Review Article : Will Your Breast Cancer Patient's Mortality Go Up in Smoke?
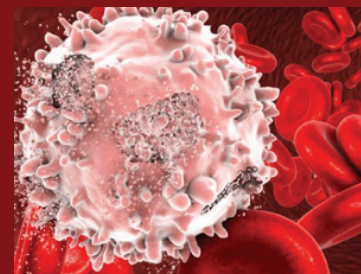
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Abstract:
Dedicated smokers who receive breast radiation may pay an unexpected price- in both recurrence risk and in mortality. Smoking during radiation therapy (RT) noticeably increases (and accelerates) the recurrence risk, but it also increases long-term risks of lung and heart mortality. The recurrence risk probably derives from (temporary) smoking - caused hypoxia. On the other hand, concurrent RT and smoking produces synergistic and permanent heart and lung damage. Tumor cell hypoxia can be exogenous (via smoking) or endogenous (inadequate capillary perfusion) or possibly even environmental (at high altitudes). However it occurs, though, it is a major contributor to treatment failure. Techniques for addressing hypoxia - both currently in the clinic, and on the technological horizon - are briefly reviewed here. These include photoacoustics, FLASH radiotherapy, and Cherenkov - Excited Luminescence Imaging (CELI).

Keywords: FLASH radiotherapy, radiation, hypoxia, smoking, radio sensitivity, hyperbaric oxygen, photoacoustics, breast cancer, CELI

Dedicated Smokers with Breast Cancer

A 50 year old African-American female has just presented for breast radiation therapy (RT). She is ER+ PR+ ERBB2- and has had an adequate partial mastectomy for a 1.2 cm, moderately differentiated, outer quadrant, invasive ductal cancer - with no positive sentinel lymph nodes. She is otherwise healthy and has a negative medical history. However, she started smoking one pack of cigarettes/day at age 18, and she continues to smoke at that rate. She has failed several cessation attempts and does not wish to try again. She asks you what additional risks she will encounter just because she continues to smoke during RT.

You explain that her breast recurrence risk could be 6.7 times higher - merely because she continues to smoke. She may also recur sooner than a non smoker. This is based on 624 patients (52 current smokers) who had a partial mastectomy followed by RT.[i] Of these women, 83% were stages 0-1, while 15% were stage 2 and only 2% were stage 3. Among patients who quit smoking before RT, no such higher recurrence rate was seen. However, overall survival was not impacted, at least during the mean follow-up of 45 months. African-American women were much more likely to be current smokers (22% vs. 7%, p < 0.001). African-American women also have a greater mortality from breast cancer, so this study raises the question of whether concurrent smoking, besides an advanced stage at presentation, may contribute to their mortality. Of course, adverse biology may also be guilty, e.g., smokers have increased rates of p53 mutations.

Unfortunately, she faces even more risks from persistent smoking. In a meta-analysis of 40,781 breast cancer patients[ii] randomly assigned to RT versus no RT in 75 trials (2010-2015), the whole lung got 5.7 Gy and the whole heart got 4.4 Gy. The median year for RT was 2010. The relative risk (RR) of lung cancer (after 10 years) was 2.10 (p < 0.001). The relative risk (RR) for cardiac mortality was 1.30 (p < 0.001). The estimated absolute risk of lung cancer was 4% for continuing smokers, versus 0.3% for non-smokers. The absolute risk for cardiac mortality was 1% for smokers and 0.3% for non-smokers. Independent of RT, the authors emphasize that women

who smoke throughout adulthood face a 20-fold higher risk of lung cancer and a 4-fold higher risk of cardiac death. On the other hand, after one year of cessation, her cardiac risk would be cut in half, while after 10 years of cessation her risk of lung, pancreatic, and head and neck cancers would also be halved. Interestingly, *excess* lung mortality (from concurrent smoking) was only seen 10 years after RT. In other words, if this patient had been older than 70 years (at presentation), then the adverse impact of concurrent smoking might almost be ignored. Despite this, the authors emphasize that most patients would still benefit from smoking cessation before RT.

