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Artykuł na zaproszenie • Invited article

From conventional averages to individual dose painting in radiotherapy for human tumours: challenge to non-uniformity

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The exploitation of a number of current clinical trials and reports on outcomes after radiation therapy (i.e. breast, head and neck, prostate) in clinical practice reflects many limitations for conventional techniques and dose-fractionation schedules and for "average" conclusions. Even after decades of evolution of radiation therapy we still do not know how to optimize treatment for the individual patient and only have "averages" and ill-defined "probabilities" to guide treatment prescription. Wide clinical and biological heterogeneity within the groups of patients recruited into clinical trials with a few-fold variation in tumour volume within one stage of disease is obvious. Basic radiobiological guidelines concerning average cell killing of uniformly distributed and equally radiosensitive tumour cells arose from elegant but idealistic in vitro experiments and seem to be of uncertain validity. Therefore, we are confronted with more dilemmas than dogmas. Nonlinearity and in homogeneity of human tumour pattern and response to irradiation are discussed. The purpose of this paper is to present and discuss various aspects of non-uniform tumour cell targeted radiotherapy using conformal and dose intensity modulated techniques.

Od konwencjonalnych uogólnień do indywidualnego „dose painting" w radioterapii nowotworów u ludzi: wyzwanie dla niejednorodności

Praktyczne wykorzystanie wyników kontrolowanych badań klinicznych i doniesień dotyczących wyników leczenia promieniami (pierś, region głowy i szyi, gruczoł krokowy) wskazuje na szereg ograniczeń w stosowaniu konwencjonalnych technik i sposobów frakcjonowania dawki promieniowania oraz „średnich" i uogólnionych wskazań i wniosków. Pomimo rozwoju radioterapii w ostatnich dziesięcioleciach nie wiadomo, jak optymalizować tę metodę leczenia u indywidualnego pacjenta i przewodnikiem dla planowania radioterapii nadal pozostają wskazówki „uśrednione" i nieprecyzyjnie zdefiniowane „prawdopodobieństwa". Powszechnie wiadomo, że grupy chorych kwalifikowanych do kontrolowanych badań klinicznych charakteryzuje duża niejednorodność kliniczna i biologiczna i że w obrębie jednego stopnia zaawansowania objętość guzów nowotworowych może różnić się kilkakrotnie. To czyni wątpliwą wiarygodność przesłanek radiobiologicznych, dotyczących średnich wskaźników popromiennej śmierci jednakowo promienioczułych i równomiernie rozmieszczonych komórek w guzie nowotworowym. Te przesłanki wynikają z eleganckich, ale idealistycznych badań in vitro i mają wątpliwe przełożenie kliniczne. Tak więc współczesny radioterapeuta napotyka na więcej dylematów niż dogmatów. W pracy dyskutowana jest niejednorodność biologicznej charakterystyki nowotworów u ludzi i ich nieliniowa odpowiedź na promieniowanie. Przedstawiono różne aspekty niejednorodnej, komórkowo zogniskowanej radioterapii przy użyciu technik konformalnych i modulacji intensywności dawki.

Key words: radiotherapy, tumour cell heterogeneity, non-uniform dose distribution
Słowa kluczowe: radioterapia, różnorodność komórkowa nowotworu, niejednorodny rozkład dawki promieniowania

"The traditional understanding of the dose response relationships for irradiated cells was that equal dose increments cause a constant decrease in cell survival. This reflects a random process of cell killing. It means, that if 100 lethal hits are distributed randomly throughout 100 equally radiation sensitive cells they will not kill them all, and on average 37 cells will survive" – over the years, this has been a dogma and a guideline for clinical radiotherapy [1].

For any given patient, success or failure in radiotherapy is an "all or none" phenomenon; if one tumour clonogenic cell survives all the dose is effectively wasted. However, for a series of tumours of the same type and stage, the dose-response is represented by a tumour control probability curve (TCP) the shape of which may differ because cell killing is a random process affected

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by biological variables. After exposure of a series of identical (cell sensitivity and density) tumours to a given dose (single or fractionated) there is a Poisson distribution of the number of surviving clonogenic cells per tumour. If, for example, a certain dose reduces the cell survival to an average of one clonogen per tumour there will be 37% of tumours sterilized and the remaining 63% not cured, with one or more surviving cells, although the total number of surviving clonogens will be the same as the number of tumours irradiated. Does it work in the clinic and are the averages useful in daily practice in radiotherapy?

Dogma of "averages" and value of "probabilities"

In oncology, the major interest is focused on improvement of long-term treatment outcome (disease-free and overall survival) by testing new methods of therapy or their combinations. Retrospective studies are usually the source of indirect guidelines for designing randomized prospective trials. Patient recruitment is almost always based on TNM stage and tumour site, and on a few clinical or histopathological predictors, and the results are presented as crude or actuarial averages.

Breast cancer

There are only a few topics in oncology that have generated so much controversy over the years as has post-mastectomy radiotherapy (RT).

The DBCG 82 trial from Denmark [2] is one of the most representative and often cited trials. It gathered 3100 postmenopausal high-risk breast cancer patients after mastectomy. They were randomized either into (arm A) 8 CMF cycles with post op-RT with 50 Gy in 25 fractions given between the first and the second cycle or into (arm B) of 9 CMF cycles only. There was a 15% gain in 10-year disease-free survival (DFS) and 9% in 18-year overall survival (OS), but there was no difference in the incidence of distant metastasis. Survival benefit for small tumours and/or 1-3 positive nodes was at least of the same magnitude as for large tumours.

