

# Individually personalized radiotherapy vs. evidence (trials) based standards – paradigms and dilemmas

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This paper opens up to discussion whether some questions, points of view, and doubts counterbalance the belief and dogmas that randomized clinical trials (mainly in radiotherapy) should be considered as the only source of guidelines to design novel therapeutic standards in radiotherapy. A number of the physics, radiotherapy, clinical radiobiology and genetic and molecular tumor's characteristics suggest that radiotherapy protocols based on the "evidence based trials" seem to be antonymous to individually personalized therapy. The major goal of this paper is to consider and discuss whether individually personalized radiotherapy is already attainable and reliable or still remains the exception.

**Key words:** physical vs. biological doses, randomized trials, personalized radiotherapy, *caveat emptor*

## Introduction

During the previous century, the use of ionizing radiation to treat malignant tumors has led to various assessments of the effectiveness of radiotherapy (RT): optimistic or rather critical? Fulfilled the aims and expectations? mainly successes or some disappointments? There is no single and simple unequivocal and convincing answer, but it raises some important doubts and uncertainties. Subsequently, such a situation presents a forum for discussion.

## Physics!... physics?

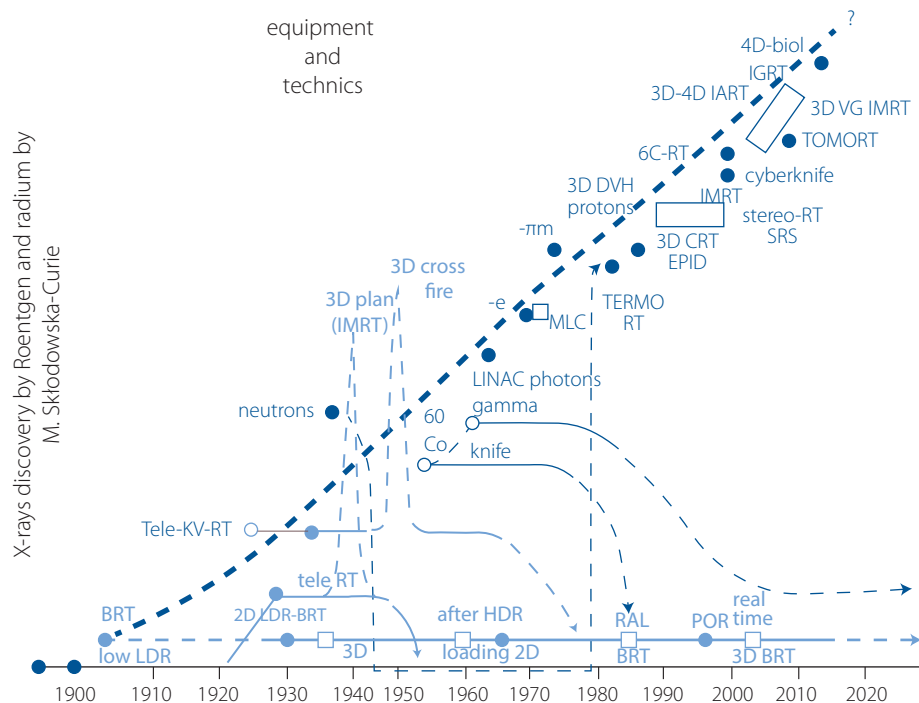
The role of radiotherapy as an effective method of treatment for malignant tumors is unquestioned. Technological and methodological progress in this field since its beginning is highly impressive (fig. 1). Orthovoltage machines and cobalt "units" have been replaced by sophisticated linear accelerators emitting photon and/or electron beams with a wide range of energy. Neutron, proton, and recently, boron therapy are all being used. Instead of simple planning of the two-dimensional isodose distributions of the depth doses, the computerized 3D

planning systems, e.g. 3, 4D-CRT, IMRT, IART, Vmat, respiratory gating and volumetric dose-volume-histograms (DVH) are being widely used in daily practice. The general "belief" in the system's individualized reliability and precision is increasingly common. Is it certainly unquestioned? Are the doses absorbed in the defined target volumes the same as those which were planned and reported in the treatment charts? Not necessarily! This has been clearly documented by the dosimetry *in vivo*. A relatively high rate of inconsistency has been noted between the absorbed and planned dose in the tumor's target. This fact is not a mere suggestion but proof that dosimetry *in vivo* should be an inherent attribute of quality control in radiotherapy (RT), but it is still uncommon.

