

Hypoxic Radiosensitization: Adored and Ignored

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ABSTRACT

Since observations from the beginning of the last century, it has become well established that solid tumors may contain oxygen-deficient hypoxic areas and that cells in such areas may cause tumors to become radioresistant. Identifying hypoxic cells in human tumors has improved by the help of new imaging and physiologic techniques, and a substantial amount of data indicates the presence of hypoxia in many types of human tumors, although with a considerable heterogeneity among individual tumors. Controlled clinical trials during the last 40 years have indicated that this source of radiation resistance can be eliminated or modified by normobaric or hyperbaric oxygen or by the use of nitroimidazoles as hypoxic radiation sensitizers. More recently, attention has been given to hypoxic cytotoxins, a group of drugs that selectively or preferably destroys cells in a hypoxic environment. An updated systematic review identified 10,108 patients in 86 randomized trials designed to modify tumor hypoxia in patients treated with curative attempted primary radiation therapy alone. Overall modification of tumor hypoxia significantly improved the effect of radiotherapy, with an odds ratio of 0.77 (95% CI, 0.71 to 0.86) for the outcome of locoregional control and with an associated significant overall survival benefit (odds ratio = 0.87; 95% CI, 0.80 to 0.95). No significant influence was found on the incidence of distant metastases or on the risk of radiation-related complications. Ample data exist to support a high level of evidence for the benefit of hypoxic modification. However, hypoxic modification still has no impact on general clinical practice.

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INTRODUCTION

Since the first clinical description by Gottwald Schwartz^{1,2} in 1909 of the phenomenon of clinical radioresistance (Fig 1), which would later be known as hypoxic radioresistance, for almost 100 years, the issue has both haunted and fascinated researchers within the field of radiotherapy and related disciplines. This is illustrated by an overview of the 10 most cited papers in each of the four top ranked international radiotherapy journals. Not only do three of the four most cited papers in the journals deal with hypoxia,³⁻⁵ but also, among the 40 most cited papers, 17 (43%) are related to hypoxia and radiation resistance. More recently, the issue of hypoxia has been described as an important factor for development of tumor aggressiveness, and there is probably an overlap between this phenomenon and the poor outcome of hypoxic tumors to radiotherapy.^{6,7} However, the present article will not deal with all of these issues but, instead, will focus on the simple phenomenon that tumors and tumor cells that are deprived of oxygen are simply resistant to radiotherapy as it is delivered by most conventional methods.

The hypoxic cell radioresistance is a result of lack of oxygen in the radiochemical process by

which ionizing radiation is known to interact with cells. The magnitude is well described by the oxygen enhancement ratio, which characteristically is in the order of 2.7 to 3.0. The phenomenon is most clearly seen after large single doses of radiation but also exists in normal fractionated radiotherapy. It is typically only observed in solid tumors, whereas normal tissues tend to have sufficient amounts of oxygen from a radiosensitization point of view. The level of hypoxia that causes radioresistance is in the order of 5 mmHg or less, which is in the more extreme end of the hypoxic scale, whereas the influence of other hypoxic-related biologic phenomena may happen at hypoxia levels that are less severe and range between 20 and 5 mmHg. In this respect, it should be noted that hypoxia, strangely enough, is more accurately defined as being less than the normal oxygenation level, rather than defined by itself per se. Thus, hypoxia ranges widely, and the biologic processes that may be influenced and induced by hypoxia may be strongly dependent on the extent and time of persistence of hypoxia.

From a radiobiologic point of view, hypoxia generally occurs in solid tumors mainly as a function of insufficient vascularization.^{5,8-10} Thus, cells situated with sufficient long distance from a functional blood vessel will become deprived of oxygen as a

