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Theragnostic Radiotherapy

Radioterapia teragnostyczna

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S u m m a r y

Present paper presents actual controversial problems of radiotherapy, new technological and therapeutic developments and future perspectives. Some old dogmas are critically discussed. In the era of 3D imaging (CT, MRI, PET) volumetric staging should be used rather than classic rank TNM. Optimal and individual dose and fractionation should be taylored to the initial tumour cell number (volume) but not to T stage. Fundamental dogma that equal doses (fractions) kill the some rate of cancer cells is not longer valid. Biological concept and practical consequence of "hypofractionation back to bedside" is presented. Clinical practice shows that many of 3D conformal RT methods still do not reach level I or II evidence. Proteomic and molecular tumour profiling have been advocated as the next "Holly Grail" for radiotherapy. However many studies show that this promising issue seems to be more complex and heterogeneous as it has been assumed previously. In the light of the present achievements and disappointments, "Theragnostic Radiotherapy" (Oncology) provides some promising perspective. This term means to explore knowledge and experience by tumour-type oriented multidisciplinary team of oncologists to plan individually personalized combination of treatment methods, its sequence and restricted timing.

Key words: theragnostic radiotherapy, hypofractionation, tumour volume, molecular profiles

S t r e s z c z e n i e

Praca prezentuje aktualne problemy radioterapii, nowe rozwiązania technologiczne i terapeutyczne oraz perspektywy postępu. Niektóre stare dogmaty są przedmiotem krytycznej dyskusji. W erze 3D obrazowania (TK, NMR, PET) klasyfikacja zaawansowania wolumetrycznego wydaje się konkurencyjna w stosunku do klasycznego rangowego systemu TNM. Dawka i jej frakcjonowanie wymaga indywidualnego dopasowania do wyjściowej liczby komórek nowotworowych (objętość), a nie do stopnia zaawansowania T. Fundamentalny dogmat, że takie same dawki (frakcje) skutkują śmiercią takiego samego odsetka komórek nowotworowych utracił wiarygodność. Praktyka kliniczna wskazuje, że szereg metod 3D konformalnej radioterapii ciągle nie wykazała dowodu I lub II stopnia. W profilowaniu proteomicznym i molekularnym indywidualnych guzów nowotworowych upatrywano następnego „Świętego Grala" dla radioterapii. Jednak szereg badań dowodzi, że ta obiecująca perspektywa wydaje się znacznie bardziej złożona i niejednorodna niż początkowo sądzono. W świetle dotychczasowych osiągnięć i rozczarowań „Radioterapia (Onkologia) Teragnostyczna" jest obiecująca. To pojęcie oznacza wykorzystanie wiedzy i doświadczenia multidyscyplinarnego zespołu narządowego w celu zaplanowania zindywidualizowanej kombinacji metod terapeutycznych, ich sekwencji i ścisłego reżimu czasowego.

Słowa kluczowe: radioterapia teragnostyczna, hipofrakcjonowanie, objętość guza, profile molekularne

This is difficult to cover a large field of many different initiatives and innovations leading to progress in oncology and specifically radiation therapy and to present only major achievements in this field. Therefore, we deliberately resign to review the results of translation studies and clinical trials and we focus on some dogmas, new concepts and developments, doubts and uncertainties.

DOGMAS DIE SLOWLY

Since Fletcher defined radiobiological basis for fractionated radiotherapy that equal doses of radiation (also chemotherapy agents) kill the same rate (not a number) of cancer clonogenic cells is unalterably accepted in the practice although it is no longer true. Time factor was misprized for a long time until late eighties. It was an obvious and groundless dogma that solid tumours generally grow slowly and therefore there is no need to complete the treatment in less than 6-7 weeks. Well documented phenomenon of accelerated repopulation of clonogenic cancer cells became an important factor for treatment outcome. Any extension of treatment time results in significant decrease in local tumour control (fig. 1), including duration of chemotherapy and any

