Invited article

Review article

Boost in radiotherapy: external beam sunset, brachytherapy sunrise

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Abstract

Radiobiological limitations for dose escalation in external radiotherapy are presented. Biological and clinical concept of brachytherapy boost to increase treatment efficacy is discussed, and different methods are compared. Oncentra Prostate 3D conformal real-time ultrasound-guided brachytherapy is presented as a solution for boost or sole therapy.

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Key words: brachytherapy, radiobiological rationale, boost techniques.

Since 1958, when Gilbert Fletcher proposed a radiobiological rationale for radiotherapy [1], for the next decades, the dogma that equal dose fractions produce the same rate (not the same number) of cell killing has been inalterably accepted although present knowledge on tumour biology and cell characteristics strongly suggests that this is a naive simplification. Based on this dogma tumour cell kill as a function of dose gets asymptotically closer and closer to zero which is never reached. It means that 100% local control can never be achieved and practice and clinical studies undoubtedly prove this. As a consequence of that, our language to the patients uses "probability" instead of "certainly". However, we are able to cure permanently more and more patients as a result of continuous conceptual and technological progress in radiotherapy, but cure rate remains still below 100%.

This reflects the random nature of cell killing. In some tumours all cells are dead. In others one or more cells survive giving an average cure rate (i.e. an average survival 1 cell per tumour results in 37% tumours cured and 63% failed: $e^{-1} = 0.37$). This is theoretically true if regular tumour cell density and its equal radiosensitivity to consecutive dose fractions is assumed. This assumption leads to homogenous dose distribution within irradiated targets. Dose homogeneity seems a logical solution for homogenous tumours, and it is clear why such a guideline was widely accepted for 2D-standard radiotherapy. However, it has also been extended to 3D-conformal dose intensity modulated radiotherapy where a sharp bend down DVH curve for the tumour is the optimal solution.

The dogma of tumour homogeneity ignores the tumour biology and its cell pattern. Nature is relentlessly non-linear. This means that human beings are widely heterogeneous, and therefore also their malignant tumours. Therefore, the term heterogeneity should completely change the present philosophy of radiation treatment planning.

Is there clinical evidence of tumour heterogeneity?

The concept of the 4R for radiotherapy defines at least 4 subpopulations of tumour cells, i. eq. fast repopulating, hypoxic, with high potential of sublethal damage repair, and quiescent cells ready to redistribution into cell cycle. Moreover, there are apoptotic resistant cells, as well as endothelial cells of the tumour vascular network.

Tumour clonogens accelerated repopulation is very well documented in many clinical studies [2, 3]. In the late eighties, the retrospective study by Withers, Maciejewski and Taylor on head-and-neck cancer radiotherapy showed that beyond week 3-4 of conventional irradiation about 0.6 Gy per day is compensated by repopulation. The RTOG 83-13 study on hyperfractionation for H&N cancers clearly showed that increasing the total dose from 72 Gy to 76.8 Gy and to 81.6 Gy together with extension overall treatment time (OTT) did not produce any increase in long-term locoregional control (Fig. 1).

From this study one may calculate that for OTT longer than 6 weeks tumour clonogens repopulation counter-balances a cell kill effect of 1.6 Gy per each one day of the OTT extension. It suggests a continuously accelerated repopulation depending on time itself. Moreover, the RTOG study illustrates a "plateau effect" (Fig. 1) which reflects an impact of repopulation on tumour control. One cannot expect any benefit in the treatment

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efficacy if the dose is escalated with extension of the OTT because the dose intensity remains unchanged. The term "Dose Intensity (DI)" means the number of Grays per one day of treatment. Therefore, 60 Gy in 42 days, 70 Gy in 49 days, 80 Gy in 56 days, etc. are in fact equally effective because the DI of 1.44 Gy/day remains constant. Expecting higher efficacy one may suggest to increase the fraction size to 3 Gy and after a basic schedule of 72 Gy in 24 fractions in 42 days to use a boost of 15 Gy given in 8 days extension. For the basic schedule the isoeffective total dose would be $78_{bioGy2.0}$ (α/β = 10 Gy) with a DI of 1.85 Gy/d, and after delivery the boost isoeffective dose would increase to $92.4_{bioGy2.0}$. However, the DI which remains 1.85 Gy/d because of the OTT extension, and such dose planning is misleading and treatment intensity illusive. In the late sixties, Fletcher already pointed out that "physical boost is not a boost in a biological sense". Therefore, radiation intensity might be increased by shortening the OTT without change in total dose or by increasing the dose without change in the OTT.