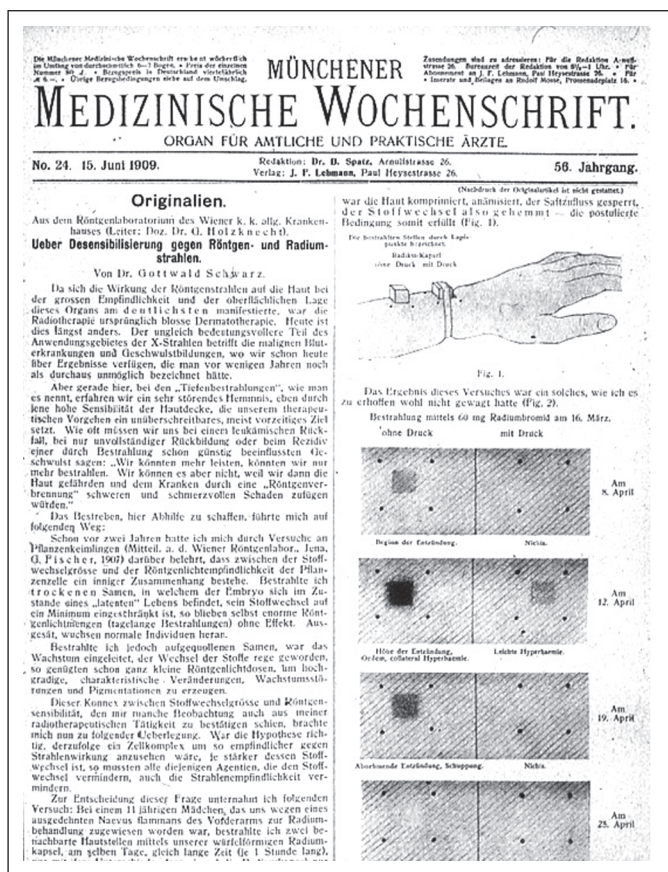


Fig 1. Article by Gottwald Schwarz¹ (1880-1959) describing the first clinical observation of the importance of hypoxia. The findings of Gottwald Schwarz were used to introduce the concept of “kompressionsanämie” by which the skin was made anemic, thereby allowing a higher dose to be given to deeply situated tumors, a biologic concept in “Röntgentherapie.” In 1914, he also observed the magnitude of the oxygen enhancement ratio²: “Kompressionsanämie der Haut setzt die Röntgenempfindlichkeit derselben auf ein Drittel herab,” but without realizing that oxygen was the causal factor.

result of limited diffusion. In addition, hypoxia may occur on a more intermittent basis in areas of tumors where blood vessels could be temporarily shut off, and thus, the section of the tumor that is supplied by such a closed vessel will render hypoxic for a limited time (transient hypoxia). To what extent the two phenomena exist in all tumors and how they interact is not known, but, probably, the diffusion-limited hypoxia is the prevailing cause of hypoxia in most solid tumors. If tumor cells outgrow their functional vasculature supply, diffusion-limited hypoxia is likely to occur, and the importance of this in terms of radiation resistance depends on to what extent such hypoxic cells are stem cells with a maintained potential of renewed growth if not eradicated. Thus, the practical magnitude of hypoxia depends on the presence of clonogenic hypoxic stem cells and the capability of such cells to stay alive during extreme prolonged hypoxia. It is likely that this differs among tumor types, and it is tempting to assume that especially squamous cell carcinomas, which have origin in a nonvascularized epithelium and thereby under their normal conditions may be in a rather hypoxic state, are more likely to maintain a clonogenic potential during long-term hypoxia. Experimental data are in favor of such a hypothesis, and this may also explain why squamous cell carcinomas in practice have been shown to be the tumors that are most

modifiable by manipulation of hypoxia. Other tumors that tend to be extremely hypoxic in terms of turning into necrosis include, among others, sarcomas. It might be that cells in such tumors have a short life expectancy when they become hypoxic and, therefore, rapidly turn into necrosis. This implies that the hypoxic problem in terms of radioresistance may be more limited because, in reality, such cells are doomed to die anyway.

During the first half of the last century, the radiobiologic focus was mainly associated with normal tissue hypoxia and the means of using this to reduce acute normal tissue morbidity by so-called compression anemia, thereby allowing larger doses to penetrate into tumors. It was not until 1953, when Gray et al¹¹ not only pointed toward the importance of tumor hypoxia as a cause of radioresistance, but also described potential modifications such as by hyperbaric oxygen (HBO),¹² that the issue gained wider attention. Since then, both experimental and clinical research has focused toward means of modifying hypoxia, but although numerous clinical trials have been performed, hypoxic modification has not reached a platform where it has become an issue in daily radiotherapy practice. In fact, there exists a kind of schizophrenia in the sense that hypoxia is still one of the most widely quoted issues of radioresistance and almost any clinical related research application in radiotherapy brings hypoxia up as an important factor and yet its routine clinical use is very limited. If one makes a search of articles on hypoxia and radiotherapy in Medline, one will find that, among the several thousands of publications dealing with the issue, only approximately 3% are addressing hypoxia in the therapeutic clinical setting.

Thus, hypoxia is adored and ignored: adored in the laboratory and ignored in the routine clinical situation. Therefore, the renewed interest in hypoxia is not so much caused by the fact that new information or methods have become available; it is merely the normal fluctuation in interest that follows the change of generations, and although new methods of radiotherapy delivery, more fancy biologic imaging methods, and computerized possibilities in modeling make the issue more interesting at a more sophisticated level, the problem is still the same old theoretical and experimental discussion of a topic that has great difficulties in finding its place in normal practice. The reasons for this are plentiful, but although a new drug has recently been explored,^{13,14} this area is basically characterized by a limited commercial interest because most of the solutions are represented by fairly inexpensive drugs and other methods that are not subjected to patent and, thereby, provide no major incentive for exploration in expensive clinical trials. The other point is a more critical professional issue, namely that, despite our hailing of evidence-based medicine as a platform, the profession often neglects the evidence unless it is associated with new technologic gadgets or/and it is commercially presented and marketed. However, this factor does not make hypoxia less interesting or important, as will be discussed in the following sections.