S. Darby, et al. have shown that breast RT improves absolute survival after 15 years by 2-5%.[iii] However - and critically - this improved benefit is not seen for good-prognosis patients. Even the intermediate risk patients in this meta-analysis showed only a 1.1% risk reduction in mortality (not different from zero), compared to 7.8% in the high risk group. In other words, breast RT would not increase our patient's longevity - as is true for most contemporary breast patients. But she would still face a 4% risk of lung cancer after 10 years. Therefore, RT might actually *decrease* her overall survival after 10 years! The lesson is clear: Concurrent smokers (especially those younger than 70) must be asked about their pulmonary and cardiac histories before starting RT. A positive history, in the face of persistent smoking, might cause this patient to choose a mastectomy (with possible reconstruction) rather than RT.

Two questions were not addressed in the foregoing articles:

1. Did lung cancer occur more commonly on the side of breast RT?

2. Was cardiac mortality higher in women who got left sided RT?

Hypoxia in Other Cancers

In both head and neck cancer[iv, v] and in lung cancer[vi] concurrent (during RT) smokers have noticeably worse mortality from their treated cancer. (In head and neck cancer, however, reformed smokers gain appreciable survival[vii]) These facts remind us of the critical role of oxygen in RT. In order to fix (i.e., make permanent) the damage from RT, oxygen radicals are essential. Although tobacco smoke delivers legions of toxic agents, its adverse effect on RT likely derives chiefly from hypoxia. Harrison's Figure 2 (reprinted from Vaupel)[viii] displays relative radio sensitivity versus tissue pO_2. A radio sensitivity of nearly 3 at 100 mm Hg falls to 2 at about 7 mm Hg, and to 1 at 0.1 mm Hg. (Standard atmospheric pressure is 760 mm Hg. Normal tissues are at about 40 mm Hg, about the same as ambient oxygen on Mount Everest.) So, we would expect cure rates to suffer a major setback just due to hypoxia—perhaps even by a factor of 2-3. Harrison and Blackwell conclude: Tumor control is clearly worse in hypoxic head and neck patients. For another example, in advanced cervix cancer, a value of $pO_2 \leq 10$ mm Hg discriminated (in recurrence risk and in overall survival) between hypoxic and nonhypoxic cancers ($p \leq 0.002$). Results have been similar in soft tissue sarcomas.

RT for rectal cancer is another concern. Since smoking (even without RT) increases the risk of bladder cancer, pre-op rectal cancer patients who smoke might invite higher risks of subsequent bladder cancers. Even absent smoking, we already know that females face higher risks of gynecologic cancers (4.5%) from rectal RT, as compared to those who only had surgery (1.5%), with p < 0.001 for uterine cancer and p < 0.007 for ovarian cancer[ix]. This data may well accelerate the use of short course pre-op RT (5 fractions) for rectal cancer instead of the still widely used 5-6 weeks of daily RT (with concurrent chemotherapy).

These issues led to trials with hyperbaric oxygen (HBO) during RT. (Hyperbaric oxygen is not limited by hemoglobin levels because, during HBO, oxygen is dissolved directly in the plasma.) In 19 randomized trials with 2286 participants, Bennett et al.[x] reported reduced 5-year mortality in head and neck cancers. However, the rate of RT injury was severe (RR = 2.6), including a risk of seizures during RT. Furthermore, the inconvenience of delivering HBO led to wildly varying RT schedules. On the other hand, for cervix cancer, no decrease was seen in 5 year cancer mortality.

Carbogen is a normal pressure gas of 95% oxygen and 5% carbon dioxide. Is this a better choice than HBO? In a rat model, HBO significantly increased tissue pO_2 but carbogen did not.[xi] Nonetheless, the authors report:

"The RT doses to control 50% of tumors were 38.0 Gy, 29.5 Gy, and 25.0 Gy for air, carbogen, and HBO, respectively. Both high oxygen content gas inspirations led to significantly improved tumor responses with oxygen enhancement ratios (OERs) of 1.3 for normobaric carbogen and 1.5 for HBO."