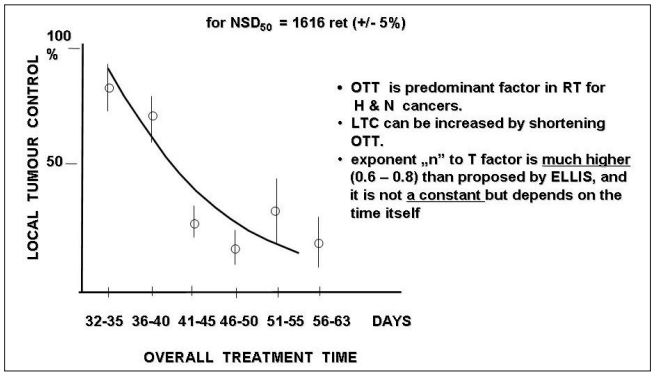

Fig. 1. Local tumour control (Maciejewski and Trott, 1983) as a function of overall treatment time for 310 T3-4N0 laryngeal cancers irradiated with a total dose for 50% local tumour control (TCD50) equivalent to Nominal Standard Dose NSD50 = 1616 reto (± 5%). For constant dose, extension of overall treatment time results in significant decrease of local tumour control.

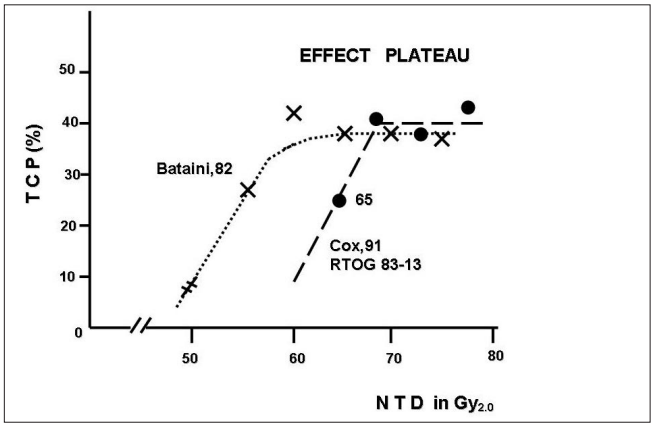

Fig. 2. "Effect plateau" for H & N radiotherapy. Any increase in total dose above 60 Gy with the respective extension of overall treatment time does not produce any therapeutic gain.

time intervals between various treatment modalities used in combined therapy. Individual tumour cel characteristics are no longer considered as homogenous. The size and localization within the tumour burden of the subpopulations of clonogenic, quiescent, hypoxic, potentially apoptotic and intrinsically resistant cells are highly heterogenous and they need heteregenous dose distribution (including chemotherapy agents). This dogma should die but it does not.

The next even more important dogma relates to the use of the TNM staging (FIGO, UICC a bit later) as a fundamental criteria for qualification to therapy irrespectively what treatment modality is selected. In the former time, the TNM staging was based on clinical examination and very simple 2D radiologic imaging. For decades technologic revolution has offered many exquisite radiologic devices, e.g. CT, MRI, MRI Spect, US, PET, CBCT which provide functional and quantitative volumetric imaging of the primary and/or metastatic tumour(s). Moreover, radiotherapy has changed from 2D to 3D (or even 4D) including palliation but the dogmatic TNM staging is still used for treatment planning. This seems to be unexplicable nonsense. For example conventional 70 Gy in 35 fraction given to $T_2N_0M_0$ oral cavity sq.c.c. might be enough for 2.1 cm (4.1 cm^3 = 4 x 10^9 cells) tumour but definitely not for 3.9 cm (33 cm^3 = 3.3 x 10^{10} cells) tumour. The TNM stage likely works for surgery (it is not important whether 2 cm or 4 cm tumour is excised) but it is definitively not predictive for individual dose fractionation. There is about 10 fold difference in tumour volume of the smallest and the largest T_2 tumour what gives difference of 1 decade (1 log) of tumour cells. Therefore the largest tumours in this category should receive about 7-10 Gy[1*] higher total dose (with no change in the OTT) than the smallest ones. However it did not become a rule in daily practice. Trends of the OTT and initial tumour volume (T_v) are very similar – local tumour control (LTC) dramatically decreases with extension of the OTT (fig. 1) and increase of the T_v.