Metaanalysis of 36 trials including 28500 patients showed equivalent 10-year survival for more extensive radical surgery as for breast conserving surgery with postoperative RT [3]. In the EORTC trial 10001 and 22881-10881 testing efficacy of the boost dose for T1, T2 breast cancers, the average decrease in local recurrence rate was by 3-6% in favour of 16 Gy boost, with no difference in local regional control, distant metastases and overall survival [4, 5].

These few "key" studies on more than 30000 patients show that, on average, a subgroup of breast cancer patients could benefit from postmastectomy radiotherapy. But indications for this method of combined therapy are still an issue for debate and the question of who may not benefit from loco-regional irradiation remains open. Except for breast preservation (cosmetic result is often controversial) there is no convincing advantage of conserving surgery with irradiation over radical mastectomy. To the question of whether a boost of 16 Gy is on average beneficial, the answer is that on average it is not. It is still an unanswered question how to identify a subgroup of patients with early breast cancer and with very high risk of distant failure. Therefore, average results lead us to average conclusions only.

Head and neck cancers

The main lesson we learned from retrospective studies supported by clinical trials is that accelerated repopulation of surviving tumour (epithelial) clonogenic cells reduces the net cell kill effect of daily irradiation above week 4, and above week 6 of treatment it may neutralize most or even all the cell kill effect of daily fractions. The evidence of that is the existence of an "effect plateau" (Figure 1A), which means that each extra dose given beyond week 6 of RT is practically lost (no increase in loco-regional control) [1, 6]. These findings lead to the idea that by shortening overall treatment time (OTT) and/or by increase in total dose (TD) giving two- or three daily fractions one may expect significant benefit in long-term local tumour control for locally advanced H & N cancers. Recent studies suggest that the relationship between tumour control probability and OTT (TCP-OTT) might be nonlinear [7]. This means that the benefit from shortening OTT may not be quite as great as the detriment from equivalent protraction of OTT.

Careful and precise meta-analysis (MARCH) of 15 well known trials on H & N cancers (13600 patients) gives an average absolute 6-year survival benefit of 3% and a 7% benefit for loco-regional control (LRC) for altered RT [8]. Any subgroup of patients defined according to the tumour site did not benefit more or less from altered RT than any other groups. This study shows that the averages, even being significant, are not promising but rather discouraging. Interpretation of particular trials is also confusing [6]. CHART showed no benefit for T1-2 oral cavity, oropharyngeal and hypopharyngeal cancers. In contrast, the PMH-Toronto trial produced LRC benefit of 12% for small tumours (especially hypopharynx) but no gain for larger ones. In the EORTC 22851 trial, 18% LRC benefit has been noted for advanced and unfavourable T & N patterns but when consequential and late complications were accounted for therapeutic gain dropped down to zero. In RTOG 9003 and in EORTC 22791 trials, hyperfractionation (HF) schedules were almost the same but LRC benefit was about 3.5 times higher in the EORTC trial (4.4% vs. 16.2%). Even within the same institution (MDACC) two trials testing efficacy of the concomitant boost (72 Gy in 42 fractions) showed at least a 2 fold difference [6] in the LRC benefit although in both trials similar tumour sites and stages were included. One of the earliest trials (RTOG 83-13) including various tumour sites and stages clearly showed an "effect plateau" [8]. Increase in total dose from 72 Gy through 76.8 Gy, to 81.6 did not produce any increase in the LRC (OTT was also prolonged respectively).

All these examples are not deliberately selected for this paper but they are taken from well known and often cited European and US studies. Wide variations in total doses (TD), doses per fraction (d_x), overall treatment times (OTT), tumour sizes and sites do not allow separation of the effect of dose from that of OTT, and to define which individual tumours may benefit from altered radiotherapy.

Prostate cancer

Large clinical studies on conventional radiotherapy for locally advanced prostate cancers (LAPC) provide many controversies [10-14]. Because the LAPC is a very heterogenous group of tumours some studies support, whereas others question a dose-response effect which makes any conclusion uncertain.

It is impossible to separate importance of clinical and histological predictors (T stage, PSA, Gleason Score) from the effect of dose escalation. Lyons et al. [12] postulate that dose escalation plays an important role for intermediate risk patients whereas for low- and high risk patients the PSA and the GS are more important than the dose. Although a few studies identify radiation dose as an independent predictor they are mostly retrospective and include heterogenous groups of patients. Among clinical trials only one seems to support a dose-effect relationship [11]. Moreover, interpretation of the results is complicated by the fact that the end-points for biochemical complete regression and biochemical progression differ significantly from study to study. There is general belief that high-risk patients need postprostatectomy radiotherapy, but recent analyses of a large body of clinical data [13, 14] have shown no difference in 10-year survival between postoperative RT and prostatectomy alone. Pooling together the most reliable data, the dose-response curve shows an "effect plateau" (Figure 1, curve B), similar to that observed for squamous cell carcinomas of the head and neck. However, the origin of the plateau for each of them seems to be quite different. Possible explanations for this are illustrated in Figure 2 (I and II). Whereas for H & N cancers (Figure 1-(I)) accelerated repopulation could be the major determinant of the "effect plateau", for adenocarcinoma of the prostate (Figure 1-(II)), which is in general a very slowly proliferating tumour, persistent hypoxia and a lesser average response to 2 Gy fractions, may explain no gain above 74-76 Gy.

