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Once upon a time in oncology: will we ever win the war against cancer? Critical review of the progresses in cancer therapies

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The aim of the present review of various classic and novel therapeutic strategies in oncology is critical discussion of its efficacy to answer the question: is it realistic and even possible to win the war against cancer. Although technological progress in radiotherapy (RT) has led to the development of many sophisticated 3D, 4D techniques, the use of RT as a sole modality has become more and more limited to the tumors in the early stage of disease, in favor of combined surgery-RT-chemotherapy (CHT) therapies. Nevertheless, patients' curability has never reached a level higher than 95% (stereotactic hypofractionated RT – limited to small tumors only). The CHT for solid malignant tumors is not effective enough, and therefore it is mainly combined with surgery and RT as a method of the boost. Common use of partial or complete regression (PR, CR) as end-points of its efficacy is irrelevant, since it is quasi-quantified tumor cell clearance but not cell kill effects, and the regrowth delay (the time the tumor takes to regrow to the size [volume] at the beginning of therapy) is the only proper end-point. The efficacy of various genetic, molecular, immuno, and antiangiogenic modalities tested in many clinical studies is critically discussed, and it has generally showed some therapeutic benefits, but somewhat unspectacular. It has been well documented that genotypes and phenotypes of the tumors (even within the same location, stage, and histology) are individually highly heterogeneous. Therefore, the term "average probability" referred to individual patients becomes meaningless, and moreover, this term has never been replaced by "certainty" yet. Statistics of many studies and trials consist of various pitfalls and biases. Thus, although we and our patients are more often winners on the individual battlefields, the winning, of the whole war against cancer seems to be possible (hope), but not for sure (real).

Key words: malignant solid tumors, efficacy of various therapeutic modalities, probability *vs.* certainty, statistical pitfalls and biases

The first thought which crosses one's mind as one tries to answer the title question might be "never say never", but "once upon a time" would sound more promising. A plethora of studies in many fields of oncology, genetics, molecular biology and tumor immunology have gathered large swathes of results and comments, which although looking promising, do not necessarily encourage. Therefore, to work out the dilemma whether one can win or not, one needs to consider and discuss

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the results and achievements of various classic, recent and novel therapeutic modalities used or tested in the realm of oncology.

Innovations in radiotherapy – physics but not only

Technological progress in radiotherapy has brought to the market a wide sort of high-tech accelerators emitting high energy photons, electrons, protons and particle beams, which have been used to develop a precise 3, 4D conformal IMRT, IGRT, IART techniques. Sophisticated algorithms optimizing dose distribution to maximize therapeutic differences between tumor and normal tissue responses have arrived to daily practice, based on an interplay of physics, biology, and clinical oncology [1–11]. It may look like the promise of a new era in radiotherapy. However, sometimes it remains as a promise only, although the RT offers a wide range of treatment time and dose intensity. Expectations of the outcome improvement are immutably based on the simple assumption (or even belief) that the tumor appearing on the CT/MRI images is limited to its bounds, which is often not true at all.

The RT seems to be an attractive offer, because it often claims a success, but it remains unclear what that "success" actually refers to: permanent curability or to local tumor control only. Withers [10], Le [11] and Glatstein [17] have warned that 3D conformal RT techniques result in a heterogeneous dose distribution, which hides discrepancy between physical and biological doses, and the risk of "overconformality". Some tumors with an indolent proliferation activity, such as prostate cancer, chordomas, meningiomas, acoustic neuromas, and some normal tissues as well, are highly sensitive to change in the dose per fraction, expressed by a low α/β ratio. For a long time, we have been convinced fans of the α/β concept. However, with the passing of time, some uncertainty has been steadily growing, suggesting that tumor and surrounding normal tissues consist of various cellular structures, as blood vessels and its epithelium, hypoxic cellular microlesions, muscles, nerves, etc., which respective α/β values differ, and therefore, an average α/β may also differ as well. Therefore, it is unknown, whether alpha, beta or perhaps even gamma value is correct [18], which can result in misleading conclusions and results. In fact, the α/β formalism is rather incidentally used in the daily RT planning.