ALTERED RADIOTHERAPY – DOES HOLLY GRAIL EXIST?

During the last 25 years phenomenon of accelerated repopulation (1) of tumour clonogens (significant decrease in the local control (LTC) with extension overall treatment time (fig. 1) has led to more that 40 different clinical trials on altered dose fractionation with more than 20 000 patients involved. However, overall results are rather disappointing. Among 26 well known trials in H&N cancer only 15 were included into meta-analysis (2). Therapeutic gain in 5-year locoregional control (LRC) was 4-6% and 8% in overall survival but mainly in favour of hyperfractionation. It seems very naive to expect any therapeutic benefit using the same dose and fractionation for variety of tumour sites and stages. These studies clearly show that a single altered fractionation regimen can never be a "Holly Grail" for many different tumours, even within the single region, as head and neck, and average results can never be used as optimal predictors to treat individuals.

The CAIR-I and CAIR-II showed about 40% increase in the 5-year LRC for $T_{3-4}N_{0-1}M_0$ oral cavity and oropharyngeal cancer, but in CAIR-II 5-day-concomitant boost has appeared similarly effective as 7-day irradiation. At the first glance one may say that altered radiotherapy generally failed. On the other hand more optimistic conclusion is that there are likely a few "Holly Grails" for more homogenous subset patients when the TNM staging would be supplemented with the volumetric one.

The next practical conclusion is that any extra dose (popularly called "escalation") together with the respective OTT extension does not produce any gain. Doses of 60 Gy/30 fx in 42 days, 70 Gy/35 fx in 49 days and 80 Gy/40 fx in 56 days are equally effective (fig. 2).

[1*]Increase in tumour volume by 1 decades on reflects an increase in the number of tumour cells e.q. from 10^9 to 10^{10} cells. Assuming D_{10} = 7-10 Gy (dose which kills 1 log of cells) than total dose of 70 Gy for small tumours should increase to 77-80 Gy for large ones for the same TCP = 90%)

Suwiński and Withers (3) have defined this phenomenon as "effect plateau". Although a universal "Holly Grail" has not be found the OTT should be as short as possible but not less than 4 weeks with no change in total dose, and the treatment should always start on Monday but never completed on Monday.

HYPO – BACK TO FUTURE

At the beginning era of radiotherapy hyperfractionation was the major, and in some countries, the only schedule of radiation dose delivery. It was mainly advocated by Germans and Swedish and was still popular even when such giants as Regaund and Coutard introduced multifractionated treatment. HYPO was abandoned as radical treatment, because of a high risk of serious late complications, and used only as palliation. The comeback of HYPO started in early 50-ties when neuronavigation has developed (stereotaxy). The next step was Gamma Knife and recently Cyber Knife. This technology has led to stereotactic body radiotherapy (SBRT) with large single fractions of 8 Gy to even 22 Gy to relatively small the target volumes. The HYPO offers two major advantages: short time of treatment and short hospitalization and it became the domain of radiobiology (4). According to Fowler, any tumour radioresistance has no chance to be converted into radiosensitivity if a single fraction is given. However, a few fractions can in principle improve radiosensitivity. Moderate HYPO with fraction dose of 4-8 Gy has been widely popularized. In rectal cancer, preoperative 5 x 5 Gy followed by total mesorectal excision resulted in significant therapeutic gain and about 65-75% sphincter preservation. Three fractions of 22 Gy given over a few weeks to T_{1-2} NSCLC resulted in 95% 2-yr LRC and 56% OS. Partial-breast irradiation with the dose of 34-38.5 Gy in 10 fractions given using 3D conformal radiotherapy after breast-conserving surgery produces none local recurrence and 90-92% excellent cosmetic outcome in the study of Beaumont Centre (4).

