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Review article

Radiotherapy

Do malignant tumors need oxygen to survive radiotherapy?

Bogusław Maciejewski[1], Rafał Suwiński[2]

[1]Department Radiotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland
[2]II Radiotherapy and Chemotherapy Clinic, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland

The pathological vascular network in malignant tumors is generally irregular and chaotic. Euoxic clonogenic tumor cells (radiosensitive) are gathered around the vessels, which are unevenly distributed within the tumor volume. The results of many clinical studies [mainly on head and neck (H&N) cancers] have convincingly shown that extension of the overall irradiation time (OTT) needs a pronounced increase in the total dose (TD). It was strongly suggested that the results reflect an accelerated clonogens repopulation, which likely neutralizes about 30% of the cell kill effect of each dose fraction, and it potentially increases to even 80% towards the end of conventional irradiation. However so far, this mechanism's activity seems to be quantitatively exaggerated, since towards the end of irradiation, residual 10^1–10^2 cancer cells likely become hypoxic and highly resistant to 2 Gy fractions. Thus, local hypoxia should likely be considered as a dominant process responsible for clinical failure. Accelerated repopulation of only a few cellular survivors does not seem reliable. The efficacy of various chemical radiosensitizers, bioreductive drugs, and immuno-boosts are presented and discussed. Finally, it becomes clear that conventional 2 Gy fractionated radiotherapy should no longer be considered as an effective regimen to achieve local tumor control of locally advanced cancer higher than 50%. Pronounced improvement of the RT might be expected using an initial conventional dose of 50 Gy given in 25 fractions followed by a boost of 4–5 large dose (hypo) fractions of 5–6 Gy or by local brachytherapy.

Keywords: tumor oxygenation, cell kill effect, hypoxia, radiosensitizers, immuno-boosts

The impact of oxygen on tumor response to radiotherapy

Since the early 1950s, the role of oxygen pressure in the tumor and its impact on cancer cells' radiosensitivity has been extensively studied *in vitro* and *in vivo*. Thomlinson, Gray and Denekamp [1, 2] clearly documented that the growing solid tumors develope own vascular network to supply the tumor's metabolism and cell proliferation; the neo-vascular network is generally chaotic with an uneven pattern.

An imbalance usually exists between blood vessel branching and the kinetics of tumor cell proliferation. Analyzing the histological sections of human bronchus cancer, Thomlinson and Gray designed the 70–90 µm cylindrical model of highly proliferative euoxic cancer cells clustered around the blood vessels [1], and therefore radiosensitive due to the O_2 pressure of about 20 µm Hg or higher. Further increases of oxygen pressure does not however increase their radiosensitivity (Fig. 1). But if the O_2 gets below 10 mm Hg cell radiosensitivity dramatically decreases, and the cells turn into poorly oxygenated, hypoxic and finally anoxic cells (< 5 mm Hg), with death being irreversible.

Euoxic cancer cells are the principal targets of radiation, e.g. induced secondary electrons [3]. Theoretically, consecutive

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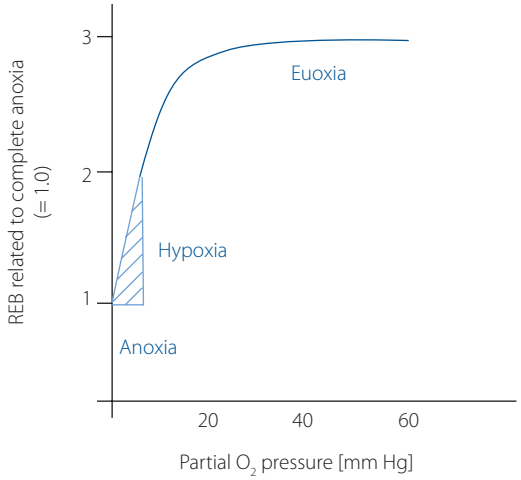

Figure 1. Dependence of the oxygen enhancement ratio (OER) on partial O_2 pressure [OER = dose in CO_2/dose in O_2] (adopted from Denekamp [2]); RBE – relative biological effectivenes