Spatial dose distribution is rarely verified during fractionated RT, although tumor regression during RT results in changes in its topography and the surrounding normal tissues. As a consequence, no one can be sure that the high dose gradient beyond the tumor's boundary remains unchanged during fractionated radiotherapy, and in fact, it does not (may be except bone or maxillary tumors). Tumor regression du-

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**Figure 1.** A key-points in the progress in radiotherapy equipment and techniques during 1900–2020

ring RT usually changes the topography of both the tumor and the surrounding normal tissue. As a result, normal tissues are shifted into the region of the higher dose than that which had been preliminarily planned, and it likely may lead to an increased risk of late complications.

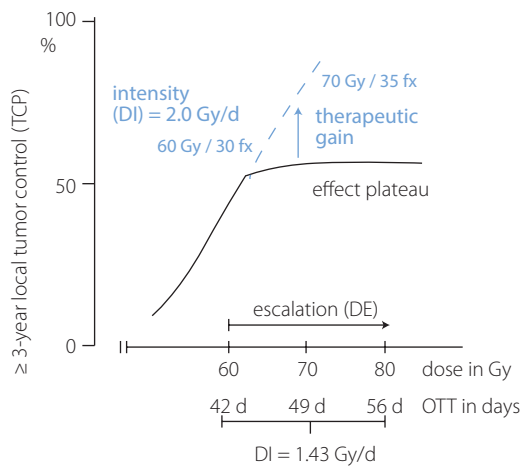
Radiotherapy 3D is called “conformal”, which means that instead of geometrically regular radiation beams, individually shaped beams are adjusted to an irregular tumor’s margins. This allows a heterogeneous dose distribution to be achieved; high within the tumor volume and with a large gradient in the surrounding normal tissue. The other side of this coin is that the risk of dose heterogeneity within the gross tumor volume (GTV) is often ignored. According to the International Commission on Radiation Units and Measurements (ICRU) recommendations, dose  $TD_{95}$  (95% isodose) is usually accepted as the GTV reference dose. Meanwhile, Fowler [1, 2] definitely pointed out that for 3D-RT dose  $D_{100}$  should only be used to cover homogeneously the whole GTV volume. An underdose ( $TD < D_{100}$ ), delivered even to a small part of the tumor volume (the so-called “cold spot”) almost always ruins preliminarily predicted local tumor control probability (TCP) – usually pretty high for early T and N0M0 tumors [3, 4]. Withers, Peters and Thames [5, 6] convincingly pointed out that in contrary to treatment planning and to tumor control expectations, the delivery of an extra dose (boost) in such cases can be ineffective, because it does not prevent the repair of the biological effects in the previous underdosed part of the tumor GTV.

In daily practice, the following two terms of “optimization” of RT planning are usually used by radiation oncologists – “dose

escalation” (DE) and “dose intensity” (DI). The term “optimization” means that the planned dose fractionation and the technique of irradiation offer the highest effectiveness as possible (the highest probability of local tumor control [LTC]). Is this also true when only a single RT plan is evaluated? In fact, “optimization” is the choice of the best DVH among a few [3–4] RT plans, but such a procedure happens rarely.

The term dose escalation is often abused and improperly interpreted. This term belongs to physics, and it exclusively means an increase in the total dose, e.g. from 60 Gy to 70 Gy or to 80 Gy, and nothing else. However, it is generally assumed that dose escalation also leads to higher effectiveness of RT, which is not true. In conventional radiotherapy, an increase in the total dose (TD) is inseparably accompanied by an extension of the overall treatment time (OTT). Delivery of 60 Gy needs on average OTT of 42 days, 70 Gy – 49 days, 80 Gy – 56 days, but the treatment efficacy does not change a lot.

