

Learning from Failure; Hypoxia is an Evil Foe.

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Microsoft founder, Bill Gates once said, "Success is a lousy teacher. It seduces smart people into thinking they can't lose." The corollary of this is that failure can be instructive. I am sure that the authors of the elegantly designed and methodologically rigorous study reported by Vera et al. (Insert reference) would have been disappointed when they analyzed their results and found that they had failed to achieve, by radiation dose escalation, their primary aim of improving outcomes of patients identified as having hypoxic non-small cell lung cancer (NSCLC). Nevertheless, they are commended for their effort and we can learn a lot from their failure. As Sir Winston Churchill once commented, "“However beautiful the strategy, you should occasionally look at the results.”"

The premise of the study was sound. It has been proven, through the seminal work of L. H. Gray over 50 years ago, that hypoxia increases radioresistance ¹. Furthermore, the presence of hypoxia leads to complex changes in tumor biology, which include alterations in cellular metabolism ², impaired DNA-repair and resulting genomic instability ³. Many of these effects are mediated by genes in the hypoxia-inducible factor (HIF) heterodimer. HIF target genes include *MYC*, which increases expression of the GLUT1 transporter and hexokinase ⁴, which, in turn, drive glycolytic metabolism. Additional effects include increased angiogenesis and tumor growth ⁵. Studies in non-small cell lung cancer have demonstrated increased HIF expression in NSCLC is both prevalent and adversely impacts overall survival ⁶. There is also evidence that hypoxia can be imaged in NSCLC and is associated with an adverse prognosis ⁷.

Accordingly, increasing radiation dose is a logical means to overcome the radioresistance and adverse prognostic implications associated with hypoxia. However, dose-limiting toxicity in adjacent tissues mandates that this can only be achieved by reducing radiation treatment volumes ⁸. To address, this challenge a consortium of 15 academic PET facilities sought to address the poor outcomes in NSCLC treated with radiotherapy by escalating radiation to sub-regions identified to be hypoxic on fluorine-18 fluoro-misonidazole (FMISO) PET/CT. Within tolerance, radiation dose was increased to up to 86 Gy in patients who had positive FMISO PET/CT studies compared to a planned treatment of 66 Gy in the absence of hypoxia. Despite this therapeutic intervention, the presence of imageable hypoxia remained strongly predictive of adverse disease-free survival (DFS), with a trend also for adverse overall survival, despite failing to reach statistical significance. Moreover, in patients with positive FMISO scans, there was no difference in DFS of patients with positive FMISO PET in whom dose could be escalated compared to those in whom dose was limited to 66 Gy and both group had worse DFS than patients with negative FMISO studies who received standard therapy. Additionally, response (CR and PR) at 3 months post-radiotherapy based on RECIST 1.1 criteria in the FMISO positive patients was seen in 12/24 (50% [95% confidence limits 31% - 69%]) after the escalated

radiotherapy doses and in 5/10 (50% [24% - 76%]) after 66 Gy. So, the study failed to achieve its primary aim of improving response rates by dose escalation.

What can we salvage from this experience? First, the authors have demonstrated that implementing complex multi-center trials that utilize PET as an imaging biomarker to guide adaptive therapies are feasible. Second, they have confirmed earlier studies that suggested that hypoxia as imaged by PET has a reasonably high prevalence in NSCLC⁹ and again demonstrated the adverse prognostic significance of imageable hypoxia, which has also been shown in head and neck cancer using FMISO PET¹⁰. Finally, and perhaps most importantly, these data suggest that the modest increments on radiation dose that are achievable in a clinical setting are probably insufficient to overcome the radioresistance imparted by hypoxia, or the influence of hypoxia on a tumor's predisposition for tissue invasion and metastatic spread¹¹, which may lead to adverse outcomes even in the setting of adequate local disease control.

The challenge of overcoming hypoxia by simply increasing radiation dose is underpinned by the so-called oxygen-enhancement ratio (OER), which is the degree to which oxygenation increases radiosensitivity. Conversely, the OER influences the radiation dose required to overcome hypoxia. Depending on the extent of hypoxia, this may be a factor of 2-3 and is probably not achievable with conventional radiotherapy techniques. It is also important to recognize that hypoxia is not the only cause of treatment failure. This was emphasized by Rod Withers' 4Rs, namely; **R**epair of sub lethal/potentially lethal damage; **R**eassortment of surviving cells within the division cycle; **R**eoxygenation of erstwhile hypoxic cells during fractionated treatment; and **R**epopulation of surviving clonogenic cells during a course of treatment to which a fifth R (**R**adiosensitivity of clonogenic cells) has since been added¹².

An alternative approach to overcome the adverse significance of hypoxia has been to use it as a therapeutic target by combining hypoxia-activated cytotoxic chemotherapy agents, such as tirapazamine, with external beam radiotherapy. Preliminary studies in advanced head and neck cancer demonstrated both a very high prevalence of imageable hypoxia and response to this combination¹³ and led to a randomized phase II trial of chemoradiation with and without tirapazamine, which confirmed the benefit of adding a hypoxia-sensitizing agent to radiation in the presence of FMISO uptake in head and neck tumors¹⁴. Despite the promise of this therapy, it failed to improve the outcome in a phase III study that lacked cohort enrichment for, or even characterization of, tumor hypoxia¹⁵. A subgroup analysis of patients within this trial who had undergone hypoxia imaging with an alternative hypoxia-imaging agent, F-18 fluoro-azomycin-aribinoside (FAZA) demonstrated again the prognostic significance of hypoxia on PET imaging with patients with a positive FAZA PET treated with conventional chemoradiation having a significantly worse prognosis than those receiving radiation with tirapazamine¹⁶. Studies combining novel radiosensitizing agents with radiation in patients with positive PET hypoxia-imaging studies may be warranted in light of these studies. The presence of hypoxia, by invoking genomic instability, may also increase neoantigenic challenge and underlie the favorable responses being seen with immunotherapy in patients with advanced NSCLC¹⁷. This may also be relevant to radiotherapy outcomes with evidence that there may be synergy between radiation and check-point immunotherapy¹⁸.

Clearly, hypoxia remains an evil foe in our battle to achieve better outcomes in non-small cell cancer but by demonstrating its important, Vera and colleagues pose us the challenge to design new combination therapies. As indicated by Amos Bronson Alcott, "Success is sweet and sweeter if long delayed and gotten through many struggles and defeats."

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The Journal of
NUCLEAR MEDICINE

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J Nucl Med.

Published online: March 30, 2017.

Doi: 10.2967/jnumed.117.191510

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The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

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