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In the paper by Durmo et al., differential diagnosis between high grade gliomas, low grade gliomas and metastases was achieved through the use of multibiometric evaluation of MRI scans.
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A 38-year-old woman with Hodgkin lymphoma was referred for staging fludeoxyglucose (18F) positron emission tomography/computed tomography (FDG PET/CT) that showed widespread intensely FDG-avid disease in multiple nodal stations above the diaphragm and spleen and extranodal involvement in the lungs and vertebral bodies. She underwent chemotherapy and radiotherapy. Progress FDG PET/CT 5 months later showed significant metabolic and anatomic response. Repeat FDG PET/CT 1 month later was highly suspicious of recurrent disseminated FDG-avid lymphoma in multiple nodal stations above and below the diaphragm, spleen, multiple bones, and lungs. Subsequent bone marrow biopsy showed sarcoïd-like granulomatous inflammation with no evidence of lymphoma. The patient was clinically well and no active treatment was instituted. Subsequent FDG PET/CT 2 months later showed complete resolution of metabolic activity.

INTRODUCTION
Fludeoxyglucose (18F) (FDG) uptake in positron emission tomography/computed tomography (FDG PET/CT) is based on identifying increased glycolytic activity in malignant cells. Lymphoma is a malignancy that originates in the lymphocytes. FDG-PET/CT has high sensitivity in detecting nodal disease and extranodal in lymphoma (Hodgkin and non-Hodgkin) and is currently the preferred method of staging, assessment of treatment response, restaging, and surveillance. FDG PET/CT has supplanted conventional imaging techniques such as gallium scintigraphy, computed tomography (CT) or magnetic resonance imaging (1).

Nonmalignant processes such as infection, inflammation, and granulomatous disease (such as sarcoidosis or sarcoïd-like reaction) can also show high FDG uptake and can mimic a malignant process on FDG PET/CT. Nonmalignant conditions causing FDG uptake in lymph nodes (enlarged or nonenlarged) such as infection and granulomatous disease are not infrequent; however, the coexistence of a malignant disease increases the possibility of lymphadenopathy being malignant in nature (2). The differentiation between malignant and nonmalignant FDG uptake may require histopathological confirmation.

Sarcoïd-like reaction has been reported to be associated with malignancy and/or therapy (3). This case highlights the importance of confirming unexpected FDG PET/CT findings with histopathology to avoid unnecessary treatment in nonneoplastic conditions.
The patient did not receive any treatment. A further FDG PET/CT 8 months following diagnosis confirmed resolution of uptake in lymph nodes, spleen, and bone (Figure 4).

DISCUSSION

Granulomatous lymphadenitis is a rare condition and is classified into 2 different groups: noninfectious and infectious. The noninfectious type includes berylliosis, Hodgkin lymphoma, non-Hodgkin lymphoma, lymph node-draining neoplasms (sarcoid–like granuloma), and sarcoidosis. The infectious type can be categorized into suppurative lymphadenitis and nonsuppurative lymphadenitis. Suppurative lymphadenitis occurs in tularemia, cat scratch disease, Yersinia lymphadenitis, and lymphogranuloma venereum. Nonsuppurative lymphadenitis includes tuberculosis and Bacille Calmette–Guerin (BCG) lymphadenitis (4, 5).

Sarcoidosis is a disease of unknown origin, with a global incidence of cases 8/100 000. It involves multiple organs, including pulmonary hilar lymph nodes, lungs, eyes, and skin (4). Useful diagnostic tests include demonstration of bilateral hilar lymphadenopathy on X-ray or CT, hypercalcemia, elevated angiotensin–converting enzyme level, and negative tuberculin test and histopathology (4).

Sarcoid-like reaction refers to the presence of noncaseating granuloma in regional lymph nodes in patients with occult or evident disease without fulfilling the criteria for systemic sarcoidosis (6) and may occur in many solid tumors and draining lymph nodes, such as those draining carcinomas of lung, stomach, uterus, ovaries, and melanoma (7, 8, 9). Sarcoid-like reaction has also been reported in tumors that have been treated with chemotherapy and radiotherapy (10, 11) and in nonregional tissue including bone marrow and spleen (12). The reported incidence is 13.8% of Hodgkin lymphoma and 7.3% of non-Hodgkin lymphomas (12). The clinical symptoms usually depend on the underlying disease. There is no hilar lymphadenopathy on X-ray and the tuberculin test is also negative. A biological defense mechanism in regional lymph nodes against antigens produced by tumor cells is postulated to be the reason for this reaction (13).

Tularemia is a zoonotic infection, a rare, often serious, disease, which affects ~125 people in the USA annually. The average incubation period is 3–5 days. The disease starts with an acute onset of nonspecific symptoms including, fever, anorexia, and general weakness. The diagnosis is confirmed by serology, polymerase chain reaction, and culture (14).

Other infectious types of granulomatous lymphadenitis can be diagnosed with serology, and culture with histopathology of...
the lymph node may be helpful (4). The distribution is variable with cat scratch disease and tularemia usually involving the cervical and axillary nodes, while Yersinia lymphadenitis involves mesenteric nodes and lymphogranuloma venereum the inguinal nodes (4).

CONCLUSION

This case illustrates the importance of confirming unexpected PET/CT findings with histopathology in avoiding unnecessary toxic treatment in non-neoplastic conditions.

REFERENCES

Assessing Mucosal Inflammation in a DSS-Induced Colitis Mouse Model by MR Colonography

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Key Words: magnetic resonance imaging, MR colonography, T2 map, inflammatory bowel disease, ulcerative colitis

Abbreviations: inflammatory bowel disease (IBD), magnetic resonance imaging (MRI), ulcerative colitis (UC), Crohn’s disease (CD), computed tomography (CT), T2-weighted (T2W), magnetic resonance (MR), dextran sodium sulfate (DSS), hematoxylin and eosin (H&E)

INTRODUCTION

Inflammatory bowel disease (IBD) encompasses 2 major forms of intestinal inflammation—ulcerative colitis (UC) and Crohn’s disease (CD)—both of which are characterized by chronic exacerbations of inflammation in the gastrointestinal tract (1). IBD is a global disease of increasing prevalence. More than 1 million individuals in the USA and 2.5 million in Europe are estimated to have IBD, with annual health-care costs of $6 billion and €4.6–5.6 billion, respectively (2, 3). Patients with IBD experience clinical gastrointestinal indications, as well as chronic emotional symptoms, that can severely reduce quality of life and ability to work. Imaging techniques can play a key role in the diagnosis and lifelong evaluation of patients with IBD. In particular, the development of noninvasive imaging techniques that can perform the initial screening and diagnosis of IBD, in particular, at early stages, will be of considerable value.

The clinical severity of IBD is usually proportional to the extent of bowel involved and the intensity of the inflammation process in the affected tissue (4). The inflammation in CD may potentially extend to any part of the gastrointestinal tract, whereas inflammation in UC extends from the rectum and involves the distal part of the colon (5). The inflammatory process in UC is typically confined to the innermost lining or mucosa and may involve all of the gastrointestinal tract continuously, whereas the inflammatory process in CD may involve all layers of the intestine, but a “skip lesion” appears between the healthy and affected tissue (6). The etiology of both diseases remains unclear, although a combination of genetic, environmental, and immunological factors contributes to disease initiation and progression (7).

IBD is, in general, diagnosed on the basis of a combination of clinical, pathological, radiological, endoscopic, and laboratory indications (8). To determined disease activity and tailor IBD therapy, the inflammatory state of the colon should be assessed. However, clinical features alone are neither sensitive nor specific enough for grading lesion severity in IBD, and imaging plays a key role in its diagnosis (9, 10). Endoscopy is the gold-standard technique for diagnosis of IBD, aiding direct visualization of the colonic mucosa, the target of the disease. Endoscopy helps to identify inflammation, including its location and severity, and obtain biopsies needed to confirm the diagnosis. However, endoscopy is an invasive technique that requires patient preparation and discomfort, and interpretation of its results is highly operator/radiologist-dependent (11, 12). Therefore, alter-
Assessing Mucosal Inflammation by MR Colonography

METHODOLOGY

Animals

Animal experiments were approved by the Weizmann Institute Animal Care and Use Committee following Israeli, US National Institutes of Health, and European Commission guidelines. Eight-week-old male C57BL/6 mice (n = 26) were obtained from Envigo (Rehovot, Israel). Mice were treated with 0%-2% (wt/vol) DSS (MP Biomedicals; molecular weight, 36,000–50,000 Da) in drinking water for 7 days, followed by 5 days of regular water (7). The mice were divided into the following 5 groups: untreated (n = 6), 0.5% DSS (n = 5), 1% DSS (n = 5), 1.5% DSS (n = 5), and 2% DSS (n = 5) treated mice. Survival and changes in body weight of the animals were monitored daily over the course of colitis development. Mice were monitored throughout the experiment, and any that showed extreme distress, became moribund, or lost more than 20% of initial body weight were euthanized.

MRI

All mice were imaged on days 7 and 11 post DSS treatment. Prior to imaging, animals were anesthetized using intramuscular injection of a mix of Domitor (Medetomidine, 1 mg/kg; Orion Corporation, Espoo, Finland) and Ketamine (75 mg/kg; Vetoquinol, Lure, France) and were administered successive warm saline enemas (~2 mL) to clear the colon of solid fecal material. Two milliliters of perfluorinated oil (Fomblin Y LVAC 06/6 perfluoropolyether oil; Sigma-Aldrich, St. Louis, MO) were introduced via a rectal catheter consisting of microbore tubing (20G cannula, Delta Med). The setup of the mice in the MRI animal holder is shown in Figure 1A. At the end of the MRI protocol, the anesthetized mice were injected intraperitoneally with Antisedan (1 mg/kg; Orion Corporation).

MRI experiments were performed on 9.4 Tesla BioSpec Magnet 94/20 USR system (Bruker BioSpin Corporation, Billerica, MA) equipped with a gradient coil system capable of producing pulsed gradients of up to 40 G/cm in each of 3 orthogonal directions. MR images were acquired using a quadrature volume coil with 35-mm inner diameter (Bruker). The T2 maps...
were acquired using multisection spin-echo imaging, with interleaved sections and the following parameters: a repetition delay of 3000 milliseconds, 16 time echo increments (linearly from 10 to 160 milliseconds), matrix dimension of $256 \times 128$ (interpolated to $256 \times 256$) and 2 averages, corresponding to an image acquisition time of 12 minutes 48 seconds. Fourteen contiguous, 1-mm-thick sections, were acquired, with a field of view of $3.0 \times 2.5 \text{ cm}^2$.

**Endoscopy**

Colonoscopy was performed on days 7 and 11 post DSS treatment to monitor the severity of colitis. Colitis was scored by a single rater according to the Murine Endoscopic Index of Colitis Severity (MEICS), considering five factors: (i) thickening of the colon wall; (ii) changes in vascular pattern; (iii) presence of fibrin; (iv) mucosal granularity; and (v) stool consistency. Each factor was scored with a value between 0 and 3. The cumulative score ranged from 0 (no signs of inflammation) to 15 (signs of very severe inflammation) (22). Healthy mice typically have cumulative scores of 0–3.

**Histopathology**

On the day of sacrifice (day 11), the colons were removed and their lengths measured. They were then fixed in 2.5% paraformaldehyde solution overnight at 4°C, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E). H&E-stained tissue was examined in a blinded manner by a gastrointestinal pathologist. Tissues were graded on a 0–4 scale based on the parameters of inflammation severity (7), according to the following scoring system: 0, no evidence of inflammation; 1, low level of inflammation with scattered infiltrating mononuclear cells, 1–2 foci; 2, moderate inflammation with multiple foci; 3, high level of inflammation with increased vascular density and marked wall thickening; and 4, maximal severity of inflammation with transmural leukocyte infiltration and loss of goblet cells.

**Image Analysis**

All image analyses were performed using purpose-written MATLAB (R2013B) scripts. Quantitative T2 maps were generated from multiecho, T2W images by fitting the multiecho signal as a monoexponential decay. Colon walls were manually segmented as hyperintense (compared with muscle tissue) regions in T2W spin-echo images. T2 maps of the colon were calculated on a pixel-by-pixel basis and overlaid on T2W images. Two regions of interest were drawn on each map, representing the inner (red) and outer (yellow) radii of the colon (Figure 1B). Mean T2 value and apparent thickness were calculated for each section of the colon.

**Statistical Methods**

The results are reported as mean ± SD. Student t-test was used to compare means of 2 groups, with $P < .05$ defining statistical significance.

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**Figure 1.** In vivo mouse magnetic resonance imaging (MRI) colonoscopy experiment. Mice were set up in a dedicated MRI animal holder (A). The length of the scanned colon was ~1 cm. Histological sections were taken from 4 regions (in red, sections (a)–(d)) of this area. The most distal portion of the colon is defined as (a) and the most proximal portion as (d). T2 maps of the colon, calculated on a pixel-by-pixel basis, with selection of two regions of interest, yellow and red, representing the outer and inner colon radii, respectively (B). Mean T2 value and apparent thickness were calculated for each section of the colon.
RESULTS

In Vivo MRI Colonoscopy of Untreated Mice

Multisection MR images were collected in a cohort of untreated control mice, and revealed clear differences along the length of the colon in these animals. T2 maps, shown in Figure 2A, illustrate a trend of increasing T2, from distal to proximal end, along the measured region of the colon. Quantitative measurement of T2 values of the colon wall, plotted in Figure 2B, shows significantly higher values in proximal vs distal regions (71 ± 1 milliseconds for the most proximal image section vs 54 ± 1 milliseconds for the most distal section). However, as shown in Figure 2C, no significant differences were observed in mean colon wall thickness along the length of the colon (0.50 ± 0.07 mm for the most proximal image section vs 0.56 ± 0.14 mm for the most distal section).

Histological examination of untreated colon at 4 different points along the measured colon confirmed the MRI colonoscopic observation (Figure 2D). There were no signs of inflammation or crypt damage and no variation in the thickness of the colonic wall. Nonetheless, microscopic examination of the colon at 4 different points along its length showed differences in tissue architecture, consistent with the positional-dependent T2 values measured in the MRI colonoscopy experiment. The thickness of the muscular layer, in particular that of the circular layer, decreases from distal to proximal (23). The diameter of the colon is also dependent on the presence or absence of fecal pellets [present in (c) and (d), but not in (a) or (b)].

In Vivo MRI Colonoscopy of 1% DSS-Induced Acute Colitis

To induce colitis, a cohort of mice was treated with 1% DSS, administered in drinking water for 7 days, followed by 5 days of untreated water. These mice showed decreases in body weight of 4% and 9% at days 7 and 11, respectively. Ex vivo pathological
analysis showed significantly shorter colons, owing to inflammation and edema, in the 1% DSS-treated mice (5.4 ± 0.2 cm) vs untreated controls (7.2 ± 0.4 cm, P < .0001).

Figure 3 shows in vivo MRI data from a representative untreated mouse (top row) and a 1% DSS-treated mouse at days 7 (middle row) and 11 (bottom row). Examples of T2-weighted images, both full (Figure 3, A–C) and expanded (Figure 3, D–F) and expanded T2 maps (Figure 3, G–I) are shown. In the T2-weighted MR images, the signal of the colon wall of the 1% DSS-treated mouse at days 7 and 11 is hyperintense compared with that of the untreated mouse. Also, these images reveal a significant change in the colon diameters of the treated mice at day 11. T2 maps show higher T2 values for the DSS-treated colon at days 7 and day 11 (yellow and red pixels) than for the colon of an untreated mouse (blue pixels).