The great leap forward in RT equipment and techniques is not supported by long-term local cure benefits, which turns out to be lower than expected. In the past, the results of a large number of the trials on altered fractionation was rather disappointing lesson, with an average 6% tumor control benefit [12–15]. Patients with generally poor prognosis are candidates to studies on new RT strategies. The question is whether objective evaluation of 3D IMRT, IGRT, IART efficacy has ever been done or not [18, 19]. There are obviously no convincing results regarding lung cancer [16–19], and some other advanced cancers, irrespective of any theoretical rationale for potential benefits.

Patients expected to live long (e.g., breast or pediatric cancers, etc.) may manifest some unforeseen morbidities that have not yet been precisely reported. Before the start of therapy, prediction of the events, (tumor control, late side effect) has in the past been based on the gathered incidences of such events, but it has never been judged whether a specific event will occur for sure, or not. There is true inconsistency between tumor control probability (TCP), expected before the treatment, and local tumor control (LTC), which is achieved as the result of therapy. The TCP or the risk of complication (NTCP) is the frequency of the event which may occur, and it is considered as a numerical mapping of the degree to which we believe the event will occur. Therefore, "Is this a game of chance?" – "No, it is the way we play it" (W.C. Fields in 36).

Radio-biological principles are rather rarely accounted for in RT planning. Assumption TCP, of let's say 99% ($TCP = e^{-0.01}$), suggests that 10 of 1000 patients, or 100 of 10,000 patients will fail, that means RT local curability is not universal. In the case of the SHRT, an LTC of 85–95% can be achieved using single dose or a few high fractions, but for small tumors only. On the other hand, using the 3D IMRT, IGRT, IART techniques, even a small "cold spot" within the PTV (overconformality), often missed during evaluation of the DVHs, can lead to a significant decrease in the TCP, and therefore, in the LTC as well. Heraclitus' sentence "you can't step in the same river twice" – means for RT, that the same tumor should not be irradiated twice, and re-irradiation is seldom used and rarely effectively. The simple reason is that the planned reirradiation dose is inexplicably but commonly lower (40–50 Gy) than the curative one, although regrowing tumor cells proliferate much faster than native cancer cells, and therefore a recurrent tumor logically needs a higher radical dose than primarily delivered.

RT and surgery as local therapeutic modalities are directed to where the tumor exists, and the theoretical aim is complete elimination of clonogenic cancer cells, proliferating unlimitedly, which can theoretically lead to a cure for the patient. However, it remains unknown whether and how many microcolonies of cancer cells are beyond surgical or irradiated margins, and where they really are. Clinical situations, where RT or surgery is used alone, have been significantly reduced, replaced by pre- or post-operative radiotherapy, and/or chemotherapy. Such combinations of two or three modalities have been found to be successful for head and neck cancer, but not necessarily for lung or rectal cancers [20–23].

Till the mid 80s, various treatment modalities offered for locally advanced cancers were mainly palliative options. Then, reconstructive surgery initiated in the US in the 1980s, later in western European countries, and around 2000 in Poland, made a breakthrough in the treatment of these tumors, mainly H&N, sarcomas and childhood solid malignancies. But that method is limited to individually selected patients. Although the overall therapeutic benefit increased somewhat, it was not significant.

The major failure of many tumors is almost the same – distant metastases, which can subclinically be present even at the time of treatment or likely for some time before [21, 24]. It remains unknown how effective numerical eradication of clonogenic cancer cells is, being below the level of its clinical detection. If a few cancer cells survive, they will be the source of local recurrence for sure, and in the case of cell mutations, also the source of metastatic lesions. In the case of ovarian cancer, distant metastases are a major cause of failure, since the cancer cells spread over the whole abdominal cavity, and they grow intensively and reveal clinically as advanced disease. Thus, surgery is usually limited to palliative cytoreduction, followed by chemotherapy. There is no room for RT, although in the 60s some attempts were made, using the "moving strips" technique. However, that method was abandoned, because the strips overlapped and resulted in serious acute intestinal and bone marrow complications.

