Letters to the Editor

Systemic Effects of Local Tumor Ablation: Oncogenesis and Antitumor Induced Immunity

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Editor:

In the August 2015 issue of *Radiology*, Drs Chapiro and Geschwind, in their commentary entitled "Science to Practice: The Changing Face of Local Tumor Therapies—Do We Have to Think Systemically When Treating Cancer Locally?" (1), highlighted the actual need of a better comprehension of the systemic effects of local tumor ablation, challenging the interventional oncology community to work on adjuvant therapy to counter this new and relevant problem. This commentary was in reference to recent studies that reported that local ablation may stimulate distant tumor growth (2,3). Rozenblum et al (3) showed an increased tumor load and reduced survival after ablation of 3.5% of the liver in comparison to controls in an animal model. They identified pro-regenerative pathways that can trigger tumor growth stimulation after ablation. They also demonstrated how a molecularly targeted approach could reduce the pro-oncogenic effect of ablation.

Although these articles (2,3) present strong evidence of the pro-oncogenic systemic effect of local ablations, there is another side of the issue that should be considered. Other studies have highlighted the observation that local ablation may stimulate an immune response that can ultimately contribute to tumor control (4–6). It has been postulated that thermal ablation of a tumor, by determining an exposure of tumoral antigens, may trigger a sort of "in vivo vaccination" against tumor (4–6), with the production of antibodies that can contribute to local tumor eradication, control of distant metastases, and establishment of an antitumor immunological memory (4). Cases of regression of distant metastases after ablation have been reported (6–8). This phenomenon has been referred to as "antitumoral induced immunity." Sánchez-Ortiz et al (6) reported the disappearance of a lung metastasis after ablation of the primary renal tumor, Kim et al (7) the regression of pulmonary and adrenal metastases after ablation of a recurrent renal carcinoma, and Rao et al (8) the regression of multiple pulmonary metastases after ablation of a single metastasis.

Thus, further understanding the full range of systemic effects of local ablative therapies and the balance between the pro-oncogenic effect and the immuno-mediated antitumoral effect will be crucial in identifying the optimal treatment to patients and will present an exciting challenge to investigators in the upcoming years.

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Response

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We read with great interest and appreciation the letter by Dr Mauri and colleagues written in response to the article by Rozenblum et al titled "Oncogenesis: An "Off-Target" Effect of Radiofrequency Ablation" (1) and our associated Science to Practice commentary (2).

We thank Dr Mauri and colleagues for pointing out that the inflammatory and systemic effects of radiofrequency ablation and other interventional oncology therapies are likely to extend beyond liver regeneration and tumorigenesis—the primary focus of our article and editorial. Dr Mauri and colleagues are correct to note that some evidence exists in support of a positive immune response to thermal tumor ablation, which might very well trigger "abscopic" anti-tumor effects by means of tumor antigen exposure. Yet, in comparison to the fairly detailed mechanistic evidence in support of protumorigenic "off-target" effects of thermal ablation presented in this work, to date only limited mechanistic evidence regarding abscopic effects is available.

We acknowledge the need for further study of both potential postablation pathways and specifically support the call to further investigate a broad variety of potential positive and negative downstream effects of interventional oncology procedures. Accordingly, it will be up to the scientific community to define under what conditions each reaction predominates as the ablation device selected, tumor and organ types, and immune status of the patient are likely to influence the balance between immunologic and tumorigenic secondary effects of interventional oncology therapies. Only such study will enable us to effectively tailor our therapeutic regimens on what is likely to be a patient-by-patient basis to achieve what we believe ought to be the overall primary objective—maximizing success by achieving optimal clinical outcomes.

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Gadolinium Deposition in the Brain: Do We Know Enough to Change Practice?

From
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Editor:

We read with interest the article by Dr Radbruch and colleagues in the June 2015 issue of *Radiology* investigating gadolinium deposition in the brains of patients with repeated gadolinium exposure (1) along with the follow-up editorial by Kanal and Tweedle (2) in the same issue.

Dr Radbruch and colleagues describe their elegant study of patients who received multiple doses of gadoterate

meglumine or gadopentatate dimeglumine. A statistically significant and dose-dependent increase in precontrast T1-weighted signal intensity was seen in the deep nuclei of the brain after exposure to gadopentatate, but not gadoterate. This adds to observations of gadolinium deposition in patients receiving multiple doses of gadolinium and raises questions regarding the long-term safety of repeated exposures.