MEASUREMENT OF HYPOXIA

We have a fairly detailed knowledge about hypoxic distribution and variation in human tumors and tissues, but to some extent, it represents another paradox, namely that most of the clinical trials on hypoxic modification were performed before our knowledge of clinical measurements of tumor hypoxia. In fact, most studies were performed on indicia derived from animal experiments and where the

only clinical indication of hypoxia was the presence of necrosis within a certain distance from small blood vessels,¹⁵ which just suggested the indication of the earlier-mentioned diffusion-limited hypoxia. Thus, no clinical trials exist that are based on prior knowledge of hypoxia in the individual tumors in question or that stratify according to extent of hypoxia, although such information is currently being derived retrospectively.

The principles for measuring hypoxia in human tumors are mainly based on three different principles^{3,16-22} (Table 1). The first includes measurement of the physical amount of oxygen in a tissue. The second is the use of hypoxic markers that are reduced under the presence of hypoxia and can subsequently be identified by various imaging methods such as immunohistochemistry or positron emission tomography. These markers tend to measure the presence of hypoxic metabolic active cells, and in contrast to the physical method, this method does not measure necrosis. The third principle is more indirect because it is an identification of biologic processes, gene expression, and so on that are known to be caused by the presence of hypoxia. Most of this is associated with the hypoxia inducible factor-1 alpha cascade (hypoxia inducible factor-1 alpha and carbonic anhydrase IX) or other processes involved in hypoxia.^{6,18,23} Most recently, focus has been given to the expression of lysyl oxidase, which is currently one of the most promising markers for radiobiologic hypoxia.^{6,24}

In addition to the direct hypoxic estimation, other more indirect imaging parameters are also of use, especially measurement of vascular density and blood flow by magnetic resonance imaging and computed tomography. On the basis of these methods, hypoxia has been described to various intents in most human tumors and clearly constitutes a feature associated with solid malignancies.^{17,25}

The presence of measurable hypoxia is associated with poor outcome.^{6,7,21} This is seen not only after treatment with radiotherapy, but also has been described as a phenomenon linked with a more aggressive tumor phenotype (eg, the presence of severe hypoxia in sarcomas is a prominent sign of poor prognosis). Concerning the relationship between hypoxia and outcome after radiotherapy, there are numerous studies, especially in squamous cell carcinomas, indicating that hypoxic tumors do have a significantly poorer outcome than tumors that express less hypoxic features.^{3,16,19,21} However, it should be made clear that practically all of such associations between hypoxia and outcome after radiotherapy are made in studies where the comparison has been between more and less hypoxia, not hypoxia and no hypoxia. Although at times these studies are taken as an indication that a link exists between radiotherapy and hypoxia in terms of outcome, it should be noted that, with a single exception, all the studies showing a relationship in fact are just demonstrating that hypoxia is associated with poor prognosis after radiotherapy; they do not show that modifying the hypoxia will render the treatment outcome more

beneficial. In other words, these studies do not demonstrate that hypoxia can be modified and result in better response to radiotherapy; thus, the observation of the hypoxic status may be prognostic rather than predictive.

There is an obvious schism between the observation that most human tumors are found to contain hypoxic areas⁴ and the fact that they can be controlled by relatively small doses of radiation. The reason for this is either that the described hypoxia is unimportant by not involving clonogenic cells or, more likely, that significant reoxygenation may occur during fractionated radiotherapy. There is experimental evidence for such a phenomenon²⁶ and also strong clinical indications, although indirectly in the form of repeated positron emission tomography measurements with hypoxic tracers.^{27,28} The magnitude and time course of reoxygenation may be fractionation sensitive, and tumors treated with hypofractionated radiotherapy (administering larger but fewer doses per fraction) are most likely to express radiotherapy-related hypoxic resistance as a result of lack of sufficient reoxygenation.⁵

Our knowledge related to the hypoxic status of tumors is rather recent and has mainly been gained years after many of the clinical trials attempting to overcome hypoxia were performed. The indication for hypoxia-modifying studies was based on the histopathologic observation of necrosis and distance from capillaries in human tumors¹³ and not on more elaborate measurements or other characteristics. Thus, our knowledge in this field has been generated in retrospect.

