NOWOTWORY Journal of Oncology • 2006 • volume 56
Number 3 • 242–248

From static 3D-conformal to dynamic 4D-imaging and molecular guided gating radiotherapy

Bogusław Maciejewski, Leszek Miszczyk, Rafał Tarnawski, Rafał Suwiński

This is a review of the topics and comments to the 7th International Conference "Dose, Time and Fractionation in Radiation Oncology" in Madison in 2005. The problems which have been discussed during the conference are presented in three sections – tumour delineation and organ motion, dose fractionation and molecular modulation of tumour response with authors' comments. New radiotherapy goals mainly concern increasing precision of treatment planning and dose delivery by dynamic fusions of morphological and functional CT-NMR-PET images, and to a growing extent, studies on molecular predictors and modifiers of radiation treatment. These two major fields of interest are intensively explored in many centres worldwide. There is convincing evidence that in many clinical situations radiotherapy used as sole treatment is effectively replaced by concurrent radiochemotherapy, however "chemo" does not longer refer to cytostatic drugs only but also to molecular compounds and radiation modifiers.

Key words: molecular and imaging guided conformal radiotherapy, fractionation, chemo-radiation

Conference "Dose, Time and Fractionation" is recognized worldwide, with a long tradition of over 28 years. It is always organized in Madison, Wisconsin in the US. The number of participants and invited speakers is rather restricted yet every four years it is an important event in the itinerary of radiotherapy meetings. The important advantage of this conference is that it is always aimed at presenting what has been done in the past four years and what are the new and the most promising developments which should be challenged in the next four years. Over the last decade there have been significant technological, physical, molecular and biochemical developments in radiation oncology that have created a tremendous potential for dose escalation in the delivery of radiation treatment. New tools allow higher confidence in tumour targeting and normal tissue sparing by providing conformal dose distribution. This allows to shift the dose distribution to the surface of the target volume with a rapid "fall off" in the normal tissues. While the previous 6th Conference concentrated on altered fractionation and treatment outcomes, the present 7th Conference has focused on precision of target delineation, static 3D- and dynamic 4D- imaging and molecular guided dose painting and molecular modulation.

According to Bentzen we are progressively moving toward theragnostic radiotherapy (i.e. with knowledge how to treat) which refers to biological information at the level of the individual patient which allows selecting a specific therapy and improving the therapeutic outcome in each individual case – relative to the outcome after standard therapy.

Department of Radiotherapy
M. Skłodowska-Curie Memorial Cancer Centre
and Institute of Oncology
Gliwice Branch, Poland

Tumour imaging and target delineation

Evolution from static (diagnostic and planning) toward dynamic imaging (treatment monitoring) became crucial for the precision of planning and dose delivery, especially for 3D-4D conformal and IMRT radiotherapy. Haslam from Chicago has shown that static treatment plan evaluation using single dose volume histograms only may not be representative for the dose delivered to the selected structures and may lead to underdosing the clinical target volume (CTV), or overdosing the organs of risk (OARs). Gregoire from Brussels has shown extensive studies on delineation errors of the primary tumour GTV, and large variations in definition of CTV_1, and CTV_2 due to unprecise interpretation of static CT images. New imaging modalities, such as dynamic enhanced DCE NMR (presented by Ling form Sloan Kettering CC, New York), FDG-PET, 18F-MISO PET, and 3'-deoxy-fluoro-thymidine FLT-PET (Jeraj from Madison) together with image-fusion allow to increase the precision of tumour and organ-at-risk delineation, and provide functional images of tumour hypoxia and tumour repopulation intensity. According to Ling, FLT-PET images can be considered as a surrogate for tumour proliferation. Increases in FLT indicate early accelerated repopulation whereas significant decreases in FLT strongly correlated

with tumour-cell clearance. Metcalfe from Australia presented a dynamic program of Beam-Eye-Views (BEVs) which allows to validate radiotherapy planning dose prediction for IMRT technology.

