expect it to be sufficient. Indeed, our previous experience with clinical translation of fluorescent tracers showed that TBR > 2 is sufficient for MFGS, depending on the tumor type, after injection with an IRDye800CW-labeled antibody 2 to 4 days prior to imaging.[7]

To further explore the use of bevacizumab-IRDye800CW in a more clinical setting, meningioma specimens of all WHO grades containing both dura mater and tumor bulk were incubated with bevacizumab-IRDye800CW. In addition, we showed that MFGS using bevacizumab-IRDye800CW can be successfully applied to detect small tumor lesions perioperatively in animals undergoing postmortem resection with fluorescence imaging using both the SurgVision and Pearl systems. This illustrates the utility of MFGS for the detection of small residual lesions.

In the clinical specimens, we distinguished between tumor bulk and healthy dura mater on the basis of bevacizumab-IRDye800CW uptake. We again showed that the fluorescence signal correlated with VEGFα expression. In a clinical setting, this could be helpful to distinguish dural tails, skull base meningiomas, and recurrent meningiomas.

Although an intracranial model may be more representative of human meningiomas, a heterotopic subcutaneous model remains representative of the bioavailability of bevacizumab-IRDye800CW because meningiomas are located outside the blood-brain barrier. Additionally, a subcutaneous tumor model allows for the growth of larger tumors that are necessary for both in vivo and ex vivo fluorescence analysis. Furthermore, the current results are descriptive, but they are strengthened by comparison with data from our previous studies with IgG and carboxylated IRDye800CW control groups.

Prior to future clinical application, a new tracer has to undergo safety evaluations, such as toxicity experiments and stability testing. Fortunately, this has already been performed for bevacizumab-IRDye800CW: no toxicity was observed after administration of the tracer, and the product proved stable and applicable for human use.[6] Additionally, bevacizumab-IRDye800CW has already been applied in multiple phase I–II trials involving more than 250 patients with (for example) breast, colorectal, and esophageal cancers. These trials have shown that intraoperative visualization of tumor tissue improved with the use of bevacizumab-IRDye800CW in the majority of the included patients without any serious adverse events.[7,8] The next phase in the development of bevacizumab-IRDye800CW for application in patients with meningiomas consists of clinical trials to determine feasibility (phase I) and optimal dose (phase II). On the basis of our findings, such a proof-of-principle clinical study—the LUMINA trial (EU Clinical Trials Register no. EUCTR2020-006141-19-NL)—is currently enrolling participants. The aim of this trial is to determine the feasibility and optimal dose of bevacizumab-IRDye800CW for MFGS in patients with an intracranial meningioma. For that purpose, patients will receive an intravenous bolus of 4.5–25 mg bevacizumab-IRDye800CW 2–4 days prior to surgery. Fluorescence imaging will be performed both intraoperatively and postoperatively. The primary outcome measure is TBR based on fluorescence in the tumor tissue and adjacent healthy dura mater.

Conclusions

Bevacizumab-IRDye800CW could serve as a helpful tool to further improve the intraoperative detection of meningioma tissue. In this study, we obtained a high ex vivo TBR in a xenograft model, showed (VEGFα-mediated) fluorescent uptake in meningiomas with all WHO grades, and distinguished dura mater from tumor bulk after incubation with the tracer. Therefore, this technique is expected to improve distinction between healthy dura mater, the dural tail, and bone invasion in patients with both (complex) primary and recurrent meningiomas. If additional tumor tissue can be safely removed, extent of resection will increase and this may lead to lower recurrence rates.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Groen, Dijkstra, Nonnekens, Nagengast, Kruijff, Kruyt. Acquisition of data: Dijkstra, Meersma. Analysis and interpretation of data: Groen, Dijkstra, Nonnekens, Kruijff, den Dunnen, Kruyt. Drafting the article: Dijkstra. Critically revising the article: Groen, Dijkstra, Nonnekens. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Groen. Statistical analysis: Groen, Dijkstra, Nonnekens. Administrative/technical/material support: Dijkstra. Study supervision: Groen, den Dunnen, Kruyt.

Supplemental Information

Videos

Video 1. https://vimeo.com/750000681.

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