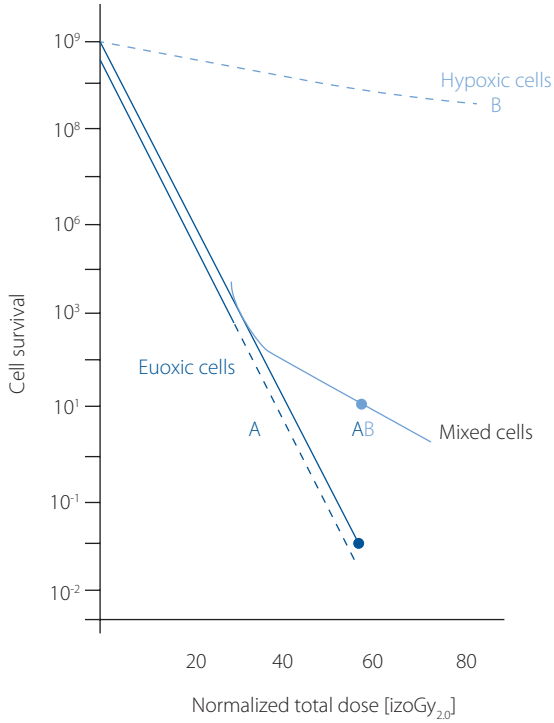

Figure 2. Cell survival after 2 Gy fractions depending on hypoxic and mixed euoxic/hypoxic cells (based on Horsman et al. [3])

fractions of, e.g. 2 Gy, should definitely eliminate (kill) the same rate of euoxic epithelial cancer cells (0.5). The same rate does not however mean the same number of cells. If the tumor contains initially 1 bln cells (10^9), after 2 Gy will survive 500 mln cells ($10^{8.7}$), but after 4–5 weeks of its number is reduced to 1000 cells (10^3), and to 500 cells ($10^{2.7}$) after the next 2 Gy fraction. It has essential sense when one wants to compare the numerical cell kill effects of 2 Gy fractions during the first 2–3 weeks of irradiation with the effect of the same number of fractions but during the last two weeks of conventional irradiation. When the euoxic cells are killed by successive fraction doses, then the hypoxic ones may get closer to the vascular network and may transform into being well oxygenated. This phenomenon was termed as reoxygenation. Generally, it is a pretty fast process within a few hours, and highly effective during the first few fractions [2]. However, it has never been quantitatively measured in human tumors, yet. Moreover, during treatment, radiation also deteriorates vascular network by killing the vessels endothelium. Thus reoxygenation might but may not necessarily be effective. It seems more and more reliable that a "final battle" against the surviving cancer cells (mainly hypoxic) occurs during the last few fractions of conventional radiotherapy.

Figure 2 illustrates the responses of oxic and hypoxic tumor cells to 2 Gy fractions [3]. This radiobiologically idealistic model *in vitro*, likely assumes that after 2 Gy (SF_2) a surviving fraction of the oxic cells equals 0.5, and oxygen enhancement ratio (OER) is 2.8–3 higher compared with the fully hypoxic fraction. If the tumor would contained only oxic cells, they will be completely eliminated (Fig. 3, curve A), which theoretically should lead to permanent local tumor control (LTC). But tumors also contain a few hypoxic cells (< 0.1%). Each successive 2 Gy fraction likely kills fewer and fewer clonogens accompanied with progressive reduction of vascular density. Consequently the number of hypoxic cells increases (Fig. 3, curve AB). If the tumor is completely hypoxic, it will ignore 2 Gy fractions and the LTC gain can likely never be expected. This plausible model is based on reliable values of the D_{10} of about 5–7 Gy for oxic tumor cells, and about 15 Gy for hypoxic cells, as proposed by Overgaard [4]. However, such a model does not directly reflect situations in clinical radiotherapy, thus an important question arises, whether at least some radiobiological principles (and which specifically) work in the clinic? To solve such a dilemma, results of the head and neck cancer radiotherapy seem be a suitable model, since the tumors are localized in a single part of the body, the vast majority of them are squamous cell cancers, and its metastases develop, at first, in the regional neck lymph nodes.