Among a long list of malignancies, glioblastoma multiforme is unique. Although surgery and/or RT, with or without temodal, are used with radical intent, neither long-term LTC nor DFS have ever been achieved and reported, and the OS is also very short. The enigma of this malignancy is that even if the gross tumor mass disappears as a result of local therapy, malignant glioma cells already circulate in the brain blood vessels network, controlled by the feedback regulatory system of the hypoxic and angiogenetic processes, which mutually activate each other.

Distant metastases are not the only attribute of advanced tumors. Even in the case of early stages of the cancer (e.g. breast cancer), distant metastases (DM) may occur early within the first 18 months of follow-up, with the rate of 8–23%, as was reported by Kryj et al. [26], suggesting that distant metastases can already be present at the time of surgery. Thomlinson [25] rightly pointed out, that breast cancer should be considered a systemic disease, and cytotoxic chemotherapy should be the modality used at the beginning of therapy. Therefore, it should not surprise, that in contrast to high-tech innovations, the use of RT as a sole treatment has been more and more limited in favor of combined therapies whose sequences are individually tailored, and defined as theragnostic oncology.

The power of chemotherapy – sequential or concurrent

Chemotherapy (CHT) acts within and out of the tumor bounds. In general, the candidates for that form of therapy are advanced tumors with a pronounced risk of dissemination. When cytotoxic agents are injected intravenously, there is however, no further control and a lack of knowledge about their destination. Therefore, the principal cause of CHT failure is inadequate delivery of the drug to some parts of the tumor because of poor local blood flow, which in clinical situations can sometimes only be deduced, but not measured. However, this is not the only reason.

Thomlinson [24, 25] designed and carried out a milestone study, which included 62,000 measurements of tumor volumes made in 239 breast cancer patients, treated with RT or CHT, producing 748 tumor regression curves. The Achilles' heel of the CHT is that multiagent cycles are spaced out by 1–3 weeks, to overcome epithelial and lymphopenia side effects, and to limit its severity to the level of patient tolerance. Making frequent measurements of tumor size (volume) of the breast cancers, Thomlinson [24] noted that tumors partly regress directly after each cycle of the CHT, and regrow later in a cyclic manner during sparing breaks between cycles (fig. 1C). This universal pattern was termed as "Jeffs phenomenon". It clearly shows that, although the intensity of the acute side effects decreases during breaks between the CHT cycles, clonogenic tumor cells do not sleep and wait, but repopulate pretty fast, resulting in tumor regrowth. Therefore, the resultant average tumor regression curve is much shallover than that noted directly after each single cycle. After surgery or RT, tumor deceleration is much deeper (fig. 1A and B), than after CHT, but the final number of surviving tumor cells also remains unknown. When the average number of surviving tumor cells would be equal to 0.001, then the LTC will raise to 99.9% (unrealistic). It means that 10 of 10,000 patients may fail after treatment, and, in fact, 100% cancer curability can never be predicted and achieved, since the cell survival rate is the result of random cell killing, and decreases asymptotically with no chance to reach zero.