Table 1 shows mean colon T2 values and apparent colon thickness, calculated from the T2 maps, as averages across all image sections. The mean T2 values for colons from the 1% DSS-treated mice were significantly higher on days 7 (83 ± 15 milliseconds) and 11 (88 ± 6 milliseconds) than for colons from untreated mice (61 ± 2 milliseconds, P < .05 and P < .0001 vs post-DSS-treatment days 7 and 11, respectively). Although no significant change in colon thickness was observed on post-treatment day 7, an increase in the mean apparent colon thickness after 1% DSS treatment was observed at day 11 (0.90 ± 0.07 cm) vs untreated colon (0.51 ± 0.03 cm, P < .005).

Mean colon T2 values and thicknesses, calculated on a section-by-section basis, are shown in Figure 4. Unlike untreated, control animals, mean T2 values of the colon wall in mice treated with 1% DSS show little positional dependence, at either day 7 or 11. Thus, because of the positional variation seen in controls, changes in mean T2 in treated mice are more pronounced in the distal part of the colon than in the proximal part (Figure 4A). For example, increases in mean T2 values in the most proximal imaging section were 22% ± 20% (day 7) and 18% ± 6% (day 11), while corresponding increases in the most distal section were 44% ± 28% (day 7) and 66% ± 10% (day 11), respectively. At day 11, there is a trend toward increased thickness from distal-to-proximal positions within the colon (Figure 4B). Relative to controls, the effect of the DSS treatment on mean apparent colon thickness is more pronounced in the proximal portion of the colon (increase of 93% ± 45% for the most proximal image section) than in the distal portion (62% ± 24%).

**Evaluation of Dose-Dependent DSS-Induced Colitis by Endoscopy, Histology, and MRI Colonoscopy**

To characterize the dose dependence of DSS-induced colitis, separate cohorts of mice were treated with 0.5%, 1%, 1.5%, or 2% DSS, administered in the drinking water for 7 days, followed by 5 days of untreated water. Mice treated with 1.5% or 2% DSS...
showed a decrease in body weight of up to 24% on day 7 and up to 31% on day 11. Ex vivo analysis revealed significantly shorter colons in mice treated with 1%, 1.5%, or 2% DSS-treated mice [average colon lengths, 5.4 shorter colons in mice treated with 1%, 1.5%, or 2% DSS-treated mice (7.2 ± 0.4 cm). No significant differences were observed between the untreated and 0.5% DSS-treated colons (7.2 ± 0.4 cm). Mice treated with 0.5%, 1%, 1.5% or 2% DSS were also characterized, in detail, by endoscopy, histology, and MRI colonoscopy.

As described in Methods/Endoscopy, the endoscopy scoring is based on colon wall thickening, vascularity, presence of fibrin, mucosal granularity, and stool consistency. Each parameter receives a score of 0, 1, 2, or 3, and the composite endoscopy score is the sum of all of the parameter scores. The endoscopy scores for the 0.5%, 1%, 1.5%, and 2% DSS-treated mice were 2.5 ± 0.6, 3.3 ± 1.4, 8.6 ± 1.3, and 10.3 ± 0.6 at day 7, and 4.3 ± 0.8, 10.0 ± 1.2, 10.8 ± 1.3, and 13.7 ± 0.6 at day 11, respectively. P-values calculated by comparing these values with endoscopy scores for the untreated groups were all <.001. On both days 7 and 11, endoscopy scores were higher for higher levels of DSS treatment, and scores increased between days 7 and 11 for all treatment groups.

Figure 5A shows representative H&E-stained sections and corresponding endoscopy images of the colon on day 11 for mice treated with 0.5%, 1%, 1.5%, and 2% DSS. Colons of untreated mice had intact mucosa, as shown in Figure 2D. There was neither endoscopic nor microscopic evidence of colitis in the 0.5% DSS group. In colons of the 1%, 1.5%, and 2% DSS groups, there was extensive to diffuse crypt loss and ulceration, accompanied by severe submucosal edema (arrows in Figure 5A) and variable inflammatory infiltration. In the 1.5% and 2% DSS-treated mice, there was free blood in the intestinal lumen (marked with *). As detailed in Methods/Histopathology, mice were scored on a histology scale ranging from 0 (no evidence of inflammation) to 4 (severe inflammation with transmural leukocyte infiltration and loss of goblet cells). The histology scores for the 0.5%, 1%, 1.5%, and 2% DSS-treated mice were 0.2 ± 0.3, 2.1 ± 0.8, 3.1 ± 0.5, and 4.0 ± 0.1, respectively, on day 11. A good correlation was found between the in vivo endoscopy scores and the histology scores (Figure 5B).

Representative T2 maps from mice treated with 0.5%, 1%, 1.5%, or 2% DSS are shown in Figure 6A. The image intensities of the colons of these mice were elevated at both days 7 and 11. The maps of the 0.5% DSS group were similar to those of untreated controls. Mean colon T2 values and apparent colon thicknesses, extracted from the T2 maps and averaged across all imaging sections, are shown in Figure 6B and 6C, respectively. DSS treatment, at levels of 1%–2%, caused significant increases in mean colon T2 values at days 7 and 11, whereas no significant differences were measured at either time point for mice treated with 0.5% DSS. Apparent colon thickness followed a different pattern of response to DSS treatment. On day 7, no significant changes in colon thickness were observed at any level of DSS treatment, whereas on day 11, significant increases (P < .02) in wall thickness were observed for mice treated with 1% or greater DSS.

Mean colon T2 values and mean apparent colon thickness parameters were also calculated on a section-by-section basis for each DSS level (Figure 7). For all levels of DSS treatment, section-by-section analysis of apparent colon thickness showed no significant changes on day 7 (Figure 7A). No changes were observed on day 11 for the 0.5% DSS-treated mice. However, at all section positions, there was a significant increase in the mean apparent colon thickness on day 11 for all mice treated with >0.5% DSS (Figure 7B), and a significantly higher mean apparent colon thickness was observed for all mice treated with >0.5% DSS. Somewhat surprisingly, the highest mean apparent colon thickness was found in 1% DSS-treated mice.

Figure 4. Quantitative analysis of T2 maps calculated from a section-by-section analysis of untreated and treated mice. Mean colon T2 values (A), mean apparent colon thickness as function of section position along the colon in the untreated colon (n = 6), and treated mice with 1% DSS on day 7 (n = 5) and 11 (n = 5) (B). Values are reported as mean ± SD. *P < .05 Student 2-tailed t test, for all section positions, for both mean colon T2 values, and mean apparent colon thickness, except for the mean colon T2 values at a section position of 7 mm.
On day 7, mean colon T2 values for the cohort of 0.5% DSS-treated mice were very similar to those for the untreated group (Figure 7C), with the same trend of increasing T2, proximal to distal, observed in both groups. On day 11, the same proximal-to-distal trend was seen, although a small but significant increase in mean T2 values was observed in the 0.5% DSS-treated mice (Figure 6D). In animals treated with >0.5% DSS, mean colon T2 values increased significantly at all section positions on both day 7 and day 11. The graphs in Figure 7, C–D also show that the effect of DSS treatment (0.5%) is more pronounced in the distal part of the colon, in particular at day 11.

A Pearson product–moment correlation coefficient was computed to assess the relationship between the MR colonography parameters (average T2 value and colon thickness across all sections) and endoscopy and histology findings at day 11 in the 1% DSS-treated mice. The correlations between average T2 value and measures of endoscopy and histology were significant (Pearson $r = 0.77$ and $0.66$, respectively), whereas the corresponding correlations between average colon thickness and these same measures were much weaker (Pearson $r = 0.59$ and $0.50$, respectively).

DISCUSSION

UC is a serious and often debilitating condition, with significant long-term consequences for patients. Early detection of UC increases treatment options and improves outcomes, but robust techniques for early detection and accurate monitoring of in vivo treatment response in UC patients are lacking. This study aimed to show the use of a noninvasive MR imaging technique, T2 mapping, for identifying and quantitatively grading UC in a chemically induced mouse model. We showed clearly that our T2-based MR experiments and analysis can provide a quantitative measure of UC inflammation on a positional (ie, section-by-section) basis along the colon. Our MRI findings were validated by endoscopic evaluation and colon biopsies. The quantitative information about colitis activity and colon wall thickness derived from noninvasive MR experiments can be readily translated to the clinic for improved early detection of UC and monitoring of the efficacy of treatment in UC patients.

As noted earlier, MRI-derived metrics, including measures of colon wall thickness and inflammation and gadolinium (contrast-agent) enhancement, have established MRI as an important, noninvasive imaging modality for detecting morphologic changes and inflammatory activity associated with IBD. However, these findings are consistently observed in only severe and active UC. In moderate and quiescent stages of UC disease, no effect on the colon wall thickness is found (15), and current MRI methods are not sensitive enough for robust detection of UC. Herein, we show quantitative T2 mapping, including both positional dependence and average along the colon, as a method for improving evaluation of the extent and severity of UC, thereby improving early, accurate diagnosis.

Our initial experiments focused on the characterization of healthy, untreated colon. As expected, no significant differences were found in the mean colon wall thickness along the length of the colon. Somewhat surprisingly, T2 mapping revealed higher T2 values in proximal vs distal regions, findings that correlated with positionally dependent differences in tissue architecture and cellular composition. These findings were mirrored in differences observed histologically. The mouse basic bowel wall structure includes the mucosa, submucosa, muscularis, and serosa. The mouse muscularis propria has inner circular and outer longitudinal layers. The mouse cecal muscular layers are thinner than the more distal colon muscular layers. The muscular tunics increase in thickness progressively in the distal and
descending colon. The mucosa of mouse proximal colon has transverse folds that are longer than those present in the cecum. Mouse midcolonic mucosa is flat with no mucosal folds. The distal colon of the mouse has longitudinal mucosal folds.

In UC in human, ulcers gradually spread upward from their points of origin, until the entire colon is involved. Thus, a method that can improve diagnostic sensitivity on a positional basis has direct translational importance. Our MRI-derived metrics, which showed sensitivity to positionally dependent colon thickening and inflammation, may have clinical relevance to the diagnosis of UC, in particular at early stages of the disease.

One of the significant differences between this work and earlier studies is the examination of the effects of lower levels of DSS treatment. Although most previous experiments were performed with high dosage (≥2% wt/vol) of DSS in the drinking water (7-9, 20), here, we examined mice treated with as little as 0.5% DSS. The development of imaging markers in these lower-dosage studies has potential importance for the early-stage diagnosis of IBD. Below 1% DSS, our T2-based, MR colonography tool was unable to detect changes in the colon, an observation that was consistent with colonoscopy and, in particular, histology in these same mice. However, in 1% DSS-treated animals, the in vivo MRI-grading tool revealed significant inflammation at post-treatment days 7 and 11, as reflected by increases in mean colon T2 of 36% and 45%, respectively. Section-by-section analysis of T2 maps showed that the inflammation was positionally dependent along the colon, being more pronounced distally than proximally. This finding is consistent with a report by Suzuki et al., that the severity of inflammation, measured by histology, was the greatest in the distal region of the colon in a DSS colitis mouse model initiated with azoxymethane (24).

Figure 6. DSS dosage response. The T2 maps of representative treated mice with different DSS ratio from 0.5% to 2% on day 7 and 11 (A). Quantitative analysis of T2 maps, as an average value across all sections of untreated and treated mice, at different DSS ratios. Mean colon T2 values (B), Mean apparent colon thickness in untreated (0% DSS) colon (n = 6), and treated mice with 0.5%–2% DSS on day 7 (n = 5) and 11 (n = 5) (C). Values are reported as mean ± SD. *P < .05 Student 2-tailed t test.
Of note, MRI-derived colon wall thickness was unaffected at post-treatment day 7 following 1% DSS administration. Thus, T2 mapping proved more sensitive to early DSS-induced pathology than wall thickness. By post-treatment day 11, the colon wall thickness was increased, with greater thickening of the wall in the proximal portion of the colon than in the distal portion.

In the current study, colonoscopy and histology scores at post-treatment day 11 increased with increasing DSS dose (above 0.5% DSS). MRI findings at days 7 and 11 provided important insights into the dose dependence of DSS-induced injury. Based upon observed increases in T2, DSS dose-dependent colonic inflammation was similar at days 7 and 11 for all DSS levels >0.5%, and showed little positional dependence along the colon. However, compared with T2 values for normal colon, T2 increases for DSS levels >0.5% were greater in the distal region of the colon.

A different pattern was observed for MRI-derived colon wall thickness as a function of DSS level. At post-treatment day 7, colon wall thickness for all DSS levels was similar to normal colon, and was positionally independent. By contrast, at day 11, significant increases in colon wall thicknesses were observed for DSS levels >0.5%. Again, no positional dependence of wall thickness was observed. Interestingly, the greatest increase in the colon wall thickness at day 11 was observed for mice treated with 1% DSS. In total, our MRI results suggest that treating mice with 1% DSS in drinking water for 7 days, followed by 5 days of regular water, produces the most severe colitis, with better reproducibility and lower mortality than higher doses of DSS.

The use of sensitive T2 mapping-based MR colonography, together with improved reproducibility and lower mortality of the murine 1% DSS-induced colitis model, will provide new opportunities for studying therapeutic drugs to combat the disease. MR imaging will allow longitudinal monitoring of therapeutic response and improve sensitivity for detecting healing at specific locations along the colon.

In summary, findings from the present study suggest that the established, T2 mapping-based MR colonography tool can be used to reliably characterize colon damage in a chemically induced mouse model. It was demonstrated clearly that colon...
thickness, measured via conventional, T2-weighted sequences, is insufficient for assessing disease severity, in particular, in the early stages. Mean T2 value, an MR biomarker of inflammation, was found to be quantitative and sensitive to disease severity.

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REFERENCES
Brain Tumor Characterization Using Multibiometric Evaluation of MRI

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ABSTRACT
The aim was to evaluate volume, diffusion, and perfusion metrics for better presurgical differentiation between high-grade gliomas (HGG), low-grade gliomas (LGG), and metastases (MET). For this retrospective study, 43 patients with histologically verified intracranial HGG (n = 18), LGG (n = 10), and MET (n = 15) were chosen. Preoperative magnetic resonance data included pre- and post-gadolinium contrast-enhanced T1-weighted fluid-attenuated inversion recovery, cerebral blood flow (CBF), cerebral blood volume (CBV), fractional anisotropy, and apparent diffusion coefficient maps used for quantification of magnetic resonance biometrics by manual delineation of regions of interest. A binary logistic regression model was applied for multiparametric analysis and receiver operating characteristic (ROC) analysis. Statistically significant differences were found for normalized-ADC-tumor (nADC-T), normalized-CBF-tumor (nCBF-T), normalized-CBV-tumor (nCBV-T), and normalized-CBF-edema (nCBF-E) between LGG and HGG, and when these metrics were combined, HGG could be distinguished from LGG with a sensitivity and specificity of 100%. The only metric to distinguish HGG from MET was the normalized-ADC-E with a sensitivity of 68.8% and a specificity of 80%. LGG can be distinguished from MET by combining edema volume (Vol-E), Vol-E/tumor volume (Vol-T), nADC-T, nCBF-T, nCBV-T, and nADC-E with a sensitivity of 93.3% and a specificity of 100%. The present study confirms the usability of a multibiometric approach including volume, perfusion, and diffusion metrics in differentially diagnosing brain tumors in preoperative patients and adds to the growing body of evidence in the clinical field in need of validation and standardization.

INTRODUCTION
Glioblastomas are the most common malignant neoplasms of the brain and together with metastatic tumors comprise half of all the malignant tumors of the brain (1). The recent published 2016 World Health Organization (WHO) classification of the central nervous system tumors incorporates, for the first time, molecular parameters in addition to histology to define brain tumors (2). The 2016 WHO central nervous system tumor classification divides glioblastoma tumors into (1) glioblastoma isocitrate dehydrogenase (IDH)-wild type (90% of cases, presenting de novo in elderly patients), (2) glioblastoma IDH-mutant (10% of cases, the so-called secondary glioblastoma as the tumor often progresses from a low-grade tumor, predominately seen in younger patients), and (3) glioblastoma not-otherwise-specified tumor, in which complete IDH evaluation and histopathology cannot be performed or is inconclusive (2). The risk to develop a glioma of a certain grade increases with certain mutations (3).