Long clinical practice has shown that linear quadratic model and α/β factor likely do not work for doses below 1 Gy and above 8-10 Gy. Ritter and Fowler reported an α/β value lower than 2 Gy for prostate cancer (less than for spinal cord) and it was almost like "October Revolution". Prostate cancer Immediately became a target for HYPO, and 5 x 5.5-7 Gy have been mandatory employed in the USA and Canada. Martinez introduced 4 x 8.5, 9, 9.5 Gy schedules as a sole treatment and noted acceptable incidence of late effects similar to conventional RT with pronounced benefit in LRC. It was found as a challenge to conventional treatment, and Fuks with Zelefsky from Sloan Kettering Cancer Institute in New York used high-tech 3D-conformal IMRT "dose painting" with 1.8 Gy/fractional given up to 90-92 Gy. Is has been recognized as "High Society" of radiotherapy because treatment planning was based on MRI-PET fusion biological imaging of tumour subvolumes with hypoxia, high proliferation, or cell density, intrinsic resistance and with individual dose painting according to the resistance of subvolumes.

Although the HYPO has made very fast career, the challenge between HYPO, HYPER, Brachytherapy and in the field boost IMRT (SIB-IMRT) continues, and till now there is no clear advantage of one of them.

3D-4D-IMRT, IGRT, SBRT, IART, IORT – SERIES OF BANK SAFE CODES! WHICH ONE WORKS?

After disappointment with altered fractionation High-Tech revolution in radiotherapy has appeared as the next promising "Holly Grail". It offers precise conformal delivery of individually shaped radiation beams focused within the tumour target. Dose can be escalated and normal tissue better protected. Stereotaxy and dose intensity modulation can even be shaped in the tumour in high degree of freedom and with higher doses in some specified subvolumes (IMRT).

Substantial changes in the topography of tumour and surrounding normal tissues interrelations caused by tumour regression together with correction to organ motion (IGRT) were also accounted for three dimensional planning and treatment, and it made one step forward to the 4D therapy. Kinetics and degree of tumour regression can not be precisely anticipated based on the treatment planning. Single replanning and resimulation during the treatment seems to be not enough. Wang et al. (5) clearly documented that dose delivery based on a single planning prior the treatment may lead to overdose in spinal cord by 10 Gy, in parotid gland by 8.5 Gy and underdose in the tumour by 5-6% in 95% of the CTV. Therefore it led to development of the 3-4 D adaptive IMRT A(MR) with real time image guidance to minimize geometric uncertainly. The onboard CBCT provides possibility for dosimetric verification. Methods of offline, online or interfraction corrections have developed. Such technological progress opened a new era for very sophisticated daily CBCT guided 4D gated adaptive radiotherapy with breath controlling or holding techniques. It showed that techniques allow to decrease geometric error from 6-8% when single planning CT and skin marks are used to 4-6% for daily ultrasound and to only 1.5% for daily CBCT.

However, the ability to predict outcome to a given irradiation is not the only one the radiation oncologist would like to know. The next step what the treatment could be also or even more effective. Therapeutic advantage of these high-tech RT is still not well proven. In Gliwice Institute 3D-CRT for H&N cancer produces therapeutic gain of about 20% compared with conventional 2D-RT. Sloan Kettering Cancer Center has documented increase in 5-year BNED for prostate cancer using 3D-AIMRT with biological imaging and planning. By improving techniques of RT for prostate cancer Martinez from Beaumont Institute noted an increase in the 5-year BNED from 51% in 1987-1990, through 83% in 1996-2000, to 92% in 2001-2005, with very low (0-2%) risk of late GU and GI grade III complications.