CLINICAL MODIFICATION OF HYPOXIA

The methods of clinically attempting to overcome hypoxic radioresistance are listed in Table 2.^{5,8,10,12,29-36} With the exception of high linear energy transfer irradiation, which from a radiobiologic point of view may eliminate the importance of hypoxic radioresistance by having a more direct target of radiation in the cells, the other principles can be separated into three different groups. One group is increasing delivery of oxygen through the blood. This may happen by HBO breathing, which in principle will result in a physical increase of the oxygen content in the blood. Typically, this is taking place with the use of the 3-atmosphere HBO, a method by which the first randomized clinical trials were performed (Fig 2).^{12,29,34,37} Also, normobaric oxygen/carbonogen has also been applied and, at times, combined with nicotinamide, a B₆ vitamin analog that is known to counteract the acute hypoxia³⁶ and, thus, may be useful in combination with the oxygen delivery method that, otherwise, is only targeted toward reducing the diffusion-limiting hypoxia. The latter combination is among other combinations known from the so-called ARCON strategy, which is currently tested in a large clinical trial in the Netherlands.³⁸

Table 1. Principles of Measurement of Hypoxia in Human Tumors

Measuring the physical amount of oxygen (eg, Eppendorf electrode); this will include values from in necrotic tissue
Labeling of metabolic active hypoxic cells by their ability to reduce specific compounds (eg, pimonidazole, PET scanning with Cu-ATSM, [¹⁸ F]misonidazole, or 18FAZA)
Identification of cells with hypoxic induced gene activation and related molecular activity (eg, HIF-1 α , CA IX, OPN, LOX)
Abbreviations: PET, positron emission tomography; Cu-ATSM, copper-diacyetyl-bis(N[4]-methylthiosemicarbazone); 18FAZA, [¹⁸ F]fluoroazomycinarabinofuranoside; HIF-1 α , hypoxia inducible factor-1 alpha; CA IX, carbonic anhydrase IX; OPN, osteopontin; LOX, lysyl oxidase.

Table 2. Methods of Modification of Hypoxic Radioresistance in Clinical Trials

Increased oxygen delivery by the blood
Hyperbaric oxygen
Normobaric oxygen/carbogen breathing
Nicotinamide
Blood transfusion, erythropoietin
Mimic of oxygen in the radiochemical process
Nitroimidazoles
Destruction of hypoxic cells
Hypoxic cytotoxins
Hyperthermia
Elimination of OER
High LET

Abbreviations: OER, oxygen enhancement ratio; LET, linear energy transfer.

The second main principle of hypoxic cell radiosensitization is the use of nitroimidazoles, which are found to mimic the effect of oxygen in the radiochemical process, although to a lesser extent.^{29,35} Thus, at a clinically acceptable toxicity level, an expected oxygen enhancement ratio of, at the most, 1.5 to 2.0 can be theoretically achieved. Early drug development was focused around misonidazole and its derivatives, but now it is more focused on 5-nitroimidazoles, which may express clinically relevant sensitization together with less severe toxicity (Fig 2).³⁹ The dose-limiting factor for the 2-nitroimidazoles is a delayed peripheral neuropathy, which is the main reason why the most used drug in this area (misonidazole) was unable to reach routine clinical use. There exists within the clinical range a relationship between the amount of nitroimidazoles and the extent of hypoxic radiosensitization. This is linked with an overall cumulative tolerance as well, which in turn, makes it difficult to secure an optimal drug schedule together with the most beneficial radiotherapy fractionation schedule. Most of the recent trials with hypoxic modification have been performed with hypoxic cell radiosensitizers, but although they have shown significant efficacy, the effect has been too small to secure a broader interest in this area.

The third group is the so-called hypoxic cytotoxins, which, rather than sensitize, are aimed at destroying hypoxic cells.^{8,13} Thus, this category of drugs is known to be strongly cytotoxic for cells under hypoxic conditions in an almost selective manner and will, therefore,

eliminate the problem of hypoxia by successfully killing such cells. In addition, these drugs are dose dependent in both time and concentration, but the most prominent of them (tirapazamine) has been tested in phase III randomized clinical trials that have not yet been published.

Over the years, the clinical importance of hypoxia and its potential modification has been one of the most investigated issues in radiotherapy. Numerous clinical trials have explored the various means of modifying hypoxia, but most have been inconclusive, partly because they are small and underpowered, and others have used techniques that are difficult to practice routinely today (eg, HBO). Furthermore, many of the trials were performed in the 1970s and 1980s at a time when clinical trial methodology was less rigorous, and thus, the information from the individual studies may have limitations compared with what is normally recorded today. However, there is still substantial information to be gained from these studies, and with the continuous interest for hypoxic modification in mind, knowledge of past experience is of great value.

There have been several overviews dealing with this topic,^{5,8,29-33,40-42} either related to a specific type of hypoxic modification, such as the use of nitroimidazoles^{30,31,41,42} or HBO,⁴⁰ or in specific tumor sites.^{41,42} In addition, in 1996, we performed an overview of all randomized trials known so far.⁵ Since then, an additional number of relatively large clinical trials have been published or updated, and therefore, it seems appropriate to modify and update the overview analysis.