Once the tumor gets larger, the number of hypoxic cells will increase, which are usually chaotically spread within the tumor volume, and its precise quantitation is not possible, so far. The probability of LTC and the respective dose (TCD) can only be assessed on average, since radiation cell killing is random in nature and focused on proliferating, euoxic cells as the targets, whereas radioresistant hypoxic cells are unaffected and in fact ignore small 2 Gy fractions. They can only be killed by much higher doses (D_{10} ~ 15 Gy). Thus, after conventionally fractionated doses, the LTC of head and neck (H&N) cancers are usually lower than theoretically assumed. For T_1–T_2 tumors, the LTC may reach a level of 80–90%, but for advanced T_3–T_4 tumors, the LTCs rarely reach levels higher than 30–45%.

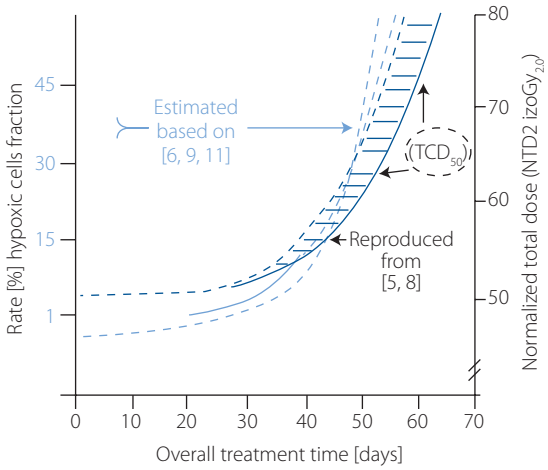

Figure 3. The dose-time relationship for 50% (TCD_{50}) [50% local tumor control (LTC) *versus* overall treatment time (OTT)]. Hypoxic fractions (red line) related to the OTT (estimated from the reports [6, 9, 11])

The first sign of what happens during irradiation at the cellular level below the clinically evident "sea surface" was experimentally documented in 1969 by Hermens and Bardensen [5]. They clearly counted clonogenic tumor cells which intensively repopulated during clinically evident regression of the gross tumor. This observation has generally been ignored until the 1990s, when Maciejewski, Withers [6–12] and Trott [13] analyzed the retrospective results of about 850 patients with H&N cancer treated in a single institution with RT alone. They showed that for a given total dose (TD), an extension of overall treatment time (OTT) leads to a dramatic decrease in 3-year LTC by about 1.5% per each additional day of time extension. The results of these quantitative analyses [6–8, 11–19] were used to estimate a bi-phasic dose-tumor response curve (Fig. 3, black curve). This has led to the conclusion that after the first two-three weeks of fractionated irradiation, the dose controlling 50% or 90% of the H&N cancer (TCD_{50} or TCD_{90}) sharply increases with the OTT extension. This tendency has been interpreted as the result of accelerated repopulation of euoxic tumor clonogens [4, 9]. From the bi-phasic LTC-DOSE curve, it was estimated that repopulation around the third week of irradiation counterbalances the cell kill effect of about 0.6 Gy of each daily 2 Gy fraction, and it continuously increases to even 1.4–1.6 Gy/day around week 6 of the OTT and longer. It was estimated from the results of the Cox et al. [14] trial 83–13, which showed that although the TD increased by 9.6 Gy during an extra 6 days, the LTC of 44% remained unchanged. It likely suggests that the effect of 1.6 Gy of daily 2 Gy might be neutralized by the repopulation. Thus, it was widely agreed that repopulation seems to be a major process responsible for local tumor failures. Such conviction led to many altered fractionation schedules tested in clinical trials. After over 25 years and over 50 studies, overall therapeutic gain appeared surprisingly low (7%) and disappointing. No improvement in the LTC after the TD higher than 60 Gy graphically reflects the flattened shape of the dose-response curve [15–17], which Suwiński and Withers [18] the defined as "effect plateau".