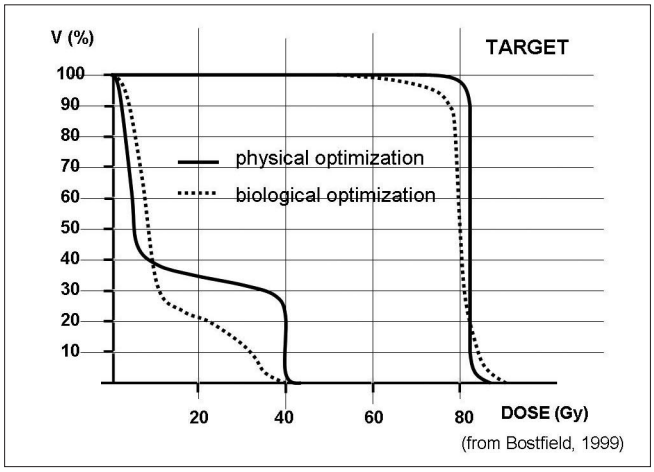

Fig. 3. Simulation of Dose Volume Histogram (DVH) for physical (solid line) and biological (dotted line) doses.

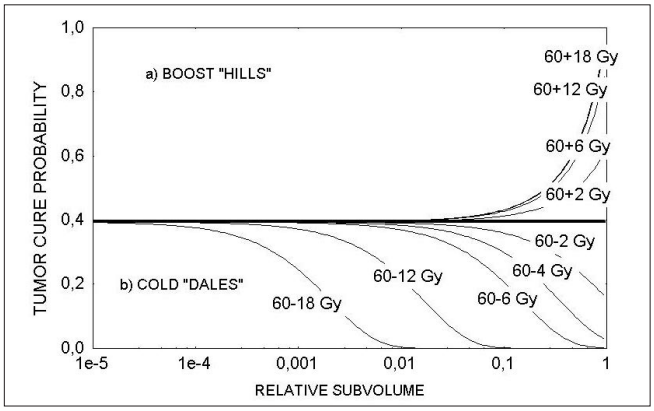

Fig. 4. Tumour Cure Probability for the boost dose given after 60 Gy/30 fractions producing 40% TCP. Upper past illustrates increased by the boost doses in the range of 2-18 Gy. Lower part shows situation of geographical error in the rate of sobvolume.

One has to keep in mind that all promising developments bring also some traps and uncertainties. One important trap is that dose distribution with a high dose gradient within very short distance is no longer physics. This is radiobiological planning of biological dose. Figure 3 illustrates this problem. Position of physical dose curves on the DVH can be misleading. In fact curves for biological doses are shifted to the left in the dose coordinate[2*]. It may lead to underdose within normal tissues at risk which is a "good news" but also to underdose in a part of tumour which might be a very "bad news". If there is underdose by 5% (e.g. 3 Gy of 60 Gy) in 50% target volume then tumour control probability (TCP) dramatically drops down even to zero.

The next trap might be no correction for tumour motion. Gotein has calculated the situation when 90% of tumour volume is within the beams for whole treatment time and 10% of tumour volume moves out of the beam by 20% of treatment time, then predicted TCP of 90% may individually decrease to zero, and randomly to about 70%.

Another trap relates to the boost dose planning, it may occur mainly for H&N, prostate, rectal cancers. First of all, conventionally fractionated boost should never be used (no effect with the OTT extension). Simultaneous in field boost-IMRT (not for hypoxic tumours) or 1-3 fractions of brachytherapy (for hypoxic tumours) are a proper solution. The point, however, is that it should be planned when the predicted TCP is below 60% to at least 80% of primary tumour volume, and using at least 2-3 D_{10} (D_{10} is dose decelerating the tumour cells by 1 log) that is 14-21 Gy. So, the trap is geometric error. Total dose lower by 10% delivered to 10% of tumour subvolume effectively ruins all advantages expected from well planned and delivered Boost-Dose (fig. 4).