The criterion for inclusion in the present overview analysis has been that the treatment should be curatively intended primary radiotherapy alone with random assignment to a hypoxic modifier that should be known only to influence hypoxic radioresistance and have no other cytotoxic effect. Thus, studies involving chemoradiotherapy, either as baseline treatment or as an intended hypoxic modifier (eg, mitomycin), or hyperthermia are not included. Studies of patients with metastatic disease are also not included because the analysis focuses on the effect of curatively intended radiotherapy. The hypoxic modification in the trials has been either oxygen breathing under normobaric or hyperbaric pressure or the use of nitroimidazoles. The few studies with hemoglobin modification by either transfusion or the use of erythropoietin are not included because there has been some uncertainty about their interpretation and also the

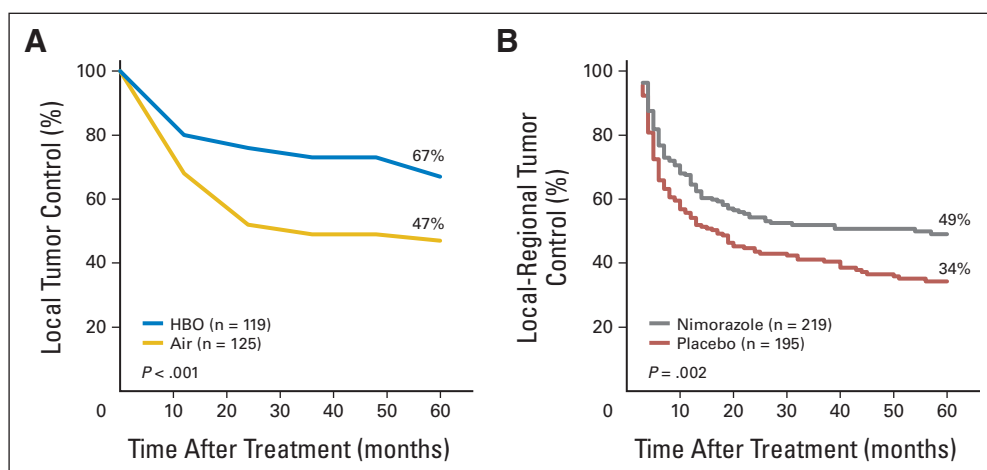


Fig 2. Examples on outcome of clinical trials with hypoxic modification. (A) The Medical Research Council (MRC) multicenter trial with hyperbaric oxygen in advanced uterine cervix³² and (B) the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5 trial using nimorazole in treatment of advanced squamous cell carcinoma of the head and neck.³⁴ HBO, hyperbaric oxygen.

erythropoietin-related studies are not available in sufficient detail and are currently under intense scrutinization.

The present knowledge about the randomized trials with hypoxic modification has been gained by a systematic search through Medline using the following search terms: hypoxia OR hypoxic OR oxygen OR hyperbaric OR nitroimidazoles AND (radiotherapy OR irradiation) AND (cancer OR neoplasms) AND human AND randomized clinical trials. This search initially yielded 169 references and included all but one previously (to the author) known published articles in the peer-reviewed literature (only one article in French language was not detected). The search further included all relevant referred literature found in the identified publications plus a scan of abstracts from relevant scientific meetings (eg, American Society of Therapeutic Radiology and Oncology, European Society for Therapeutic Radiation and Oncology, specific meetings on hypoxic modification, and so on). In addition, investigators from large multicenter cooperative groups and relevant pharmaceutical companies were contacted. The author has been active in this field for more than 30 years and has, in addition, a wide personal network within this field of research that further was used to explore unknown trials. The use of the described search strategy, however, identified all the included studies, although a few were in the format of abstracts of which some had subsequently been published, and some other studies have been updated and published in more detailed. Therefore, the following overview of the literature should be considered to cover the international experience so far. The references to the older trials can be found in previously published overview analyses,^{5,8,30-32,40-44} whereas the most recently published studies are directly referred to in the present article.^{39,45-66}

Unfortunately, it has been impossible to collect individual patient data from many, especially old, trials because much of the material no longer exists; therefore, the overview is based on an extract of information from the published articles. Because there is some variation in the observation time, the studies are evaluated by the use of an odds ratio (OR) analysis, which is considered to be one of the more robust, although crude, methods.⁶⁷⁻⁶⁹ The numbers of events are taken either directly from the published information or, if not possible, from measurement of published survival curves as previously described.⁶⁸ The following end points have been addressed: locoregional control, overall survival, frequency of distant metastases, and radiation-related complications. The updated overview will only give a summary of the recorded information; however, this should be sufficient to give the necessary impression of the potential impact of hypoxic modification.

The survey identified 10,108 patients treated in 86 randomized trials applying HBO (26 trials), normobaric oxygen or carbogen (five

trials), hypoxic radiosensitizers (54 trials), or both HBO and hypoxic sensitizer (one trial). An additional two trials were excluded because of lack of useful data. The tumor sites investigated were bladder (11 trials), uterine cervix (19 trials), head and neck (31 trials), CNS (10 trials), lung (10 trials), and other (esophagus, pancreas, and mixed sites; five trials). The trials were analyzed with regard to locoregional control (70 trials), overall survival (84 trials), distant metastases (28 trials), and radiation-related complications (21 trials). Most of the trials have both outcomes related to locoregional control and survival, except for the CNS studies where the only end point analyzed was survival.