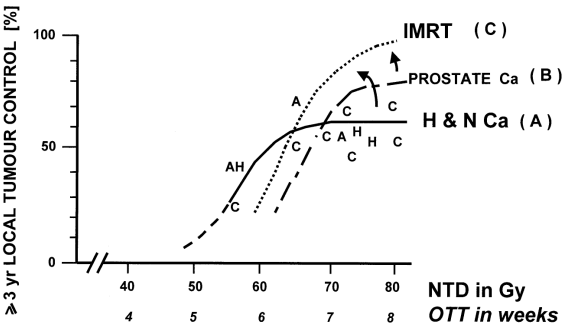

Figure 1. Dose-response for (A) head and neck cancer; (B) prostate cancer; (C) IMRT. TCP curves have been estimated based on the published clinical data and results [6, 8-11, 14, 17, 18, 20]. Solid and dashed curves represent conventional techniques. The capital letters refer to the results of trials of treatment of H&N cancer using conventional (C), hyperfractionated (H) or accelerated – hyperfractionated (AH) irradiation. Dotted curve for IMRT indirectly drawn from the recently published data [11, 17, 20] shows steeper slope than those for conventional RT and that by using IMRT the plateau effect might be reduced.

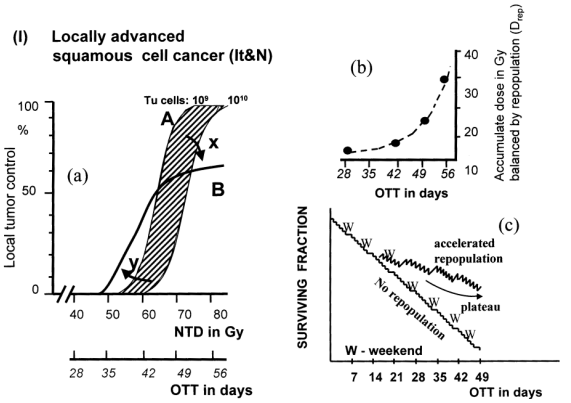

Figure 2.I.

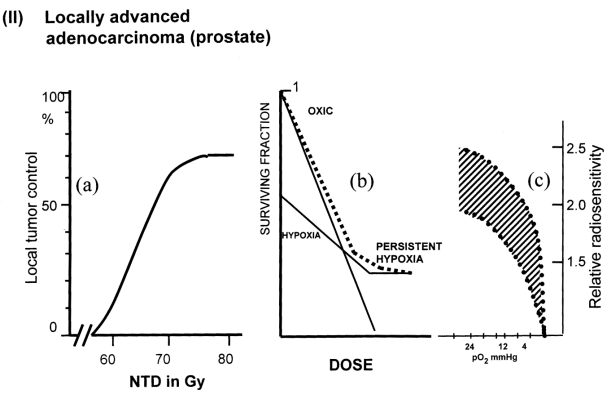

Figure 2.II.

Figure 2. Theoretical and graphical illustration of two different mechanisms which likely lead to the effect plateau in conventional radiotherapy:
(I-a) – Dashed area represents TCP-dose relationship for tumours with 10^9-10^{10} equally radiosensitive tumour cells (D_{10}=7 Gy) with no repopulation. A shift of these curves to the region of lower doses (solid line -y) suggests that in fact epithelial cancers contains one or two logarithms of cells more sensitive than the average. Flattening the upper part of the TCP curves in the region of higher doses is the result of decrease in *"effective dose"* due to gradual increase of *"wasted dose"* compensated by repopulation.
(I-b) – The longer OTT is the more dose is balanced by accelerated repopulation whole cell kill effect might be compensated by repopulation of tumour cells surviving daily fraction doses (I-c) and the TCP-plateau reflects the cell surviving plateau. Therefore time is the major determinant, although a subpopulation of radioresistant cells could contribute to a plateau.
(II-a) – TCP-plateau for prostate cancer may reflect on increasing size of initial hypoxic subpopulation because conventional 2 Gy fractions are not effective enough to kill hypoxic cells, and/or pO_2 gradually decreases (II-b). Time becomes unimportant and the size of dose per fraction and intensity of its accumulation in consecutive weeks of treatment play the major role.

In summary, even after decades of evolution of radiation therapy we still do not know how to optimize treatment for the individual patient and only have "averages" and ill-defined "probabilities" to guide treatment prescription. The major problem is that patients recruited into clinical trials are heterogeneous in their radiation responses and their tumours have heterogeneous subpopulations and responses despite having what appear, at first glance, to be uniform characteristics on which they are randomized. Another uncertainty is that the TNM or AJCC systems are useful for surgery because they are relevant to removal of bulky tumours or nodes, but is not so logical for radiotherapy in which the only aim is to sterilize all cancer cells. In this sense it is volume, not stage of disease which is relevant. Within one stage there can be a ten-fold variation in tumour volume. Finally, basic radiobiological guidelines concerning *average cell killing of "uniformly distributed" and "equally radiosensitive tumour cells"* arose from elegant but idealistic in vitro experiments and seem to be of uncertain validity. Radiobiological models for cell killing fit experimental data but they have not been proven "correct" for clinical data. Nowadays, therefore, we are confronted with more dilemmas than dogmas.