It must be emphasized that the effectiveness of the proliferative potential of euoxic tumor clonogens as a dominant or a single process induced by irradiation has only been deduced but not proven. Moreover, the events of self-sensitizing of the quiescent tumor cells and its reoxygenation have been anticipated but never quantitated as yet. Despite the belief that the increase of the total dose may overcome the repopulation, the LTC for advanced H&N cancers immutably remains around 50%, although many various sophisticated techniques and dose fractionation regimes have been tested since 1980. Through all these years, it remains intriguing as to why the use of more and more aggressive fractionated regimens did not resulted in a higher local control rate of the advanced tumors; conventional dose fractionation regimes have deliberately been continued, based on the assumption only that the each dose fraction kills a constant rate of the cancer cells. As a matter of fact, radiation effects relate to the cell numbers, which are not constant but markedly decrease during fractionated irradiation.

It has to be remembered that irradiation eliminates not only tumor clonogens but also vascular endothelial cells, with the network of oxygen supply becoming weaker and weaker, and therefore an "army" of hypoxic cells increases and begin to dominate towards the end of irradiation (Fig. 3, dotted curve). Undoubtedly, these cells are about 3 times more resistant to 2 Gy fractions than euoxic clonogens. Therefore, the logical conclusion would be that natural tumor growth definitely needs oxygen, but during fractionated irradiation, and oxygen assigns cancers cells to death a few moments after the radiation beam is delivered, and it does not give them a comfort to survive.

Hypoxia supports cancer cells to survive the course of radiotherapy

The first clear evidence that hypoxic cells exist in malignant tumors was documented by Thomlinson and Gray in 1955 [1]. Denekamp [2] pointed out that tumors' hypoxic cells are radioresistant as the result of vascular insufficiency. Chaotic and very primitive patterns of pathologic tumor neo-vasculature is not efficient enough to provide the increasing nutrient needed for the rapidly growing cancer cells. Microregional cellular foci within the tumor mass become nutritionally deprived what promotes the increasing number of hypoxic cells. They may stay alive, and when microenvironmental conditions will improve they may proliferate once again due to reoxygenation (e.g. local recurrence).

The radiation response of the hypoxic tumor cells is represented by cell survival curve B on Figure 2, which shows no cell kill after low fraction doses (≤ 2.5 Gy). Next, the bi-phasic cell survival curve (Fig. 2, AB) illustrates a mixed cell population, inflected by a proportion of resistant hypoxic cells.

Generally, curve A on Figure 2 seems to be relevant to a selected group of small (≤ 2.5 cm in diameter) epithelial cancers. On the contrary, the theoretical curve B represents a purely hypoxic tumor with LTC probability almost close to zero after conventional 2 Gy fractionated schedules.

Advanced tumors are usually heterogeneous with a mixed population of euoxic and hypoxic cells. During the first three--four weeks of irradiation, the initial part of curve AB (Fig. 2) is similar to curve A. However, towards the end of irradiation, hypoxic cells begin to dominate and the respective cell survival curve bends horizontally. An important question arises, whether any clinical results reflect these purely radiobiological principles, and the answer is "yes", there are a few.

Following the Thomlinson's recommendations [20], the present author [21] has measured the volumes of over 600 H&N tumors and more than 280 metastatic lymph nodes during the period of 1975–1986. The normalized total doses for 90% Local Nodal Control (NTD_{90}) were estimated and plotted against initial nodal volumes. Figure 4 shows that the nodal dose-response curve clearly reflects experimental estimates (Fig. 2, AB). Nodes with volume larger than 10 cm^3 (2.5 cm in diameter) characterize "the tail" on Figure 4, which suggests that the larger nodal metastases may likely contain some rate of the hypoxic cells, and they should need an extra dose of about 10 Gy to be locally controlled.

On the other hand, some other authors [17, 22] documented the adverse impact of lymph node involvement on local control of the primary H&N tumors compared to those with the N_0 stage. When total nodal volume increased above 30 cm^3, then a primary tumor needed an extra 6–7 Gy to be controlled with the same rate as those with the N_0 stage. This is still ignored in the clinical settings. Peters et al. [22, 23] pointed out that one plausible explanation of such an adverse effect could be that some "joungly" cancer cells escape into lymphatics to develop metastatic lesions, whereas the cells which remain in the primary tumor likely become synchronized in the most resistant phase of the cell cycle (G_0), and become even more resistant than hypoxic cells. Peters defined it as "probabilistic radioresistance".