Meanwhile, in 57 humans with high grade gliomas, a combination of HBO with procarbazine, nimustine, and vincristine, and 60 Gy has proven safe.[xii]

In an excellent recent (2020) review of tumor hypoxia by Zhu, et al. [xiii] the authors cite the above glioma work, but also list other hypoxia options: perfluorocarbon-based oxygen carriers, metronomic chemotherapy, calcium peroxide nanoparticles, and even metformin, which reduces tumor oxygen consumption and thereby increases tumor oxygenation. In particular, mice so treated were clearly much less hypoxic.

Meanwhile, until these new approaches are fit for the clinic, what options are available to us? We know that carbon monoxide (CO) competes - tenaciously - in binding to hemoglobin. Oxygen is rudely kicked off hemoglobin by CO, so smokers have high levels of CO after smoking. The elimination half-life of CO (while breathing room air) is about 4.5 hours. (It is only 90 minutes while on 100% oxygen.) Therefore, if patients must smoke during RT, they should at least refrain for 4-12 hours prior to daily RT. I routinely offer this option to all my curative patients. For breast patients over age 70 this may not be critical, but then today most good-prognosis patients over age 70 are often best managed via observation only. In practice this means that smokers will be treated in the morning - after no smoking overnight. Or, if they must be treated directly after smoking, perhaps they should first breath 100% oxygen for several hours before (and maybe even during) daily RT.

One more reason for treating head and neck patients in the morning derives from Bjarnason and colleagues at the Canadian NCI. [xiv]

A total of 205 patients were evaluable, but in a subgroup of 111 patients treated to 66-70 Gy in 33 - 35 fractions, morning patients

had much less toxicity than afternoon patients (p < 0.022). Although concurrent smoking usually worsens mucositis, even the 53 concurrent smokers had significantly less mucositis if treated in the morning. Five months later, the morning patients had lost noticeably less weight than the nonsmokers (p < 0.024). The authors did not report whether these morning smokers actually lit up before daily RT; if not, they should have done better (especially after overnight cessation) - as opposed to the afternoon patients who would have lit up many times before daily RT (and therefore would have repetitively raised their CO levels throughout the day). On the other hand, this favorable morning outcome might have arisen (at least partly) from normal circadian rhythms, which the authors consider: laboratory studies had suggested that twice as many cells would be in the G_2/M phase in the afternoon than in the morning. They therefore predicted that, in the morning, most healthy mucosal cells were in the G_1 phase and therefore less vulnerable to mucositis from RT. Based on this article and on the elevated CO in concurrent smokers, I have routinely preferred treating head and neck patients in the morning.

Pulse oximeters should not be relied on here: they measure dissolved oxygen and are not affected by carboxyhemoglobin. Furthermore, oximeters cannot distinguish between carboxyhemoglobin and normal hemoglobin, so put your oximeters away. Furthermore, noninvasive CO detectors are useless for diagnosing CO exposure. (However, household CO detectors are useful for prevention of CO poisoning.)

Can High Altitudes Worsen Tumor Hypoxia?

A corollary issue is whether RT in high altitude clinics is less effective. This appears to be unexamined. For example, Figure 1 below displays "Oxygen Saturations at Altitude." Note that the left ordinate is PaO_2 (arterial partial pressure of oxygen) while the right ordinate is SaO_2 (saturation percentage). The highest North American RT clinic known to me is in Breckinridge, Colorado, at an elevation of 9600 feet (2926 meters). I have characterized their values in Figure 1. The question is obvious: Do these patients have a lower cure rate as a result of the low ambient oxygen? On the other hand, chronic high altitude exposure typically triggers higher hemoglobin levels, but one study examined urine pO_2, as an estimate of renal tissue oxygenation and found that at 6 hours, urine pO_2 decreased at all altitudes. It returned to baseline by 24 hours at the lowest altitude (1,780–2,085 m), although not after exposure at the highest altitude (2,454–2,800 m).[xv] The Breckinridge RT clinic is even higher than that.

