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LETTER TO THE EDITOR

The limits of the "holy gray" in radioembolization and beyond

Beyond the "holy Gray"

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Dear Sir,

With interest, we have read the letter by Kao [1] which was written in response to our previous editorial [2]. Certainly, the author presents an interesting summary of recent advances and insights in the benefit of dosimetry-guided therapy in radioembolization. Certainly, as we are also aware, in recent years radioembolization has effectively become the first branch of therapeutic application of radionuclides where dosimetry has not only taken hold, but has become the de-facto standard of care.

However, even within radioembolization the points we brought up in our editorial [3] still hold true. There is a large heterogeneity in the clinical dose–response relationship in the target tissue, especially between different cancer entities [4], the cause of which is unknown. Certainly, even in high mean achieved doses to target tissue radioembolization may prolong life, but will not achieve complete eradication of tumor tissue as nicely shown, e.g., by Garin et al. [5]: a delivered dose of on average > 205 Gy prolonged median survival from 11 months after treatment in controls to 27 months in treated patients—however, in this same study, after 3 years only 2 patients were alive in each of these groups. This still shows that even high absorbed doses to the target tissue will leave behind a contingent of cells that for some mostly not fully understood reason did not respond adequately to a high dose of radiation.

It is exactly this heterogeneity, the cause of which remains largely unexplored, which in our opinion is one of the main limits of purely physical dosimetry procedures. Here, biodosimetry studies are still urgently needed to better understand the mechanisms of resistance to radiation, which may eventually lead to novel strategies to overcome the same.

While we agree that true radioresistance, as Kao points out, may in a purely physical sense not exist in that any cell, structure, or even every solitary chemical compound will eventually break down given sufficient radiation exposure, we do believe that in a medical sense it does exist. Even in radioembolization, there is a limit to the activity that can be administered without causing undue complications in a palliative setting—where first and foremost the retention or, preferably, improvement of quality of life is paramount.

And of course, radioembolization is not representative for radionuclide therapy at large. Radioembolization in effect functions in analogy to brachytherapy, where spheres containing radiation are targeted directly toward the target tissue through local application and will stay there for the duration of physical radiation decay. This removes a number of the previously [2] discussed variables that play an important role in cell specific entity targeted therapy, such as via receptors, where the distribution volume of the patient and renal and biliary excretion as well as tumor-related factors such as expression level of the receptor and locus of expression play a role in determining both the total uptake and effective half-life. Furthermore, non-target exposure in such therapies plays a far stronger limiting role in activity prescription than in selectively infused radioembolization. All these factors, too, are subject to research in order to improve both the delivery of radiation to target and the reduction of exposure of non-target tissue.

In that sense, whereas we do believe that the "holy gray" has a value in the total complex of dosimetry-based

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individualized patient care, it certainly has its limits. Many biological factors play a role which go beyond pure dosimetry which remain largely unexplored, and hence, we would here once again like to emphasize the paramount importance of further research into radiobiology into realms uncharted beyond the "holy gray."

Declarations

Ethics approval Not required for a literature-based letter.

Conflict of interest The authors declare no competing interests.

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