Grading presumes biological behavior or phenotype of a lesion and is, together with molecular testing, of high clinical relevance. The 2016 WHO glioma grading system classifies gliomas into one of the following grades: grade I (World Health Organization [WHO] grade I), grade II (WHO grade II), grade III (WHO grade III), or grade IV (WHO grade IV). 

Key Words: MRI, diffusion-weighted imaging, perfusion-weighted imaging, brain tumor, brain metastasis, sensitivity, specificity, glioma
Abbreviations: High-grade gliomas (HGG), low-grade gliomas (LGG), metastases (MET), cerebral blood flow (CBF), cerebral blood volume (CBV), receiver operating characteristic (ROC), isocitrate dehydrogenase (IDH), magnetic resonance imaging (MRI), gadolinium (Gd), diffusion-weighted imaging (DWI), tumor volume (Vol-T), normalized cerebral blood flow (nCBF-T), normalized cerebral blood volume-tumor (nCBV-T), normalized fractional anisotropy-tumor (nFA-T), normalized fractional anisotropy-edema (nFA-E), nCBF-edema (nCBF-E), nCBV-edema (nCBV-E), mean time to progression (MTP), overall survival (OS), fluid attenuated inversion recovery (FLAIR), region of interest (ROI), normal-appearing white matter (NAWM), area under the curve (AUC)
importance for therapy selection; adjuvant radiation, chemotherapy, surgical or palliative treatment. Gliomas of different grades may at presentation or over time exhibit morphological similarities on magnetic resonance imaging (MRI) (3).

In the present study, full molecular testing of the tumors was not performed in the majority of the patients. Therefore, they are referred to as high-grade gliomas (HGGs), that is, grades III–IV glioblastoma or low-grade gliomas (LGGs) according to the WHO classification 2016, with no reference to different mutations (2). MRI is considered the standard modality for diagnosis and prognosis of brain tumors, based primarily on gadolinium (Gd) contrast medium enhancement, biological behavior including location, and progression over time. This concept, however, is challenging, as not all HGGs show Gd enhancement. Further, 10% of glioblastomas and 30% of anaplastic astrocytomas do not enhance, whereas few LGGs occasionally do enhance (4). Clinical distinction between LGG and HGG is important, as the treatment options between these groups may significantly differ. The clinically estimated prognosis for each patient with a certain type of tumor includes prognostic factors such as age of patient, tumor location, contrast enhancement, and residual postoperative tumor volume (5–9). The largest tumor diameter has an impact on survival for patients with LGG, and extensive surgical resection is beneficial (10). However, HGGs are today treated more aggressively than LGGs, as the overall survival (OS) for patients with LGG is substantially longer than that for patients with HGG (2). Intracranial metastases (MET) may have a similar imaging appearance, as solid or ring-enhancing cystic lesions may, in the initial stage, complicate the differentiation toward HGG (11). Different MRI techniques such as perfusion-weighted MRI, diffusion-weighted imaging (DWI), and diffusion tensor imaging have a diagnostic value for the discrimination between LGG and HGG and for identifying the glioma grade (12, 13).

In this study, it is proposed that LGG/HGG/MET have sufficiently different manifestations at early presentation of the disease, allowing for clinically acceptable discrimination by utilization of several MRI protocols. Aggressive growth in HGG is hypothesized to manifest with a higher tumor volume (Vol-T), normalized cerebral blood flow (nCBF-T), normalized cerebral blood volume-tumor (nCBV-T), normalized fractional anisotropy-tumor (nFA-T), normalized fractional anisotropy-edema (nFA-E), nCBF-edema (nCBF-E), and nCBV-edema (nCBV-E), and a lower nADC-T, nADC-E, ratio edema volume to tumor volume (Vol-E/Vol-T), compared with LGG and MET. It is hypothesized that the differences between MET and HGG, both presenting as highly malignant and proliferating entities, are distinguishable, albeit having smaller differences than when comparing LGG and HGG owing to LGG’s generally low proliferating state. It is hypothesized that aggressive growth is associated with higher vascularity, cellular density, and destruction of the myelin, which, in turn, is quantifiable by measuring diffusion, perfusion, and volumes of tumor and edema. Aggressive growth as seen in HGG, is hypothesized to manifest with higher intratumoral and peritumoral perfusion, greater tumor volume, and lower diffusion when compared with MET and LGG. The low proliferative state of LGG and the probable vasogenic edema around MET are hypothesized to result in lower perfusion values and higher diffusion values in edematous tissue than in edematous tissue of HGGs, which probably has a more infiltrative component than LGG and MET.

Utilization of the microstructure either within the tumor or adjacent to the tumor, that is, perilesional tissue, has been reported with varying degrees of success in differential diagnosis between MET and HGG (13). Tumoral and peritumoral CBV, ADC, and FA provide diagnostic information in the differentiation between LGG and HGG (13). In addition, there is potential in measuring the ratio between Vol-E and Vol-T for the differentiation between MET and what was formerly categorized by WHO as glioblastoma multiforme (14). However, conflicting evidence exists, in which imaging biomarkers are optimal and should be used for the distinction between HGG, LGG, and MET (12, 15). A similar morphological appearance on MRI, along with varying treatment options and varying overall prognoses, raises the necessity for standardized and verified protocols to increase the specificity of MRI regarding the differentiation of HGG, LGG, and MET.

Because the further treatment approach is reflected by the suspected diagnosis, the possibility to separate these entities may reduce the need for surgery and histopathology confirmation, particularly between LGG and MET and HGG and MET. Ultimately, this study, when externally validated, may help to establish a minimally invasive approach to earlier screening for disease, more rapid diagnosis of patients, and decision support for clinicians (16).

The aim of this study is to evaluate the sensitivity and specificity of advanced magnetic resonance (MR) imaging metrics for DWI, perfusion-weighted MRI and tumor and edema volume for tumor type differentiation in a cohort of patients with HGG, LGG, and MET.

**MATERIALS AND METHODS**

The initial cohort of this retrospective study consisted of 60 consecutive patients. After excluding patients with meningioma, lesions at the skull base, and those that had limited preoperative MR examination, the final cohort consisted of 43 patients; 18 HGG (15 glioblastomas, grade IV; 2 oligoastrocytomas, grade III; 1 anaplastic oligoastrocytoma, grade III), 10 LGG (3 diffuse astrocytomas, grade II; 4 astrocytomas, grade II; 2 oligodendrogliomas, grade II; and 1 oligoastrocytoma, grade II), and 15 MET (9 adenocarcinomas with gastrointestinal, lung, or breast origin; 4 malignant melanomas; 1 invasive lobular breast carcinoma; and 1 anaplastic thyroid cancer). There were 30 male patients and 13 female patients with a mean age at diagnosis of 64 (range, 48 – 79) years for HGG, 45 (range, 20 – 66) years for LGG, and 59 (range, 30 – 81) years for MET. Study inclusion criteria were age >18 years, histologically verified intracranial glial tumor of de novo origin or brain MET and MRI performed before surgery. The study has been approved by the local ethical committee, and written informed consent was obtained from all study subjects (#2010/199, 2012/188, 2014/368).

**Clinical Data**

Histological diagnosis of tumors was obtained surgically by resection (n = 12 HGG, 6 LGG, 15 MET) or biopsy (n = 6 HGG, 4 LGG) (Table 1). Mean time to progression (MTP) (measured in days after initial MR imaging, on the basis of which the tumor was detected) and mean OS (measured in months after the
<table>
<thead>
<tr>
<th>Patient/Sex/Age/Tumor Type</th>
<th>Histopathology (grade)</th>
<th>Location of Tumor</th>
<th>Type of Surgery</th>
<th>MTP</th>
<th>OS</th>
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<td>&gt;55</td>
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<td>Exirpation</td>
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</table>

Abbreviations: GB, glioblastoma; OA, oligoastrocytoma; MET, metastasis; AC, adenocarcinoma; LT, left; RT, right.
* Data not obtainable; resection refers to partial resection of the tumor; extirpation refers to total resection of the tumor.
aforementioned initial MRI examination until death or last available follow-up) were calculated for each group (Table 1) and derived from patients’ medical records based on the combination of clinical evaluation and radiological findings. For the radiological decision, the RANO (Response Assessment in Neuro-Oncology) criteria were used.

**Study Protocol**

MRI was performed on a 3 T Siemens MAGNETOM Skyra® (Erlangen, Germany), with a 20-channel head/neck coil. The MR protocol included the following sequences: axial T2 2D Turbo spin-echo (TSE); axial 2D fluid attenuated inversion recovery (FLAIR); T1 3D magnetization prepared rapid gradient echo (MPRAGE), pre- and post-Gd contrast administration with 1-mm isotropic resolution; DWI; diffusion tensor imaging with diffusion-sensitized single-shot echo planar imaging (SSEPI) using 30 noncollinear diffusion gradient directions, with b-values of 0 and 1000 s/mm², and a spatial resolution of 2.0 × 2.0 × 2.0 mm²; dynamic susceptibility contrast perfusion MR with a time resolution of 1.5 seconds, using a single-shot gradient echo EPI-gradient sequence, with a spatial resolution of 1.7 × 1.7 × 5.0 mm³ and an echo time of 28 milliseconds. The total examination time was approximately 1 hour.

**Postprocessing**

All data were anonymized before any processing or export, according to local policies and stated in the ethical permission and written informed consent form. ADC and FA maps were calculated using in-house–developed software, based on the MATLAB framework. T1-weighted and FLAIR maps used for volume measurements were also calculated using the in-house–developed software, whereas the resulting perfusion maps were calculated using singular value decomposition with a truncated singular value decomposition and the software package Nordic ICE (NordicNeuroLab, Bergen, Norway; http://www.nordicneurolab.com/). All obtained perfusion maps were leakage-corrected with Boxerman and gamma fitting (Nordic ICE; NordicNeuroLab).

**Biometrics**

Tumor tissue was defined as a deranged tissue structure with or without Gd-enhancement, mass effect, hemorrhage, or necrosis but not solemnly attributed to perilesional edema. Biometrics included volume (Vol), nADC, nFA, nCBV, and nCBF for tumor and edema (Figure 1, A–N).

Manual region of interest (ROI) delineation has an advantage over semiautomatic segmentation for measurements on T2-weighted image maps, whereas semiquantitative methods of measurement underappreciate tumor volumes, suggesting that the manual approach is the method of choice for volumetric measurements on maps of T1-weighted image as well as T2-weighted image (17). In addition, manual ROI delineation is a clinically acceptable method for the measurement of nCBV. Elliptic ROIs of a similar size and shape were chosen to reduce the risk of underappreciating the true value of the intended measurement. Also, the elliptical ROI was chosen to include more volume/area/tissue when measuring and to reduce the risk of encompassing tissues that do not require measurement, that is, not choosing a square ROI. The ROI location for normalization was consistent for all modalities, that is, centrum semiovale, contralateral to the tumor. The in-house–developed program chosen for the measurements produced a mean of the measured values and also provided a histogram of the values within the measurements; care was taken to produce measurements with a normal distribution on histograms. In our cohort,
rectangular ROIs of size between 15 and 20 pixels produced poorer histograms than elliptical ROIs, probably owing to the inclusion of tissue that did not require measurement, that is, a rectangular-shaped ROI of size $\frac{H_{15}}{H_{15}}$ pixels was not optimal for measurement. For CBF in edema, a rectangular-shaped ROI of size 4 pixels was chosen. The reduced-size ROI was used because of the hypothesis that the edematous tissue could be more prone to the partial volume effect. Regardless of the ROI size, the sampled value was averaged automatically by the program in which the measurements were made. Obtaining significant values across different modalities was an insurance of the stability of the measurements, as it showed that the method was reproducible. Therefore, an averaged measurement with a pixel size between 4 and 20 is sufficient for measurement.

### Volume Metrics.

For lesion volume (Vol-L), the outer margin of the entire lesion including tumor and edema was outlined on each section on the FLAIR maps, also referencing to T1- and T2-weighted maps. Total Vol-T was outlined in each section on the Gd-enhanced T1-weighted images, also referencing to FLAIR and T2-weighted maps. Total edema volume (Vol-E) was calculated by subtraction of Vol-T, measured on the postcontrast T1-weighted images, from Vol-L; the entire Vol-L was measured on the FLAIR images for respective patients. Vol-E/Vol-T was calculated for all tumors. A neuroradiologist with 20 years of experience reassessed the volume delineation derived by a trainee MD and a PhD student.

### Diffusion Metrics.

Mean ADC and mean FA were measured for tumor and edema tissue (ADC-T, ADC-E, FA-T, and FA-E) in each patient. ROIs were defined on ADC and FA maps with reference to morphological images, avoiding necrotic, cystic, and hemorrhagic areas. For normalized values of ADC and FA, 1 ellipsoid ROI was placed on each of 3–4 sections (105–408 pixels in total for 3–4 ROIs per patient) in the normal-appearing white matter (NAWM) in the contralateral hemisphere using the centrum semiovale, more precisely craniocaudally oriented corona radiata fibers, for obtaining both nADC and nFA to obtain substantial representative tissue for mean FA-NAWM and mean ADC-NAWM values. This assumption for the normalization is supported by previous studies showing that normalized ADC values are more standardized than non-normalized values (15) and that ADC and FA values may be affected by age of the patients and tumor location in the brain (18). Normalized diffusion metrics were defined accordingly as nADC = ADC/ADC-NAWM and nFA = FA/FA-NAWM.