Although tomotherapy (IMRT combined with CT on time and on line) has been known since the late nineties, mainly in Madison, a few new centres have recently been developed in the US and in Canada. Kupelian from Orlando has presented an elegant technique of IMRT/tomotherapy for prostate cancer. In-room, cone-beam CVCT imaging is adapted to the TomoTherapy HiArt II helical accelerator to perform highly adaptive radiation therapy. A motorized couch driven by an on-board computer makes inverse treatment planning possible with different pitch ratios, jaw widths, and modulation factor and thus it is possible to use an optimal plan for a specific treatment site. CT images with a delivered dose of 1-3 cGy per scan are generated prior to each treatment and fused with original planning CT images to reposition patients to the simulated and planning positions. Daily evaluation of dose, including dosimetric variations in target and normal tissues, leads to image- and dose-guided radiotherapy.

Apart from uncertainties in the delineation of the GTV, CTV_1, CTV_2 volumes, organ motions become one of the most important aspects of precision in radiotherapy. Organ motion due to physiological functions can be substantial. For example, the liver can move up to five centimeters in the caudal-cranial direction during free breathing, causing motion of the entire upper abdominal and lower thoracic cavity. Organ motion due to cardiac function, gastrointestinal peristalsis, stomach filling, rectal filling, bladder filling and swallowing can also occur during therapy. Furthermore, patients may involuntarily change their position during the treatment session, due to discomfort or session prolongation.

Dawson from PMH in Toronto has focused on strategies to compensate for breathing motion, including voluntary shallow breathing, deep inspiration, breath holds at variable phases of the respiratory cycle, gated radiotherapy and real-time tumour tracking. Among the many techniques gated radiotherapy with the beam triggered only at the same phase of the respiratory cycle appears to be the most efficient. The real-time tracking system consisting of fluoroscopic x-ray tubes in the treatment rooms and allows visualization of radio-opaque markers. The linear accelerator is triggered to irradiate only when the marker is located within the planned treatment region. As the tumour shifts outside the treatment region the multileaf collimators, the couch position or the entire accelerator may move with it tumour to ensure adequate tumour coverage at all times. The diagram on Figure 1 shows step-by-step procedures starting with the collecting of topographic and functional images for 3D-contouring of the defined targets. 3D-planning is based on a series of DVHs to optimize the treatment plan. The simplest solution is that the radiation beam is delivered only during the same phase of the respiratory cycle. The conceptof this method resembles that behind tomotherapy and pulsed brachytherapy.

To summarize, at presernt it is obvious that the use of the DVHs based on unfrequent series of CT images or even the use of the MLC does not automatically render planning and dose delivery conformal. During the Conference it has been clearly pointed out that the name "conformal" is often overused. High-tech accelerators and other tools are tools only and do not automatically legitimate conformity. Knowledge and experience are also important, and probably even more so. Therefore, sometimes conformal radiotherapy is onl;y the term used, and in fact not performed. The criteria for conformal radiotherapy recommended during the conference are