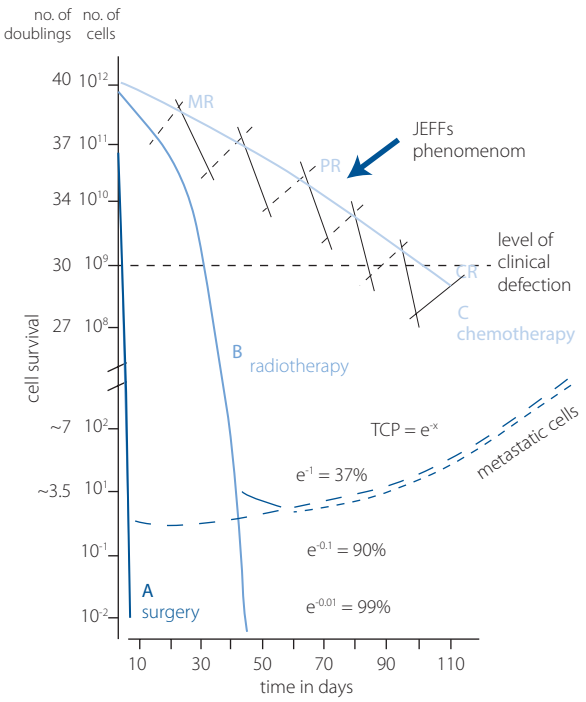

Figure 1. Theoretical tumor cell survival curves after: A – surgery; B – radiotherapy; C – chemotherapy. MR – minimal response; PR – partial regression; CR – complete regression; x – average number of survived cells. CHT curves-reprinted from Thomlinson [24]

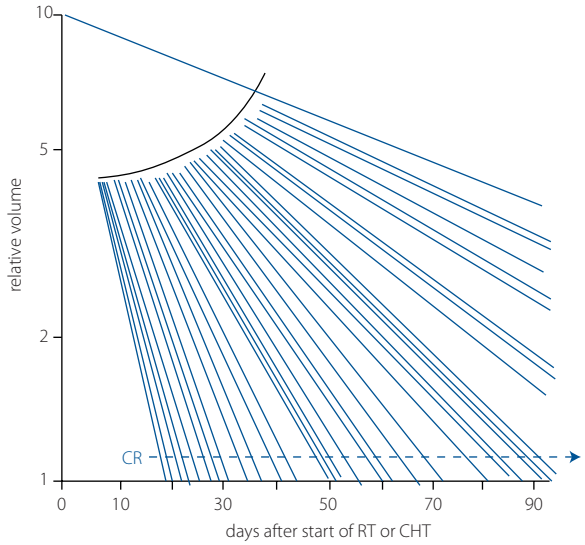

Figure 2. Spectrum of regression rate of breast cancers after delivery of a same and constant dose of the RT or CHT, estimated by Thomlinson [24, 25]

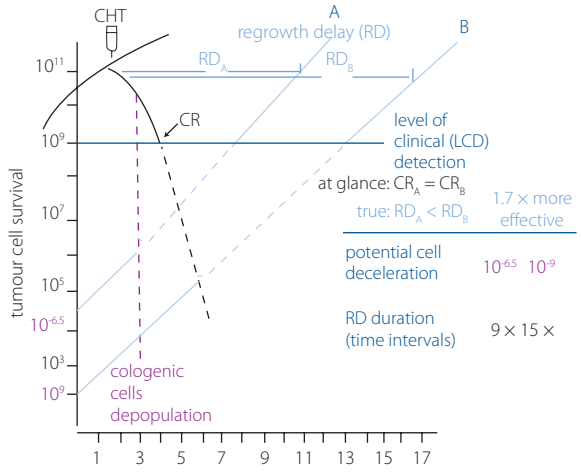

Figure 3. Scheme illustrating how to measure "regrowth delay" as the only quantitative end-point of CHT efficacy. Extrapolation of the tumor regrowth curves (dotted blue lines) back to the cell survival coordinate allows for an estimation of the approximate decrease in the cell kill effect of a given CHT