Meanwhile dose intensity is more clinically important, which is the number of Gy delivered per day (or per hour). For total doses mentioned earlier, the value of the DI is the same, and it equals 1.43 Gy/day. Therefore, it should not be surprising that their efficacy is also similar. For the majority of epithelial cancers (e.g. in the head and neck region), the respective part of the dose-tumor response curve flattens (effect plateau) when increasing the DE, resulting in no gain in the LTC (fig. 2). What can be expected is a higher risk of late complications (which does not depend on the OTT), as a result of the accumulation of the higher TD in normal tissue. On the contrary, the increase of the DI, e.g. from 1.43 Gy/day



**Figure 2.** Radiotherapy effectiveness (tumor cure probability – TCP) depending on dose escalation (DE) compared with dose intensity (DI) [DE = TD +  $\Delta$ D +  $\Delta$ OTT; DI = TD/OTT]; TD – total dose;  $\Delta$ D – dose increment;  $\Delta$ OTT – overall treatment time extension

to 2.0 Gy/day or even 3.0 Gy/day (as a result of shortening the OTT) results in higher biological intensity (higher efficacy) of the delivered total dose in a shorter OTT. Therefore, it seems that DI should be considered as a more clinically useful radiobiological parameter than a physical one (DE).

### Is radiobiology meaningful for radiotherapy – yes or not necessarily?

Has radiobiology had any impact on clinical radiotherapy or it is only a theoretical field of research? Empirical clinical experience gathered throughout decades has proven that radiobiology is the essential and unquestioned basis for radiotherapy. The skeptics consider radiobiology as an experimental science and research because it uses cell line colonies, or transplanted animal tumors, and it does not necessarily concern clinical radiotherapy. On the contrary, advocates try to argue that radiobiology has always been the basis for clinical RT, and all radiobiological mechanisms always somehow occur during fractionated RT, but they are not clearly manifested; they are hidden in the shadow of much more complex and heterogeneous mechanisms of radiation response of human tumors than those which appear in genetically and morphologically homogenous experimental cell lines or animal tumors.

All processes discovered and defined by experimental radiobiology always have clinical implications. The scope of this article will not permit us to discuss all of them in detail, and therefore we will concentrate only on two of them which have had a pronounced and undeniable impact on progress in clinical radiotherapy.

The first one is the “time factor”. For a long time (over the course of the first 70 years of radiotherapy) there was a general belief that the natural growth of the majority of human tumors was generally slow, with volume doubling time taking about 50–60 days. During 6–7 week fractionated irradiation,

tumors are unable to double their volume, and therefore the time factor had been considered as much less important, and usually ignored.

A few retrospective clinical studies [7, 9, 11] in the 1980s (not clinical trials) convincingly proved the key-role of treatment time as a major determinant of RT efficacy. It was clearly documented that with the extension of the OTT tumor cells which survived consecutive dose fractions begin to repopulate faster and faster; at the end of the sixth week of irradiation cell kill effect of more than a half of 2.0 Gy of the daily fraction is counterbalanced by altered repopulation of the survived cancer cells. Therefore, after a 2.5-day weekend (from Friday afternoon till Monday morning) 10 Gy of the previous weekly dose reduces the effective dose to only 7 Gy. Due to accelerated repopulation of cancer cells, the OTT extension by 1 day decreases the LTC probability by about 1.5–1.6% [1, 9]. It became obvious that during the RT, the natural tumor doubling time of 50–60 days rapidly decreases to only 4–5 days. The time factor is no longer being ignored but is recognized as a crucial factor to initiate clinical studies on various novel altered fractionation regimes with the shorter OTT.

The radiobiological “time phenomenon” concerns not only RT but also surgery and chemotherapy. If surgery is microscopically non-radical, then the doubling time of cancer cell microlesions beyond surgical margins accelerates to about 10–11 days, similarly as to what happens during the time intervals between subsequent chemotherapy cycles. The general belief that cancer treatment should begin directly after diagnosis, without any unnecessary delay has been commonly accepted as the most important prognosticator. However, on the contrary, Withers [11] decidedly argued that therapy can be delayed and can start even 60 days after diagnosis; the crucial point is that once therapy has begun, it should be completed in the shortest overall time period as possible. This conclusion should be considered as a key-paradigm of radiotherapy and combined treatment modalities as well.

The unquestioned importance of the time factor has led to many studies on various fractionation regimes with a shorter OTT than conventional. Finally, it has resulted in the revival of hypofractionated radiotherapy with high single (10–12 Gy) or a few large fraction doses (e.g. 5 x 9 Gy), called “stereotactic hypofractionated radiotherapy or radiosurgery (SHRS)”. For these regimes, the DI increases from conventional 1.43 Gy/day to 9 Gy/day or even 12–20 Gy/day. This also allows for a shortening of the patient’s hospitalization from weeks to days.