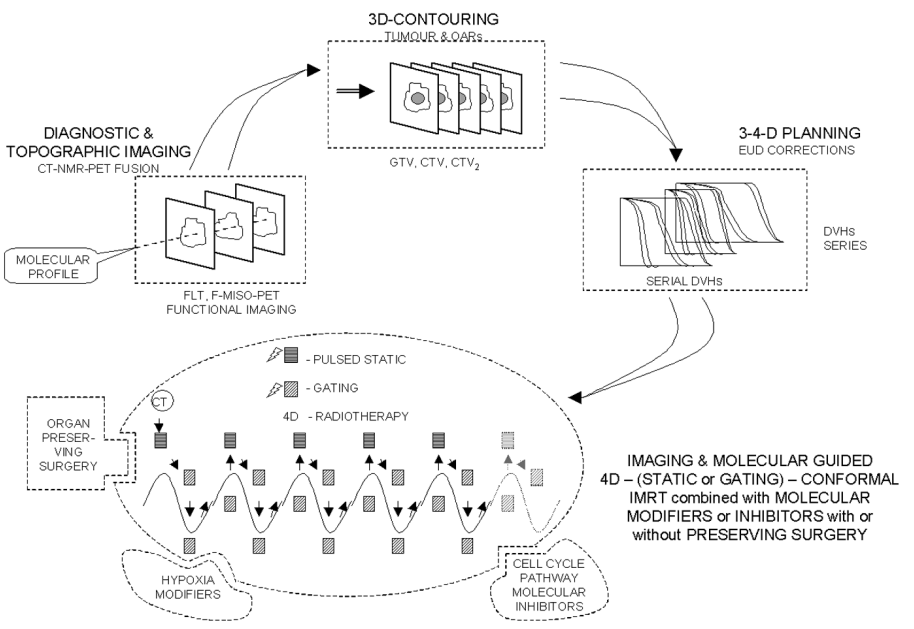

Figure 1. Step-by-step diagram of 4D-gating radiotherapy

Table I. Criteria for 3D-Conformal (IMRT) radiotherapy recommended at present

Procedures and steps	Who should do it?
WHO and WHAT? (qualification)	
Tumours close to critical normal organs (OARs) the tolerance of which is much lower that the predicted TCD	RO
Tumour contours relatively well defined with predictable microscopic spread	RO
Tumours with moderate or low radiosensitivity, with heterogeneous cell density, and/or with present or deducable hypoxia sublesions	RO
Mainly tumours with an average and lower local control probability (TCP ≤50%)	
WHEN?	
Sole treatment with dose escalation intent (SIB)	RO
Pre- or postoperative (with uncertain margins close to OARs)	RO, S
As a boost after conventional techniques	RO
Combined with concurrent chemotherapy	RO, MO
HOW?	
3D-CT frequent images (~every 5 mm)	RO, RD
3D-targest reconstructions	RO, RD
GTV, CTV1.... CTVn, PTV delineations	RO (PH)
3D simulation with BEV	RTT, RO
3D treatment planning with at least a few DVHs and BN-DVHs (to make optimal choice)	RO, PH
Interpretation of OAR constraints and dose-volume distribution for OARs on BN-DVHs beyond the constraints (critical!)	RO
Choice of optimal solution	RO
Patient immobilization, and set-up at the first session, PVI, Exac-Track, dosimetry in vivo	RTT, PH, RO
Every session PVI monitoring (come-beam CT)	RTT
Standard dosimetry in vivo after delivery of a half of the planned dose or after pronounced tumours regression	PH
Resimulation repositoning, replanning if needed	RO, PH, RTT

Legend TCD – Tumours Cure Dose, OAR – organ(s) at risk, SIB – Simultaneous Infield Boost, BEV – Beam-Eye-View, BN-DVH – Biologically Normalized Dose Volume Histogram, PVI – Portal Vision Imaging, RO – radiation oncologist, S – surgeon, MO – medical oncologist, PH – medical physicist, RTT – radiation technologist

presented in Table I. However, one has to bear in mind that step-by-step procedures of 3D-conformal and IMRT radiotherapy can be the source of numerous uncertainties, including delineation errors, margin errors due to the presence of microscopic disease and set-up errors, which may significantly decrease the estimated probability of tumour control. Even very small and physical cold spots within the CTVs may overrule all advantages of the method. On the other hand, organ motion becomes a critical issue when all procedures are precisely and properly performed. Precise inaccuracy might be the potential risk of high-tech radiotherapy. It may explain why there is an urgent need to replace static images by dynamic images, CT-NMR-PET fusions, functional images of tumour hypoxia, proliferation including molecular tumour profile to improve tumour and normal tissue contouring, organ stability defining and tumour heterogeneity, and all of them can be an important step forward to increase therapeutic gain in radiotherapy. Moreover, Bentzen, Niemierko and Withers have clearly documented, that in order to take full advantage of technological and imaging capabilities an improved biological knowledgebase is required. For 3D and 4D conformal, IMRT irradiation, single and static DVHs providing physical dose-volume relationships may often be misleading while the radiation-bioeffect estimates based on linear-quadratic model, which in turn can help to define how far dose-fractionation can be utilized may be necessary.