### Table 2. Median Values With Range and Minimum and Maximum Values for Evaluated Biometrics for HGG, LGG, and MET

<table>
<thead>
<tr>
<th>Groups</th>
<th>Vol-T (mL)</th>
<th>Vol-E (mL)</th>
<th>Vol-E/Vol-T</th>
<th>nFA-T</th>
<th>nADC-T</th>
<th>nFA-E</th>
<th>nADC-E</th>
<th>nCBF-T</th>
<th>nCBV-T</th>
<th>nCBF-E</th>
<th>nCBV-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Median</td>
<td>40.25</td>
<td>26.58</td>
<td>0.83</td>
<td>0.40</td>
<td>1.52</td>
<td>0.47</td>
<td>1.49</td>
<td>7.91</td>
<td>6.65</td>
<td>0.59</td>
<td>0.68</td>
</tr>
<tr>
<td>Range</td>
<td>93.40</td>
<td>155.79</td>
<td>9.40</td>
<td>0.41</td>
<td>0.93</td>
<td>0.33</td>
<td>1.49</td>
<td>9.63</td>
<td>5.75</td>
<td>0.93</td>
<td>1.01</td>
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<td>0.46</td>
<td>0.01</td>
<td>0.15</td>
<td>1.16</td>
<td>0.23</td>
<td>1.13</td>
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<td>2.70</td>
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<tr>
<td>Maximum</td>
<td>94.96</td>
<td>156.25</td>
<td>9.41</td>
<td>0.56</td>
<td>2.09</td>
<td>0.56</td>
<td>2.63</td>
<td>12.18</td>
<td>8.45</td>
<td>1.33</td>
<td>1.35</td>
</tr>
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<td>LGG</td>
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<td></td>
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<td>Median</td>
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<td>10.15</td>
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<td>0.25</td>
<td>1.86</td>
<td>0.44</td>
<td>1.46</td>
<td>2.80</td>
<td>3.33</td>
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<td>0.94</td>
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<td>Range</td>
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<td>0.16</td>
<td>0.85</td>
<td>0.24</td>
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<td>4.97</td>
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<td>3.06</td>
<td>0.16</td>
<td>0.19</td>
<td>1.67</td>
<td>0.32</td>
<td>1.39</td>
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<td>1.26</td>
<td>0.52</td>
<td>0.54</td>
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<tr>
<td>Maximum</td>
<td>67.14</td>
<td>41.13</td>
<td>1.01</td>
<td>0.35</td>
<td>2.52</td>
<td>0.56</td>
<td>1.96</td>
<td>3.79</td>
<td>6.22</td>
<td>1.86</td>
<td>1.74</td>
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<tr>
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</tr>
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<td>50.28</td>
<td>2.88</td>
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<td>0.41</td>
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<td>7.70</td>
<td>6.91</td>
<td>0.73</td>
<td>0.86</td>
</tr>
<tr>
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<td>6.51</td>
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<td>1.14</td>
<td>0.24</td>
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<td>8.17</td>
<td>9.29</td>
<td>1.12</td>
<td>1.95</td>
</tr>
<tr>
<td>Minimum</td>
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<td>2.20</td>
<td>0.33</td>
<td>0.18</td>
<td>1.14</td>
<td>0.27</td>
<td>1.39</td>
<td>2.49</td>
<td>3.55</td>
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<tr>
<td>Maximum</td>
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<td>111.58</td>
<td>6.84</td>
<td>0.49</td>
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<td>10.67</td>
<td>12.84</td>
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</tr>
<tr>
<td>Median</td>
<td>16.36</td>
<td>26.39</td>
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<td>0.31</td>
<td>1.60</td>
<td>0.43</td>
<td>1.60</td>
<td>6.67</td>
<td>6.25</td>
<td>0.83</td>
<td>0.78</td>
</tr>
<tr>
<td>Range</td>
<td>93.40</td>
<td>155.79</td>
<td>9.40</td>
<td>0.41</td>
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<td>0.33</td>
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<td>10.71</td>
<td>11.58</td>
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<td>1.95</td>
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<td>Minimum</td>
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<td>0.01</td>
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<td>1.47</td>
<td>1.26</td>
<td>0.40</td>
<td>0.31</td>
</tr>
<tr>
<td>Maximum</td>
<td>94.96</td>
<td>156.25</td>
<td>9.41</td>
<td>0.56</td>
<td>2.52</td>
<td>0.56</td>
<td>2.68</td>
<td>12.18</td>
<td>12.84</td>
<td>1.86</td>
<td>2.25</td>
</tr>
</tbody>
</table>

Abbreviations: HGG, high-grade gliomas; LGG, low-grade gliomas; MET, metastases; nFA-T, normalized fractional anisotropy-tumor; nADC-T, normalized ADC-tumor; nFA-E, normalized fractional anisotropy-edema; nADC-E, normalized ADC-edema; nCBF-T, normalized cerebral blood flow-tumor; nCBV-T, normalized cerebral blood volume-tumor; nCBF-E, nCBF-edema; nCBV-E, nCBV-edema.
**Perfusion Metrics.** Areas with highest CBF and CBV values in tumor and edema areas were obtained by analysis of color-coded blood flow and volume maps as previously described (19). As suggested and used previously (20–22), four ellipsoid ROIs, each of size 18–20 pixels, were placed in areas of highest perfusion for each patient with reference to morphological images while avoiding necrotic, cystic, and hemorrhagic areas for maximum CBF-T and CBV-T values. The ellipsoid ROI with the highest CBF-T and CBV-T was then chosen to represent the maximum value; the other 3 ROIs were discarded. The maximum CBV-E and CBF-E values were obtained by means of an identical methodology with the exception of using a smaller rectangular ROI in edematous tissue versus tumor, that is, 1 rectangular ROI of 4 pixels on 1 section per patient.

The maximum CBV-T and CBV-E and CBF-T and CBF-E values were normalized to normal-appearing contralateral white matter using 1 rectangular ROI (38–40 pixels) placed in the contralateral hemisphere in the normal-appearing periventricular white matter in 1 section and by dividing tumor and edema values for each biometric by corresponding values of normal-appearing contralateral white matter, for example, nCBV-T = CBV-T/CBV-NAWM, as previously described (20). Because the present perfusion method does not allow for absolute values of CBV and CBF, the relative CBV and CBF value was calculated according to the standard method (23).

**Statistical Analysis**

Statistical analysis was performed with SPSS® v. 23.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). A normality plot with a Shapiro–Wilks test was performed and Kruskal–Wallis test was used for pairwise comparison between the groups and biometrics found to have statistically significant differences with Kruskal–Wallis H test. A binary logistic regression model was then used and an ROC analysis and univariate and multivariate analyses were performed with sensitivity and specificity calculated for each significant biometric. A multiple logistic regression analysis was performed and the probabilities were used in the ROC analysis.

Area under the curve (AUC), specificity, and sensitivity were used as indicators of performance for each ROC analysis (25). Finally, a Kaplan–Meier survival analysis was performed between the 3 groups. Statistical significance was set to P-value <.05.

**RESULTS**

Table 1 shows the demographics of the 43 patients included in this study. Of the 43 included, 4 patients with HGG were not evaluated for all biometrics because of the following technical issues: data were nonobtainable because of not performed or technical issues with selected sequences (FLAIR, nADC, nFA, nCBV, and nCBF) on the initial preoperative MRI examination (3 subjects) and extensive hemorrhagic volume in peritumoral edematous tissue for nCBF-E and nCBV-E (1 subject).

**Mean Time to Progression and Overall Mean Survival**

MTP for patients with HGG was 172 days (n = 18; 95% CI 7–32) was 20.1 months (Table 1). Differences in MTP for patients with LGG was 211 days (n = 4). The Kaplan–Meier survival analysis showed that there were significant differences between the 3 groups with regard to OS; log rank, Breslow, Tarone–Ware P-value <.14; 0.01 and .01, respectively. OS for HGG (n = 18; 95% CI 14–23) was 18.7 months, for LGG (n = 10; 95% CI 34–57) was 46.2 months, and for MET (n = 15; 95% CI 7–32) was 20.1 months (Table 1). Differences in MTP
between HGG and LGG could not be statistically evaluated owing to the sample consisting of fewer patients with LGG (n = 4).

**Biometrics**

Median, minimum, and maximum values for the evaluated biometrics are given for the 3 groups of HGG, LGG, and MET in Table 2. The Kruskal–Wallis H testing showed no significant differences between HGG, LGG, and MET for the following variables: Vol-T, nFA-T, and nFA-E and nCBV-E (Table 3). Pairwise differences between HGG, LGG, and MET for the following variables: Vol-E, Vol-E/Vol-T, nADC-T, nADC-E, nCBF-T, and nCBV-T was found to be effect size for the 3 groups and Vol-E, Vol-E/Vol-T, nADC-T, nADC-E, nCBF-T, and nCBV-T showed a significant predictive ability for all 4 biometrics. However, nCBF-T (AUC = 0.95; P-value <.001) had the highest predictive capacity with a cutoff value of 4.12, sensitivity of 93.3%, and specificity of 100% (Figure 2, A and B; Table 7).

**Post Hoc Analysis**

Bonferroni adjustment with a corrected alpha was performed and a conservative significance level of P-value <.016 (~0.0166) was chosen for post hoc testing. nADC-T, nCBF-T, nCBV-T, and nCBF-E in HGG differed significantly compared with LGG (Table 4). Further, nADC-E in HGG was significantly lower than that in MET (P = 0.015) with a cutoff value of 4.35 AUC (0.95; P-value <.001), sensitivity of 93.3%, and specificity of 100%. In addition, Vol-E, Vol-E/Vol-T, nADC-T, nCBF-T, nCBV-T, and nCBF-E in LGG differed significantly compared with those in MET (Table 6). For specific values, see Table 2.

**Binary Logistic Regression Model**

The binary logistic regression model for HGG and LGG showed a P-value of <.001 for the model in the Omnibus tests and a Nagelkerke $R^2 = 0.87$, as well as P-values of <.010, <.003, <.007, and <.002 for Vol-E, Vol-E/Vol-T, nADC-T, nADC-E, nCBF-T, and nCBV-T, respectively. For LGG and MET, the binary logistic model showed a P-value of <.001 for the model in the Omnibus tests and a Nagelkerke $R^2 = 0.87$, as well as P-values of <.010, <.003, <.007, <.001, and <.003 for Vol-E, Vol-E/Vol-T, nADC-T, nADC-E, nCBF-T, and nCBV-T, respectively. Statistical significant P-values and high Nagelkerke $R^2$ values disclosed that the model was adequate for the prediction of tumor type, which was also strengthened by the fact that 100% of the variance in the outcome was predicted for LGG and HGG by the statistically significant predictors, namely, nADC-T, nCBF-T, nCBF-E, and nCBV-T. In addition, Vol-E, Vol-E/Vol-T, nADC-T, nCBF-T, nCBV-T, and nCBF-E in LGG differed significantly compared with those in MET (Table 6).

### Table 5. Comparison Between HGG and MET Using Mann–Whitney U Test for HGG and MET on Previous Statistical Significant Biometrics

<table>
<thead>
<tr>
<th></th>
<th>Vol-E (mL)</th>
<th>Vol-E/Vol T</th>
<th>nADC-T</th>
<th>nADC-E</th>
<th>nCBF-T</th>
<th>nCBV-T</th>
<th>nCBF-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann–Whitney U</td>
<td>103.00</td>
<td>85.00</td>
<td>116.00</td>
<td>58.00</td>
<td>92.00</td>
<td>100.00</td>
<td>97.00</td>
</tr>
<tr>
<td>P-value &lt;</td>
<td>0.355</td>
<td>0.109</td>
<td>0.874</td>
<td>0.014</td>
<td>0.395</td>
<td>0.604</td>
<td>0.727</td>
</tr>
</tbody>
</table>

Abbreviations: HGG, high-grade gliomas; LGG, low-grade gliomas; MET, metastases; nADC-T, normalized-ADC-tumor; nADC-E, normalized-ADC-edema; nCBF-T, normalized cerebral blood flow-tumor; nCBV-T, normalized cerebral blood volume-tumor; nCBF-E, nCBF-edema.

Significance after Bonferroni adjustment set at P-value <.016.

### Table 6. Comparison Between LGG and MET Using Mann–Whitney U Test Performed for LGG and MET on Previous Statistically Significant Biometrics

<table>
<thead>
<tr>
<th></th>
<th>Vol-E (mL)</th>
<th>Vol-E/Vol T</th>
<th>nADC-T</th>
<th>nADC-E</th>
<th>nCBF-T</th>
<th>nCBV-T</th>
<th>nCBF-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann–Whitney U</td>
<td>29.00</td>
<td>13.00</td>
<td>15.00</td>
<td>28.00</td>
<td>8.00</td>
<td>19.00</td>
<td>34.00</td>
</tr>
<tr>
<td>P-value &lt;</td>
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<td>0.001</td>
<td>0.001</td>
<td>0.009</td>
<td>0.001</td>
<td>0.002</td>
<td>0.023</td>
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</tbody>
</table>

Abbreviations: HGG, high-grade gliomas; LGG, low-grade gliomas; MET, metastases; nADC-T, normalized-ADC-tumor; nADC-E, normalized-ADC-edema; nCBF-T, normalized cerebral blood flow-tumor; nCBV-T, normalized cerebral blood volume-tumor; nCBF-E, nCBF-edema.

Significance after Bonferroni adjustment set at P-value <.016.
pared with nCBF-T, the biometrics Vol-E/Vol-T and nCBV-T showed equal specificity of 100%, albeit a lower AUC (0.91; $P$-value $<.001$) and lower sensitivity (80% and 60%, respectively) (Figure 4, A and B; Table 7).

Multivariate ROC analysis with combined significant biometrics for discrepancy between LGG and MET and biometrics Vol-E, Vol-E/Vol-T, nADC-T, nADC-E, nCBF-T, and nCBV-T (AUC = 0.95; $P$-value $<.001$) with a probability cutoff value of 0.50, generated by the logistic regression model, showed a sensitivity of 93% and a specificity of 100% in differentiation between HGG and LGG (Figure 5B; Table 7).

The cutoff values for differentiation between HGG and LGG, HGG and MET, and LGG and MET are presented in Table 7.

**DISCUSSION**

In this present study, significant differences between normalized values of volumetric, perfusion, and diffusion biometrics are shown in the differentiation between LGG, HGG, and MET. Cutoff values are proposed in Table 7. The most prominent cutoff values for distinction between HGG/LGG and LGG/MET are the combined biometrics of nADC-T, nCBF-T, nCBV-T, and nCBF-E with cut-off value of 0.50 for prediction probability, sensitivity of 100%, and specificity of 100% in differentiation between HGG and LGG (Figure 5B; Table 7).

Table 7. ROC Analysis Performed on Biometrics for HGG, LGG, and MET

<table>
<thead>
<tr>
<th>Group &amp; Biometric</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Cutoff Value</th>
<th>AUC (Area Under the Curve)</th>
<th>95 % CI (Confidence Interval)</th>
<th>$P$-Value</th>
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</thead>
<tbody>
<tr>
<td>HGG/LGG</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>nADC-T</td>
<td>85.7</td>
<td>80</td>
<td>1.76</td>
<td>0.87</td>
<td>0.73-1.00</td>
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<tr>
<td>nCBF-T</td>
<td>93.3</td>
<td>100</td>
<td>4.12</td>
<td>0.95</td>
<td>0.86-1.00</td>
<td>$&lt;.001$</td>
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<td>nCBV-T</td>
<td>80</td>
<td>90</td>
<td>6.06</td>
<td>0.91</td>
<td>0.79-1.00</td>
<td>$&lt;.001$</td>
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<td>nCBF-E</td>
<td>92.9</td>
<td>70</td>
<td>1.03</td>
<td>0.82</td>
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<tr>
<td>Combined biometrics$^a$</td>
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<td>100</td>
<td>0.50*</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>$&lt;.001$</td>
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<tr>
<td>HGG/MET</td>
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<tr>
<td>nADCE</td>
<td>68.8</td>
<td>80</td>
<td>1.63</td>
<td>0.76</td>
<td>0.58-0.94</td>
<td>$&lt;.015$</td>
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<tr>
<td>LGG/MET</td>
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</tr>
<tr>
<td>Vol-E (mL)</td>
<td>73.3</td>
<td>90</td>
<td>22.39</td>
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<tr>
<td>Vol-E/Vol-T</td>
<td>80</td>
<td>100</td>
<td>1.05</td>
<td>0.91</td>
<td>0.80-1.00</td>
<td>$&lt;.001$</td>
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<tr>
<td>nADC-T</td>
<td>86.7</td>
<td>90</td>
<td>1.71</td>
<td>0.90</td>
<td>0.77-1.00</td>
<td>$&lt;.001$</td>
</tr>
<tr>
<td>nADC-E</td>
<td>80</td>
<td>90</td>
<td>1.62</td>
<td>0.81</td>
<td>0.63-1.00</td>
<td>$&lt;.010$</td>
</tr>
<tr>
<td>nCBF-T</td>
<td>93.3</td>
<td>100</td>
<td>4.35</td>
<td>0.95</td>
<td>0.84-1.00</td>
<td>$&lt;.001$</td>
</tr>
<tr>
<td>nCBV-T</td>
<td>60</td>
<td>100</td>
<td>6.37</td>
<td>0.87</td>
<td>0.74-1.00</td>
<td>$&lt;.002$</td>
</tr>
<tr>
<td>Combined biometrics$^b$</td>
<td>93.3</td>
<td>100</td>
<td>0.60*</td>
<td>0.96</td>
<td>0.88-1.00</td>
<td>$&lt;.001$</td>
</tr>
</tbody>
</table>

Abbreviations: receiver operating characteristic; HGG, high-grade gliomas; LGG, low-grade gliomas; MET, metastases; nFA-T, normalized fractional anisotropy-tumor; nADC-T, normalized-ADC-tumor; nFA-E, normalized fractional anisotropy-edema; nADC-E, normalized-ADC-edema; nCBF-T, normalized cerebral blood flow-tumor; nCBV-T, normalized cerebral blood volume-tumor; nCBF-E, nCBF-edema; nCBV-E, nCBV-edema.