Nolinearity and individual inhomogeneity

In 1981 Stewart pointed out that *"Nature is relentlessly nonlinear"*. This raises questions about the salient aspects of fundamental radiobiology, identification of the causal roles in tumour response of the factors of time, total dose, dose per fraction and of target volume and the validity of current methods and techniques of irradiation. Real-time image-guided radiotherapy needs urgent replacement of model-driven methods by data-driven methods which enable radiation oncologists and physicists to deal with the tumours and their characteristics as they really are, rather than as they can be simulated by models. For the last few years this process is already in progress and it has been quickened in 2001 by the *6th Conference on Dose, Time and Fractionation Radiation Oncology* in Madison, USA.

It is no longer necessary to impose the assumption (often incorrect) of a normal (Gaussian) distribution of a set of clinical data in order to derive the p-values of classical statistics. Nor, is it necessary to assume (almost always incorrectly) that the patient's target volume is a regular solid. Thus classical statistics providing estimates of the significance of the probability of obtaining the current set of data given the null hypothesis are replaced by Bayesian statistics which provides estimates of the probability of a hypothesis, or of a future observation, given the current set of real-data. That eliminates averages, uniform cell density and equal radiosensitivity. Consequently, radiation killing of a constant cell fraction by consecutive and equal daily fractions should be questioned and may be revised. The model concept of equal cell killing per treatment day may or may not work from tumour to tumour, and this could be supported by the flattening of dose-response curves and the "effect plateau" already derived from clinical data for many tumours (Figure 1).

Studies on tumour cellularity strongly suggest that it is far more diverse and heterogenous than we think. Recently, Wilson from Gray Cancer Institute [15] presented a cellular model of the tumour with molecular pathways of its growth (Figure 3) which is more complex than in previously widely accepted radiobiological models. It shows that the tumour is composed of heterogenous

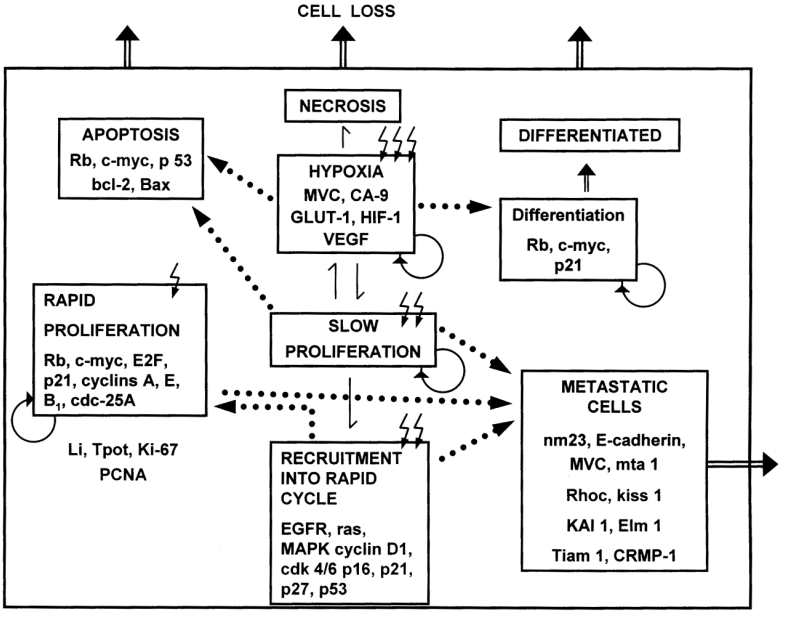

Figure 3. Scheme of cell subpopulations in the epithelial tumour with the key pathways and genes involved in tumour growth, modified from Wilson [14]. Flash arrows to the targets illustrate their relative radioresistance.

subpopulations of cells, whose fate may be natural (e.g. exfoliation, apoptosis) or cytotoxic death from chemotherapy, or removal (surgical excision), but others may persist in a viable state for long periods and could be recruited back into the cell cycle. There are also subpopulations of metastatic cells which may migrate out of the tumour. Therefore, we are dealing in daily practice with heterogenous individual tumours even if clinical classification puts some of them into the same TNM stage.

It is important to recognize gross tumour mass and subclinical deposits of tumour cells. Available images (CT, MRI, PET with image fusion) allow gross tumour delineation with relatively high precision. The next important step is to localize and measure the size and density of tumour cell subpopulations of differing radiosensitivities which have to be destroyed. Although our skills in this field are improving, we are not able yet to achieve this goal.

In 2000 Hellman and Heimann 16] proposed to define breast cancer as a "spectrum of disease" instead of the popular description as "systemic disease," arguing that such a definition covers all possible evolutions of the disease; those which will never develop distant metastases (DM), which already demonstrate DM at the time of diagnosis, and those which will surely develop DM sooner or later (from subclinical deposits already present during the first admission or from locally persistent primary or nodal failures). It is well documented that for node-negative (N0) cases long-term survival after local therapy is about 80% and among T1-T2N0 patients treated radically on an average 10-15% will fail because of DM. Analyzing a database of 2136 N0 patients who underwent mastectomy only, in the same centre, the authors found that evaluation of selected molecular markers, i.e. MVC (microvessel count), E-cadherin, nm23 and p53 allowed separation of N0 cases with very low (close to zero) risk of DM from those with high risk.