However, we are concerned that history may be repeating itself to the detriment of our patients. Nephrogenic systemic fibrosis (NSF) is a serious condition with convincing paired data relating NSF to gadolinium exposure in renal failure. After NSF was identified, there was a lengthy period of uncertainty based on a lack of reliable data. The lack of data contributed to an unprecedented gadolinium-phobia and denial of medically important imaging studies. The overall impact on human health from denial of imaging will never be known, but in our opinion likely exceeded the potential risks of NSF.

Unlike NSF, gadolinium deposition, although concerning, lacks paired evidence of adverse neurologic or biologic outcomes. Therefore, we are not able to comprehend which, if any, practical recommendations are appropriate at this stage. We also suggest caution in concluding that gadolinium retention is "dependent on the class of contrast agent." Although findings from recent publications are consistent with this statement (1,3), we find this broad conclusion premature, as additional work evaluating all agents is needed. Is it prudent to switch preferentially to a class of pharmaceutical agents, some of which are expensive, purely on the basis of imaging observations? This is fraught with potential for abuse from pharmaceutical companies and legal firms to seize on this controversy to their financial benefit.

We are reminded of the adage: "Treat the patient, not the picture."

We urge caution in the interpretation of these data. Additional studies are warranted, but the development of "practical implications" such as withholding gadolinium or promoting macrocyclic agents is premature.

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Response

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We thank Drs Reeder and Gulani for the appreciation of our work as well as for their constructive criticism. We agree on a lot of—however, not on all—the points raised by Drs Reeder and Gulani.

First, we concur that the entirety of the marketed gadolinium-based contrast agents (GBCAs) has to be assessed in order to conclude that a signal intensity increase in the deep nuclei is dependent on the class of contrast agent. In our article, we have taken this into account by stating that "only two of the nine available GBCAs on the market have been analyzed" (1) and by concluding that future studies including other GBCAs should be conducted. Nonetheless, considering all evidence from the hitherto published in vitro (2) and in vivo (1, 3–10) data (with the exception of one recently published study [11]), we hypothesize that the differentiation in macrocyclic and linear GBCAs is most likely the crucial factor when looking at causes for a potential signal intensity increase in the deep nuclei (12), even though this is not proven yet.

Second, we agree that gadolinium deposition in the deep nuclei "lacks paired evidence of adverse neurologic or biologic outcomes" and clearly state this in our article. However, it should also be mentioned that clinically relevant sequalae of gadolinium retention in the brain cannot be excluded and—given the fact that there is histologically proved accumulation in the brain (7,8)—it is important to prove that there is no clinical damage rather than to prove that there is damage.

Third, we agree that the findings of gadolinium deposition in the brain can potentially cause a "gadolinium-phobia." However, we are convinced that the best way to manage this scenario is to continue conducting evidence-based studies and—just as important—to provide our patients with comprehensive information about the contrast agent they receive. This includes the varying potential of GBCAs to cause hyperintensities in the deep nuclei in the brain, the currently unknown clinical relevance of these hyperintensities, and the varying prices of the contrast agents. Only by proactively addressing the issue of gadolinium retention in the brain

will we be able to prevent the unreasonable decline of gadolinium-enhanced magnetic resonance (MR) imaging.

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Response

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We thank Drs Reeder and Gulani for their insightful comments. We agree that unwarranted fear of GBCA is inappropriate and potentially harmful. Drs Reeder and Gulani highlight the lack of evidence of potential adverse effects relating to intracranial gadolinium accumulation (IGA) yet readily admit that such accumulation is "concerning." Common sense demands that we decrease that concern by means of reasonable and readily implementable steps, such as prescribing agents that seem to accumulate less intracranially per administered dose.

We also concur that concluding at this point that IGA is dependent on the contrast agent class is premature. We therefore carefully avoided such conclusions and insist on further studies before sound conclusions can be drawn. This is especially imperative now that the literature has documented that one macrocyclic agent is associated with these effects (1) whereas two other macrocycles may not be (2,3). Moreover, some linear agents exhibit these effects to a greater extent than do others (3–6).

We also wish to "treat the patient, not the picture." We don't advocate treating images, but rather responding to the new pharmacokinetic data they revealed, namely, marked differences in IGA following administration of various GBCAs. This was not considered in the past but, appropriately, is a focus of our attention today.