It should be remembered that deceleration in the proliferative compartment due to radiation cell kill induces a reverse effect of recruitment of the quiescent cells into proliferative phase even when tumours regression is observed and more and more cells divide symmetrically. Getting a smaller cellular pattern of the tumour changes into more aggressive and growth fraction increases. On the other hand, islands of hypoxic, apoptotic resistant cells could be another cause of local failure if the planned dose is homogenously distributed. Although reoxygenation is a fast and highly effective process during the first few days of fractionated irradiation, the chance of local control may be seriously disturbed by acute hypoxia which could occur in various unpredictable parts of the tumour.

There is clinical evidence supporting radiobiological experiments which convincingly proves that conventional homogenous radiotherapy has likely reached the upper limit of its efficacy, mainly due to "plateau effect", and there is no reason to escalate physical dose if the OTT also increases. It has also become clear that a tumour being heterogeneous in its biology and cellular pattern need a higher dose intensity together with its heterogeneous distribution (Fig. 2).

Tumour heterogeneity – dose painting – boost supremacy

It is obvious that tumours within a single location may differ by their TNM stage. But it is very naive to assume that tumours within a single stage, i.e. $T_2N_0M_0$, are a homogeneous group. In fact, there can be a 8-fold difference in their volume. Ignoring such a possibility, in many clinical trials the same total dose is given to all $T_2N_0M_0$ tumours and T_3N_3 tumours as well. Meta-analysis MATCH of many altered fractionation schedules has shown an average therapeutic gain of 7%, much less than expected [4]. It is difficult to refer evidence based averages to different clinical situations reflecting heterogeneity of tumour stages, localizations and its biology. It therefore suggests that except some palliative cases the term "homogeneity" should not be longer an attribute for radical dose distribution planning and delivery.

Nowadays, thanks to serial CT, MRI images, a precise delineation of tumour volume has become possible, which indirectly reflects the initial number of tumour cells. This should be a basic parameter for defining the total dose and fractionation scheme, by the simple assumption of 7 Gy for the D_{10}* for oxic cells. In some centres biological imaging of the PET-CT fusion is already available. It allows visualising subpopulations of hypoxic, fast proliferating, neoangiogenic regions to design heterogeneous dose distribution with higher dose to more resistant subregions of the tumour (dose painting). It is also possible to modify total dose individually by using the boost techniques. However, external irradiation boost does not seem effective enough. Teo et al. used external irradiation with 62.5 Gy in 6.5 weeks plus a boost with 3 fractions of 8 Gy in an extra 15 days for nasopharyngeal cancers. Although

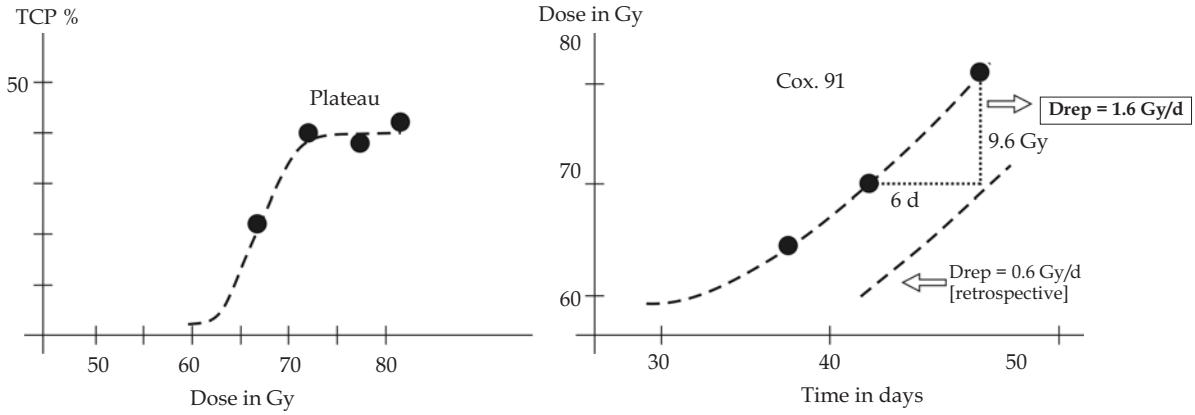

Fig. 1. RTOG 88-13 illustrates "effect plateau" – increase in total dose with extension overall treatment time total doe with extension overall treatment time does not improve locoregional control (TCP) because of accelerated repopulation with increasing Drep even to 1.6 Gy/day towards the end of treatment longer than 6 weeks