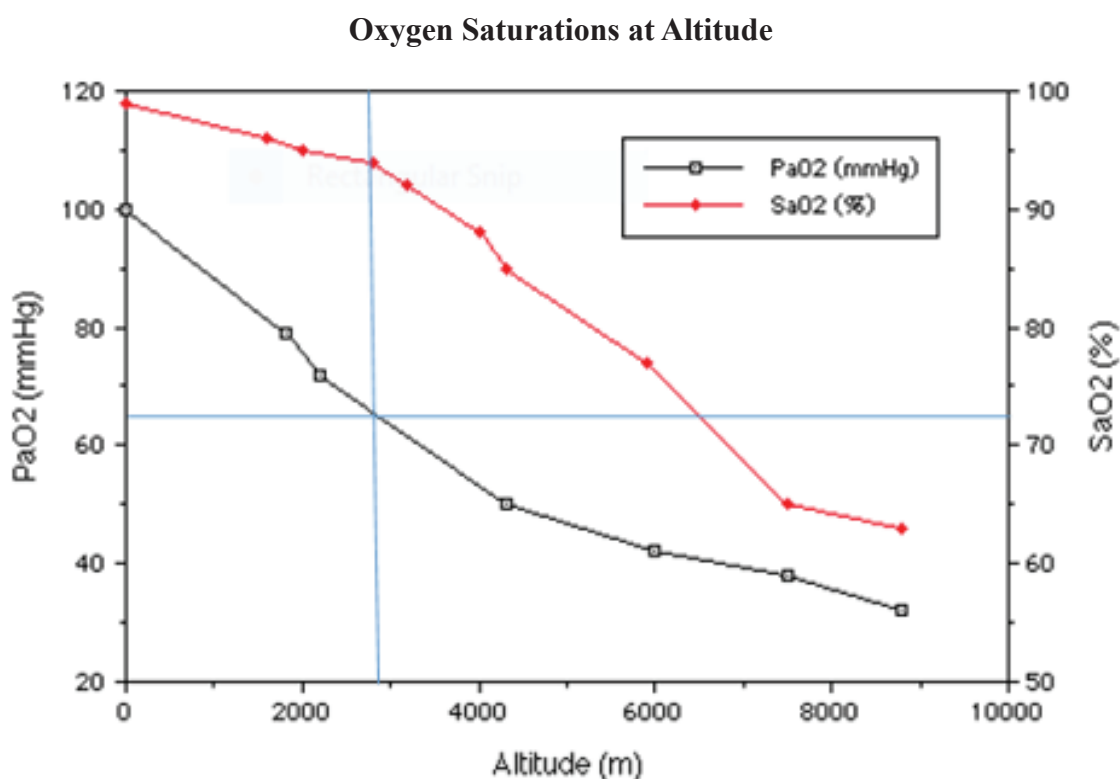## Oxygen Saturations at Altitude

Figure1. Breckenridge is characterized by the thin orthogonal lines.

At 490 meters, median cerebral tissue oxygenation was 85%, while peripheral oxygen saturation as measured by pulse oximetry (SpO2), was 93%. At 2,590 meters, the corresponding values were 59% and 86%, respectively (p < .05). [xvi] So, we can conclude: Tissue oxygenation is seriously affected by ambient oxygen pressures.

Can We Now Image and Even Measure Tumor Hypoxia?

The real issue, of course, is not normal tissue oxygenation, but rather *tumor* oxygenation. The literature on this, as a function of altitude, is almost nonexistent but that may change, due to our recent ability to image hypoxia. [xvii] Using the photoacoustic effect, [xviii] Klibanov and Hu *noninvasively* were able to measure tumor hypoxia. (This effect was first discovered in 1881 by Alexander Graham Bell.) The modern technique employs rapid heating during nanoseconds with non-ionizing lasers. As this energy is absorbed, the tissue heats and undergoes thermoelastic expansion; that expansion spontaneously produces wideband

(i.e., MHz) ultrasonic emission. These waves are then detected via ultrasonic transducers and subsequently analyzed to produce images. The magnitude of the ultrasonic emission reveals the contrasts in physiologically specific optical absorption spectra. To be specific, the level of blood oxygenation defines the hemoglobin absorption spectrum. As the blood oxygenation level changes, so does the shape of the spectrum, and that permits calculation of tissue hypoxia. See Figure 2.