Optimizing dose fractionation

Assuming that treatment planning and radiation delivery is highly precise, all possible technical and physical dosimetric errors can be minimized by daily monitoring using interfraction dynamic CT (PET) imaging. It allows to correct deviations between the actually delivered and the prescribed dose. With tumour (node) regression during treatment it has to be remembered that the primary topography of the tumour and organs at risk usually changes, in some cases even significantly, thus calling for resimulation and replanning due to which the delivery is reoptimized, and thus throughout the entire treatment course the dose can be maintained as closely as possible to that originally planned. The so-called daily image guidance has already been introduced into daily practice in some centres. This process is referred to as "generalized adaptive radiotherapy". The idea is that the

tumour and organs at risk receive the doses which have been planned to be delivered. Therefore the unrepaired DNA damage can be modulated in space and time. These concepts, and their practical application, have been clearly illustrated by a few speakers, mainly by Mackie from Madison, USA, Metcalfe from Wollongong in Australia, and by Altman from Chicago.

When optimal technical and physical precision is achieved, dose fractionation becomes the major attribute of therapeutic benefit. K. Ang from MDACC in Houston has presented an elegant review of the results of many clinical trials on altered radiotherapy recommending some of them as a standard regimens (Table II) Bentzen has postulated that if the boost dose is needed, it should be at least 14 Gy, although according to the available clinical data a dose close to 21 Gy is preferred. It is important to remember, that the boost should be delivered as fast as possible. Continuing this topic Withers and Lee have clearly demonstrated that the beneficial effect of the boost strongly depends on local tumour control probability (LTCP) predicted prior to the treatment, and on the boost volume. The greatest benefit can be expected only when pretreatment LTCP is moderate (≤50%) and if the boost volume is similar to the primary GTV. Therefore there is no reason to boost through a very small field or in early stages of cancer when the LTCP is already high (≥80%).

Maciejewski presented long-term results of 7-day regimen (CAIR-I) showing that 6-year LTC and disease-free survival keep higher by 35% comparing with conventional standard 5-day regimen. By decreasing the dose per fraction one develops the 7-day regimen, which is undoubtedly safe and acute mucosal reactions, although severe, are found tolerable by patients. However the question whether 7 fractions in 7 day (weekend-in) is similar or more effective tthan 7 fractions in 5 days (weekend-off concomitant boost) still remains open because the CAIR-II trial dedicated to this issue is still ongoing. On the other hand, CAIR-I and CAIR-II have provided important observations concerning acute mucosal reactions. First of all, the five-grade EORTC/RTOG scale has been shown not to be precise enough to score the severity of acute mucositis, because grade 4 severity varies significantly among individual patients, and all, more or less serious, functional and subjective problems occur above grade 4 although they are all accounted for within this very grade. Therefore the Dische system is much more suitable for scoring and recording acute mucosal reactions. Second, the frequency of taking the score is crucial to render a precise and true to life pattern of acute effects. Interim results of CAIR-II have shown that the severity of acute confluent mucositis is wave-like and could be quantified precisely only with regular, at least trice-a-week scoring. Irregular or regular weekly scoring procedures allow to miss a substantial number of cases of confluent mucositis and their incidence can be underestimated even by about 30-40%.