* D_{10} – is a dose which decrease cell survival by one decade (1 log), i.e. for TCP of 90% for a tumour with 10^9 cells, 10 logs of cells should be killed ($10^9 \times 10^{-10} = 0.1$, TCP = $e^{-0.1}$ = 90%) which gives total dose of at least 70 Gy ($10 \times D_{10} = 10 \times 7$ Gy = 70 Gy)

the total physical dose was escalated to 86.5 Gy, the biological dose only increased by 1.5 Gy (22.5 Gy was balances by repopulation). Therefore, one could not expect any therapeutic gain which in fact was only 1% (from 62% to 63%), likely being within the statistical error margin.

Yet when a brachytherapy boost was used instead of external irradiation, the therapeutic gain was much higher and significant (Table 1). An average 30% therapeutic gain reflects about one extra log of cell kill. Going back to the bench, hypoxic or apoptotic resistant cells need about 2.5-3 times higher dose than oxic cells to achieve a biologically equivalent cell death rate. Assuming on average 7 Gy as a D_{10} for oxic epithelial cancer cells, the equivalent D_{10} for hypoxic cells should be within the range of 14-21 Gy. The brachytherapy boost used in clinical studies is usually within the range of 20-35 Gy, producing extra 1.0-1.5 logs of cell kill. The boost is necessary at the end of external irradiation when residual tumour is persistent or subclinical deposits of resistant cancer cells are likely to survive. The biological aim of the boost is to kill cancer cells and to kill them all. A boost should not give these cells any chance and time to repopulate or to repair sublethal change. Therefore, a relatively large dose (assuming the cells are hypoxic or intrinsically resistant) should be delivered within minutes and not in days. A high dose given in minutes corresponds more or less with external hypofractionation. Hypofractionation in radical radiotherapy has been abandoned for years because it was considered too toxic to surrounding normal tissues. Nowadays, there is a return to this schedule as a radical treatment, probably due to low α/β value estimated for some malignant tumours (prostate, rectum). Extracranial stereotactic radiotherapy shows that

Table 1. Impact of external vs. brachytherpay boost on long-term locoregional control for head and neck cancer [6]

Tumour	Treatment schedule control	5-year locoregional control	Author
Nasopharynx	EXRT + EXRT boost	60%	Wang, 1991
	EXRT + BRT boost (20 Gy)	91%	
Tonsil	EXRT	40%	Puthawala, 1985
	EXRT + BRT boost	70%	
Oral cavity	EXRT	58%	Chao, 2001
	IMRT (SIB)	80%	
	EXRT	54%	Perez, 2004
	EXRT + BRT boost	84%	

EXRT – external irradiation, BRT – brachytherapy, IMRT – 3D-dose modulated external irradiation, SIB – simultaneous infield boost