Tumor gets smaller (regression) during and after therapy, only when dead clonogenic cells are removed out of the tumor. Thomlinson [24, 25] clearly documented that the regression rate of the same tumor type varies individually, and its spectrum is about 50-fold wide after an identical and constant dose of RT or CHT (fig. 2). There are three formal, clinical end-points to quantify the CHT efficacy in the clinic, i.e. Minimal response (who knows what it quantitively means?), partial regression and complete regression (fig. 1C). This is astounding, that for more than 5 decades, the PR and CR have been persistently used in practice, despite the fact that they are clinically irrelevant and it makes no adds, since they mark the removal of already dead cells by various heterolytic processes only, resulting in the decrease of tumor doublings from about 35–36 (e.g. 3.5–4 cm tumor diameter) to 29–30 (0.5 cm^3 tumor), which is still not enough to achieve the local tumor control. Therefore, the PR and CR with no doubts, do not quantify the CHT cell kill effect. A long time ago, it was clearly pointed out that the only proper quantitative end-point for the CHT effect is the regrowth delay (RD), which measures the time period during which recurrent tumors regrow to the size (volume) at the start of the CHT (fig. 3). In the case of long-term LTC, the RD achieved infinity.

The CHT used as a sole modality to treat solid malignant tumors is not radical, curative therapy, except leukemias and some lymphomas. Therefore, it has often been used as neo- or adjuvant tools. However, metaanalysis of the CHT combined with RT [27] revealed only an average 2% therapeutic benefit after neo- or adjuvant CHT (the result seems to be within the range of statistical error). Concurrent chemo-radiation produces a bit higher LTC gain of about 6% [28]. Such, an average benefit looks suspectedly too low. Therefore, to check that results, we reviewed 15 well documented studies on concurrent RT-CHT (cisplatin, 5-Fu or paclitaxel) carried-out in world-leading cancer centers (3300 H&N cancers). The 3-year LTC has been higher by about 20% [11–26%] than the RT alone. So, previous metaanalysis results recommended as an "evidence" guide seem at least doubtful. A large number of studies suggest that surgery (fig. 1A) and radiotherapy (fig. 1B) have possible but not certain curative power (100% LTC has never been achieved), but not the CHT (fig. 1C). So, we can win some individual battles with cancer, but are not yet in a position to win the whole war.

Genetic and molecular tumor biology and therapeutic perspectives – belief on, or not

During the last 3–4 decades, enormous amount of data has been gathered regarding genomics, proteomics, radiomics and tumor biology [29–31]. Growing recognition of the heterogeneity of genotypes and phenotypes of tumor cells, tumor suppressor genes and intra-cellular multisignaling pathways has led to the initiation of many attempts to develop and test in practice various specific antibodies, which could modify and enhance the therapeutic power of classic treatment modalities. One of the most interesting approaches is targeting the signaling axes of cancer stem cells (CSC) alone or in combination with CHT and/or RT. It has been proven that the survival of even one CSC leads to recurrence for sure. Actually, the combination of CHT with CSC inhibitor GDC-0449 has been tested for the advanced, primary or recurrent small-cell lung cancer. In the case of melanoma, the use of immune check-point inhibitors targeting cytotoxic T-lymphocyte-associated protein CTL4 has clinically promising. Preclinical studies on TGF-β1-neutralizing antibodies have offered an interesting strategy to prevent radiation induced fibrosis. Some experimental studies have shown that the VEGFR2 blocking antibody may decrease the dose of fractionated radiotherapy. By contrast to

the fear of destruction of tumor vasculature by antiangiogenic therapy, some studies have shown the normalization of tumor vasculature in various pilot clinical studies on HER2-negative breast cancer, NSCLC, rectal, hepatocellular, ovary cancers and glioblastoma multiforme. Regarding the last malignancy, a concept has developed that a block of more than one cellular receptors could be more efficient, and pilot the US study on anti-VEGFR2 together with anti-EGFR were combined with the RT. The results were highly disappointing, with no therapeutic benefit, but with a high rate, over 50% of brain lethal necrosis. It may likely suggest that the use of more than one antibody is too much to be tolerated by patients.