Sensitivity, specificity, cutoff value, AUC, 95% confidence interval and $P$-value; significance level set at $P$-value $<.05$.

$^*$ Probability cutoff value generated by regression model.

$^a$ Combination of nADC-T, nCBF-T, nCBV-T, and nCBF-E.

$^b$ Combination of Vol-E, Vol-E/Vol-T, nADC-T, nADC-E, nCBF-T, and nCBV-T.

Figure 2. ROC analysis for nADC-T and nCBF-E (A) and nCBF-T and nCBV-T (B) for distinguishing between high-grade glioma (HGG) and low-grade glioma (LGG).
combined biometrics of Vol-E, Vol-E/Vol-T, nADC-T, nADC-E, nCBF-T, nCBV-T with cut-off value of 0.60 for LGG/MET, respectively. In addition, nCBF-T is the best single biometric, with a cutoff value of 4.12 for HGG/LGG and 4.35 for LGG/MET, resulting in a sensitivity of 93.3% and a specificity of 100% for both these groups.

The imaging characteristics of HGG and MET can be similar, as both may present with a ring enhancing partly cystic or necrotic lesion and surrounding edema (11). This can, particularly in cases of unknown primary cancer to support the diagnosis metastasis, be a diagnostic challenge. In addition, the differentiation between HGG and LGG cannot solely depend on the presence or absence of contrast enhancement (4). Therefore, a need exists for more accurate diagnostic tools and methods in addition to conventional MRI to improve radiological differentiation between intracranial lesions, as this may have a clinical impact in terms of treatment choice and overall prognosis for the patients (3, 12). The present multiparametric study has shown, when comparing the best single diagnostic biometric with the integrated approach, that the multiparametric approach exhibits higher sensitivity and AUC for differentiation between HGG and LGG and a higher AUC for differentiation between MET and LGG. In essence, the present study confirms the usability of volume, perfusion, and diffusion metrics for differential diagnosis in patients with primary or secondary brain tumors.

This is in accordance with some previous studies that have reported the ability of both biometrics and conventional MRI for differentiation between LGG and HGG, with some providing sensitivity and specificity for ADC, CBV, CBF, and FA (12). In addition, a previous meta-analysis study reported that the best differentiator between LGG and HGG is CBV-T (15). Our study showed that nCBF-T is the single best biometric for differentiation between LGG and HGG and between LGG and MET, whereas nADC-E, even if weak, is the sole biometric that can differentiate between HGG and MET. However, when combining imaging biometrics from both perfusion and diffusion measures such as nADC-T, nCBF-T, nCBV-T, and nCBF-E, a sensitivity and specificity of 100% can be achieved in distinguishing HGG from LGG.

Our findings of lower nCBV and nCBF in LGG compared with those in HGG are in accordance with previous studies (19, 26). The present study’s ROC analysis when combining, in our case, nADC-T, nCBF-T, nCBF-E and nCBV-T, yields an ROC curve with AUC = 1.00 (P-value <.001) with a sensitivity and specificity of 100% to differentiate between HGG and LGG. This is well in accordance with the accuracy for the combination of nCBF-T and nCBV-T, with a sensitivity of 100% and a specificity

![Figure 3. Receiver operating characteristic (ROC) analysis for normalized-ADC-edema (nADC-E) for distinguishing between HGG and MET](image)

![Figure 4. ROC analysis for Vol-E, Vol-E/Vol-T, nADC-E, nCBF-T, and nCBV-T (A) and nADC-T for distinguishing between LGG and MET (B).](image)
of 90.9% and AUC = 0.992, reported in a previous study (19), as well as other studies that have shown that nCBF and nCBV have the highest specificity and sensitivity in differentiating between LGG and HGG (27–29).

A significant difference within edematous tissue between HGG and LGG was the presence of only reduced nCBF values in the peritumoral edematous tissue in the LGG compared with that in the HGG. A possible explanation for the differences may be that perfusion may be reduced owing to an increase in the local pressure exerted upon vasculature because of fluid leakage into an enclosed space as suggested by some authors (30, 31). HGG showed the highest median Vol-T (40.25 mL), the lowest Vol-E (26.58 mL), and the highest nCBF-T (7.91). Intratumoral compressive growth-induced stress results not only in the formation of necrosis within the tumor interior but also deforms and compresses vessels. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium presses vessels. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium. Defect tumor vessels owing to angiogenesis result in hyperpermeability and increased fluid flux into the interstitium.

In the present study, combining VOL-E, VOL-E/VOL-T, nADC-T, nADC-E, nCBF-T, nCBV-T yielded a sensitivity of 93.3% but still 100% specificity for distinguishing LGG from MET. Even though nCBF-T also reached the same level of accuracy with regards to sensitivity and specificity, the combined approach had higher AUC, suggesting that the combined approach is more plausible to use.

Although perfusion metrics such as nCBV and nCBF in both tumor and edema could differentiate between HGG and LGG, only nADC in the tumor (nADC-T) could distinguish HGG from LGG and MET. Cellular density is correlated with the pathological grades of glioma, that is, glioma with a higher cell density has lower ADC values than gliomas with a lower cell density (33). This may explain our finding of significantly higher nADC-T in LGG compared with that in HGG and MET. As we excluded cystic, hemorrhagic, or necrotic parts in our measurement, we can speculate that higher nADC values imply less density of cells in selected volumes of tissue in LGG and higher cell density in the HGG, reflecting the lower nADC-T in HGG when compared with LGG. Also, the similar median values of nADC-T for MET and HGG imply that these 2 groups have a similar cellular density in the central parts of the tumor. However, the median nADC-E being higher in MET than in HGG can be explained by MET having few pathological cellular components in the surrounding perilesional edema tissue secondary to higher tissue displacement and increased water content (34). In addition, it has been shown that MET had higher ADC in peritumoral necrosis than HGG, suggestive of higher fluid production/extravasation (30). At the same time, there is also the possibility that the higher ADC in MET is because a more rapid fluid expansion per time unit than HGG and LGG in the early phases of tumor manifestation in the brain; this is further supported by MET also having the largest Vol-E (50.28 mL) and the largest Vol-E/Vol-T ratio (2.88) of the 3 groups. Our findings of highest diffusion in the perilesional edema of MET compared with HGG is in accordance with the findings of a previous study (35).

Contradictory to the present and most previous studies (35, 36), significant differences between maximum intratumor FA values between LGG and HGG have been reported in 1 study (37). However, the result from that study might be questionable, as the authors did not correlate their maximum FA values with maximum FA values for normal tissue, and thus, they did not adjust for intraindividual variations. In the present study, comparison was made with normalized values to give the best inter- and intraobserver reproducibility as reported previously (20–22). Minor differences between our study and previous studies in terms of specificity may be because of inconsistencies in the sample size or methodology, in which some studies chose not to normalize biometrics with contralateral normal-appearing tissue. This may have implications, as some biometrics that are not significantly differing between groups may be reported as such owing to intraindividual differences.

There are some incongruences in the literature with regard to differentiation between MET and HGG by means of nCBV-T and nADC-T, as some previous studies have shown difficulties in differentiating HGG from MET using quantitative biometrics such as nCBV-T (30, 38), and other studies have shown that normalized CBV in perilesional edema can help differentiate MET from HGG with 90% sensitivity and 100% specificity (29).
Furthermore, several other studies have shown higher ADC-values in perilesional edema of MET compared with the corresponding tissue in HGG; however, these studies did not provide sensitivity, specificity, or cutoff values for the distinction between tumor types (30, 39). Particularly surprising were the findings in a larger cohort of patients with MET, which showed that nADC-T and n-CBV-T values do not differ between histologically different MET (40). Furthermore, a meta-study concludes that MET cannot be differentiated reliably from HGG on the basis of ADC and CBV (15). This present study found that only nADC-E could distinguish HGG from MET.

In contrast to the difficulties in differentiating HGG from MET, several biometrics investigated here differentiated LGG from MET. Vol-E, Vol-E/Vol-T, nADC-T, and nADC-E, as well as nCBF-T and n-CBV-T, can all be used for differential diagnosis between LGG and MET. Findings, which are supported by some previous studies, showed significantly lower nCBV in LGG compared with MET and HGG and higher minimum ADC levels in LGG compared with MET (15, 41).

Finally, it is acknowledged that the present study has some limitations such as the relatively small group sizes; even though the size is adequate for performing the statistical evaluations, one should not exclude the possibility that sampling errors may occur or that tumors have nonlinear behavior or growth. At the time of this study, IDH was not assessed in all patients with glioblastoma. IDH mutations are, therefore, not included as a confounder in the analysis. Histopathological diagnosis of the tumors was presumed to be 100% correct.

We have not correlated our measurements with the results of a possible treatment with steroids, a drug that may have some effect on the perfusion metrics and reduce the perilesional edema.

In addition, the probabilities generated by the logistic regression model used for the ROC analysis, the chosen method, that is, machine learning algorithm, cannot generate further cutoff values, that is, the exact cutoff values in each biometric in the combined analysis, than is already provided via the ROC analysis, that is, probability values (Table 7).

There may be further value in the proposed model for predictions on the prognosis of OS and MTP; albeit this being out of the scope of this study, it is reasonable to externally validate the model on a larger cohort of patients and conduct follow-ups with regard to OS and MTP.

**CONCLUSION**

The present study clearly shows and confirms the advantages of an integrative approach by measuring the volume, perfusion, and diffusion metrics. Such an integrated approach can, as presented in this study, yield cutoff values and improve sensitivity and specificity while aiding the clinician in preoperative differentiation between LGG, HGG, and MET. Furthermore, this study adds to the growing body of evidence in a clinical field in need of validation and standardization.

**ACKNOWLEDGEMENTS**

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Evaluation of Brain Tumors by Multibiometric MRI


Feature Tracking Cardiac MRI Reveals Abnormalities in Ventricular Function in Patients With Bicuspid Aortic Valve and Preserved Ejection Fraction

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Key Words: Bicuspid aortic valve, diastolic dysfunction, cardiac MRI, feature-tracking, strain
Abbreviations: Bicuspid aortic valve (BAV), feature-tracking cardiovascular magnetic resonance (CMR-FT), ejection fraction (EF), electrocardiogram (ECG), magnetic resonance imaging (MRI), steady-state free precession (SSFP)

Subclinical systolic and diastolic left ventricular (LV) dysfunction has been reported in previous echocardiographic studies on congenital bicuspid aortic valve (BAV). Patients with BAV commonly undergo evaluation with magnetic resonance imaging, and feature-tracking cardiovascular magnetic resonance (CMR-FT) is an emerging technique that assesses myocardial strain using standard cine sequences. This study investigated differences in myocardial strain between patients with BAV with preserved ejection fraction (EF) and controls using CMR-FT. Patients with isolated BAV and preserved EF, who had previously undergone CMR (n = 42; mean age, 41.2 ± 13.9) were compared with controls (n = 19; 36.6 ± 9.8; P = .2). Investigational CMR-FT strain analysis software was used to measure circumferential systolic and diastolic strain values, as well as standard LV volumetric and functional parameters. The majority of patients with BAV had mild or no valve dysfunction, and LV myocardial mass end-diastolic volume indices were similar between groups. Peak diastolic circumferential strain rate was lower in patients with BAV than in controls (0.89 ± 0.27 vs 1.21 ± 0.21 s⁻¹, P = .003). After adjusting for covariates, only myocardial mass index was independently associated with peak circumferential systolic strain and diastolic strain rate. Feature-tracking CMR can identify abnormalities of LV strain in a clinical cohort of asymptomatic patients with BAV with preserved EF. Decreases in circumferential diastolic strain rate in patients with BAV suggest evidence of early diastolic dysfunction.

INTRODUCTION

Bicuspid aortic valve (BAV) is commonly identified in asymptomatic young adults with normal or mildly impaired valve function. Current clinical guidelines recommend these patients to undergo regular echocardiography for assessing valve and ventricular function, with surgery indicated only when the patient becomes symptomatic or has evidence of left dysfunction/dilation by imaging (1). The latency period from the time of diagnosis to the development of symptoms is often long and is characterized by progressive valvular obstruction and myocardial pressure overload (2). The typical ventricular adaptation to chronic pressure overload is myocardial hypertrophy, and although beneficial in maintaining left ventricular (LV) systolic function, hypertrophy is associated with deleterious chronic effects such as the development of myocardial fibrosis, decreased coronary blood flow reserve, impaired diastolic function, and increased risk of death from cardiovascular disease (2, 3). Specifically, the development of myocardial fibrosis has been proposed as a marker of chronic myocardial injury and can predict ventricular decompensation in patients with aortic stenosis (4, 5).

To improve the early detection of myocardial dysfunction, imaging-based techniques, including echocardiography-based techniques such as tissue Doppler imaging and speckle-tracking, and magnetic resonance imaging (MRI)-based techniques, including tagging for myocardial strain assessment and T1-mapping myocardial fibrosis assessment, have been developed for a detailed assessment of myocardial function. In brief, myocardial strain is a measurement of the myocardial deformation, related to shortening/lengthening and thickening of the myocardial fibers throughout the cardiac cycle, and it can be measured in three directions along the ventricular axis, namely, circumferential, longitudinal, and radial. By convention, higher degrees of shortening (ie, systolic contraction) and lengthening (ie, diastolic relaxation) are represented by more negative and positive

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values, respectively. Several recent studies of patients with BAV among whom speckle-tracking echocardiography was used have shown decreased systolic strain values despite preserved ejection fraction (EF) and lack of significant valve disease, suggesting that subclinical myocardial dysfunction exists in otherwise asymptomatic patients with BAV (6, 7). Furthermore, despite a well-established relationship between hypertrophy and diastolic dysfunction, and clearly demonstrated increased myocardial mass in asymptomatic patients with BAV, little has been reported about the role of hypertrophy in diastolic function in patients with BAV (8).

Feature-tracking cardiac magnetic resonance (CMR-FT) is a relatively new technique that, similar to speckle-tracking echocardiography, assesses ventricular function in detail by measuring a variety of strain parameters. CMR-FT allows strain analysis, a significant benefit, that uses standard steady-state free precession (SSFP) cine images obtained during clinical cardiac MRI examinations; therefore, unlike in tagging techniques, CMR-FT images can be retrospectively analyzed. CMR-FT has been previously used to assess ventricular function in a variety of diseases including myocardial ischemia, congenital heart disease, and nonischemic cardiomyopathy; however, few studies have used CMR-FT to assess ventricular function in either acquired or congenital aortic valve disease (9-11).

The aim of this study was to investigate the utility of CMR-FT in assessing LV function in a cohort of asymptomatic patients with congenital BAV who were undergoing clinical CMR evaluation, and to determine associations between strain parameters and traditional imaging and clinical parameters. Furthermore, we aim to identify differences in systolic and diastolic LV function between this cohort of patients with BAV and a group of controls by the use of the CMR-FT technique. We hypothesized that among patients with BAV with preserved EF, there are abnormalities of systolic and diastolic function that are not apparent by standard clinical imaging evaluation.