The group from Sloan Kettering Cancer Centre in New York [17, 18] has used PET for imaging hypoxic cell deposits within the prostate tumour target in order to escalate and modulate dose distribution in these regions. Furthermore, they found greater tumour cell density in the apex and the lower posterior part of the prostate. Van der Kogel from Cancer Institute in Nijmegen (The Netherlands) developed assays for molecular mapping of hypoxic cells in head and neck tumours. These examples show that theoretical and practical changes from uniformity to heterogeneity in radiotherapy are in progress.

Non-uniformity and dose painting

For decades radiation oncologists have aimed for precise and uniform dose distribution within the target volume because through all these years till now the rule of random cell killing of equally distributed and equally radiosensitive tumour cells was widely accepted. Technological innovations such as high-tech linear accelerators with portal vision, multileaf colimators, exact track correcting for organ movements, 3D treatment planning with CT and MRI images to construct Dose-Volume Histograms (DVH) led to conformal (3D-CRT) non-coplanar (3D-NRT), stereotactic (3D-SRT), dose intensity modulated (IMRT), and recently 4D-Synergy (gating) IMRT techniques. The advantage offered by 3(4)D-CRT and IMRT over conventional RT is that conformally tailored IMRT is individually capable of delivering different doses to multiple target sites with extremely high dose gradient between tumour and critical normal tissues.

The DVH clearly illustrates the advantage of 3D-CRT over conventional RT (Figure 4A – dashed vs.

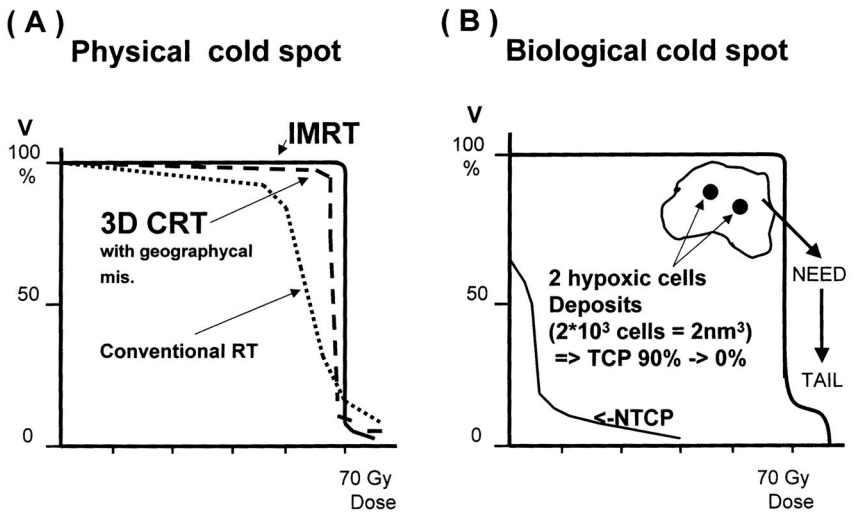

Figure 4. Examples of Dose-Volume Histograms (DVH) – with physical (A) and biological (B) cold spots. Upper-right corner of DVH (A) should be of the major interest. Any shallowness of this part may reflect physical cold spots. Optimal DVH with uniform dose distribution within the target may cover up biological cols spot (B) caused by relatively resistant hypoxic cells which would need an extra boost dose (tail on the DVH).

dotted line). The critical part of the DVH in predicting tumour control probability is its upper-right corner. Sharp bending of the DVH curve in this corner illustrates uniform dose distribution within the tumour target. IMRT can provide a more precise DVH than 3D-CRT (Figure 4A – solid vs. dashed line). However precise definition of the visible tumour (GTV) then becomes critical. The CTV is drawn subjectively based on the assumption of local subclinical spread and no imaging methods can improve its precision. In contrast, the PTV can probably be shrunk by improving set-up accuracy.

Compared with conventional techniques and dose fractionation (Figure 1A,B) IMRT allows to achieve increased steepness of the TCP curve (Figure 1C). The effect plateau may disappear due to increasing the dose within a precisely defined target, and sparing of critical organs enlarges the "safety window" (higher TCP with lower risk of late side effects). Thus, higher therapeutic benefit can be expected [17-20]. On the other hand, a high dose gradient (and dose per fraction), within relatively short distances increases the risk of geographical miss, and pure physical DVH can be misleading. The rapid change in dose per fraction, as well as in total dose suggests that physical DVHs should be converted into Biologically Normalized DVHs (BNDVH) reflecting, at least, corrections for change in dose per fraction [19].

Because IMRT allows margins to be reduced, the danger of edge misses enlarges (Figure 4A – dashed line). Any cold spot within the edge of the tumour ruins the potential benefit of higher doses for increasing of local tumour control (TCP). A 50% dose deficit (dose gradient) in only 1% of the volume reduces TCP to zero, and a 25% dose deficit in 2% of the volume reduces TCP from 90 % to less than 30%. Considering all the advantages and risks of 3D-CRT and IMRT an important question arises – *do we really need dose distribution as uniform as possible within heterogenous tumours?*