Suwiński has presented an interim report on postoperative CAIR for H&N cancers showing a higher incidence, severity and duration of confluent mucositis in the study-arm as compared with the conventional postoperative regimen, but these reactions were well tolerated by the patients. Miszczyk has shown that a hyperfractionated accelerated split-course regimen with 64 Gy in 28 days (CHA-CHA) is an effective 4-week treatment for advanced T_{3-4} N_{2-3} head and neck caner allowing for a 44% 2-year locoregional control. Tarnawski, by analyzing spectroscopic signals of 1H-MRS in vivo has demonstrated that postirradiation biochemical changes in normal brain occur also outside the irradiated volume, what may suggest that an acute reaction in normal tissue may not be a local effect restricted to the irradiation

Table II. Altered fractionation regimens for IMRT more effective than conventional 66-70 Gy in 2 Gy fractions, recommended by K. K. Ang

General
66-72 Gy in 1.8-2.0 Gy fractions over 6 weeks (twice-a-day for 5-12 days) or 79,2-81,6 Gy 79.2-81.6 Gy in 1.2 Gy fractions over 7 weeks (twice-a-day during whole therapy
Specific IMRT
for T_1-T_2 CTV_1: 66 Gy in 30 fractions over 6 weeks (dx = 2.2 Gy) CTV_2: 54 Gy in 30 fractions over 6 weeks (dx = 1.8 Gy) [subclinical disease]
for T_3-T_4 CTV_1: 70 Gy in 35 fractions over 6 weeks (dx = 2.0 Gy) CTV_2: 56-59.5 Gy in 35 fractions over 6 weeks (dx = 1.6-1.7 Gy) [no concurrent chemotherapy is planned]
IMRT with concurrent chemotherapy
CTV_1: 70 Gy in 35 fractions over 7 weeks CTV_2: 52.5-56 Gy in 35 fractions over 7 weeks (dx=1.5–1.6 Gy)

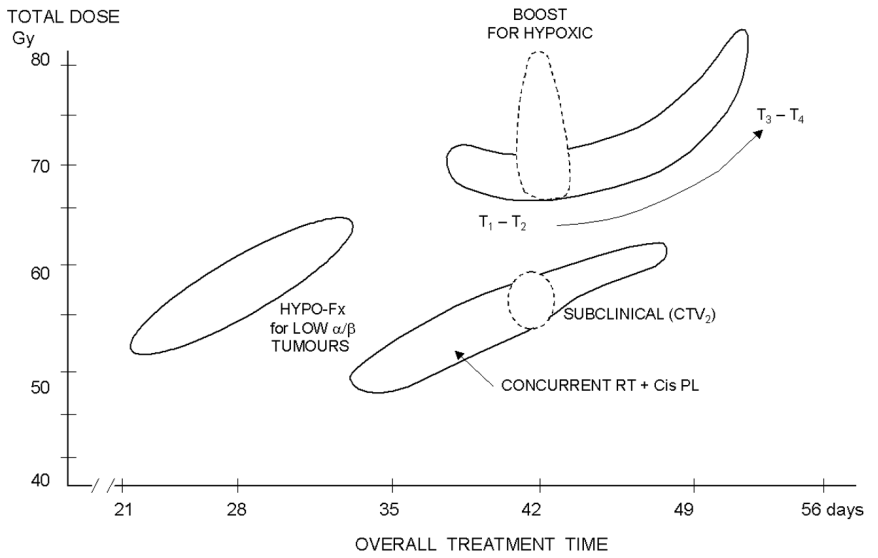

Figure 2. Ranges of dose and time for IMRT for head and neck and prostate cancers recommended by 7th Conference "DTF"

volume but it may have generalized biochemical and functional consequences.

Although the evidence of a low alpha/beta ratio for prostate cancer is criticized by some authors, Ritter from Madison has presented the preliminary results of a three-level hypofractionated trial with fractionation regimens designed by J. Fowler. The three dose fractionation levels are: 64.7 Gy in 22 fractions with dx=2.94 Gy, 58.08 Gy in 16 fractions of 3.63 Gy and 51.6 Gy in 12 fractions of 4.3 Gy delivered in three randomized groups of patients with prostate cancer using image-guided IMRT. Acute rectal and bladder toxicity were moderate and well tolerated by patients independently of the dose-fraction delivery in four or five fractions per week. According to the Madison group hypofractionation offers the potential for therapeutic gain and economic and logistic advantage.