The final "cell kill battle" concerns the last few dose fractions, delivered to a few surviving tumor cells of about 10^1–10^2. It is radiobiologically impossible that a smaller and smaller number of cells have the potential to repopulate faster and faster to neutralize about 80% of successive 2 Gy doses. It could theoretically happen only if the cell cycle turnover time was shortened by 15–20 times, but it is biological nonsense, since its duration is always constant throughout the whole treatment. Therefore, the belief that tumor clonogens intensively repopulate during the whole course of treatment and accelerate towards the end of conventional 2 Gy irradiation (Fig. 3) is not entirely credible and true. Conventional 1.5–2 Gy fractions are too weak to trigger cell-kill of residual hypoxic and radioresistant cells, and any increase of a conventionally fractionated

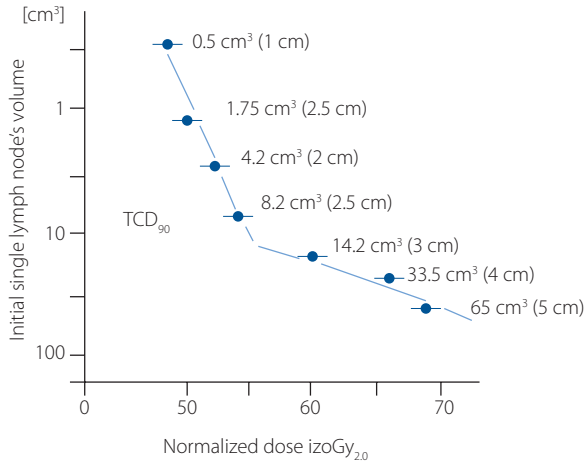

Figure 4. The local nodal control (LNC) Doses (TCD_{90}) related to initial node volumes (from Maciejewski [21]); TCD_{90} – tumor cure dose for 90% patients

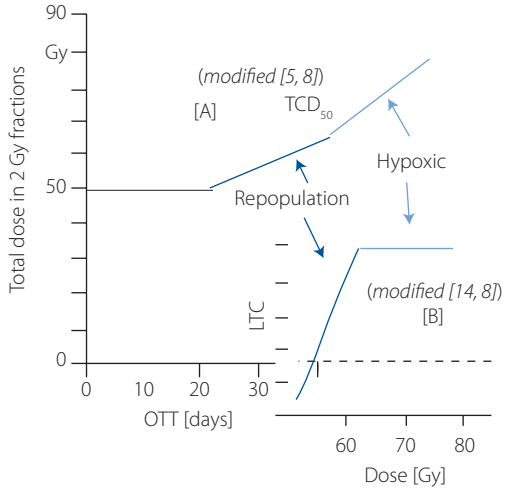

Figure 5. Modified (**A**) dose-time relationship for 50% (TCD_{50}) and (**B**) local tumor control (LTC) — dose "effect plateau" for head and neck (H&N) cancers; Blue — reflects effect of repopulation; red — reflects effect of hypoxia; OTT — overall irradiation time

total dose with an extension of the OTT above week 5 is likely wasted and seems clinically useless.

If 1 or 3 hypoxic cells survive at the end of irradiation, which may likely happen in locally advanced H&N cancers, then the LTC of about 37% should not surprise ($TCP = e^{-x} = e^{-1} = 0.37$). Such final cellular pattern calls for modification of the LTC-DOSE relationship (at least for the H&N cancers), shown on Figure 5. When the tumor completely regresses, the only one or a few hypoxic cells will survive, then they likely will lead to the tumor regrowth, and finally to local recurrence and/or dissemination [24, 25]. In humans, many biological and molecular changes during hypoxia are controlled by activation the HIF family of transcription factors. Both HIF-1 and HIF-2 regulate more than 100 different genes during hypoxia, controlling several processes including erythropoiesis, angiogenesis, metabolic activity cell invasion, proliferation

and survival of hypoxic cells. It suggests the credible and cautious conclusion that the hypoxic cells likely dominate towards the end of irradiation, what likely is an important or even a key hallmark of advanced malignant (at least epithelial) tumors, and the LTC gain above 45–50 % can never be achieved using conventional radiotherapy, which should be modify to strengthen its efficacy.