The general outcome is seen in Figure 3, which shows that, overall, there is a significant OR of 0.77 (95% CI, 0.71 to 0.86) for the outcome of locoregional control. There is a similar significant survival benefit, with an OR of 0.87 (95% CI, 0.80 to 0.95). The use of hypoxic modification yielded no significant difference in the risk of developing distant metastases (OR, 0.93; 95% CI 0.81 to 1.07), and it also did not have any significant influence on the overall risk of radiation-related complications.

When the locoregional outcome data were analyzed according to tumor site, the same overall trend was observed at all tumor sites (Fig 4); however, only the head and neck and uterine cervix had sufficient numbers of trials and patients to secure a significant tumor site-specific benefit. Similar findings were observed regarding overall survival (Fig 5), where all studies except CNS showed a favorable outcome when treated with hypoxic modification. The survival benefit was somewhat less than for the locoregional control response, which is as expected for this more indirect end point. However, the overall survival value did also include the outcome of CNS tumors (where no locoregional data were available). Despite the initial enthusiasm that was expressed by one of the first clinical trials with hypoxic sensitizers by Urtasun et al,⁷⁰ the subsequent evaluation of nitroimidazoles in gliomas and astrocytomas has shown to be without benefit, and the relatively large number of trials indicate conclusively that hypoxic modification with nitroimidazoles has no benefit in this tumor localization.

When analyzed according to the method of hypoxic modification without taking other factors into consideration, HBO seems to be more beneficial than normobaric oxygen or hypoxic modification (Fig 6). Whether this is a true observation or a result of the fact that many hyperbaric trials were performed with high doses per fraction, which is known to increase the hypoxic radioresistance, remains to be shown. Most detailed experience comes from the head and neck studies, where there exists a clear dose-response relationship, with the hypoxic modification being most prominent when hypofractionation

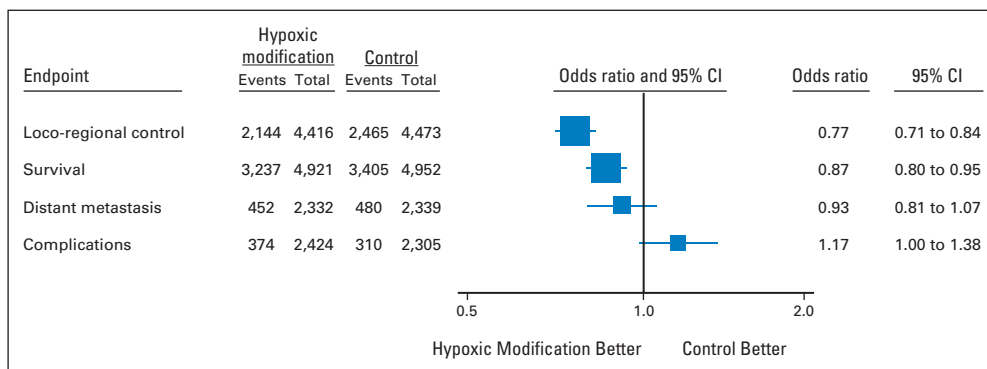


Fig 3. Overview of hypoxic modification of radiotherapy. Data are from 86 randomized trials including 10,108 patients.

Hypoxic Radiosensitization

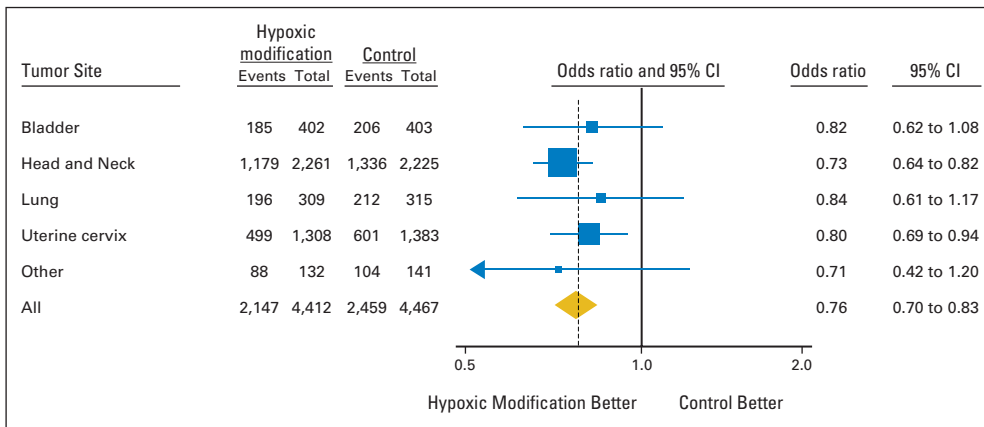


Fig 4. Hypoxic modification of radiotherapy. Influence on locoregional control as a function of tumor site.