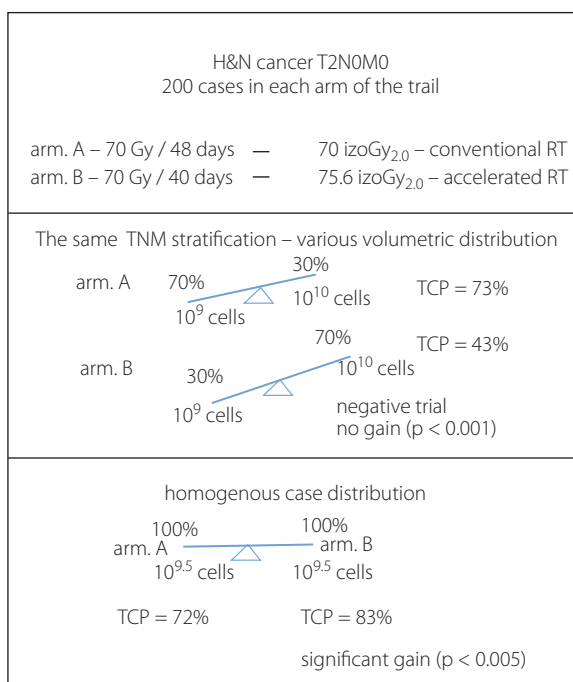
The second important contribution radiobiology has made to radiotherapy is to dispute TNM system credibility in radiotherapy. The proper choice of dose and fractionation based on a given T or N quasi-quantitative ranks might be uncertain. There is no doubt that the sole aim of irradiation is to kill all cancer cells, which should lead to the irreversible elimina-

tion of two major attributes of malignant cells: immortality and repopulation.

Experimental tumor cell cultures *in vitro* or transplanted animal tumors endlessly guarantee these two attributes, due to colony forming and the ability to produce subsequent generations of descendants, but it (at least immortality) does not concern human tumors. They stay alive and grow by exploiting the host (patient) as a supplier of nutrients and oxygen which the tumor needs to survive. These processes last as long as the tumor sponges on the host, but it ultimately leads to host death, which automatically causes the tumor's death also. Tumor cell repopulation can be reduced by radiation and/or chemotherapy. The more aggressive therapy is the lower and lower chance for tumor cells to produce descendants until zero, which results in definitive tumor death, whereas the patient will survive and will be cured. To achieve such a goal, dose-time fractionation should be tailored to the initial number of tumor clonogenic cells. Assuming that  $D_{10}$  equals 7 Gy ( $D_{10}$  is the dose which reduces cell survival by one decade [e.g. from  $10^{10}$  to  $10^9$ ]), then a tumor with  $10^{10}$  clonogens needs  $11 \times 7$  Gy (77 Gy) to reduce tumor cell survival to on average  $10^{-1}$  (0.1 cell/tumor), which corresponds with the LTC of 90% ( $TCP = e^{-0.1} = 0.9$ ). The initial number of tumor cells can be easily estimated based on initial tumor volume (e.g. GTV), which can be simply counted from serial CT scans. Therefore, it seems logical that tumor (or neck node) volumetric staging is a proper criterion for tailoring the most effective fractionated radiotherapy, instead of the TNM rank system "what's that got to do with anything".

The initial number of tumor clonogens varies even within a given T category. For example, the initial number of tumor clonogens in the smallest and largest tumors within the T2N0M0 category differs by at least one decade ( $10^{9.5}$  vs.  $10^{10.5}$ ). Therefore, it is logical that the largest tumor should receive a total dose higher by at least 7 Gy than the smallest one. Meanwhile, in daily practice using "evidence based" protocols, the planned total dose is usually the same for different tumor volumes within the same T category. While for the smallest tumors, 90% TCP can be predicted ( $e^{-0.1}$ ), whereas for the largest, within the same T category, the TCP would decrease to 37% ( $e^{-1}$ ). If the total dose is tailored based on the T category, it should not be surprising that an average overall TCP would not be higher than 60–70%, or even less. Therefore, the overall TCP will depend on the advantage of smaller or larger tumors in the study group (fig. 3).