Many studies focused on antiangiogenic therapy (fig. 4), have finally shown a surprisingly short and disappointing extension of progression-free survival, by only 1.2–6 months, in addition to very low improvements in overall survival (by 1.4–4.7 months), achieved only for the selected patients [29], although many pilot and randomized studies documented the feasibility and reliability of molecular modifiers combined with CHT-RT for different malignant tumors [30–34]. Similarly, quests of validity molecular predictors [34] have shown that some of them correlate with higher LTC or even DFS. However, it has to be pointed out that an interpretation of the correlation's power may differ, and the correlation coefficient of r = 1.0 only, defines a strong and absolute "predictor-effect" relationship, whereas in many relevant studies, the factor r, even if it is higher than 0.5, has never reached 1.0. So far, the clinical power of the family of tested genetic and molecular predictors can only be interpreted in the category of "likelihood", but not as an absolute and undoubtful guideline. Numerous clinical studies, which extensively explore growing knowledge on genomics and the proteomics of human malignant tumors to test novel concepts of combined therapeutic strategies, are very important and should not be ignored, but the progress in the patients' curability can only be achieved by small steps forward, and for complete victory of the war against cancer we still have to wait.

An interesting aim of some experimental and clinical studies is to intensify processes of the host immune response against primary and metastatic cancer cells by immunotherapy combined with the RT and/or CHT. It has been found out that immunogenicity is mediated by the DNA exonuclease Trex1, which could be used as a potential biomodulator to optimize the RT combined with the CHT. The complimentary pathway is TGF-β, which promotes the RT to induce antitumor immunity. Actual results convince the stereotactic hypofractionated RT (SHRT) should be considered a potentially highly effective treatment, since the use of a large single dose or a few large fractions effectively boosts the tumor immune-response (fig. 5), triggering *in situ* vaccination, T-cell promising infiltration, and immunogenetic killing [30, 32]. Large doses of RT induce Fas-receptors which activate the T-cells. Pre- and clinical studies have shown a complexity of the processes optimizing radiation-immunotherapy interactions. The SHRT frequently used in the setting of limited extra- and intracranial metastases combined with immunotherapy could provide not only LTC improvement, but also distant control as well. Immune agents approved for cancer therapy include cytokines, oncolytic viruses, dendritic-cell vaccine and check-point inhibitors. There is well-grounded excitement regarding design studies exploring RT combined with available immunotherapeutic strategies.

Another fast-growing field in oncologic therapies is a combination of diagnostic and therapeutic modalities with nanoparticles [30]. The use of a nano-radiation dose enhancer (Nano-RDE) to improve RT efficacy has been one of the explored fields by experimental and pilot clinical studies, and has been termed as a "SMART combined modality therapy" [30]. Gold nano-particles (Au NP) have been tested to intensify

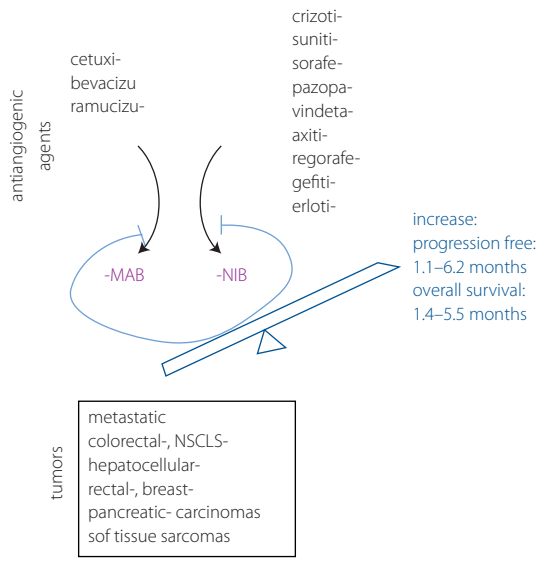

Figure 4. PFS and OS improvement after antiangiogenic therapy (taken from Jain et al. review [29])