Hypoxia radiosensitizers

Since the role of hypoxic cancer cells was recognized as a meaningful factor for radiotherapy failure, a number of various approaches have been clinically tested to overcome hypoxic radioresistance [26]. One of the earliest clinical attempts proposed in 1968 by Churchill Davidson was hyperbaric oxygen therapy (HBO) [27]. High oxygen breathing (usually 95% oxygen + 5% carbon dioxide) was clinically tested to radiosensitize tumors. Over 20 trials including almost 3000 patients, mainly with locally advanced cancers, were carried out by the British Medical Research Council (MRC). Because of high oxygen pressure up to about 3 atmospheres, HBO radiotherapy was delivered through a glass window in a hermetic capsule. The overall benefit in LTC was unexpectedly low (7%) (Tab. I). No benefit was achieved in bladder, lung and esophageal cancer [28–31]. Relatively higher LTC (28%) was noted for uterine cervix cancer only [31], however it was not possible settle the doubts whether the LTC gain attributes to the HBO or rather the use of a few large daily fractions. Finally, HBO therapy was discontinued because of the high rate of serious complications (life-threatening complications caused by patient's decompression during leaving the capsule) and since chemical radiosensitizers [26] have appeared on the therapeutic market.

In 1969, the concept of chemical radiosensitizers was developed by Adams and Cooke [26]. They found certain compounds were able to mimic oxygen, and therefore to enhance radiation damage of primarily hypoxic cancer cells. The nitroimidazoles were the first electron-affinic compounds, which experimentally showed a radiosensitizing effect. Animal studies indicated misonidazole as the most promising, with a sensitizing enhancement ratio (SER) of > 2.0, and toxicity mainly directed at hypoxic cells. However once again, many clinical trials did not document the LTC benefit [28, 29, 31], as the misonidazole dose was found to be too low to sensitize hypoxic cells, but the use of higher doses immediately resulted in serious neurotoxicity as the first effect.

Failure of these clinical trials has led to test more effective radiosensitizers. Among many compounds, nimorazole, etanidazole and pimonidazole have been found to be the most promising. The first was tested in the DAHANCA 5 trial [28, 30, 31] and resulted in a highly significant benefit in the LTC, and nimorazole became a part of standard therapy for H&N cancers in Denmark. In contrast to this compound, the use of etanidazole or pimonidazole did not produce any clinical benefit (Tab. I). Moreover, the trial on pimonidazole combined with radiotherapy for cervix cancer was stopped, since the preliminary results were worse than that noted for the control group.

Results on the use of oxygen-mimic agents have generally been disappointing, and therefore bioreductive drugs became the next option of clinical interest, since they occurred to be highly cytotoxic to hypoxic cells [32–34]. Mitomicin-C, Nicotinamide (ARCON) and Tirapazamine were recognized as clinically effective, producing an increase in the LTC of H&N cancers by 18–20% (Tab. I). The interest was mainly focused

Table I. Clinical results [3 years local tumor control (LTC) gain due to the use of hypoxic sensitizers combined with fractionated radiotherapy]

Hypoxia sensitizers	No. trials (patients)	3 years LTC improvement *vs.* control
HBO [25, 27–31] Cervix cancer	24 (~ 2700 pts) 4 (~ 290 pts)	9% (58 *vs.* 49%) 28% (76 *vs.* 48%)
OXYGEN [27, 30–32] Mimetic sensitizers	41 (5970 pts)	7% (49 *vs.* 42%)
— misonidazole [29]	5 (626 pts)	No gain
— nimorazole [31]	2 (414 pts)	19% (52 *vs.* 33%)
— etanidazole [33]	1 (523 pts)	No gain
— pimonidazole [31]	1 (~ 80 pts)	Worse LTC (trial stopped)
BIOREDUCTIVE agents — mitomycin C [34]	3 (480 pts)	17–22% (76 *vs.* 54%) (48 *vs.* 31%)
— ARCON [32] (nicotinamide)	1 (215 pts)	20–25% (70 *vs.* 45%) (larynx, hypopharynx only)
— tirapazamine [34]	1 (230 pts)	18% (84 *vs.* 66%) (early H&N cancer)
TRANSFUSION [25, 31] Hb increase	2 (235 pts)	15% (84 *vs.* 69%) (early H&N cancer)