The situation becomes even more complex when the study group includes patients with various T stage (from T2 to T4). As long as the RT protocols are designed based on the TNM rank system, therapeutic gain (TCP improvement) will remain expectable but not necessarily achievable. It is difficult to understand why such an inaccurate system is still persistently used in practice, against all logic and the available genetic, molecular and imaging diagnostics. Unfortunately, in such



**Figure 3.** Theoretical example of a trial showing the effectiveness of the arm B > A (evidence based?) occurs untrue and proper statistical analysis shows lack of evidence

situations, the more and more often used term "individually personalized radiotherapy" remains unjustified.

### Evidence-based radiotherapy: belief or proven facts?

This is often forced out (belief rather than conviction) that the results of randomized clinical trials should be considered as the one and only reliable source of facts, which should be the basis to design novel, modified therapeutic protocols, recommended as obligatory standards.

It is often suggested that the novel "evidence based" strategies should replace empirical clinical experience and retrospective studies. Some authors believe that the results of evidence based studies should be taken for granted, if the statistical significance is below 0.05.

Bentzen [4, 17] and Glatstein [18] have convincingly questioned the logic and reliability of the "result-significance-certainty-belief" relationships and their impact on the results of the trials accepted as "evidence based". Meta-analyses of numerous studies on altered radiotherapy and radiochemotherapy carried out for head and neck cancers [10, 12, 14] revealed an average overall therapeutic gain of only 6%. Should this be proof and evidence in favor of altered radiotherapy? If yes, immediately the next question arises: which schedule should then be recommended? At which tumor stage and localization? The reliability and strength of such far from unequivocal clinical evidence seems uncertain and doubtful.

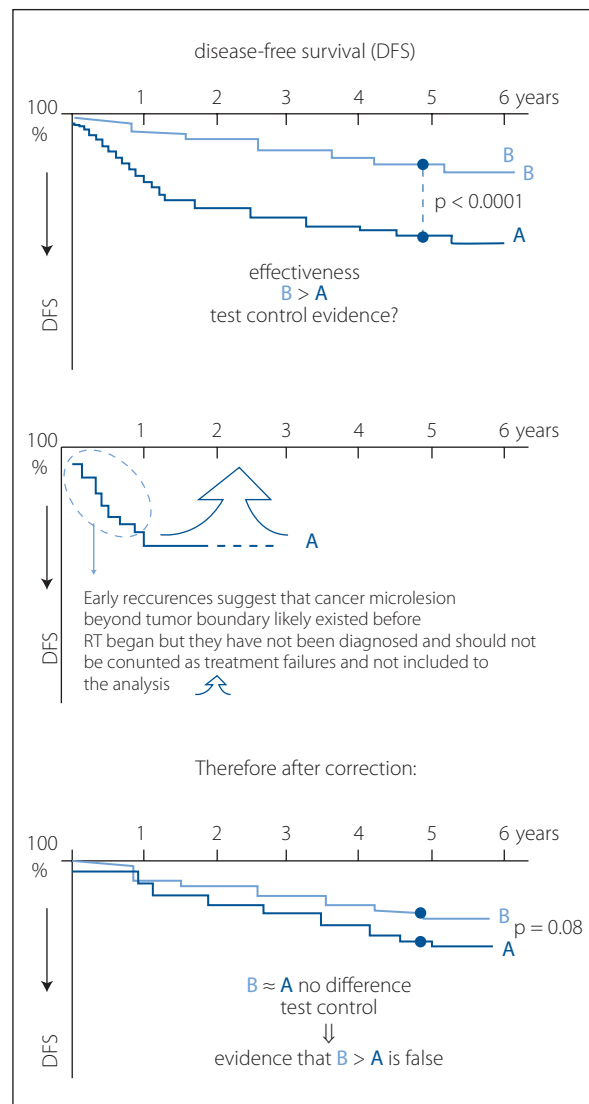
Why meta-analyses included only 19 among the 50 trials still remains unexplained; in each arm of these trials there were

a wide range of various tumor localizations and TNM stages recruited. Such huge clinical heterogeneity becomes even larger, when the TNM ranks are replaced by tumor volumetric staging. Moreover, it is surprising that the local control rates noted for the tested arm in some trials were almost the same as those for the control arm in other trials. Where is the proof of evidence in these trials, if their expected advantage and reliability generates so many uncertainties and doubts. The head and neck trials are not the only example [19].