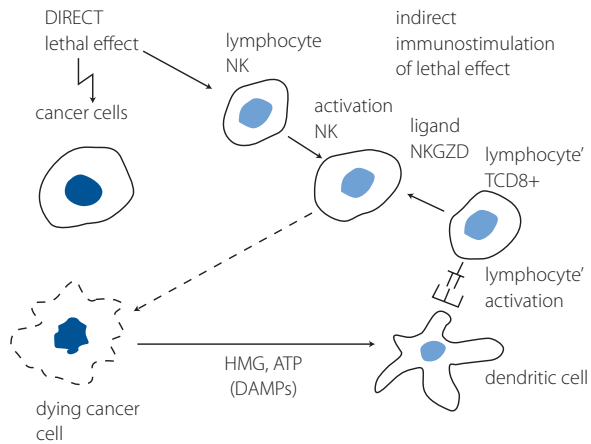

Figure 5. Scheme of immunostimulation of the indirect cancer cell death induced by high doses of the SHRT [32]. DAMPs – set of molecular factors which induce indirect immunological lethal effect

both the CHT and the RT efficacy. The TNFα – colloidal gold nanoparticle (CYT-6091) selectively delivered to the cancer cells intensifies the apoptotic effect of the RT dose. However, till now, such compounds are not used in routine daily RT practice yet. Nevertheless, an interesting approach concerns the use of direct conjugation of antibody labeled with radionuclide, compatible with SPECT or PET imaging, to localize antibodies in the tumor, inducing a cytoreductive and potentially curative effect (targeted drugs). Major obstacle is, however, insufficient dose delivery to solid tumors because of poor penetration. With no doubts, all these new approaches are very interesting and encouraging, but they are still at the beginning of "a long, long way to Tipperary". As it happened before, some of them will likely be abandoned, and others will be extensively explored. But, they still remain within probabilityland, and not in an absolute certaintyland of the victory.

The miracle of statistics – pitfalls and biases?

One may raise a query about statistical interpretations of clinical data [18, 19]. The roots of statistics' "cause-effect" relationships are in 19th-century laws of physics and mathematics, which are immutable. If something occurs, then that must follow. However, this does not happen in oncology at all. There is a lot of individual genetic, phenotypic, biological variables and pathways, which make a large number of more or less powerful variables of "cause-effect" relationships very difficult to be explicitly establish. Discussing the results of various brilliant concepts and attempts made to win the war against cancer, major question arises as to why the results of major therapeutic achievements are much lower than expected. It seems that one important reason is that the randomization and stratification routinely explored in the trials, produce only ostensibly homogenous groups of patients, whereas in fact, they are genetically, phenotypically and biologically highly individual tumors, and therefore highly heterogeneous, even if its localization, type, and stage are the same. Since the result of such widespread heterogeneities are usually quantified as "averages" or "median", one can generally be disappointed with the rather low therapeutic gain reported. The averages are usually recognized as significant when the "p" value is below 0.05. But according to Glatstein [18, 19], significance does not necessarily mean clinical importance. If, for example, the p-value is 0.06, the results are counted as insignificant. However, are the results really less clinically important when 94 instead of 95 out of 100 patients with cancer will be permanently cured? Somebody could say – "not at all statistically", since they differ by one patient only. But clinically – cure of the one is as important as a cure of the other 100 patients, and the p-value is just a statistical toy to play with the analyzed results of treatment.