is used but still having a significant benefit at conventional fractionation levels or even with hyperfractionation. The relationship is probably a mixture of both factors, but it certainly points toward the importance of proper fractionation, and with the increased interest in hypofractionation and with the further indirect use of larger doses per fraction with the application of intensity-modulated radiotherapy techniques, it should be kept in mind that such treatment is likely to enhance the hypoxic problems and must be considered biologically less advantageous in tumors with known hypoxic radioresistance. The use of hypoxic sensitizers has a generally less pronounced effect than the hyperbaric treatment, as discussed earlier (also when excluding CNS tumors). This may be partly because of the more conventional fractionation schedules used and partly because of less efficient drugs. However, in the largest investigated site of head and neck cancer, conventional fractionation with hypoxic modification overall yielded a significant benefit in locoregional control of a clinically important magnitude. The other large tumor site investigated is the uterine cervix, and although there is an overall small significant benefit, this group contains some of the largest variations in trial outcomes, including one of the few studies that are significantly in disfavor of hypoxic modification. Overall, this makes it more difficult to make a conclusion on the implication of hypoxic modification in this tumor site. Uterine cervix cancer probably responds like the other squamous cell carcinoma tumors, and one cannot rule out the potential importance for hypoxic modification in this site, which is one of the most obvious tumor sites to further investigate in new trials.

In 61 trials with a total of 8,889 patients, there were comparable outcome data on locoregional control and survival, and as seen in Figure 7, there is a clear correlation between the benefit achieved for locoregional control response and the consequently associated survival. The fact that, in these primarily squamous cell carcinoma tumors, an improved locoregional control translates into better survival should be a further incentive to explore the potential benefit of hypoxic modification. Figure 7 also shows that most of the studies, on an individual basis, have a favorable outcome after hypoxic modification; thus, this points toward a clear pattern of benefit, although most of the individual studies may not be statistically significant by themselves because the older studies, in general, are underpowered. The outcome of the overview points toward a likely expected benefit of hypoxic modification administered with conventional fractionation of approximately 10% improvement in locoregional control of squamous cell carcinomas. Assuming this magnitude to be true, the individual trial recruitment must be 1,000 patients to demonstrate the benefit. Therefore, the lack of significant improvement in most trials, which on an average include less than 100 patients, is no surprise and should not be taken as a sign of no benefit, but rather, these trials illustrate too much optimism and lack of understanding for proper clinical trial design.

Obviously, this trial design can be improved if existing markers of modifiable hypoxia were identified. There are several studies suggesting that this may be the case,^{14,22,71} most prominently shown by the

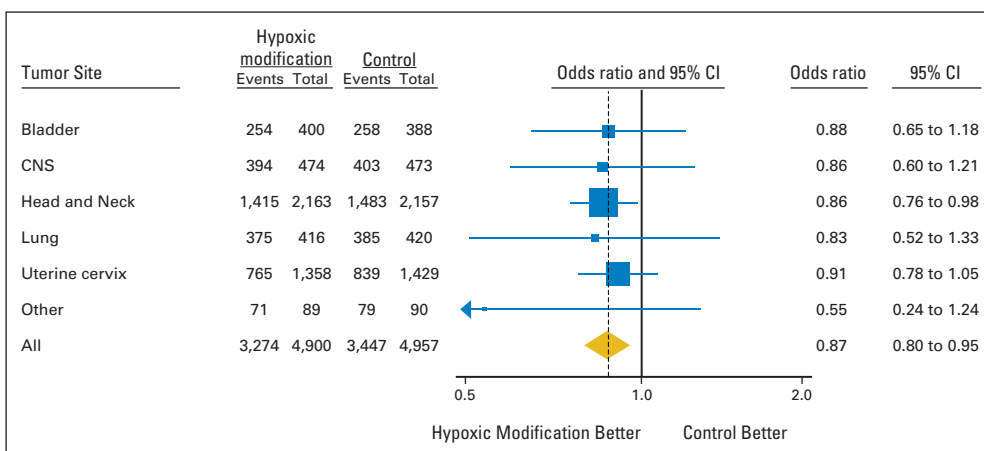


Fig 5. Hypoxic modification of radiotherapy. Influence on overall survival as a function of tumor site.