Glatstein [18] firmly warned against so-called “tyranny of mediana”, which is often used as a measure of treatment efficacy. The author pointed out that the 5-year actuarial results (e.g. survival or local tumor control), match in fact no more than 2.5 years of the real time of the follow-up for all patients (crude data). The statistics of the actuarial results can by itself be often misleading. The results of cases with even a short follow-up (even a few days) are not withdrawn but are censored. Therefore, only the initial part of the e.g. disease-free survival, should be considered as the most reliable. The shorter follow-up the lower the credibility of a middle or final part of the censored survival curves. This also concerns the median values of survival or curability estimated from those parts of the survival or local control curve. If, for example, the 5-year median value of disease-free survival after the tested therapy B would be significantly higher by 25% than that representing conventional therapy A (fig. 4), it would likely be recognized as evidence based proof that therapy B is significantly more effective than therapy A.

However, Bentzen [17] mentioned that high significance it is not necessarily unquestionable proof. Instead of the median value at the fifth year, careful analysis of a whole course of curve A reveals early incidence of failures (recurrences) during the first 12 months of the follow-up (fig. 4). It may likely suggest that tumor cell microlesions beyond the target volume had already existed but passed over the diagnosis (too small to be detected), and they were out of the irradiated volume. Therefore they should not be accounted for in the analysis, because they have not had any impact on the results of treatment A. If they are ignored then the remaining part of curve A will shift closer to curve B, showing in fact no difference in the efficacy of both therapies. Therefore, the practical value of such (false) preliminarily established evidence is zero.

The majority of cancer patients are treated beyond any trials [18], so, why evidence based results of carefully selected and randomized trials should be referred to a large number of patients who were not recruited to the trials. Bentzen [17] has warned that “the lack of significance does not necessarily mean the lack of evidence”. Glatstein [18] has pointed out that careful and critical interpretation of the retrospective results should not be ignored, and sometimes, empirical clinical experience and common sense are more important than acceptance of the trial’s evidence without criticism (*caveat emptor*).



**Figure 4.** “TNM tyranny” in clinical trials – randomization and stratification without 2 (3) arms based on the TNM system but not on volumetric staging do not assure biological homogeneity and identical (or at least similar) tumor cell numbers and other molecular and clinical predictors. It shows that the results of such a trial may differ

Belief that randomized trials are the only source of evidence to modify therapeutic modalities might be questioned because the methodical rules of the trials create the illusory conviction that two or three arms of the trial are biologically and clinically homogeneous. Theoretically, the trial could be considered as a source of reliable and unquestioned evidence based proof, if it includes cases with the same (or within a very narrow range) volumetric stage (not TNM) of primary tumor (GTV) and total nodal volume (TNM) of the regional nodes in each of the trial arms. Apart from that, the prognostic molecular profiles should also be the same, or at least similar for all patients recruited to the trial. The accomplishment of the homogeneity of all biological and clinical factors in all arms of the trial is practically unattainable, but if it could be theoretically possible, patients

recruitment will last many years. Such an idealized model is still unavailable.

The trials on altered fractionated radiotherapy for head and neck cancer enrolled patients with different tumor localizations and stages (T2N0–T3N3). The GTV volumes ranged from 0.4 cm<sup>3</sup> to more than 170 cm<sup>3</sup>. Thus, homogeneity, even within these two parameters was none, and the average therapeutic gain of 6%, estimated in the meta-analyses, does not seem reliable, but instead misleading. For example, the 5-year DFS gain of 5% in the CHART trial, after a 10-year follow-up decreased to 0%. This is one of the critical arguments against trials as carriers of the “only” evidence based guidance for radiotherapy practice. Evidence and proof of what?

Despite the fact that randomized trial results have been published in prestigious journals, their reliability and recommendations as “evidence based proof”, unfortunately remains uncertain, and therefore they should be very carefully interpreted (*caveat emptor*).

### **Individually personalized radiotherapy or “evidence based” standard protocols?**

Genetic or molecular profiles of malignant human tumors have been intensively gathered during the last 10–15 years. This has inclined radiation oncologists to utilize them in clinical practice to improve treatment efficacy (to increase LTC). Growing knowledge on individualized tumors’ geno- and phenotypes – even within the same tumor type, stage and localization – leads to the expectation that the tailoring of individually personalized therapy will be able to replace conventional “stiffed” standard protocols. It looks like a belief that we are getting closer and closer to finding where the goalposts are, whereas the goalposts are always continuously moving. Therefore, an accomplishment of the skyline remains the illusion only.