To summarize the presentations and discussion on dose fractionation – clinical practice has gained some recommendations concerning altered radiotherapy as a standard procedures (Figure 2), however in the majority of them the use of IMRT is advocated. Currently the advances in biology have inspired searches for selective enhancers of tumour response.

Novel therapeutic approaches using molecular inhibitors and modifiers

An overview of clinical trials on chemotherapy administered concurrently with radiotherapy, presented by Tannock from the PMH in Toronto, provides level 1 evidence of survival benefit for patients with head and neck, cervix and non-small cell lung cancers and level 2 evidence for brain (or gliomas), eosophagus, rectal and bladder cancers.

An increase in the therapeutic index has indeed been noted, however at the expense of an increased toxicity, but the enhancement of tumour cell kill from chemoradiation was greater than normal tissue toxicity. Generally neoadjuvant chemotherapy given prior to radiotherapy does not improve the treatment outcome or, if npresent, the benefit is very small. Adjuvant chemotherapy might likely be effective for some tumours, such as breast cancer. Cytostatic drugs may sterilize microscopic deposits of tumour cells while the primary tumour is treated effectively with surgery and radiotherapy, and therefore there is no requirement for the interaction of chemotherapy with radiotherapy or surgery. Scheduling of the modalities is not likely to be important. In case of tumour such as head and neck cancers, where distal failure is rare, chemotherapy of micrometastases is unlikely to be a major strategy leading to improved outcome, and long-term benefit is more likely to be achieved through local control improvement.

Continuing, Tannock has criticized the concept chemo-radio sensitization, since the only known process that might lead to selective radiosensitization is hypoxia, and the usual cytotoxic drugs are not hypoxic radiation sensitizers. Cytotoxic drugs activity against rapidly-proliferating tumour cells is another unlikely possibility, because the administered doses are generally insufficient to have a major cell-kill effect against subpopulations of tumour cells that have survived through radiotherapy and repopulate fast. Selective toxicity to hypoxic tumour cells also seems unlikely, because except for tiripazamine, which has this property, a maaajority of anticancer drugs are either non-selective or may be more active against aerobic cells.

Tannock has pointed to the remarkable heterogeneity of tumour sensitivity to anti-cancer drugs, regardless of whether the drug is used to kill cells, to inhibit proliferation, or for some other goal. For these reasons, the use of the same drugs with radiation to treat tumours of the same type in different patients will inevitably provide limited benefit.

Following molecular (gene-expression) profiling, molecular inhibitors and modifiers are, currently, one of

the most promising areas for the advancement of molecular-targeting radiotherapy. According to Harari from Madison, a series of EGFR inhibitors from both the monoclonal antibody (mAb) and tyrosine kinase inhibitor (TKI) class have demonstrated clear clinical activity. Three EGFR inhibitors including the mAb cetuximab (Erbitux), small molecule TKIs grefitinib (Iressa) and erlotimib (Tarceva) have been approved. A phase III trial for head and neck cancer has shownthat patients with low EGFR expression have an approximately 30% better long term prognosis. By combining EGFR inhibitor-cetuximab with radiation, a 10% increase in locoregional control and a 9% increase in overall survival has been documented. Nevertheless, the overall clinical profits associated with EGFR inhibitors are modest when analysed in view of the global cancer population. This suggests that methods of patient selection should be optimized. On the other hand, the increasing knowledge on tumour biology provides convincing evidence that tumour cells use a network of signaling pathways, and even if one pathway is blocked by a respective molecular inhibitor, the tumour cells are flexible enough to use another one to survive and to continue their life activity.

Harari and Ang have suggested that several signal-transducation levels should be blocked at the same time, e.g. simultaneous inhibition of EGFR, other ErbB receptors as HER-1, HER-3, HER-4 together with VEGFR pathways, EGFR and COX-2 signaling, P13K blockade leading to radiosensitization with VEGFR inhibitors blocking tumour angiogenesis. The use of angiogenesis inhibitors can normalize tumour vasculature and improve proliferation and oxygenation. According to Camphausen from NCI in Bethesda, VEGFR inhibitors are clinically promising in the combined treatment of glioblastoma multiform (GBM). It seems that the major reason of a poor outcome in patients with GBM is not tumour cell intrinsic resistance, but rather the tremendous potential of tumour angiogenesis. The use of VEGFR inhibitors combined with radiation has produced promising preliminary clinical results.