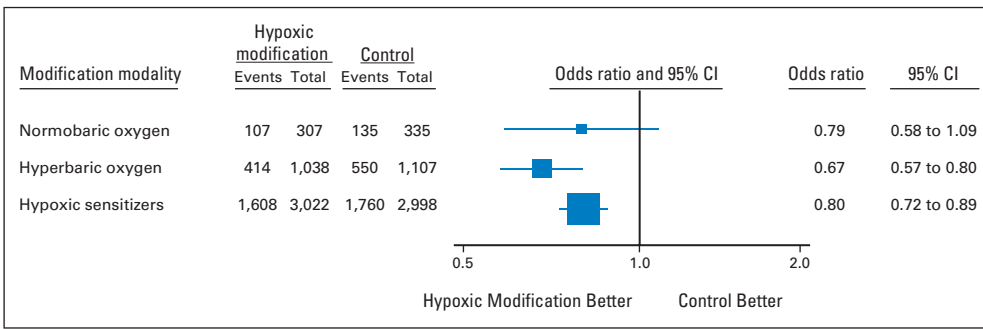


Fig 6. Hypoxic modification of radiotherapy. Influence on locoregional control as a function of type of modification.

analysis of serum osteopontin as a predictive marker for treatment with nimorazole.⁷¹ The best way to further explore such markers would be by collecting biologic specimens from past clinical trials and, if possible, applying the proposed predictive markers on such material. Only by addressing a potential predictive marker in material collected from a randomized clinical trial can the true potential of prediction be evaluated. Several markers are currently under investigation in that aspect, but with the exception of osteopontin, they have not so far been successful (eg, carbonic anhydrase IX, which has been suggested as a potential marker for hypoxia,²³ has, in several other studies, been shown to be completely without importance^{72,73}).

CONCLUSION

Today, almost 100 years since the first clinical observation of the importance of hypoxia for radiotherapy, we are in a situation where the role of hypoxia has been intensively explored with regard to both its influence on cancer progression and resistance to therapy.

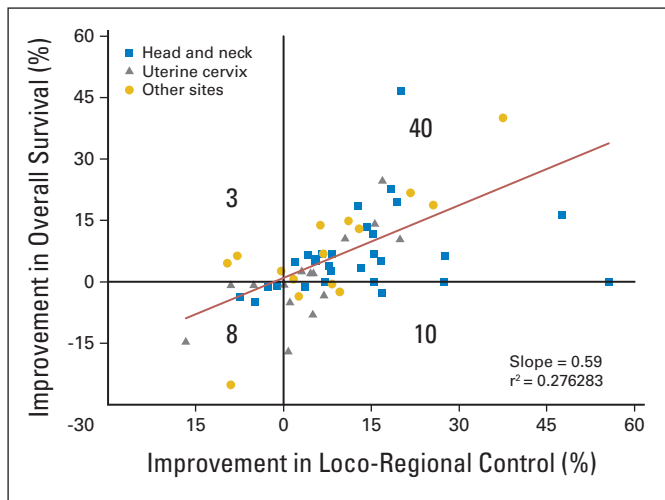


Fig 7. Relationship between locoregional control and overall survival in 61 trials with 8,889 patients. The figure shows the difference in locoregional control and its related difference in overall survival. A positive improvement indicates a beneficial outcome of the hypoxic modification. As indicated by the numbers, 50 trials had a better locoregional control after hypoxic modification, and of these, 40 trials also had improved survival. Only 11 trials showed a negative locoregional outcome, and of these, eight trials were associated with a similar poor survival. The regression line indicates that, on average, the locoregional improvement translates into a survival benefit in approximately 60% of the patients.

Abundant financial and intellectual research resources have been allocated to better describe, identify, and overcome the problems of hypoxic radioresistance. We have gained substantial clinical information that undoubtedly points toward an important radioresistance, especially in squamous cell carcinomas. Furthermore, both past and more current clinical trials have demonstrated that this hypoxic radioresistance, to some extent, can be overcome and that that may happen by the use of simple and inexpensive drugs, which, unfortunately, do not attract the pharmaceutical industry because of the lack of financial incentive. There might be those who feel that there is not enough clinical gain to be achieved by the currently available methods or that the lack of proper identification of the patients in need may be another obstacle to a more routine clinical use. However, it is characteristic that those who present this point of view also frequently are the same people who, from a research point, are still investigating the potential and, in their research application, continuously point toward the sparse clinical results achieved so far. Thus, with the substantial knowledge about hypoxic radioresistance and the means to overcome it, we have reached the point where the situation is almost schizophrenic; the increased research and preclinical interest deeply contrasts with the profession's resistance toward having the simple drugs or other means implemented to a larger extent. It certainly stresses the fact that there is no strong scientific basis for progress and achievement in clinical oncology unless it is accompanied by a continuous support and interest from the more commercial partners in the field. The story of hypoxia and hypoxic modification in radiotherapy is a clear illustration of this phenomenon, and therefore, despite 100 years of research efforts, we are still in a situation where hypoxia, now more than ever, can be considered to be both adored and ignored. Besides being an interesting phenomenon and paradox, it also sadly indicates how difficult it is to advance even sound clinical concepts and shows that there is a long way to go before true evidence-based medicine will get the platform it deserves. Or to say with a phrase from L.H. Gray⁷⁴: "Since the balance between failure and success in radiotherapy may hinge so critically on the distribution of oxygen tension throughout the tumor, it is very regrettable that we are still so ignorant on this important point."

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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