Interpretations of the "averages" usually lead to uncertainties and doubts. It is a routine procedure to comment survival (LTC, DFS, OS) curves counting actuarial *vs.* crude survival. The first one often leads to underestimations, since the cases lost during the 3-, 5-, and 10-year follow-up are censored in about 50% as relapses, whereas they might be controlled during the assumed follow-up. Another point of criticism is that the interpretation of the survival curves simplifies their courses to the one number, which is a median value. It seems that the major problem is that the interpretation is focused on one point on the survival curve and its trail is usually ignored. Meanwhile, such a curve is surrounded by the "noise" of many points, representing individual patients. If, for example in some trial, the 5-year actuarial LTC of the H&N cancer was about 85% in the tested arm and 70% in the conventional one, then such a difference would be quantified for sure as statistically significant, in favor of a novel therapy. However, what is often ignored is that, for example, in the control arm a 15% rate of local recurrence has occurred during the first 18 months of follow-up [26]. It becomes clearly evident, based on biology, and the kinetics of tumor growth, that such small subclinical tumor cell lesions beyond the irradiated or excised mass likely already existed at the time of the start the therapy. Therefore, it should not be accounted for the efficacy of the conventional therapy. When such part of the LTC curve would be excluded, then both curve become close each other and significance disappears, and the advantage of the tested therapy as well. This is a simple example of the statistical bias, which often happens.

Important trouble with interpretation of the trials and metaanalyses results is that the actuarial statistics reflect wide biological and genetic heterogeneities of patients and maldistribution of various prognostic factors, although, at first glance, they look homogenous within each study group. For head and neck cancers, about 600 genetic and proteomic predictors were analyzed a couple of years ago, and none of them turned out to be absolute and the sole prognostic predictor. However, when Buffa et al. [34], analyzed that sets of data once again using sophisticated taxonomic cluster statistics, they clearly found overexpression of the four factors as a significant prognostic predictors of the LTC gain by 20%. Similarly, Suwiński et al. [35] designed the trial, to test efficacy of the 7 fractions per week *vs.* conventional 5 fractions per week, used in the postoperative radiotherapy for H&N cancer patients with the increased risk of local recurrences. Classic, actuarial statistics have shown no difference in the effectiveness of both schedules. But, when the authors designed molecular scoring for the overexpression of the four selected genetic predictors, then the score >2 of them predicted an enormous increase in the DFS after 7 fractions/week schedule, much higher (>40%) than after 5 fractions/week. In case of the score ≤2 there is in favor of any these two schedules. These examples, as well as many others, suggest that classic statistics may provide deceptive results. Therefore, a rhetorical question may arise: what can really be considered "evidence". It seems that in many studies the importance of "evidence" remains uncertain. Thus, clinicians should likely prefer clinical importance, experience, and common sense as guidelines,

more than the results predominately based on the p-value. Glatstein [18, 19] strongly suggests that "evidence" should be weighed more carefully, and it seems that in the case of individual patients, the logic and own experience are often more important, but this does not mean that trials should be dismissed either.

Conclusions

Many years ago, the famous oncologist Vincent de Vita pointed out that "if we expect pronounced success in oncology, we have to be patient, because the progress will be realized in many small steps". For the last few decades, our knowledge on genetics, proteomics molecular predictors and modifiers has enormously increased, and we have unexpectedly learned that there are as many genetically and phenotypically different malignant diseases as there are patients suffering from them. It means, that effective combined therapy should be personally individualized, and that we are not able to win whole war against cancer just yet. However, that suggest, we should not lose hope and belief that it could happen in the future. There is a large number of winners on various, single oncologic battlefields, mainly those, which tumors are in very early stage of disease. Undoubtedly, we will likely achieve an important step forward when we will be able to replace "probabilityland" by "certaintyland", but not yet. We should also keep reasonable and limited belief on the statistics, and remember that the "averages" never represent individual heterogeneous characteristics. So far, real progress in cancer curability can likely be expected due to the increased activity and efficacy of prophylaxis and early detection of malignant tumors.

Article information and declarations

Author contributions

Bogusław Maciejewski – was responsible for the main idea, writing and editing of the article.
Daniel Bula – was responsible for supportive writing and editing of the article.
Justyna Rembak-Szynkiewicz – was responsible for supportive writing and editing of the article.

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