HBO — hyperbaric oxygen therapy; H&N — head and neck; Hb — hemoglobin

on the ARCON, which combines three potentially successful strategies, i.e. accelerated RT, HBO and a bioreductive drug. Clinical trials on agents modifying tumor hypoxia enrolled more than 11 000 patients in 91 randomized trials. The results have shown significant LTC improvement for the cervix and head and neck cancers only. The variability of the results may suggest considerable genetic heterogeneity of tumors within the same localization and histology. In order to optimize future clinical projects, detection of the hypoxic cell subpopulation and capacity for reoxygenation appears to be a key issue, something which is, however, still not quantified. Diagnostic positron emission tomography (PET) with Miso-radiotracers illuminates hypoxic cells chaotically spread within one tumor volume prior to therapy, and densely gathered within the residual volume towards the end of therapy; it would be useful to design the individual shape of the radiation beams and dose distribution but this is not routinely used in practice, yet.

One of the earlier approaches to counteract the adverse impact of hypoxia on the efficacy of RT also focused on the hemoglobin (Hb) concentration. Although mechanism of the relations between the Hb level and tumor hypoxia, is not clear, clinical studies [30, 35, 36] showed that Hb concentration below 12 g/L significantly reduces local tumor control and survival after radiotherapy. It seems that the efficacy of the oxygen homogenously delivered to the tumor by its own vascular network can be considered a key factor in intensifying radiation cell kill effect. A few clinical trials on the effect of blood transfusions in patients with low Hb levels [25, 31, 35, 36] have shown significant improvement in the LTC in cases when the advanced cervix cancer is accompanied with anemia. However, in the DAHANCA 5 trial on blood transfusions given several days prior to the RT, although indicating a rapid, albeit transient, increase of the Hb level, it finally failed to show a pronounced LTC benefit in H&N cancer patients. Low Hb level prior to the RT is commonly considered as a poor prognostic factor. However, patients with initially normal Hb levels (~ 12 g/L), and their gradual but sharp decrease during RT has been recognized as even more pronounced risk factor. An interesting but transient approach was the use of erytropoetin (EPO) producing a gradual increase in the Hb of patients with H&N cancer, but final RT results were disappointing, and the patients with EPO+ had even poorer outcomes than those with the EPO(–).

Since inadequate tumor vasculature and insufficient oxygen supply have been proven as important factors for tumor hypoxia, both angiogenesis inhibiting agents (AIA; e.g. bevacuzimab, avastin, angiostatin) and vascular disrupting agents (VDA; e.g. combrestatin, tumor necrosis factor) have been recognized as an attractive option for targeted therapy. Although some preclinical radiotherapy studies have shown that tumor oxygenation increases, the final results did not document any improvement or even deterioration in tumor oxygenation. The role of hypoxia in combination with AIA and VDA with radiation is not fully recognized, but it seems that the sequencing and timing of these two modalities looks critical in optimizing the most beneficial effects of therapy.

Immuno-boost

For decades, the importance of the immuno-modulation induced by conventional radiotherapy has been appreciated, however, local radiation is not the only immunosuppressive factor, particularly when large volumes are irradiated. During the RT, immunocompetent T-cells are severely depleted. With the advent of new imaging and radiation techniques, stereotactic-hypofractionated radiotherapy (SHRT) using single or a few large dose fractions [37] became an attractive therapeutic option producing very high LTC, but only for small tumor sizes (≤ 4 cm). The SHRT has been recognized as an "effective weapon" against residual hypoxic cells. The experimental data have indicated that high doses may effectively also induce local immunoresponse [37] activating TCD8+ lymphocytes and natural killer (NK) cells. Such a combined circle of "immunomodulated" response may contribute to more effective cell kill, but the power of such impact is not very impressive. Also, the effect of radiation outside the irradiated volume (abscopal effect) is recognized, but not strong enough and frequent to create the background for meaningful therapeutic gain.