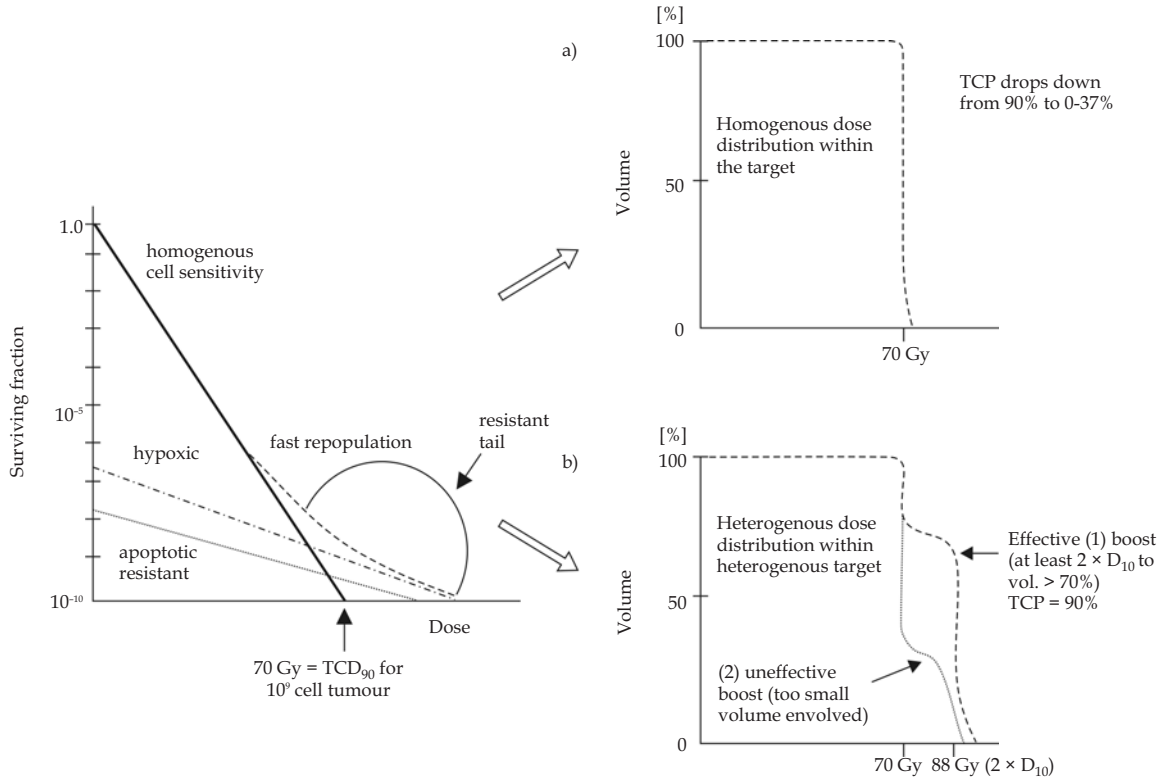

Fig. 2. Theoretical cell survival curve for fractionated irradiation. Solid line represents population of homogenously sensitive tumour cells, and each dose fraction results in the same cell kill rate. Dotted lines represent different subpopulations of more or less resistant cells which produce "resistant tail" in the survival curve. (a) DVH with homogenous dose 14 distribution for tumour with heterogeneous cellular pattern results in the decrease of the planned TCP of 90% to even 0%. (b) Heterogeneous tumours need heterogeneous DVH with the "boost-tail" to eradicate resistant cells and to keep TCP at the assumed level of 90%

a single large dose delivered to metastatic tumours in the lung is a highly effective modality and not too toxic. This leads to brachytherapy supremacy in the field of boost treatment.

Brachytherapy sunrise

The biological effectiveness of brachytherapy against resistant tumour cells is significantly higher than external fractionated irradiation (Table 2) because its dose intensity measured in minutes is higher than that of external radiotherapy measured in days. One might argue that a simultaneous infield boost (SIB) which can be used as a part of dose intensity modulated radiotherapy could be competitive to brachytherapy boost (Fig. 3). Individual planning of the SIB subvolume and dose per fraction does not change the number of fractions and the OTT. Compared to brachytherapy, the difference is that an extra boost dose is a relatively small increment of the dose per fraction which is continuously repeated during whole course of irradiation. For tumour with 10^9 cells, assuming a dose per fraction of 2 Gy to the basic PTV and 2.5 Gy to the SIB, the respective total doses given in 35 fractions and in 48 days would be 70 Gy and 87.5 Gy. At the first glance, the dose intensity (DI) for the SIB would be 1.82 Gy/day and about 25% higher than the DI for the basic PTV (1.46 Gy/day). Therefore, one may expect a 90% probability of local control within the PTV and even higher rate for the SIB. Such a calculation, however, is misleading because it is based on the assumption that tumour cells are similarly radiosensitive whereas they are not. Assuming 10 logs cell kill needed for the TCP of 90% from the SIB total dose one may calculate D_{10} of 8.75 Gy, which is much lower than about 14 Gy for hypoxic cells. On the other hand, the SIB of 87.5 Gy is not biologically equivalent to the basic 70 Gy in 35 fractions plus HDR brachytherapy boost of a single dose of 17.5 Gy although both physical total doses are the same. A brachytherapy boost of 17.5 Gy is able to eliminate at least one extra decade of residual resistant survivors which are a part of "resistant tail" on the cell survival curve (Fig. 2). Comparing the pros and cons for SIBIMRT and BRT boost, the advantages are in favour of brachytherapy (Table 3).