We have known for years (7,8) that gadolinium retention in bone differs among various GBCAs. This reinforces our concern regarding differential IGA.

We therefore respond to the question in their letter title, "Do we know enough to change practice?" with a resounding "Yes."

We agree that "withholding gadolinium or promoting macrocyclic agents is premature," and made no such recommendations. But withholding gadolinium if it is not truly indicated will benefit everyone and prescribing agents that (all else being equal) accumulate less gadolinium in the body are practical, reasonable, common sense, and easily implementable recommendations until further information becomes available.

Radiologists should therefore become more involved in deciding *(a)* whether to administer a GBCA, *(b)* which agent should be administered to which patient, and *(c)* the administered dose for each patient for whom a contrast material–enhanced MR examination is clinically requested.

Our patients would expect no less of us.

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Quantitative Dynamic Contrast-enhanced MR Imaging in Posttreatment Glioblastoma: Possible Limitations of Short Acquisition Time

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Editor:

I read with interest the article by Dr Yun and colleagues in the March 2015 issue of *Radiology* entitled "Glioblastoma Treated with Concurrent Radiation Therapy and Temozolomide Chemotherapy: Differentiation of True Progression from Pseudoprogression with Quantitative Dynamic Contrast-enhanced MR Imaging" (1). The authors demonstrated that mean volume transfer constant (K^{trans}) and extravascular extracellular space per unit volume of tissue (v_e) in true progression were significantly higher than those in pseudoprogression; however, the blood plasma volume per unit volume of tissue (v_p) was not significantly different between the true progression and pseudoprogression groups. v_p may be a marker of angiogenic activity in a tumor, and the lack of difference in v_p is somewhat unexpected and can be related to the total image acquisition time in this study, which was 1 minute 30 seconds. Larsson et al (2) investigated the effect of variations in total measurement times on the estimations of kinetic parameters derived from dynamic contrast-enhanced magnetic resonance (MR) imaging by using acquisition times of 1, 2, 3, 4, and 5 minutes and demonstrated that reduced total sampling time will result in reduced precision of the estimated values with overestimation of K^{trans} and the constant of transfer from the interstitial space to the plasma (K^{ep}) and underestimation of v_p and v_e (2). In fact, although there are some variations in the literature with regard to total image acquisition time in dyamic contrast-enhanced MR imaging, the more common acquisition time in the literature as well as my institution is approximately 5 minutes (3,4). Therefore, I believe that the results of this study should be interpreted with caution and that further studies with long acquisition times as well as cross validation of the results in a prospective study are warranted.

Disclosures of Conflicts of Interest: disclosed no relevant relationships.

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MR Imaging in the Assessment of Endometrial Cancer

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Editor:

We were pleased to read the very interesting article in the September 2015 issue of *Radiology* by Dr Nougaret and colleagues (1), who underlined that the major clinical challenge in endometrial cancer staging is to select the patients who are most likely to benefit from lymphadenectomy. This is particularly relevant in patients with type 1 endometrial cancer, as patients with type 2 cancer do require systematic pelvic and para-aortic lymphadenectomy (2). Moreover, tumor size and lymphovascular space involvement (LVSI) have no impact on survival in patients with type 2 endometrial cancer (3,4). Therefore, it is of particular interest to determine the contribution of magnetic resonance (MR) imaging in a homogeneous population of patients with type 1 endometrial cancer (59 of 70 patients in this study). In these patients with type 1 cancer, European Society for Medical Oncology (ESMO) guidelines state that patients with low or intermediate risk of recurrence who exhibit LVSI should be considered a high-risk group (2). In the study by Dr Nougaret and colleagues, a very high percentage of patients underwent para-aortic lymph node sampling (89%), which is commonly indicated in high-risk patients, who typically have comprised less than one-quarter of patients with early stage disease in previous retrospective studies (3,5). Moreover, in this study, there was a high level of LVSI (50% vs 20%–30% in previous studies) (3,5). Thus, it would be very helpful to understand in which ESMO category the patients in this study were initially classified and in how many cases the new MR imaging criteria evaluated would have modified management.

Second, in their study, Dr Nougaret and colleagues conclude that the different MR pulse sequences were equal in the evaluation of tumor size because nonsignificant differences were found. Did the authors have a sufficient study size to draw this conclusion? For that issue, the measurement of the concordance between size at histologic and MR examination would have been helpful. Is this histologic information available?