**MATERIALS AND METHODS**

**Patient Identification**

Electronic charts of the diagnostic radiology reports were reviewed at our institution from January 2005 through to August 2014; 77 patients with at least 1 echocardiography study, confirming the presence of BAV, and at least 1 clinical cardiac MRI examination that contained short-axis SSFP images covering the entire LV, were identified. Exclusion criteria for the study included age <18 years, LV EF of <50% by echocardiogram, history of aortic valve replacement, and suboptimal short-axis SSFP images (<20 frames/cardiac cycle). After application of the inclusion/exclusion criteria, 49 patients with BAV who were undergoing CMR surveillance were selected for the study. A waiver of informed consent was obtained from our institutional review board for the retrospective data analysis performed for this study, which was compliant with the Health Insurance Portability and Accountability Act. Similarly, 19 controls were identified over the same interval by a review of the clinical charts and radiology reports consisting of 5 healthy volunteers and 14 patients with CMR studies for clinical evaluation. All patients had normal CMR studies, and there was no evidence of confirmed cardiovascular disease on review of medical records. The indications for clinical CMR in the controls included evaluation for occult shunt (n = 5), arrhythmogenic right ventricular dysplasia in the setting of palpitations/family history (n = 6), and coronary anomaly in the setting of syncope (n = 3). Clinical and demographic data were obtained by a review of the relevant charts. A review of the clinical echocardiogram report closest in time to the CMR imaging aided the grading of aortic stenosis/insufficiency and diastolic dysfunction by means of echocardiography.

**MR Imaging Technique**

Scans were acquired at 1.5 Tesla Achieva (Philips Medical Systems, Best, The Netherlands), using a 5-channel surface cardiac coil. All patients had (ECG)-gated SSFP cine images in the short-axis plane covering the entirety of the LV to quantify ventricular size and function. The following are the typical imaging parameters: repetition time/echo time, 3.7/1.9 milliseconds; section thickness, 8 mm; gap, 0 mm; field of view, 340 mm; matrix, 244 × 245; phases per cardiac cycle, 16; signals acquired, 1; sensitivity encoding factor, 2; sections per breath hold, 2; and acquisition time per breath hold for a heart rate of 80 beats per minute, 15 seconds.

**LV Analysis**

Standard LV volumetric and functional analyses were performed by using commercially available cardiac MRI analysis software (cvi42®, Circle Cardiovascular Imaging Calgary, Canada) after LV endocardial and epicardial contours were segmented from base to apex on short-axis SSFP images at end diastole and end systole by use of the standard segmentation technique (12). Papillary muscles were excluded when measuring the myocardial mass and were included when measuring LV volumes. An observer (NSB) with 6 years of experience with CMR, who was blinded to the patient’s clinical and demographic information, performed the segmentation; however, blinding of BAV status during LV functional and volumetric assessment was not possible, as the aortic valve is visible on cine images being segmented for CMR-FT analysis. After ventricular segmentation, 2-dimensional tissue tracking analysis was performed on the short-axis SSFP images by use of an investigational software plugin (Tissue Tracking module, Circle Cardiovascular). In brief, the feature-tracking strain analysis involves using small windows to generate a pixel-intensity map/pattern for a small region of the myocardium on SSFP cine images, and then using algorithms to identify the most similar patterns of pixel-intensity on images from all subsequent images in the cardiac cycle, thus creating the ability to “track” a specific point in the myocardium over time. Detailed descriptions of the algorithms used by this and other software vendors remain proprietary. A more comprehensive review of the CMR-FT strain analysis technique is described in detail elsewhere (13), and a screenshot of the CMR-FT analysis software with superimposed displacement fields and strain curve analysis is shown in Figure 1. Myocardial tracking was visually assessed for adequacy, any apparent deviations of the tracking contours from the myocardial borders were corrected, and the tracking analysis was repeated. Multiple global circumferential LV strain parameters including, peak systolic strain, systolic strain rate (SR), diastolic SR, and systolic time to peak (TTP) strain were measured. Of note, systolic strain values are negative by convention, meaning that less negative peak systolic strain values indicate decreased ventricular con-
traction. For simplicity of measurement and interpretation, and given the global nature of aortic valve-related myocardial abnormalities, segmental strain data were not analyzed. Longitudinal strain parameters were not analyzed given that the horizontal long-axis SSFP images required for longitudinal strain assessment were available in only a minority of cases owing to the fact that our institutional aortic valve clinical CMR protocol did not include standard long-axis SSFP for a majority of the study period. Radial strain values were not analyzed owing to known issues of measurement inaccuracy with feature-tracking techniques (13).

Data Analysis and Statistics
Baseline characteristics were reported as mean ± SD for continuous variables and frequencies for categorical variables. Pearson correlations were used to assess associations between imaging variables and other clinical/demographic variables. Group means were compared using 2-tailed unpaired Welch unequal variances’ t-tests. Chi-square analysis and Fisher exact tests were used to evaluate difference in frequency of categorical variables. The threshold for statistical significance was prospectively set at P < .05. Pairwise correlation matrices were used to identify multicollinearity among predictor variables. Subsequently, parsimonious multiple linear regression models were used to identify independent predictors of peak systolic circumferential strain and peak diastolic strain rate among a group of potential predictor variables including age, history of hypertension, EF, myocardial mass index, and LV end-diastolic volume index and severity of aortic stenosis/insufficiency. Given the low frequency of significant aortic valve stenosis or insufficiency, valve dysfunction was analyzed as a binary variable with moderate-to-severe dysfunction considered as “significant” and none-to-mild dysfunction considered as “not significant.” All statistical analyses were performed using Stata 14.0 (StataCorp LP, College Station, TX).

RESULTS
Patient Characteristics
The average age of the patients with the BAV group was 41.2 ± 13.9 years and that for the controls was 36.6 ± 9.8 years (P = .15); male patients were marginally more in the BAV group (55% vs 39%, P = .26). There was a trend toward higher BSA (body surface area) among patients with BAV, which did not reach statistical significance (1.86 m² vs 1.74 m², P = .06). The majority of patients with BAV had either none/mild aortic stenosis (78%) and none/mild insufficiency (74%) by echocardiography. The majority of patients had no evidence of diastolic dysfunction by clinical echocardiography (81%). Patient characteristics are detailed in Table 1.

LV Parameters
There was a trend toward higher mean EF among the controls compared with patients with BAV (60.1% ± 6.0% vs 57.5% ± 4.3%, P = .10), although the mean EF in both groups was within the normal range. Heart rate was similar between patients with BAV and controls (63.6 ± 10.2 vs. 68.5 ± 8.1, P = .16). LV end-diastolic volume index, stroke volume index, and myocardial mass index were comparable between the 2 groups. Peak systolic circumferential strain was comparable between the patients with BAV and control groups (−20.0 ± 2.0% vs 19.6 ± 2.3%, P = .41); however, the mean peak diastolic strain rate was significantly lower in patients with BAV (0.89 ± 0.27 vs 1.21 ± 0.21 s⁻¹, P = .0003) (Figure 2). No significant differences were
observed between groups for circumferential systolic strain rate or time to peak strain. The statistical significance of these results did not change when patients with diastolic dysfunction by echocardiography were excluded from the analysis. LV parameters for each group are detailed in Table 2.

### Strain Parameter Correlations

Peak systolic circumferential strain showed a weak negative association with history of hypertension ($r = -0.33$, $P = .04$) and a moderate negative correlation with EF ($r = -0.49$, $P = .01$). In addition, there was a moderate positive correlation with myocardial mass index ($r = 0.51$) and a weak positive association with aortic stenosis severity ($r = 0.29$), although these associations did not reach predefined levels of statistical significance (both, $P = .06$). As a reminder, systolic strain values are negative by convention, meaning a positive correlation coefficient indicates a decrease in myocardial strain (eg, less negative values) with an increase in the clinical variable.

Peak diastolic circumferential strain rate showed moderate negative correlations with myocardial mass index ($r = -0.66$, $P = .003$) and LV end-diastolic volume index ($r = -0.5$, $P = .04$), as well as a weak-to-moderate positive correlation with heart rate ($r = 0.46$, $P = .05$). Additional weak correlations with peak diastolic circumferential strain rate were noted with a history of congenital heart disease ($r = 0.4$), and aortic insufficiency severity ($r = -0.4$) showed a weak correlation with peak diastolic strain rate.
although these correlations did not reach statistical significance. Complete correlation data are presented in Table 3.

Regression Analysis
Multiple linear regression analyses of peak systolic circumferential strain and diastolic strain rate were conducted including independent variables of age, heart rate, EF, aortic stenosis, aortic insufficiency, myocardial mass index, and LV end-diastolic volume index and history of hypertension. After adjusting for covariates, variables that were independently associated with peak systolic circumferential strain were myocardial mass index ($\beta = 0.064; \text{SE} = 0.025; 95\% \text{ CI} = 0.014, 0.114; P = .01$) and EF ($\beta = -0.16; \text{SE} = 0.058; 95\% \text{ CI} = -0.279, -0.044; P = .01$) Table 4. Similarly, after adjusting for covariates, the only variable that was independently associated with peak circumferential diastolic strain rate was myocardial mass index ($\beta = -0.019; \text{SE} = 0.008; 95\% \text{ CI} = 0.037, 0.000; P = .05$) Table 5.

DISCUSSION
The results of the present study show lower mean diastolic strain rate in a cohort of asymptomatic patients with BAV compared with controls, suggesting impaired diastolic relaxation, despite preserved EF. However, we did not find any significant abnormalities of systolic strain between patients with BAV and controls. Myocardial mass index had a moderate correlation with both peak circumferential systolic strain and diastolic strain rate, and after controlling for covariates, only myocardial mass index was independently associated with these strain parameters. Our findings suggest that CMR-FT strain analysis can detect myocardial dysfunction in asymptomatic patients with BAV in whom there is no evidence of ventricular dysfunction by routine clinical cardiac MRI techniques.

The bicuspid aortic valve is a complex spectrum of disease with genetic underpinnings, resulting in dysmorphic valve development and structural wall abnormalities of the ascending aorta that predispose to aneurysm development (14). LV dysfunction becomes clinically apparent in significant aortic valve disease. However, echocardiography studies have shown abnormal systolic and diastolic strain parameters in patients with mild or no valve dysfunction, suggesting that subclinical myocardial abnormalities exist in asymptomatic patients with BAV (7, 15, 16). Our results support these observations and lend further

### Table 2. Measured Left Ventricular Parameters

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls (n = 19)</th>
<th>Patients With BAV (n = 42)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>60.1 ± 6.0</td>
<td>57.5 ± 4.3</td>
<td>.10</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68.5 ± 8.1</td>
<td>63.6 ± 10.2</td>
<td>.16</td>
</tr>
<tr>
<td>Stroke volume index, n (%)</td>
<td>44.5 ± 13.3</td>
<td>39.8 ± 11.2</td>
<td>.19</td>
</tr>
<tr>
<td>LV EDVDI (m²)</td>
<td>74.7 ± 18.4</td>
<td>71.4 ± 18.9</td>
<td>.52</td>
</tr>
<tr>
<td>Myocardial mass index, g/m²</td>
<td>57.1 ± 17.0</td>
<td>56.7 ± 13.9</td>
<td>.94</td>
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<tr>
<td>Peak circumferential systolic strain, (%)</td>
<td>−19.6 ± 2.3</td>
<td>−20.1 ± 2.0</td>
<td>.41</td>
</tr>
<tr>
<td>Peak circumferential diastolic strain rate [s⁻¹]</td>
<td>1.21 ± 0.21</td>
<td>0.89 ± 0.27</td>
<td>.0003</td>
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</table>

### Table 3. Pearson Correlation Coefficients Between Strain Parameters and Clinical Variables in Patients With BAV

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Peak Circumferential Systolic Strain</th>
<th>Peak Circumferential Diastolic Strain Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson r</td>
<td>P-Value</td>
</tr>
<tr>
<td>Age</td>
<td>−0.06</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypertension</td>
<td>−0.33</td>
<td>0.04</td>
</tr>
<tr>
<td>Coarctation</td>
<td>−0.09</td>
<td>0.58</td>
</tr>
<tr>
<td>Congenital heart disease*</td>
<td>−0.07</td>
<td>0.68</td>
</tr>
<tr>
<td>Significant aortic stenosis</td>
<td>0.29</td>
<td>0.06</td>
</tr>
<tr>
<td>Significant aortic insufficiency</td>
<td>0.0</td>
<td>0.95</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>−0.49</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart rate</td>
<td>−0.06</td>
<td>0.73</td>
</tr>
<tr>
<td>Myocardial mass index</td>
<td>0.51</td>
<td>0.06</td>
</tr>
<tr>
<td>LV end-diastolic volume index</td>
<td>0.29</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Other than coarctation.
support for these echocardiographic observations using an MRI-based strain assessment technique.

Reduced EF—the traditional marker of a failing LV—is a relatively late finding along the path leading to myocardial decompensation. However, impaired diastolic function related to myocardial hypertrophy and fibrosis precedes systolic abnormalities and predicts surgical outcomes in patients with aortic stenosis (17, 18). Myocardial hypertrophy is known to be strongly associated with myocardial dysfunction and cardiovascular mortality. The cellular processes that lead to hypertrophy begin before clinical definitions of myocardial hypertrophy are reached, and are promoted by the increased afterload that results from fused valve leaflets, even if the valve function is classified as normal on echocardiography (19). Similar to our findings, others have observed increased LV myocardial mass among young patients with BAV with normal valve function, as well as increased myocardial interstitial fibrosis in patients with stenotic BAV, further highlighting the early deleterious effects on myocardial function that can occur with BAV (5, 8, 20).

While the mechanism of subclinical myocardial dysfunction remains an area of active research, our results further stress the potential prognostic importance of myocardial mass measurement, as it was the only variable that was associated with diastolic strain rate in our adjusted analysis. Patients with BAV have a variable clinical course, with some developing significant valve and ventricular dysfunction, while some remaining minimally symptomatic or asymptomatic throughout their life. Given this clinical variability, improved methods to detect subclinical disease and improve patient risk stratification are needed to achieve optimal treatment of patients with BAV before symptoms or overt signs of ventricular dysfunction develop. Diastolic function plays a significant role in the development of heart failure in patients with AS (21). Early detection of diastolic dysfunction could prompt changes in pharmacological treatment, such as initiation of angiotensin-converting enzyme inhibitors, or earlier surgical or transcatheter aortic valve replacement in the hopes of minimizing irreversible myocardial fibrosis (22). A recent study showed that preoperative assessment of diastolic strain rate with echocardiography predicated long-term postoperative mortality after surgical aortic valve replacement (23).

Although patients with BAV are most commonly evaluated with echocardiography, they are frequently referred for cardiac MRI/MRA, particularly when young (owing to concerns of radiation exposure) or if there are associated congenital heart abnormalities. An MRI-based method of assessing early LV dysfunction by using only standard SSFP cine images is attractive, particularly in the evaluation of diastolic function, where, unlike with echocardiography, there is currently no well-validated MRI assessment technique. Several studies have shown good agreement between echocardiographic speckle-tracking and CMR-FT techniques, although additional studies assessing the agreement between these two strain measurement techniques are required (11, 24).

### Table 4. Multilinear Regression Predictors of Peak Circumferential Systolic Strain

<table>
<thead>
<tr>
<th>Variable</th>
<th>β Coefficient</th>
<th>SE</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial mass index</td>
<td>0.064</td>
<td>0.025</td>
<td>0.014, 0.114</td>
<td>.01</td>
</tr>
<tr>
<td>Significant aortic stenosis</td>
<td>0.758</td>
<td>0.626</td>
<td>−0.519, 2.035</td>
<td>.24</td>
</tr>
<tr>
<td>Significant aortic insufficiency</td>
<td>−0.674</td>
<td>0.700</td>
<td>−2.093, 0.745</td>
<td>.34</td>
</tr>
<tr>
<td>LV end-diastolic volume index</td>
<td>−0.008</td>
<td>0.021</td>
<td>−0.051, 0.036</td>
<td>.72</td>
</tr>
<tr>
<td>Hypertension</td>
<td>−0.727</td>
<td>0.694</td>
<td>−2.141, 0.688</td>
<td>.30</td>
</tr>
<tr>
<td>Age</td>
<td>−0.001</td>
<td>0.017</td>
<td>−0.034, 0.035</td>
<td>.98</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>−0.162</td>
<td>0.058</td>
<td>−0.279, −0.044</td>
<td>.01</td>
</tr>
</tbody>
</table>

Overall model adjusted $R^2 = 0.44$.  