The results of a clinical trial presented by Mehta from Madison utilizing temozolomide with external radiotherapy over 6 weeks followed by up to 6 cycles of maintenance of this compound are also interesting. Temozolomide is an alkylating agent which methylates DNA. The key lesion is methylation of the 06 position of guanine which, under normal circumstances is repaired by the enzyme AGAT. on temozolomide administration the enzyme is methylated and therefore deactivated, which makes AGAT a suicide enzyme. Such inactivation of AGAT results in a significant survival benefit of 48% 2-year survival, as compared to 14% when the AGAT gene is active or unmethylated. However, even if the AGAT is inactivated cytotoxicy is not a universal phenomenon. Preclinical data suggest that wild type p53 may be required for inducing apoptotic death. It is not a single and simple way to eradicate GBM effectively. It is commonly known that EGFR up-regulation, especially through the expression of a mutant form of EGFR, is a frequent event in GBM and may provide a survival advantage to the tumor. A second critical pathway is the unopposed activity of P13 kinase through the mutation in the PTEN gene, which results in the abrogation of apoptosis in these tumours. Respective inhibitors have already been combined with radiotherapy for GBM and the study is still ongoing.

Conclusions

First of all, the Conference has shown the tremendous progress in radiation techniques and medical physics. Radiotherapy remains a sole treatment only in a carefully selected group of tumour sites and stages. The manufacturers provide us with high-tech tools and innovations. Static CT and NMR or PET images are widely replaced by dynamic fusion of CT-NMR-PETcombined with image monitoring during treatment. Functional images already allow to define hypoxic and highly proliferate subregions of the tumours. However, one should be very naive to think that these high-tech simulators, accelerators and supportive tools will solve all problems and they are the warranty of good clinical practice. These tools are tools only. Evidence-based criteria for 3D-conformal and IMRT radiotherapy are well defined and there is no doubt as to the fact that these techniques are very sophisticated and complicated. Moreover, organ motion, which was more or less ignored in the past, has recently become a crucial element of these procedures. It is important to continue the research into molecular imaging and treatment guidance, although these areas are still more in the field of pure science and are just beginning to have practical application.

The increasing number of the already collected experimental and clinical data in this field suggest that the genetic and molecular network of signaling pathways is complex and may vary individually. They provide clear evidence that human beings and their malignant tumours are relentlessly non-linear, i.e. they are highly heterogenous. Consequently, all accepted standards are only averaged guidelines, which should be individually modified for individual patient application. It is important that new techniques and treatment strategies are tested clinically, but they should not be indiscriminately introduced into daily practice. The road from new perspectives to new standards is long. It is one of the important conclusions of the Conference in Madison. Meanwhile, precision in target imaging, definition and monitoring, dose and fractionation planning and prescription, and dosimetry of dose delivery are the major warrants of effective radiotherapy. Therefore, training, experience and skills are the basic attributes of good practice in radiotherapy. A couple of years ago this had been defined by Fowler as 3P in radiotherapy (and also in other medical specialities) – Patients, Patience and Practice. If one wants to treat patients, and to cure them, very good performance is necessary. According to Bentzen, to know whom, when

and how to treat calls for selecting a specific therapy based on biological information and this is called theragnostic therapy.

Paper received and accepted: 29 November 2005

Professor Bogusław Maciejewski MD, PhD
Department Radiotherapy
M. Skłodowska-Curie Memorial Cancer Centre
and Institute of Oncology
Gliwice Branch
Wybrzeże Armii Krajowej St. 15
44-101 Gliwice, Poland
e-mail: bmaciejewski@io.gliwice.pl