Geographic Miss: A Cause of Treatment Failure in Radio-Oncology Applied to Intracoronary Radiation Therapy

To the Editor:

We compliment Sabaté et al on their article on geographic miss. However, we do not agree with the authors’ definition of geographic miss as requiring both low-dose radiation and injury. 

On the basis of the concepts of radiation oncology, a geographic miss occurs when any segment of the stenotic or “injured” vessel is not included in the radiation field or is treated to an inadequate dose. To clarify the terminology of this “new” phenomenon in endovascular brachytherapy, we proposed the following definitions:

1. Gross target length (GTL) is defined as the narrowed segment of the artery that requires intervention.
2. Clinical target length (CTL) is defined as the entire length of the vessel that is injured due to angioplasty, atherectomy, or stenting, including the barotramatized edges.
3. Planning target length (PTL) is the clinical target length plus a margin to account for heart/catheter/source movement and the inherent uncertainty in target localization.
4. Treatment length (TL) is the final length of the source train required for the treatment. This is the planning target length plus the penumbra, and it follows from the basic physics of a line source: at the prescribed radius from the source train (e.g., 2 mm), the prescription isodose is always shorter than the source length. This penumbra effect depends on the isotope, the length of the planned target, and the prescription radius; thus, it is unique to each source and treatment protocol.

Adoption of these definitions would assure treatment consistency among practitioners, especially for multi-institutional clinical trials. It would allow for objective dose specification, a tenet among practitioners, especially for multi-institutional clinical trials. It would allow for objective dose specification, a tenet among practitioners, especially for multi-institutional clinical trials. It would allow for objective dose specification, a tenet among practitioners, especially for multi-institutional clinical trials. It would allow for objective dose specification, a tenet among practitioners, especially for multi-institutional clinical trials.

Regarding the stimulatory effect of low-dose radiation, Weinberger et al did find increased neointima with 10 Gy; however, the reported neointimal area was not controlled for medial fracture length. Conversely, other studies have found a dose-dependent neointimal inhibition starting with doses as low as 3.5 to 5 Gy, and the GAMMA I study showed a decrease in in-stent restenosis at doses as low as 8 Gy (at a radius of 2 mm).

Sabaté et al did not observe any restenosis within the last 2 mm of the source train, despite the fact that the doses here would have been only 7.2 to 12 Gy. Where they did observe restenosis due to geographic miss (5 mm beyond the gold markers), the dose would have ranged from 6 Gy to practically zero. These are calculated doses that do not take into account the attenuation caused by the gold seed; the actual doses would be much lower. There is really no evidence in the oncology literature to support a stimulatory effect at these doses. The “edge effects” are merely instances of restenosis of injured segments of the artery (at the stent edges) in the absence of a therapeutic radiation dose. A near-total inhibition of neointimal hyperplasia within the body of the stent may also result in an apparent shift of the minimal luminal diameter to the stent edges, further contributing to this edge effect.

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Response

We thank Professor Parikh and colleagues for their comments regarding our article on geographic miss. We think that both components (low-dose radiation and injury) are needed to define the concept of geographic miss in Interventional Cardiology. As discussed in the article, if only low-dose radiation is in the equation, we are dealing with uninjured edges. And, as demonstrated in the article, no edge restenosis or late loss occurred in those uninjured edges. This confirms the hypothesis that low-dose radiation per se has no stimulatory effect and that the injury is needed to induce this edge effect. Further, if only injury is in the definition, we are dealing with the normal restenosis process. Fortunately, cells involved in the atherosclerotic process are not malignant (ie, without indefinite capacity of proliferation). It is the injury produced during the angioplasty procedure that triggers the restenotic process (as demonstrated in the experimental models of restenosis). Of course, this phenomenon is an adoption and an adaptation of the radio-oncology concept of geographic miss aimed at understanding what the pathophysiology of this edge restenosis is. It can definitely not be considered “merely instances of restenosis of injured segments,” because the incidence of this phenomenon is not as high in any of the reported trials using stent or balloon angioplasty. The apparent shift of the minimal luminal diameter to the stent edge may be a plausible explanation for the cases involving radioactive stents (not studied in our article). However, again, late loss and restenosis on the conventional stent edges have not been reported before in such a manner.

Recently, we proposed and clinically validated a new terminology to unify criteria and, especially, to avoid misleading results when a clinical trial is reported. In that article, the terms target segment, injured segment, irradiated segment, and vessel segment are incorporated in the analysis of a clinical trial. In this regard, the efficacy of the therapy itself (angioplasty and radiation) would be determined by the results at the target segment, and the effectiveness of the radiation therapy, which includes both the desired effects (ie, lumen enlargement after radiotherapy) and the side effects (ie, edge restenosis), would be defined for the entire vessel segment. Finally, analyses of the injured and irradiated segment would be helpful to identify the potential causes of failure after treatment (ie, geographic miss). The terminology proposed by Parikh et al, which is adopted from radio-oncology, almost mimics our definitions, which are expressed in a more cardiological way. It confirms the need to “talk the same language” and unify criteria when the treatment of a patient involves different clinicians and professionals of different specialties.

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