### Table 5. Multilinear Regression Predictors of Peak Diastolic Strain Rate With Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>β Coefficient</th>
<th>SE</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial mass index</td>
<td>−0.019</td>
<td>0.008</td>
<td>−0.037, −0.000</td>
<td>.05</td>
</tr>
<tr>
<td>Significant aortic stenosis</td>
<td>0.273</td>
<td>0.142</td>
<td>0.049, 0.594</td>
<td>.09</td>
</tr>
<tr>
<td>Significant aortic insufficiency</td>
<td>−0.075</td>
<td>0.162</td>
<td>−0.442, 0.292</td>
<td>.67</td>
</tr>
<tr>
<td>LV end-diastolic volume index</td>
<td>0.005</td>
<td>0.005</td>
<td>−0.006, 0.015</td>
<td>.33</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.304</td>
<td>0.242</td>
<td>−0.243, 0.851</td>
<td>.24</td>
</tr>
<tr>
<td>Age</td>
<td>0.003</td>
<td>0.006</td>
<td>−0.010, 0.015</td>
<td>.63</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.010</td>
<td>0.007</td>
<td>−0.006, 0.025</td>
<td>.21</td>
</tr>
</tbody>
</table>

Overall model adjusted $R^2 = 0.42$.
This study has several limitations. First, the BAV population was relatively small and heterogeneous; however, we made a concerted effort to control for variability in patient characteristics through adjusted analyses and exclusion of patients with clinically apparent myocardial dysfunction, and we feel that our cohort is representative of a typical population of patients with BAV referred for cardiac MRI at an academic medical center. Second, patients were not excluded on the basis of the presence of moderate/severe valve dysfunction, and while the majority of patients with BAV in our study did not have significant valve dysfunction, few did. The inclusion of such patients could contribute to the lower diastolic strain rate we observed in patients with BAV. However, interestingly, the degree of valve dysfunction did not show a significant association with diastolic strain rate on unadjusted or adjusted analyses, and our results suggest that increased myocardial mass—a downstream consequence of valve dysfunction—is more closely related to the deleterious pathomechanisms that result in diastolic dysfunction. Third, our strain analyses were limited to assessment of circumferential strain, given that the long-axis SSFP images required to measure longitudinal strain are not routinely acquired as part of our aortic valve CMR protocol. Finally, given the retrospective nature of our study, the strain measurements were based on CMR-FT, an emerging technique, with myocardial tagging techniques still considered the gold-standard for assessing myocardial strain. However, it is encouraging that our findings agree with those of other studies using echocardiographic techniques.

**CONCLUSION**

We found evidence of impaired diastolic function, in particular decreased diastolic strain rate, among a cohort of asymptomatic patients with BAV with preserved EF using CMR-FT imaging. Only myocardial mass was independently associated with circumferential diastolic strain rate on multivariate analysis, further supporting the role of myocardial hypertrophy in the development of ventricular dysfunction among patients with BAV. Considering the increasing availability of CMR, the lack of accepted CMR methods for assessing diastolic function and the fact that only standard cine images are required for analysis, CMR-FT may be a useful and practical tool for assessing ventricular function among patients with BAV. CMR-FT analysis shows promise as a method to improve risk stratification through the early detection of LV diastolic dysfunction for minimally symptomatic or asymptomatic patients with BAV prone to future ventricular dysfunction.

**REFERENCES**


Simultaneous Estimation of Bias and Resolution in PET Images With a Long-Lived “Pocket” Phantom System

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Key Words: quantitative positron emission tomography imaging, calibration, standardized uptake value, clinical trials

Abbreviations: Positron emission tomography (PET), computed tomography (CT), standardized uptake values (SUVs), full-width half-maximum (FWHM), point-spread function (PSF), ordered-subsets expectation-maximization (OSEM), 3D filtered-backprojection (FBP), regions of interest (ROIs)

A challenge in multicenter trials that use quantitative positron emission tomography (PET) imaging is the often unknown variability in PET image values, typically measured as standardized uptake values, introduced by intersite differences in global and resolution-dependent biases. We present a method for the simultaneous monitoring of scanner calibration and reconstructed image resolution on a per-scan basis using a PET/computed tomography (CT) “pocket” phantom. We use simulation and phantom studies to optimize the design and construction of the PET/CT pocket phantom (120 \times 30 \times 30 \text{ mm}). We then evaluate the performance of the PET/CT pocket phantom and accompanying software used alongside an anthropomorphic phantom when known variations in global bias (\pm 20\%, \pm 40\%) and resolution (3-, 6-, and 12-mm postreconstruction filters) are introduced. The resulting prototype PET/CT pocket phantom design uses 3 long-lived sources (15-mm diameter) containing germanium-68 and a CT contrast agent in an epoxy matrix. Activity concentrations varied from 30 to 190 kBq/mL. The pocket phantom software can accurately estimate global bias and can detect changes in resolution in measured phantom images. The pocket phantom is small enough to be scanned with patients and can potentially be used on a per-scan basis for quality assurance for clinical trials and quantitative PET imaging in general. Further studies are being performed to evaluate its performance under variations in clinical conditions that occur in practice.

INTRODUCTION

In oncology clinical trials and clinical practice, estimation of standardized uptake values (SUVs) of malignant lesions in positron emission tomography (PET) images can be used to assess response to therapy (1-6). Evaluation of response on a per-patient basis is central to the concept of precision medicine, which is prevention and treatment strategies that take individual variability into account (7). However, measured SUVs have a large degree of variability owing to physical and biological sources of error, as well as variations in image acquisition, processing, and analysis (8-10).

Important sources of variability are global shifts in SUVs due to scanner calibrations, operator error, or other reasons. During calibration, scanner sensitivity is typically measured by computing the number that scales PET images in arbitrary scanner units to match the known radiotracer concentration. SUV bias due to this scale factor, or calibration bias, is unstable even when measurements are repeated at a single site (11, 12). Further, biases of key factors in the computation of SUVs, from PET scanners and dose calibrators, are not correlated and thus do not cancel out (11, 13).

A second important source of variability in PET SUVs is a size-dependent bias caused by resolution loss, often called the partial volume error (or effect) (14, 15). This is due to a combination of the intrinsic resolution of the PET acquisition (typically leading to 5-mm full-width half-maximum [FWHM] image resolution) and smoothing applied during image reconstruction to suppress noise. In addition, this bias increases as object size decreases, leading to the well-known recovery coefficient curves (14).

Many methods have been proposed for correction of partial volume effects (15), but attempts to recover signal lost in the imaging process are often constrained either by noise amplification (if they aim to restore high spatial frequencies) or the requirement that the exact lesion geometry and the scanner’s resolution be known, so that the fraction of the lost signal can be estimated.
determined. In practice, resolution is often unknown because of its complicated dependence on both user-selected parameters, which vary widely in practice (16-18), and variations in the image reconstruction methods, which are both proprietary and scanner-specific.

Although best-case PET image resolution is on the order of 5-mm FWHM, the final image resolution in practice is typically on the order of 10-mm FWHM or more. This means that a homogeneous spherical lesion would need to be larger than roughly 30 mm in diameter to avoid SUV bias at the lesion’s center. For objects <30 mm in diameter, it is not possible to tell if a measured bias is caused by resolution effects, global calibration effects, or a combination of the 2. These effects are illustrated in Figure 1 for the 20-mm sphere. This confounding mix of biases has likely hindered the use of small calibration sources in PET scanning, even though the idea has been proposed anecdotally for several decades.

These biases are important, as both scanner bias and image resolution are prone to vary, particularly in multicenter studies. Both will contribute to increased SUV variance if they are not carefully monitored. This can reduce study power in clinical trials that use SUVs as biomarkers (19).

In this study, we develop and evaluate a “pocket phantom” system using a source small enough to be imaged with a patient, which provides simultaneous estimation of the global bias and the final resolution of the image. “Pocket” connotes the compactness of the phantom—small enough to fit in one’s pocket—compared with current quality control phantoms. First we describe the algorithm used to estimate global bias and resolution. We then use simulation and phantom studies to optimize the design and construction of the PET/computed tomography (CT) pocket phantom. We then evaluate the performance of the PET/CT pocket phantom in practice when imaged alongside an anthropomorphic phantom and propose a method for the correction of SUVs in biased images.

**METHODOLOGY**

**Pocket Phantom Estimator Method**

The pocket phantom estimation process is summarized in Figure 2. The prototype, shown in Figure 3, borrows some features, including overall geometry, from a CT-specific phantom that also used spherical inclusions to estimate image properties (20). The phantom contains spherical radioactive regions of known size and activity. The phantom active regions contain solid epoxy...
infused with $^{68}$Germanium/$^{68}$Gallium ($^{68}$Ge/$^{68}$Ga). This provides 2 advantages. First, the half-life of $^{68}$Ge, which decays to $^{68}$Ga, is 271 days. In turn, the $^{68}$Ga decays by positron emission with a half-life of 68 minutes. This decay scheme makes $^{68}$Ge/$^{68}$Ga a useful long-lived reference source, with replacement typically needed every 1–2 years. The phantom was manufactured with accurately specified radiotracer quantities that are National Institute of Standards and Technology (NIST)-traceable (21). Second, although a small phantom could be readily filled with $^{18}$F in solution, there would be an additional variance added by difficulties of accurate calibration and operator variability in filling the phantom.

The overall algorithm models bias and resolution effects to produce a synthetic PET image from the known phantom geometry. The parameters of this model are then adjusted iteratively to match measured images of the pocket phantom. For the present study, images were converted from scanner-generated Digital Imaging and Communications in Medicine (DICOM) files or variables in MATLAB (MathWorks Inc., Natick, MA) to the Meta-Image format (22). Analysis was performed in VolView (23) and MATLAB.

Imaging Model. The imaging system model used here is expressed in equation (1):

$$I(x, y, z) = g \cdot p(x, y, z) * k(\sigma_X, \sigma_Y, \sigma_Z) + n(x, y, z),$$

where $I(x, y, z)$ is the 3-dimensional (3D) image generated by the PET scanner, $g$ is a multiplicative global scale factor (ie, $g = 1$ means there is no global bias), and $p(x, y, z)$ is the true distribution of the PET signal source (ie, the physical concentration of radiotracer in the field of view). The function $k(\sigma_X, \sigma_Y, \sigma_Z)$ approximates the point-spread function (PSF) in the image with resolutions in the $(x, y, z)$ directions given by standard deviations $(\sigma_X, \sigma_Y, \sigma_Z)$. Here the PSF is assumed to be both Gaussian and spatially-invariant. The 3D convolution operation is denoted by “*”, and $n(x, y, z)$ is an additive noise vector.

Estimator Algorithm. In words, the system produces an image that is a blurred and scaled version of the true PET tracer distribution in the phantom. If we can estimate the scale factor and the PSF, we can check for consistency between different imaging centers and in test–retest studies.

The estimator algorithm uses a synthetic sphere image generator function $s(x_i, r_i, \rho_i)$, where $i$ is the index for a specific sphere. For example, if 1 pocket phantom is used, then there are 3 spheres. The location, radius, and activity for the $i$-th sphere are given by $(x_i, r_i, \rho_i)$. The radius and activity of each sphere are known a priori, and an initial estimate of the location of each sphere is obtained by segmenting the spheres from the CT image. Using the sphere image generator function, the predicted PET image is generated using the following equation:

$$\tilde{I}(x, y, z) = k(\sigma_X, \sigma_Y, \sigma_Z) * \left[ \sum_{i=1}^{N} s(x_i, r_i, g_i \cdot \rho_i) \right]$$

where $\tilde{I}(x, y, z)$ is the predicted noise-free sphere PET image, $N$ is the number of spheres, and $g_i$ is a scale factor for the activity of each sphere. A Nelder–Mead downhill simplex optimizer is used to estimate the standard deviations $(\sigma_X, \sigma_Y, \sigma_Z)$ and $(x_i, g_i)$ for $i = 1 \ldots N$ by minimizing the mean squared difference objective function $\Phi(\sigma_X, \sigma_Y, \sigma_Z, x_i, g_i) = |I(x, y, z) - \tilde{I}(x, y, z)|^2$ by using voxels in the neighborhood of the spheres. The algorithm terminates after a fixed number of iterations. The multiplicative global scale factor $g$ in equation (1) is then estimated as the average of the individual sphere scaling factors $g_i$.

Pocket Phantom Design Study

Simulated and measured PET data were used to evaluate the performance of the estimator algorithm. For a range of activity levels and sphere sizes, real and simulated phantom images were multiplied by scalars and smoothed with different filters to simulate variable scanner calibration and reconstruction settings. These tests led to the selection of design parameters for prototype pocket phantoms.

Design Study Using Simulated Data. As a first test of the estimator algorithm, a synthetic test object containing 2 spheres 15 mm in diameter having an activity concentration of 5 kBq/mL was simulated. Noise-free emission data sets (sinograms) for this object were generated using the University of Washington’s ASIM package (24). The detector configuration was modeled after a General Electric Discovery STE PET/CT scanner (General Electric Healthcare, Waukesha, Wisconsin). In MATLAB, the effects of detector parallax (25) and Poisson noise were added. Total detected coincidences were $4.8 \times 10^6$ (high noise) and $8.7 \times 10^5$ (low noise). Images were reconstructed with a fully 3D ordered-subsets expectation-maximization (OSEM) algorithm (26) or 3D filtered-backprojection (FBP) (27). For all OSEM reconstructions in this work, 4 iterations with 28 subsets were used. Voxel dimensions were $2.73 \times 2.73 \times 3.27$ mm for both OSEM and FBP. Further, 3 Gaussian postreconstruction smoothing filters (transaxial FWHM of 4, 8, and 12 mm) were also applied to the OSEM images. The axial filter FWHM for all OSEM images was 4.6 mm.

The resulting images were then rescaled such that the maximum signal was the same in each, creating images in which a calibration bias and resolution effects were mixed in ways unknown to the algorithm. The algorithm was then used to determine the image resolution parameters ($\sigma_X, \sigma_Y, \sigma_Z$). As a check of the algorithm’s accuracy, the width of the user-specified postreconstruction filter was calculated by comparison with the PSF from an unfiltered image. This was done by assuming that the intrinsic PSF and filter width added in quadrature, such that $\sigma_{\text{additional}}^2 = \sigma_{\text{filtered}}^2 - \sigma_{\text{unfiltered}}^2$.

Fillable Testbed Phantom. To estimate the effect of sphere diameter, a cast urethane disc with fillable spheres was con-
constructed (Figure 4). The disc contained 3 spheres at each of 3 diameters (10, 15, and 30 mm) and was scanned on a General Electric Discovery STE PET/CT scanner. 18F-fluorodeoxyglucose (18F-FDG) was used as the radiotracer.

A single solution of 18F-FDG was used to fill all spheres, and the phantom was scanned with all sphere centers in a single transaxial plane. CT-based attenuation correction was performed using a 120-kV CT scan. Acquisitions and reconstructions varied as shown in Table 1. OSEM images were not filtered, while the FBP reconstruction used an 8.2-mm Hanning window. The axial voxel dimension, or slice width, was 3.27 mm for all images. The estimated scale factors $g_i$ for all 9 spheres were recorded without averaging, and the bias and variance as a function of size across all 24 parameter sets were evaluated.

Testing of Pocket Phantom Prototypes

Based on the results from the simulated data and fillable phantom, 2 long-lived prototype pocket phantoms were constructed using epoxy infused with $^{68}$Ge/$^{68}$Ga. Each phantom had 3 spheres of 15 mm diameter (Figure 3) in a rectangular 3 × 3 × 12-cm cast urethane block. The activity concentrations of the 3 spheres in the first phantom were 30, 74, and 118 kBq/mL. For the second phantom, the concentrations were 47, 109, and 190 kBq/mL.