For the last few years the complexity of the cellular pattern of the tumour has become apparent (Figure 3). Subpopulations of clonogenic (stem) cells, slow or fast proliferating cells, recruited cells and hypoxic tumour cells, as well as fibrotic, inflammatory, endotherial and stromal cells representing various types of normal tissue form a whole tumour. Tumour cell pattern is further complicated by variations in cell density. In fact, neither normal cells nor some of the cancer cells (which are still alive but never will proliferate) are the real targets for radiation. Modern radiotherapy should not be considered as *"tumour focused"* but rather as *"cancer cells targeted"*. Subpopulations of *"target cells"* are not uniformly distributed within the tumour, and they may differ by localization, size, cell density, proliferative activity and radiosensitivity. Therefore, different doses with probably different fractionation are likely required to kill all of these tumour cells which are viable and proliferative. It leads to the conclusion that uniformity should no longer be considered as the primary attribute for specifying the dose within the targeted tumour, and *"cancer cell targeted radiotherapy"* needs heterogenous dose distribution with deliberately and precisely designed *"biological hot spots"*. This is the idea of so-called *"dose painting"*. Hot spots in the tumour are not dangerous, unless they are also in the wrong places (normal structure). It seems, that dose painting is not a science fiction scenario but is a real-time radiotherapy for biologically and clinically heterogenous human tumours.

To discuss the need of dose painting let's consider an example of an individual epithelial tumour with two subvolumes of 10^8 and 10^9 cells each, being of the same size, equally proliferative, radiosensitive and well oxygenated, and cell density is the only difference. Assuming D_{10} of 7 Gy*, the total dose (TD) of 63 Gy (9 x 7 Gy) will reduce the 10^8 subpopulation to an average 0.1 surviving cell which gives a TCP of 90%. If such TD would be uniformly distributed also in the second subpopulation, 1 cell will survive on average, and give TCP of 37% (e^{-1}). Therefore, for TD of 63 Gy overall TCP will decrease from the expected 90% to about 33% because the same dose is uniformly distributed within two subpopulations containing different numbers of cancer cells. To keep TCP around 90%, the 10^9 population should receive 70 Gy. The increase or decrease in TCP from changing the dose within subvolumes with inhomogenous cell densities can be estimated (Figure 5). Figure 5 shows that the benefit from overdosed subvolumes increases as control rates with standard uniform treatment decrease.

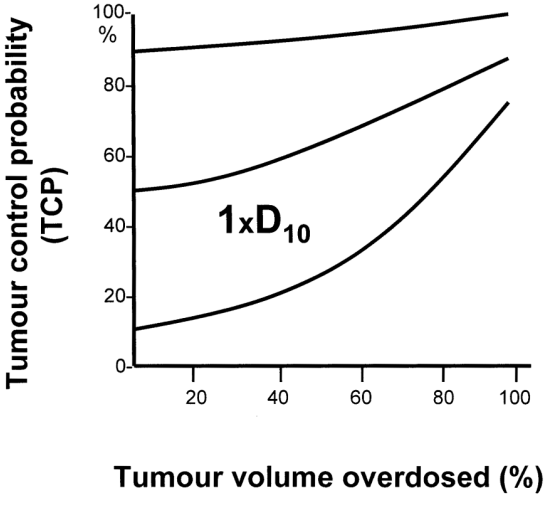

Figure 5. Predicted increase in TCP due to nonuniform dose distribution within the target (according to Withers et Lee, 20), which yields dose greater by 1 x the D_{10} value. The greatest benefit can be expected when the TCP for prescribed dose is relatively low and when the tumour subvolume receives a higher *"boost dose"*.

* D_{10} is handy parameter because it is the dose that reduces survival by one common logarithm. If the tumour has 10^8 cells then 9 x D_{10} corresponds with the TCP = 90% [TCP = e^{-x}, where "x" is an average number of cells survived; after 9 x D_{10} – x will be 0.1 and $e^{-0.1}$ = 0.9 (90%)]. D10 is about 2.3 x $_{eff}D_0$ which for squamous cancer cells and 2 Gy fractions is about 3.0 Gy, therefore D_{10} = 7 Gy.

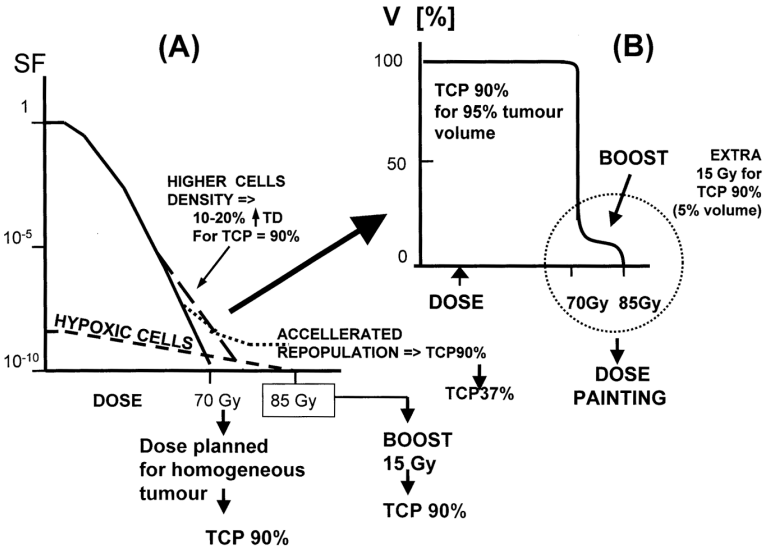

Figure 6. Multicomponent cell survival curve reflecting response of different cell-subvolumes in the tumour. This would support the use of a heterogenous dose distribution in the target volume which is graphically illustrated by the "boost tail" in the DVH.