It is already well substantiated that cancer cells have developed various molecular receptors on their surface and respective molecular inhibitors have already been produced. Cancer cells are however, “smart” enough and they develop a signaling network which transfer information from the cellular membrane receptors to the nucleus in order to survive. When one receptor is blocked by the respective inhibitor (e.g. EGFR), another signal pathway is automatically activated. Clinical studies have shown that the inactivation of a single cancer cell receptor is often not enough to cause cell death, and clinical expectations can be only partially effective.

A new concept has suggested using a few molecular inhibitors (monoclonal antibodies) instead of only one. In 2006, two inhibitors – EGFR (cetuximab) and VEGFR (PTK 787/ZK) – were used in the MD Cancer Institute in Houston to improve radiotherapy for glioblastoma multiforme. Unfortunately, no therapeutic gain occurred, but on the contrary, unacceptable high incidence of serious late complications often led to patients’ death. Although glioblastoma cells are able to

compensate for the block of the two signaling pathways by activation of other ways, it has been shown that the patient’s tolerance is limited and it does not accept the use of more than one molecular inhibitor.

Supporters of “evidence based” therapy will likely be outraged that their beliefs on the trial’s evidence is being undermined and they will use the argument that, after all, the 3D-IMRT, respiratory gating or stereotactic RT are in fact nothing more than individualized therapy. It is not easy to challenge such a point of view, except that the “individualization” of the 3D physical dose distribution within the irradiated volume often disappears when physical doses are converted into biological doses and individual tumor biology is accounted for. A tumor’s molecular profile as a prerequisite for so-called individualized therapy is not very often used. For example, although higher radiosensitivity of HPV+ p16+ oropharyngeal cancer has been quite well documented, but the suggested dose-de-escalation in such cancer patients is rather supposed. If someone decides to de-escalate the dose, it should be at least restricted to low risk T1–2N0–1 patients. A similar situation concerns breast cancer patients. Although molecular and hormonal profiles are used to modify the standards of combined therapy, radiotherapy is unvaryingly tailored to the TNM stage of the disease, what undoubtedly is antonymous to the personalized therapy?

In many studies on the geno- and phenotype heterogeneity of various human malignant tumors, more and more attention is being focused on the reserve pool and the role of cancer stem cells (CSC). Their relative higher radioresistance and lower lethal effect have already been recognized [21, 22]. If the only one CSC would survive radiotherapy, it will become the source of permanent tumor regrowth, with the ability to produce genetically mutated metastatic cells. Therefore, the quantitation of the size and localization of the CSC-lesions within the tumor volume might likely be a key-predictor to optimize mono- or combined therapy. Although the identification of CSCs using monoclonal antibodies can be partly realized (at least for some tumors, e.g. glioblastoma, breast cancer), quantitation of the CSC population and its localization within the tumor is not yet possible. The genetic plasticity of the CSC makes this situation even more complex by the presence and role of hypoxic, apoptotic and angiogenic cancer cells. Seemingly, the static tumor geno- and phenotype image established during diagnostics is unstable, but it is likely changing more or less during therapy. At the beginning of therapy, a tumor cell, e.g. type A, during subsequent mitotic cell cycles, genetically evolves into the cell genetically type B, C, etc., whereas the dose and fractionation planning is tailored for the initial profile of the cells A. Therefore, if radiotherapy is initially individualized based on the biological tumor eye-view, it should be repeated and corrected during treatment, depending on the geno-phenotypic changes, but this would be highly expensive and time-consuming.

A malignant tumor is a family of cells with various functions and with multifaceted interactions which have revolted against

physiological homeostatic mechanisms. Its individualism is binary (yes–no) but morphologically, molecularly and functionally unstable. Such a complex of characteristics and interactions cannot be quantified yet, even by very sophisticated computerized systems. This seems unlikely to quantitate some regulations among enormous number of variable abnormalities. If it would be possible, then and only then, could attributes of individually personalized therapy be fulfilled. Currently this term remains unlegitimately abused. Although perspectives may look promising, they can be paraphrased by the words of the British song “It’s a long, long way to Tipperary”. There are still many questions, controversies and uncertainties which still wait to be answered. The major message of this likely controversial article is that scientific and research progress in radiotherapy must be admired, widely recognized and continued, but the results and conclusions of many studies do not always settle an advantage of ones over the others. They should be considered with caution and criticism. We must keep in mind that common sense, logic and our own professional experience are often the most important.

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