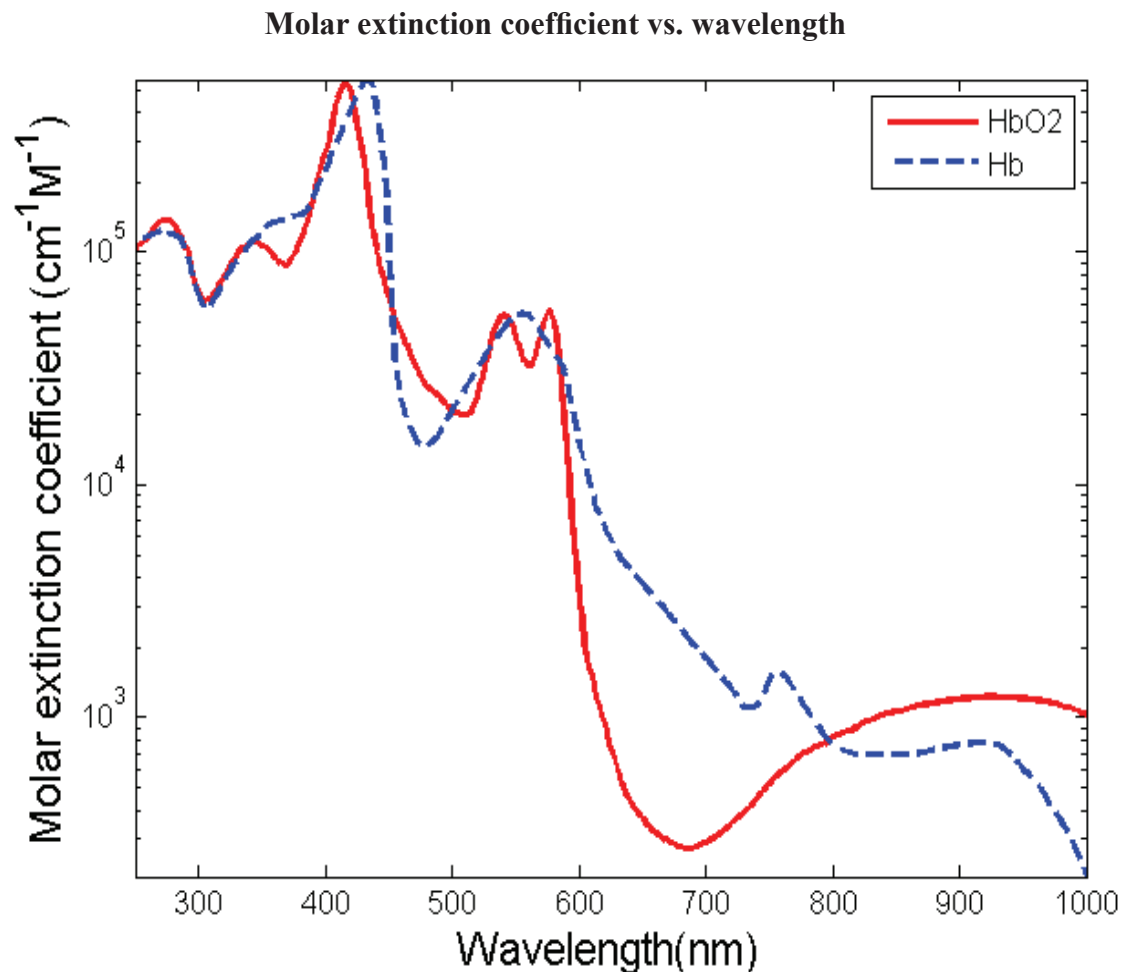## Molar extinction coefficient vs. wavelength

Figure2. Absorption spectra of oxy- and deoxy-hemoglobin

The sound waves in photoacoustics penetrate only several centimeters, so it is only useful for superficial tumors, e.g., lymph nodes in head and neck cancer. But the high resolution permits separate measurements of the (1) normoxic rim, (2) normoxic core, and the (3) hypoxic core. This study can even be performed in real time, so that changes due to inhalation of carbogen (for example) can be monitored over minutes or hours. Remarkably, after an oxygen challenge, the authors were surprised by a *reduction* of oxygen saturation level in the hypoxic core. This immediately suggests that, if carbogen is being considered, such a study must first rule out a counterproductive result. One could even consider daily or weekly monitoring of hypoxia throughout radiation therapy. Medical oncology, in particular, might profit from knowing the results produced by their chosen potions. For example, if after one cycle their results were disappointing, they might switch agents.