Geometric and biological traps are an important warning when one decides use the RT sofistatical techniques. Otherwise the belief that optimal RT with high TCP is offer to the patient can unnoticeably be illusion.

PROTEOMICS AND MOLECULAR MARKERS – TO BE OR NOT TO BE FOR RADIOTHERAPY

Impressive and fast progress in cancer genetics, proteomics and molecular markers has enlightened radiation oncologist how much they have to learn to improve knowledge and experience to optimize RT for individual patients. It has been recognized that clinical and pathological factors are not predictive enough. Gene expression and its proteins products become of obvious interest of the cancer research and clinics. Predictive value should be clearly distinguished from prognostic one. The RET expression was found as 100% predictive factor for the risk of hereditary thyroid cancer to perform prophylactic thyreoidectomy. For breast cancer, HER-2/neu amplification was established as a prognostic factor associated with a poor outcome. In a relatively short-time clinical studies have shown that HER-2 status became also as a strong predictive factor for chemotherapy combined with trastuzumab. However, even when specific molecular factor was found as a good average prognosticator it often failed as individual predictor, e.g. p53 expression.

Searching for a single molecular/genetic predictors as individual key has shown that it might be a long walk into heavy forest. Special interest on the thyrosine kinase regulatory network has resulted with very promising clinical RTOG trial on Cetuximab targeting the EGFR during fractionated radiotherapy for head and neck cancer. In 2006 Bonner et al. (6) documented 13% 3 yr DFS benefit in favour the RT + cetuximab compared with RT alone (57% vs. 44%). However, the rate of this gain looks controversial. Based on experimental enhancement ratio for cetuximab of 1.5-1.8, therapeutic benefit should increase to about 70%. The results

[2*]Assuming 70 Gy in 35 fractions is given to the CTV and a part of the organ at risk received 40 Gy. This is physical but not biological dose because it was delivered in 1.14 Gy (40 Gy/35 fx). Therefore the respective biological dose (α/β = 2.0 Gy) is: BD=TD (α/β + d)/ /(α/β + 2.0 Gy) = 40 (3.14/4) = 31.4 bioGy.

showed that among 57 of 100 patients 44 patients respond to RT despite EGFR inhibition, and only 13 pts. respond due to cetuximab inhibition whereas another 13 patient should also respond positively but they do not. Logical explanation could be that cancer cells have multipathways network, and when one of them is blocked "life signals" are passed through another one. Which one – we still don't know.

When a single moleculat modifier was found not effective enough studies on 2-3 modifiers hase been designed. Inhibitor for EGFR (gefitinib, erlotinib) with VEGFR inhibitor (PTK 787/ZK) were tested for malignant glioblastoma by RTOG and NABIC group in the US. There was no benefit at all and only 8% partial response but high incidence of very serious complications (brain oedoma, deep vein thrombosis). This study suggests that glioblastomas can compensate loss of a given downstream signaling pathway by another one and even more, that cancer cells are smart enough to fight for own life and transfer "life-signals" through the blockage, and modify own molecular profile.

Hellman and Heiman (7, 8) have elucidated this phenomenon in clinical studies on early node negative breast cancer with diameter of less than 3 cm. Answering to the question what is the mechanism responsible for a high risk of early dissemination (DM) of such tumours they define molecular signature with high level of E-Cadherin, low p53, high nm23 and low MVC which strongly correlates with very low risk of the DM and 10 yr DFS of above 95%. Contrary to that, signature with high p53 LOH, low E-Cadherin, low nm23 and high MVC is strongly predictive to more than 60% of early DM and very poor 10 yr DFS below 40%. Such molecular signature – predicts a high or low risk of DM, and therefore unsuccessful or beneficial local conserving treatment. However, it is not so simple. The authors observed that during the treatment good preliminary molecular signature can progress into very bad one with poor prognosis.