Brachytherapy boost should be planned prior to the treatment. To synchronise both plans and to improve precision and quality of the dose delivery it is important to modify the organisation of both departments connected digitally online, and to establish EXRT and BRT planning as the central part of the whole system (Fig. 4). The most important parameters of such a combined treatment are boost volume and dose. Withers [5] has estimated limits for boost volume and dose to improve locoregional control. Table 4 shows that there is no reason to plan the boost for

Table 2. External beam irradiation (EXRT) vs. brachytherapy (BRT) efficacy against subpopulations of resistant tumour cells

Subpopulations	Effectiveness EXRT	BRT
Highly proliferative	no	yes
Hypoxic	no in 2 Gy/fx	yes
Apoptotic resistent	no in 2 Gy/fx	yes
G0/G1 phase	no	yes

Table 3. Advantages and disadvantages of the SIB vs. brachytherapy boost

SIB – IMRT	BRT – BOOST
conformal	conformal
needs continuous CT monitoring	continuously monitored in real time by ultrasound
once planned remains stationary through whole course of treatment or needs replanning	dwell times and positions can be changed individually during the treatment
biologically less effective	higher HDR single or fractionated dose are more effective against resistant cells
more expensive and time consuming	short duration less expensive

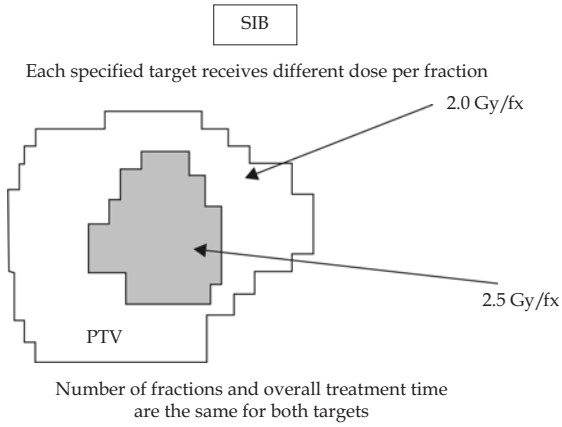

Fig. 3. Scheme of simultaneous infield boost (SIB) within the PTV. SIB area receives an extra (boost) dose with each fraction. Because number of fractions and overall treatment time are constant for a given treatment the only variable is dose per fraction which produces in the SIB area higher total dose (boost) than in the remaining PTV

Table 4. Theoretical therapeutic gain in the TCP depending on boost volume and boost dose

TCP increase by percentage points						
Boost volume	10%		50%		80%	
Boost dose in D_{10}	1 ×	2 ×	1 ×	2 ×	1 ×	2 ×
Baseline TCP						
10%	3%	3%	17%	20%	42%	50%
50%	3%	3%	17%	19%	32%	36%
90%	2%	2%	4%	4%	7%	8%