Two More Possibilities
Norman Coleman and J. C. Buchsbaum have recently reported

(in February 2021) that FLASH radiotherapy [xix] has now entered its clinical phase: bone metastases have been treated with protons via a single fraction of 8 Gy, typically delivered at 40 Gy/second over a few tenths of a second. [xx] (The first patient was treated at the University of Lausanne, Switzerland.) FLASH may succeed by overcoming tumor hypoxia. Independent of the underlying reason, though, if FLASH works in the clinic a minor revolution in RT delivery may follow. For example, as RT becomes useful for a wider variety of tumors it might invade territory previously occupied solely by medical oncology.

Xu Cao and colleagues at Dartmouth University, including the Geisel School of Medicine (named after the creator of Doctor Seuss), have used (*noninvasive*) Cherenkov-Excited Luminescence Imaging (CELI), which excites a porphyrin-like phosphor molecule (PtG4) to enter a triplet state. [xxi] (Cherenkov radiation also causes the flashes detected by optic structures in patients. [xxii]) This radiation is produced by a charged particle traversing a dielectric medium - in this case by the secondary electrons from 6 MV X-rays, while traversing an 8 mm mouse

tumor. Cherenkov radiation occurs when the speed of light (in the medium) is less than the particle speed. In water, the speed of light is only about 75% of that in a vacuum. This process is similar to the production of a sonic boom in air, where the speed of sound is less than that of the flying object (e.g., a bullet or an aircraft).

The phosphor (PtG4) was introduced via IV a day in advance, so that it was distributed throughout the tumor during radiation. A lead enclosed camera measured the emitted light intensity from the phosphor.

Its triplet state is naturally quenched by oxygen [xxiii]; therefore its intensity is an indirect measure of the tissue oxygen level. As a confirmation of their CELI data, the authors also employed an *invasive* technique with IV administered pimonidazole (as an indirect marker of hypoxia), after which the mice were sacrificed and tissue sections were stained to display pimonidazole. The authors concluded that hypoxia (defined as less than 10 mm Hg) is extremely heterogeneous on the submillimeter scale, likely due to large variations in capillary perfusion of the tumor. They found that the hypoxic fraction *decreased* significantly when the imaging resolution worsened from 0.2 mm to 3 mm. The latter is the current clinical limit of PET via fluoromisonidazole or fluoroazomycin arabinoside. However, the authors admit that the imaging depth of CELI is only 2 cm. Furthermore, the technique now provides only 2-dimensional pO_2 images, but they propose that tomographic reconstructions may become possible.

Conclusion: Practical Lessons for the Clinic

1. Breast cancer patients who are dedicated smokers do not automatically benefit from RT. In fact, good-prognosis patients might even be harmed by RT. If cessation does not occur, these patients might instead choose mastectomy or even observation.
2. Or, if they refrain from smoking for 4-12 hours before RT, they might still try RT. Another option might be oxygen for 1-2 hours just before daily RT.
3. Mortality in breast patients over age 70 is less likely to be decreased by concurrent smoking but they may still face a much higher (and earlier) recurrence risk.
4. Any curative patient (with any diagnosis) should either stop smoking, or refrain from smoking for 4-12 hours before RT. This likely means that the morning clinic will contain all current smokers, with the afternoons left for nonsmokers.
5. Patients (of all diagnoses) treated with curative intent at high altitude might instead consider migrating to a lower altitude during RT until these issues are better understood.
6. All of these lessons likely apply to curative chemotherapy, so educate your medical oncology colleagues, especially about the risks of smoking during chemotherapy.

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