Phantom Measurements. The prototype long-lived pocket phantoms were measured alongside an anthropomorphic phantom that contained 3 different concentrations of 18F-FDG radiotracer in 3 regions corresponding to liver, lung, and background. Scan parameters are shown in Table 2. The duration was 5 min and the voxel size was $2.73 \times 2.73 \times 3.27$ mm. The mean signal intensity was measured in regions of interest (ROIs) in the anthropomorphic phantom.

Addition of Known Bias and Smoothing. To simulate multicenter clinical variability of scanner calibration and image resolution, we systematically varied the global scalar bias and postreconstruction filtering of our measured prototype phantom images. As shown in Table 2, the images had 3 levels of smoothing and 5 scale factors applied. These scale factors were applied after the PET/CT scanner had applied all physical corrections to the data to generate correctly calibrated images. We denote the image for the scan with the $j$-th applied scale factor and $k$-th filter width as $I_{jk}$, and the estimated scale factor, after averaging over spheres, as $g_{jk}$.

For each image in our test-space of reconstructions, we generated a bias-corrected image, $I^b_{jk}$, according to equation (3).

$$I^b_{jk} = \frac{I_{jk}}{g_{jk}}$$

As a test of the pocket phantom system’s ability to correct scanner calibration errors, we report ROI values from the corrected and uncorrected images.

Pocket Phantom Data Rescaling. It is known that scatter and attenuation correction can lead to bias in some solid phantoms (28). Our calculation of the scale factor $g$ was therefore modified to use premeasured pocket phantom image data as a reference. As a test case, the reconstruction with a scale factor of 1.0 and a 12-mm post filter was used as a reference image. Scale factors $g_i$ from the spheres in this scan were used as normalization factors.

<table>
<thead>
<tr>
<th>Imaging Parameter</th>
<th>Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconstruction algorithm</td>
<td>OSEM, FBP</td>
</tr>
<tr>
<td>Transaxial voxel dimension (mm)</td>
<td>2.73, 5.56</td>
</tr>
<tr>
<td>Detected events (millions)</td>
<td>0.5, 0.8, 1.6</td>
</tr>
<tr>
<td>Activity concentrations (kBq/mL)</td>
<td>6.0, 32.0</td>
</tr>
<tr>
<td>Sphere diameter (mm)</td>
<td>10, 15, 30</td>
</tr>
</tbody>
</table>

Abbreviations: OSEM, ordered-subsets expectation-maximization; FBP, 3D filtered-backprojection. Twenty four reconstructed images were generated, with each image having 3 spheres at each of 3 diameters.

Table 2. Imaging Parameters for Scanning of Prototype $^{68}$Ge/$^{68}$Ga Phantoms With 18F-FDG Phantom (Figure 7)

<table>
<thead>
<tr>
<th>Imaging Parameter</th>
<th>Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconstruction method</td>
<td>OSEM</td>
</tr>
<tr>
<td>Postreconstruction transaxial smoothing FWHM (mm)</td>
<td>3, 6, 12</td>
</tr>
<tr>
<td>Postreconstruction axial smoothing FWHM (mm)</td>
<td>4.6</td>
</tr>
<tr>
<td>Simulated global scale factor $g$</td>
<td>0.6, 0.8, 1.0, 1.2, 1.4</td>
</tr>
</tbody>
</table>

Abbreviations: OSEM, ordered-subsets expectation-maximization; 18F-FDG, 18F-fluorodeoxyglucose; FWHM, full-width half-maximum.
to calculate rescaled estimates of the scale factors for the corresponding spheres in all images.

RESULTS

Design Study Results

Simulation Results. Profiles through a subset of simulated phantom spheres are shown in Figure 5. The profiles confirm that bias from either resolution losses or global scaling are not unique. In other words, the same recovery coefficient can result from different combinations of global bias and resolution bias.

Table 3 shows the true and estimated values of the applied scale factor and applied transaxial filter width [equation (1)]. Estimates of the filter width in the axial direction, which was 4.6 mm, had a distribution of 4.57 (0.16) mm over all simulated images. The performance of the pocket phantom system was similar over all simulated parameters, including variations in sphere size (data not shown). In other words, the estimator algorithm accurately predicted the applied global scale factor and image smoothing.

Figure 5. Profiles through simulated PET images (4.8 × 10^5 detected events) having different global scale factors and resolution losses that lead to the same maximum signal.

**Table 3.** Applied and Estimated Image Parameters of Simulations Having the Same Maximum Signal

<table>
<thead>
<tr>
<th>Noise Level</th>
<th>Applied Global Scale Factor</th>
<th>Estimated Global Scale Factor</th>
<th>Applied Transaxial Filter (mm)</th>
<th>Estimated Transaxial Filter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>0.76</td>
<td>0.79</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>High</td>
<td>0.94</td>
<td>0.95</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>High</td>
<td>1.35</td>
<td>1.36</td>
<td>12</td>
<td>12.4</td>
</tr>
<tr>
<td>Low</td>
<td>0.81</td>
<td>0.83</td>
<td>4</td>
<td>4.8</td>
</tr>
<tr>
<td>Low</td>
<td>0.97</td>
<td>0.98</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>Low</td>
<td>1.39</td>
<td>1.40</td>
<td>12</td>
<td>12.4</td>
</tr>
</tbody>
</table>

The “high noise” data correspond to the profile in Figure 5.

Fillable Testbed Phantom. Figure 6 shows the distribution of $g_i$ scale factor estimates for all spheres in the reconstructions listed in Table 1. In some cases, the algorithm returned anomalously low $g_i$ values for the 10-mm sphere, indicating algorithm failure for this sphere size. For the 15-mm spheres, $g_i$ had a mean of 0.868 (0.025) across all reconstructions. Performance of the algorithm with 30-mm spheres was similar. Bias estimates were stable as the reconstruction method changed. For the 15-mm sphere, $g_i$ values were 0.872 (0.036) for OSEM images and 0.869 (0.014) for FBP.

For the 15- and 30-mm spheres, the distribution of resolution estimates are shown in Table 4. Here, reported statistics are over variations in image noise and activity concentration (rows 3 and 4 of Table 1). Changing the transaxial voxel sizes in OSEM images led to changes in transaxial resolution estimates. In the axial direction, for which voxel dimensions were the same for all reconstructions (3.27 mm), the agreement was better, with average estimates from OSEM images agreeing to within 0.8 mm as sphere size and voxel size varied. Resolution estimates from FBP images showed better agreement than OSEM.

Our testing indicated that the 15-mm sphere size was optimal based on its acceptable performance in simulated and physical images.
testing and the ease of manufacturing versus 30-mm spheres in the final phantom.

**Pocket Phantom Results**

*Measured Data.* Figure 7 shows the scan configuration and representative data from the pocket phantom prototype measurements acquired with the anthropomorphic chest phantom. This scan roughly represents the intended clinical scan configuration with the pocket phantoms below the patient. The PET images and profile show that the pocket phantom images have excellent signal-to-noise properties and match the magnitude of signal in the anthropomorphic phantom.

Table 5 shows the PET signal measured in images created with the parameters of Table 2 before and after correction by equation (3). Expressed as a percentage of the range midpoint, ranges of mean ROI signal were reduced from 80% in uncorrected images to \( \frac{5}{100} \) for corrected ones, indicating that the pocket phantom system successfully compensated for the simulated scanner miscalibration in our test image set.

Figure 8 shows the measured ROI values (AROI) for the pocket phantom spheres after division by known activity concentration. The differing slopes for AROI show the dependence of partial volume effects on the variable image resolution. The square ACAL markers represent the ratio of the applied scale factor (Table 2) to the estimated scalefactor \( g \). A value of 1 for ACAL therefore corresponds to the accurate estimation of bias. After averaging over the 6 pocket phantom spheres in the images, ACAL values ranged from 0.95 to 1.06, indicating that the bias-corrected images were accurate to within 6% regardless of the changes in image filtering or global image bias.

As the reconstruction postfilter width varied between 3, 6, and 12 mm, estimates of final transaxial, or transverse, resolution varied as in Table 6. These estimates of final image resolution include effects of both the postfilter and intrinsic PSF. The small standard deviations demonstrate that transverse resolution estimates are stable as global scaling varies. In addition, axial resolution estimates are stable as transverse resolution and global scaling vary.

**DISCUSSION**

We have tested and evaluated design parameters for small phantoms that allow the simultaneous estimation of scanner global calibration bias and reconstructed image resolution. We have constructed and tested a prototype phantom on the basis of these results, and have demonstrated the ability of the phantom and software to detect changes in the bias and resolution of measured images. For the prototype phantom, the 15-mm spheres were chosen based on their providing similar performance to the 30-mm spheres while allowing the phantom itself to be smaller. The algorithm succeeded in estimating global bias independently of resolution. In particular, Table 3 shows that the variations of parameters shown in Figure 5 have been successfully separated. Table 5 shows that the range of signal biases in our set of test images was reduced to <5% using the pocket phantom correction factors regardless of changes in the applied postreconstruction smoothing. Further, bias estimates did not show any dependence on the image reconstruction method. The global scale factor for the 15-mm sphere had a coefficient of variation of <3% over all instances of parameter variations shown in Table 1. The agreement of bias estimates for these very different reconstructions suggests that the Gaussian model used by the estimator algorithm can accommodate a range of resolutions and reconstruction methods.

The absolute accuracy of bias estimates is more difficult to evaluate. In the simulated data, for which bias was known, the pocket phantom system found the global scale factor to within 3% of the true value for all resolutions tested (Table 3). In PET/CT measurements of epoxy-based solid phantoms, the PET

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**Table 4.** Estimates of Final Image Resolution (in millimeters) From the 15- and 30-mm Spheres in the Fillable Testbed Phantom Reconstructions of Table 1

<table>
<thead>
<tr>
<th></th>
<th>15-mm Spheres</th>
<th></th>
<th>30-mm Spheres</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.73-mm Voxels</td>
<td>5.46-mm Voxels</td>
<td>2.73-mm Voxels</td>
<td>5.46-mm Voxels</td>
</tr>
<tr>
<td>OSEM Transaxial</td>
<td>3.69 (0.343)</td>
<td>1.42 (0.215)</td>
<td>3.98 (0.341)</td>
<td>2.24 (1.668)</td>
</tr>
<tr>
<td>OSEM Axial</td>
<td>3.70 (0.340)</td>
<td>4.47 (0.450)</td>
<td>4.23 (0.172)</td>
<td>4.37 (0.250)</td>
</tr>
<tr>
<td>FBP Transaxial</td>
<td>9.12 (0.163)</td>
<td>9.26 (0.261)</td>
<td>9.50 (0.191)</td>
<td>9.65 (0.147)</td>
</tr>
<tr>
<td>FBP Axial</td>
<td>6.06 (0.098)</td>
<td>6.15 (0.096)</td>
<td>5.97 (0.093)</td>
<td>6.05 (0.138)</td>
</tr>
</tbody>
</table>

*Abbreviations: OSEM, ordered-subsets expectation-maximization; FBP, 3D filtered-backprojection. Columns are labeled with transaxial voxel size. Axial voxel width (slice width) was 3.27mm for all images.*
image value is known to be biased owing to attenuation correction that is not correct for synthetic materials (28). Although our scanner was carefully calibrated, Figure 6 shows global scale factor estimates were generally less than one. ROI measurements of activity in the centers of the largest spheres in the urethane fillable testbed phantom, which were not subject to partial volume effects, showed that this bias was real and not a failure of the algorithm. This prevents us from computing scanner calibration bias directly from the known radiotracer concentration. To correct this problem in our solid prototypes and future work, we have proposed and tested the use of a calibration prescan (see Section Pocket Phantom Data Rescaling) where the algorithm is precalibrated to compensate for biases in the pocket phantom signal from physical effects such as attenuation and scatter correction. With this method, the impact of scatter and attenuation correction on the pocket phantom is assumed to be constant for a given scanner. The ACal data in Figure 8 show that for our initial tests, the precalibration led to accurate correction of our simulated global image bias.

Unlike calibration bias, resolution effects cannot be easily corrected. Partial volume correction methods have been proposed, but these have been shown to add bias and variance (15, 29). However, if changes in resolution can be detected, this information can help with quality control either for clinical practice or clinical trials in which the quantitative accuracy of PET images is relied upon. For example, in clinical trials, the removal of data with uncontrolled biases, including those due to resolution, can increase the study power even if the sample size decreases (19). In our measured data (Table 6), the pocket phantom system returned estimates that were well separated when resolution varied, with standard deviations of 0.01 and 0.09 mm for the 3- and 6-mm postreconstruction filtering, respectively. Importantly, these results were stable even when global scaling was varied by up to ±40% (Figure 8).

Currently, efforts to reduce variability in PET mainly consist of accreditation procedures (30) and consensus documents on best practices (31-33). Scanner accreditation often involves “cross calibration,” in which dose calibrator and scanner measurements are required to concur, but this process may not ensure biases are stable over time (13).

Resolution may be addressed by specifying a range of acceptable signal bias for a range of lesion sizes (34) or by requiring visibility of specific features of a given size (30). Methods for quantifying resolution in the literature vary and may involve profiles through FBP images of point sources near the scanner’s center (35), ROI signal from multiple sphere sizes in a large calibration phantom (36), or solving for the radial PSF in Fourier space (37). However, we note that none of these methods is compatible with a clinical scan with a patient in the field of view.

With its unique combination of software and manufacturing, the pocket phantom system aims to provide new capabilities

### Table 5. Ranges of Measured Signal (kBq/ml) in Biased and Corrected Images

<table>
<thead>
<tr>
<th>Applied Smoothing</th>
<th>Background Region</th>
<th>Liver Region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original ROI Values</td>
<td>Corrected ROI Values</td>
</tr>
<tr>
<td>3 mm</td>
<td>1.27–2.97</td>
<td>2.07–2.14</td>
</tr>
<tr>
<td>6 mm</td>
<td>1.28–2.98</td>
<td>2.10–2.20</td>
</tr>
<tr>
<td>12 mm</td>
<td>1.28–2.98</td>
<td>2.09–2.15</td>
</tr>
</tbody>
</table>

Abbreviations: ROI, region of interest. ROI mean values are shown.
in PET quality control. The long-lived phantoms provide a more stable signal than the manually-filled phantoms used in cross calibration. The spherical symmetry of the active regions allows estimates of resolution along 3 independent directions, regardless of the phantom orientation. In particular, the spherical design offers an advantage over line sources, from which axial resolution cannot be estimated. In addition, the software modeling allows the phantoms to be small enough to be scanned with patients, enabling quality control during patient scans. Future work will address the practical requirements for translating our initial results into a more widely usable quality control system. We have already published the preliminary results on our user-facing software that will make the algorithm available to off-site imagers (38). In addition, a more detailed subsequent analysis of the phantom performance, including the dependence on scan configuration and radiotracer concentrations, will allow us to optimize the protocol for phantom scanning and finalize the manufacturing parameters. Our study has some limitations. The global bias due to CT-based attenuation correction of the epoxy-based phantom, and the precalibration workaround, have already been discussed. The dependence of resolution estimates on voxel size seen in Table 4 is likely due to the way the model images are downsampled before the smoothing of equation (3). In cases where voxel dimensions approach the resolution, the effect of downsampling may become significant and lead to unreliable resolution estimates. We note that for the more heavily smoothed FBP images, this problem did not occur. Our initial evaluation of the pocket phantom system was limited to a single scanner. Future work will include repeated measurements on different makes and models of scanners.

The pocket phantom system can estimate and correct changes in calibration bias in measured PET images, and it can simultaneously detect changes in the reconstructed image resolution. Over the imaging scenarios tested, the system returned stable estimates of both bias and resolution, as long as voxel size was not too large. This suggests that the pocket phantom system is a viable method for quality assurance in PET, particularly in clinical trials. However, the robustness of the imaging model should be further investigated for multiple imaging systems.

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Conflict of Interest: None Reported.

REFERENCES
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