This not all what cancer cell can do. According to Szala (9) some type of specialized cancer cells is able to recruit certain normal hematopoietic and mesenchymal cells (monocytes, macrophages, granulocytes, dendritic cells, fibroblasts). They undergo "education-like" phenotype reprogramming influenced by cancer cells and serve as tumour associated "slaves" (TAM, CAF) and contribute to the development of a specific microenvironment. Together with cancer cells they are engaged in the processes of defective angiogenesis which may have substantial impact on hypoxic metabolism. Another form of anecting normal cells in so-called "frog jumping" mechanism was defined by the Amsterdam group (10, 11). Squamous cancer cells in the H&N region are able to transfer some undefined signals to surrounding normal epithelial cells and induce a cascade of genetic alterations (EGFR, CCND1, cyclin D1, p53, Cox-2, LOH of 9p21, 3p, 17p13). Normal mucosa begins to transform through hyperplasia and dysplasia into carcinoma in situ. Traditionally it

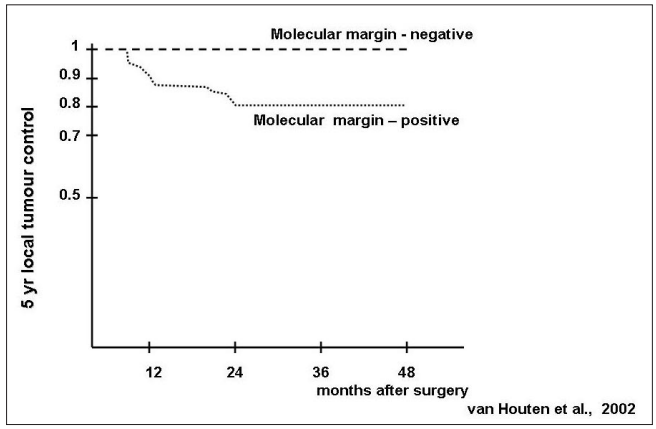

Fig. 5. Impact of surgical molecular margins of local tumour control of head and neck cancers (van Houten, 2002).

has been diagnosed (and still is) as a true second primar tumors whereas at least 50% of them is "second field" recurrence of primary tumour. Evidence of this phenomenon are positive molecular (p53+) surgical margins (fig. 5) which correlate with 26% incidence of local recurrence comparing with only 4% for negative molecular margins.

In light to the cited facts, important question arises whether significant reduction of tumour (CTV) margins is a proper solution for targeted of the IMRT, SBRT, A-IMRT. Kępka et al. (12) clearly documented therapeutic power of the threshold doses below 50 Gy to eradicate small metastatic deposits in the isolated mediastinal lymph nodes. The authors pointed out that generally ignored "disregarded doses" (incidental irradiation) beyond the boundary of interest may have important impact on treatment efficacy. Therefore, instead of targeting the dose to what "we can see" due to the best images, spectrum of interest should be widen also to what "we cannot see". Logical consequence would be to wide-field "radiation shower" with low doses and large doses to the target thereafter.

Hypoxia is another important predictor for treatment outcome (e.q. H&N, lung and breast cancers) because it correlates with poor vascular network, metastatic potential and radioresistance. The 18 FMISO-PET is an effective image of hypoxic regions within the tumour. The major problem is the lack of the method to distinguish acute from chronic hypoxia areas, because they can change localisation during the treatment.

Tumour stem cells are used to be crucial for local curability since they are the source of clonogenic cells being sensitive to cytotoxic agents. In contrary, Bao et al (13) has found that CD 133+ (phenotypic marker) glioma stem cells are radioresistant and together with a small hypoxic fraction may dictate response to (chemo-) radiotherapy.