Making the example above more complex let's assume that in the 10^9 subpopulation one logarithm of cells would be hypoxic. This will drop the TCP down to zero for TD of 63 Gy. To keep the TCP still at the same level of 90%, as for an 10^8 subpopulation, D_{10} should increase to 17.3 Gy assuming OER of 2.5**. In such a situation, TD covering the 10^9 cell tumour should increase from 63 Gy to 80.3 Gy but the size of the last 2-3 fractions should be 7.5 Gy. It would be even more effective if 17.5 Gy will be delivered as a single dose (high dose rate brachytherapy boost). Therefore this example also illustrates the need of variation in dose fractionation given as a boost. If 17.3 Gy would be given in 2 Gy fractions the boost may not work, whereas hypo-fractionated or as a single dose it will.

In clinical practice, predicting TCP is potentially complicated by many causes of heterogeneity in radiation response, such as the presence of subpopulations of rapid proliferating cells and/or intrinsically resistant cells but the common conclusion is that various regions of the tumour need, with no doubt, different total doses of radiation and likely different fractionation schedules. Therefore it seems unrealistic that a single cell survival curve (SF) could represent the response of human tumours to radiation. Rather, a series of SF curves would be more reliable (Figure 6A). Consequently the standard aim of a DVH with homogeneous dose distribution within the target and with its sharp upper-right bend would not be optimal, and the tail, representing a boost dose to biological hot spots (Figure 6B) would better reflect the tail in the survival curve (Figure 4A). Fowler pointed out that not 95% of target must receive at least 100% dose, but that one has to specify a definite minimum target dose, and the target effective uniform dose (EUD) should exceed the prescribed tumour dose [21].

As mentioned earlier, pure physical DVH (especially for IMRT) might be misleading because of physical cold spots and/or a large dose gradient within a relatively short distance. But even it these factors are accounted for and corrected by BNDVH, uncertainty does not disappear and the risk of biological cold spots remains if subvolumes of hypoxic, resistant, or fast proliferating cells exist in the tumour (Figure 4B). In such a situation it seems that dose painting is the only solution, if it can be accurately targeted.

Increasing application of 3D-CRT and IMRT in daily practice needs precise definition of *"dose escalation"* and *"dose intensity"* because they are often misinterpreted and interchangeably missused one for another. *Dose escalation (DE)* simply means the increase in total dose. It may or may not increase biological efficacy (higher TCP). If extra dose is delivered to an epithelial tumour as a fractionated boost with extension of OTT it could be completely balanced by accelerated repopulation, and such dose will be *"wasted"* but not *"escalated"* in a biological sense. By contrast, short HDR-brachytherapy boost given in the last day of fractionated radiotherapy is effective escalation of dose.

Dose intensity (DI) quantitatively describes how intensively the units of dose are accumulated during treatment time, and it is closely related to its biological efficacy. It can be expressed by the number of Gy given per one day of treatment or by the ratio of effective treatment days and overall treatment time. For example, for conventional 66 Gy in 45 days, the DI is 1.47 Gy/day whereas for 66 Gy in 35 days (DAHANCA 7 trial) the DI increases to 1.71 Gy/day. Using the time factor, 5-day a week radiotherapy describes the DI of 0.71 „effective

** For OER 2.5, ${}_{\text{eff}}D_{0\text{hypoxic}} = 2.5 \times {}_{\text{eff}}D_{0\text{oxic}} = 2.5 \times 3$ Gy = 7.5 Gy and then $D_{10} = 2.3 \times 7.5$ Gy = 17.3 Gy.

treatment time" (5/7), which increases to 0.86 for 6-day a week treatment [22]. The DI estimates should be interpreted carefully because 10-12 Gy given in the first week of RT is not biologically equivalent to 10-12 Gy given in week 6 of RT. It means that the DI is biologically higher during the first 2-3 weeks of treatment and significantly decreases with extension of overall treatment time at least for epithelial tumours. It seems likely that beyond week 6 of RT the DI may drop down to zero and result in the "effect plateau", unless accumulated dose per week is higher than 14 Gy.

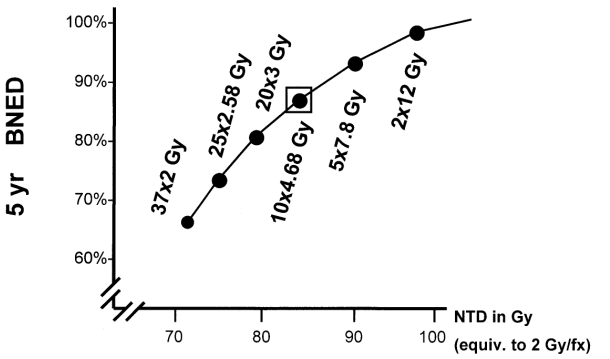

Figure 7. Dose per fraction escalation schedules (from conventional to hypofractionated) predicting tumour control benefit for prostate cancer for constant late normal tissue toxicity (from Ritter and Fowler, 23).

Is there evidence of nonuniformity and the need of dose painting

Heimann and Hellman [16] documented that by using a combination of molecular markers for metastatic potential (MVC, nm23, E-cadherin, p53) it is possible to select a subgroup of patients with T1-2N0 breast cancer with almost no risk of distant metastases (low MVC and p53, and high E-cadherin and nm23) for which 20-year disease-free survival is close to 100%.