Finally, Dr Nougaret and colleagues compared the accuracy of a number of MR pulse sequences in the evaluation of myometrial invasion. It is surprising that the authors did not compare T2- and diffusion-weighted pulse sequences with a high-spatial-resolution T1-weighted pulse sequence, which is considered as a standard in European guidelines (6). Moreover, the number of premenopausal and menopausal patients and the presence of benign uterine-associated abnormalities would be useful to discuss in the assessment of myometrial invasion.

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Response

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We thank Dr Thomassin-Naggara and colleagues for their thoughtful comments regarding our article (1).

First, as they point out, a large percentage of patients in our study underwent para-aortic lymph node sampling. The decision to proceed with para-aortic lymph node sampling was based on a combination of factors, including preoperative tumor grade, imaging findings, intraoperative assessment, and surgical templates in practice at our institution during the study period (2010–2012). We would like to emphasize that the current surgical practices are a product of ongoing revisions based on emerging new data and that these practices have un-

dergone changes since the time of our retrospective data review. Furthermore, unfortunately, there is no single universally accepted surgical approach for the treatment of endometrial carcinoma, and the practice remains nonuniform between Europe and North America, as well as amongst different institutions within North America.

Second, as Dr Thomassin-Naggara and colleagues accurately note, 50% of patients in our cohort had LVSI, which is higher than that in other reports. This may be explained by the fact that we selected patients with tumors that were large enough to undergo quantitative assessment with MR volumetry.

Third, we could not directly correlate tumor volumes at MR imaging to those at histopathologic examination because this information was not consistently available at the time of our retrospective data review.

Fourth, we would like to direct Dr Thomassin-Naggara and colleagues to table 5 and to the "Qualitative Assessment of Myometrial Invasion" section under Results for further information regarding the comparison of T2-weighted imaging with diffusion-weighted imaging and T2-weighted imaging with contrast-enhanced T1-weighted imaging in the assessment of myometrial invasion. We did not perform a subgroup analysis to examine the influence of various confounding factors such as menopausal status and benign uterine abnormalities on the performance of MR imaging for the assessment of myometrial invasion because this analysis was previously reported by Beddy et al (2).

Finally, in this study we aimed to investigate the value of quantitative tumor volume measurements and whole tumor volume apparent diffusion coefficient histogram metrics as predictive biomarkers of the depth of myometrial invasion, tumor grade, and LVSI at surgery. Although beyond the scope of our study, we concur with Dr Thomassin-Naggara and colleagues that it would be of interest for future studies to investigate how quantitative MR imaging criteria could influence surgical management of endometrial carcinoma in accordance with ESMO practice guidelines (3).

Disclosures of Conflicts of Interest: S.N. disclosed no relevant relationships. **C.R.** disclosed no relevant relationships. **Y.L.** disclosed no relevant relationships. **B.G.** disclosed no relevant relationships. **E.S.** disclosed no relevant relationships.

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Errata

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The Alzheimer Structural Connectome: Changes in Cortical Network Topology with Increased Amyloid Plaque Burden
Jeffrey W. Prescott, Arnaud Guidon, P. Murali Doraiswamy, Kingshuk Roy Choudhury, Chunlei Liu, Jeffrey R. Petrella; For the Alzheimer's Disease Neuroimaging Initiative

Erratum in:
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Quiet Submillimeter MR Imaging of the Lung Is Feasible with a PETRA Sequence at 1.5 T
Gaël Dournes, David Grodzki, Julie Macey, Pierre-Olivier Girodet, Michaël Fayon, Jean-François Chateil, Michel Montaudon, Patrick Berger, François Laurent

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Beyond the Cuff: MR Imaging of Labroligamentous Injuries in the Athletic Shoulder
Elizabeth A. Roy, Ian Cheyne, Gordon T. Andrews, Bruce B. Forster

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Incorrect Learning Objectives were published with the print article. The Learning Objectives should be as follows: **Describe correct MR imaging technique for assessment of labroligamentous injuries of the shoulder; Define common labral variants that can simulate injury; Discuss examples of sequelae of traumatic instability; Describe the SLAP tear and its major components; Discuss the concepts of external and internal impingement and their major subcategories; Describe the common nerve entrapment syndromes and their major imaging characteristics.**