Results of clinical trial on postoperative CAIR (7 fractions in 7 days) for H&N cancer clearly show that clinical prognostic factors are not strong enough to select the group of patients who can gain from this regimen. However, when Suwinski et al. (14) defined "joint mo-

lecular risk scoring system" they noted significant 68% LRC benefit in favour of the p-CAIR for the oral cavity and oropharyngeal cancer (not for larynx) with the signature of high EGFR, low p53 and low Ki-67 compared with 28% after conventional fractionation.

THERAGNOSTIC RADIOTHERAPY – REALITY OR DREAM?

Despite significant technological progress the use of radiotherapy as a sole treatment for solid tumour is more and more limited, likewise surgery and chemotherapy. In 2008 Bentzen used from the Greek a term "Theragnostic" to emphasize the importance of the therapy and knowledge, regarding individual combination of treatment methods, its sequence and timing. Theragnostic oncology is therefore Personalized Multimodality Cancer Care (as a complex of planned combined therapy). Theragnostic radiotherapy specify the RT method and its place within the sequence multimodality treatment. It is likely that average results being even important and evidence based protocols remain only average guidelines and might be unprecise for individual treatment optimization.

Despite some uncertainties, broad categories of biomarkers, molecular and functional images should be a top priority for clinical – translation radiation research. Considering the place of chemotherapy within the multimodality plan MACH-NC metaanalysis (16) of 63 trials including about 10 500 patients showed no benefit for adjuvant or neoadjuvant chemotherapy and some gain for concomitant chemoradiation, but once again large heterogeneity of clinical data and treatment regimes did not led to firm conclusions. However, it became certain there is no longer room for conventional sequential therapy. It still happens that escalation, intensity and efficacy are often mixed up and misinterpreted. Dose escalation simply means an increase in total physical dose. If the OTT is also prolonged one may expect "effect plateau" and no therapeutic gain at all. Dose intensity has a direct impact on therapeutic benefit not only for RT but also for whole multimodality strategy.

It seems possible to express intensity of surgery, chemotherapy and radiotherapy by a single value. Such concept has been defined by Withers as a BLUE (Biological Unit Effective). Excision of 3 cm tumour might be equivalent to 30 Gy/1 day (it was suggested by Paterson in late forties) and 6 courses of standard chemotherapy is likely biologically equivalent to about 21-28 Gy[3*]. Let us consider two simple clinical examples A and B.

Example A is a conventional sequential therapy surgery (3 cm excision = 30 Gy/1d) – 4 wks interval – postop. RT with 60 Gy/42 d – 3 wks interval and 6 courses chemotherapy in 105 days (equir to 28 Gy). Therefore DI_A (Dose Intensity) = 118 $_{BLUE}$ Gy/197 d and finally DI_A = 0.6 BLUE $_{Gy}$/day.

Example B is similar treatment sequence but with concomitant chemoradiation and the intervals shortened as much as possible. It gives:

Neoadj. CHT-RT = 20 Gy and 2 cycle CHT (~10 Gy)/ /in 22 days – 7 days interval – surgery (~30 Gy/1d) – 10 days interval – RT 60 Gy + 4 cycles CHT (~18 Gy), all in 63 days. Overall DI_B = 138 $_{BLUE}$ Gy/99 days = 1.4 $_{BLUE}$ Gy/day. Therefore model B is at least as twice effective as model A.

In light of all presented criticism, there is no doubt that biomarkers will likely enlarge the arsenal of predictors and prognosticators to personalize optimalize treatment strategy. However until it will become widely applicable there is practical lesson to learn. Theragnostics dictates the rule that multidisciplinary tumour-oriented team should define optimal treatment based on functional biological images and volumetric staging. Strategy should consider modalities sequence, timing and intensity based on knowledge, experience and common sense. It is important to count every single day, every single Gray and every single drug.

[3*] 6 courses of chemotherapy usually results in 3-4 Logs of cell kill. Assuming D_{10} = 7 Gy it gives (3-4) x 7 Gy = 21 – 28 Gy.

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