In DAHANCA-7 trial [22] 6-day per week RT for a clinically homogenous group of patients with supraglottic cancer has produced an average benefit of LRC of 9%, but in the selected subgroup of well differentiated cancers this benefit increased to 15%, and, within this subgroup, it further increased for a series of patients with high expression of EGFR.

The most fascinating current information is that prostate cancer appears to have an unusual radiobiology and it may likely respond to change in dose-fractionation similarly to late-responding tissue [23] because of a very low α/β ratio of 1.49 Gy (95% CI of 1.35-1.63 Gy). This offers a unique opportunity for hypofractionated radical RT to improve therapeutic ratio. Among a few schedules designed by Ritter and Fowler [23], 10 fractions of 4.68 Gy seems to be plausible (Figure 7). The low α/β ratio probably reflects the presence of inherently resistant and/or hypoxic subvolumes in the prostate cancer. Zelefsky and Ling [17, 18] have shown the potential of PET images to provide both topographical and biological data. Biological images broadly include those in the metabolic, biochemical and functional categories. The increased enthusiasm for PET is in part due to the availability of different tracers (Table I). These advances make prostate cancer an interesting candidate for IMRT dose escalation and painting. Using dose painting, high doses can be restricted to the anterior part of the rectal wall only and the benefit has been validated by recent results showing a significant decrease in late complication rate [17]. Therefore, it may suggest that conventional and prolonged fractionation may neither be necessary nor optimal for prostate cancer. Martinez' group from the Beaumont Centre indicates that 3D-real time conformal HDR brachytherapy can eliminate many of the critical problems that have hampered dose escalation with 3D-CRT (24).

There is no doubt that *dose painting* needs precise quantitative imaging of tumour cell inhomogeneity. Recent advances in nuclear medicine are dedicated to the pursuit of molecular imaging with a potential

Table I. Tumour biology images (cell subvolume characteristics and functions)

Tumour characteristics and/or functions	Method	Tracer	End-point
tumour blood perfussion, diffussion, blood-brain barrier permeability	MRI/^{1}H-MRS	Gd-DTPA (gadolinium diethylenetria-minepentaacetic acid	T1 signals ↑
blood-oxygenation level-dependent (BOLD)	MRI/^{1}H-MRS	deoxygenated Hb	Oxy – Hb ↑ T2 signals ↑
malignant/benign tumour (mainly prostate), tumour burden/cell density	MRI/^{1}H-MRS	Choline/citrate	Ch/c ratio↑
tumour oxygenation	MRI/^{1}H-MRS	Lactate FDG	Lact. ↑ - hypoxia detection, stage, recurrence
tumour oxygenation, growth	PET	^{124}I/UdR	proliferated subpopulation
tumour malignancy	PET	^{11}C – Misonidazole	hypoxic cell-subvolume
tumour growth	PET	^{11}C – Methionine	proliferative activity
tumour apoptosis	PET	^{99}Tc – Annexin V	cell death imaging

resolving power on the order of 20 μm (25). Studies with radioiodinated phospholipid ether (PLE) which is selectively trapped in the membrane of tumour cells, suggest that it could be a potential tumour-selective imaging agent [26]. Clinical studies indicate that the use of inhibitors of the EGFR and the VEGFR may enhance intrinsic radiosensitivity and thereby increase the ultimate tumour response, reducing the need for dose escalation. Intensive studies on molecular mapping together with molecular modifiers and IMRT-dose painting open a new era of *"nonuniform tumour cell-targeted radiotherapy"*.

Criticisms and perspectives

Molecular mapping and dose painting becomes a realistic scenario for the near future in radiotherapy. We learned that the human genome includes approximately 30 000 to 35 000 genes and the growth of various human tumours is initiated and regulated by only about 1000 genes, but on the other hand, by as many as 1000 genes. To learn about all their functions and interactions needs time but it may progressively change not only oncology but likely all medical practice. What we know now is that each individual tumour has its own characteristic cell-pattern which needs nonuniform dose-painting or modification or radioresistance (e.g. by eliminating the effect of hypoxia) which should also include surgery and chemotherapy in order to destroy cellular reproductive integrity of all tumour clonogens. We are not able yet to identify accurately areas of increased density, proliferative activity, resistance and hypoxia. Therefore localized dose escalation has an inherent potential for geographical errors. To achieve a benefit hypoxic subvolumes require a significant increase in dose but hypoxia might be distributed throughout the whole tumour instead of being in one or two localized areas and may change from day to day. Therefore to selectively target foci of radioresistance needs precise and repeated functional imaging.

One can be sceptical but none can ignore the perspectives. We have to be prepared for collection of a large number of genetic and molecular data in parallel with clinical data, treatment parameters and results of treatment. Therefore the latter ones should be as accurate as possible. It seems likely that the rules of randomization and clinical trials may change because we will be looking for homonogeous groups with respect to both clinical and molecular parameters relevant to radiation responsiveness. Methods of analysis may also change into comparison of two tumours with identical cell characteristics, one cured and another one failed, to establish their genetic and molecular differences in order to recognize which characteristics are responsible for the failure. Notwithstanding all of these uncertainties and criticism the conclusion seems that openess,mutual contacts and, collaboration and intensive exchange of precise information are basic and urgent fundaments for effective progress, not only in radiotherapy. In fact it might be the beginning of so-called *global oncology*.

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