The advent of novel immunocompetent drugs has changed the attitude of radiation oncologists towards the immunomodulative role of radiation. A convincing example of advantageous cooperation between radiotherapy and immunocompetent drugs is a randomized clinical trial carried out in a group of patients with stage III NSCLC [38]. Conventionally fractionated curative chemoradiotherapy as a control arm has been tested compared with the same schedule but followed by the maintenance with durvalumab for a period of 12 months. Twelve-month progression-free survival was 55.9% in the durvalumab arm and 35.3% for chemoradiotherapy alone. Such improvement attributes to immunoeffects, which have been often ignored in previous radiotherapy trials. Previous altered radiotherapy or chemoradiation did not result in a such high LTC magnitude. The NCLC results strongly suggest that immunoresponse should be considered as one of the most important processes affecting locoregional control in radiotherapy, substantially overshadowing repopulation effects.

Comments

It is obvious that oxygen is fundamental to the physiological function of normal tissues and organs, and ultimately the healthy life of human beings. But in malignant tumors, oxygen is not evenly distributed within the tumor, and some cells can already be hypoxic and radioresistant, but at the beginning of irradiation they rate is rather small. Tumor hypoxia is moved to the "shadow" because since the 90s, the general belief was begun dominate that accelerated repopulation of cancer cells counterbalances an increasing rate of 2 Gy fractions, towards

the end of fractionated radiotherapy. This process has been considered as a major (or even the only) factor leading to an increment of the total dose with overall time extension. For over 30 years, this concept has been unquestioned, however nowadays, it looks highly doubtful. It is reliable that during the last few days of irradiation, the number of hypoxic cells and their radioresistance to conventional 2 Gy fractions dominates over the kinetics of previously euoxic cells. Thus, a fair comment is that oxygen does not protect tumor cells but rather marks them to being killed by radiation.

For over 30 years the fact that the number of hypoxic tumor cells, increases during radiotherapy, even to more than 50–70% towards the end of treatment (Fig. 3) has been somehow ignored. It is radiobiologically illogical that towards the end of irradiation a few surviving cancer cells (undoubtedly hypoxic) have suddenly got enormous potential to repopulate faster than millions of euoxic clonogens during week 3 or 4 of treatment. It is amazing that up until now, nobody, including the present authors, has ever questioned that.

It seems plausible that a small number of resistant hypoxic cancer cells likely ignore and do not respond to 2 Gy [6, 9, 10, 14], and therefore any increase of the total dose, let's say above 63–65 Gy, is therefore likely to be wasted and useless. Thus, the "effect plateau", documented by Suwiński et al. [18] and Cox et al. [14], illustrates a resistance of the hypoxic cancer cells to 2 Gy fractions but not an accelerated repopulation. The minimal therapeutic gain noted after many altered fractionation schedules tested over 25 years is likely a convincing argument. Although these trials were fairly randomized and stratified, nevertheless both arms biologically remain highly heterogeneous, and it should not be surprising that fraction doses within the very narrow range of 1.15–2.0 Gy are ignored by resistant hypoxic cells.

Radiobiological concepts and clinical achievements gathered over the decades lead to the logical assumption that there is no longer room for conventional 2 Gy radiotherapy (CRT) as an effective, radical treatment for locally advanced tumors (not only for H&N cancers). Since towards the end of fractionated irradiation, hypoxic cancer cells likely dominate, the last 5–6 fractions become essential. Thus, it seems reasonable to consider a combined schedule of conventional (CRT), i.e. 50 Gy in 25 fractions (when repopulation works) followed by the last 5–6 fractions of 4–6 Gy each (SHRT anti-hypoxic boost), as a rational solution. Such doses can be delivered using external irradiation (CRT + SHRT) or brachytherapy (CRT + BRT).

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Conflicts of interest

The authors declare no conflict of interest.

Supplementary material

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Bogusław Maciejewski
Department Radiotherapy
Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch
ul. Wybrzeże Armii Krajowej 15
44–102 Gliwice, Poland
e-mail: boguslaw.maciejewski@gliwice.nio.gov.pl

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