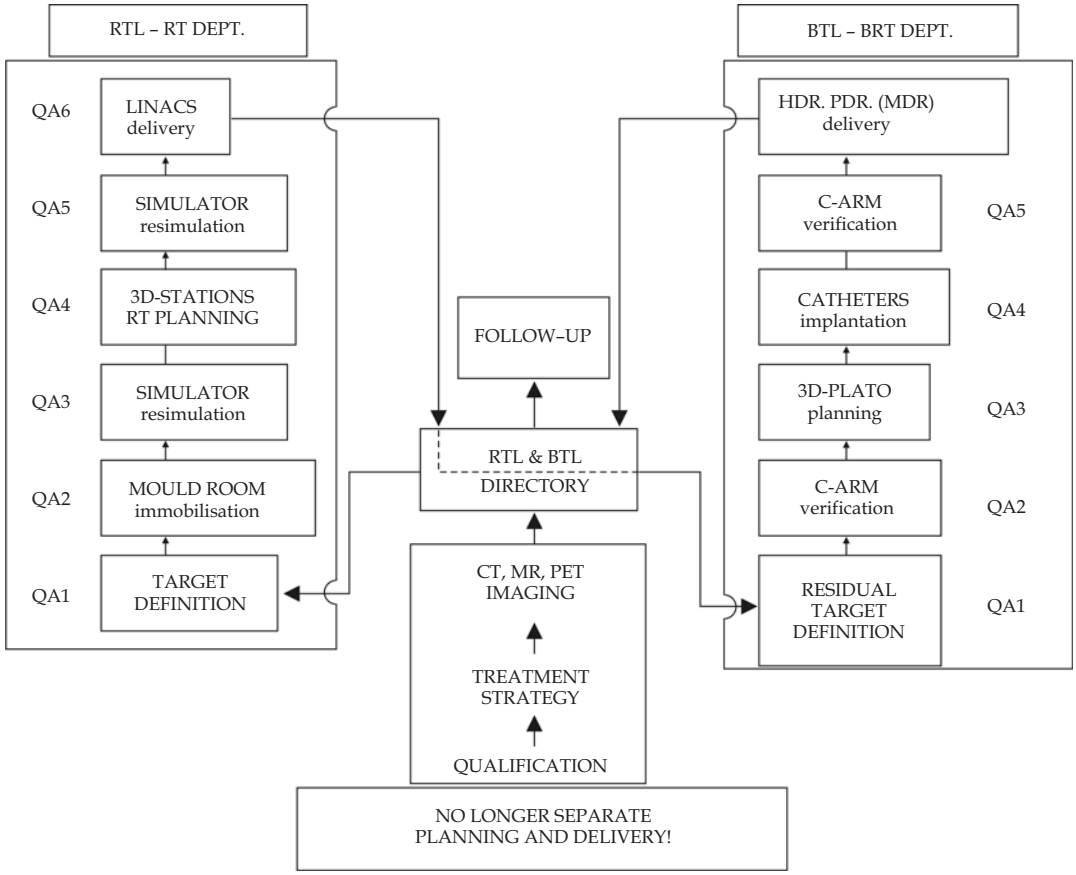

Fig. 4. Scheme of organization of the Department of Radiotherapy (RTL) and Brachytherapy (BTL) connected with Treatment Planning Dept. (Div.) through RTL & BTL Directory (QA – quality assurance audits)

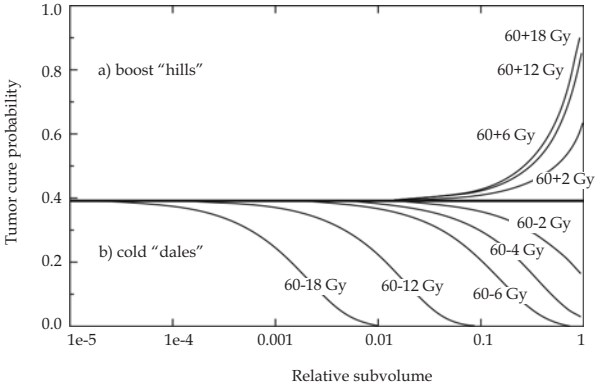

Fig. 5. Dependence of tumour control on boost advantages and on geographical or radiation delivery errors. Dose missing (cold dates) resulting in decrease of the TCP can never be corrected by the boost strategy

individual tumours with high a 90% probability of locoregional control (TCP) and for tumour with lower TCP (< 50%) if the boost volume and boost dose would be too small. The highest TCP benefit can be expected for advanced tumours if the boost volume covers at least 50% of basic PTV and if the boost dose is around 2 × D_{10}, that is 14-21 Gy. Precise dose delivery during a basic external irradiation has a fundamental impact on treatment outcome. Any geographical miss or cold spot results in a significant decrease in local control probability (Fig. 5). In such a situation any boost with a proper dose covering a large volume will not correct the previous error, and planned improvement will not be achieved. Therefore, both EXRT and BRT need the highest possible precision.

In recent years, thanks to technological progress, radiation oncologists have got the opportunity to use the *Oncentra Prostate*® (aka *SWIFT*®) system which offers 3D-conformal real time and ultrasound-guided brachytherapy for sole treatment or for boosting (3D-CRTBRT). This equipment is mainly dedicated to prostate cancer therapy. An important advantage of *Oncentra Prostate* is the possibility to make 3D-live plans until the optimal dose distribution within the planed volume is achieved. Thanks to ultrasound monitoring the dwell times and positions can be individually adapted to the topographical coordinates of the target and surrounding normal tissues.

Using *Oncentra Prostate** Gonzales at William Beaumont Hospitals in Detroit, Michigan, USA has performed pioneering studies introducing hypofractionated boost of 3 × (5.5-6.5 Gy), 2 × (8.25-11.5 Gy) after EXRT of 46 Gy in 23 fractions, and 4 × 9.5 Gy as a sole treatment for locally advanced prostate cancer with PSA < 10, Gleason ≤ 6, and with no prior treatment to be tested in an international trial. This seems a very interesting alternative to 6-7 weeks of external irradiation because the whole treatment is completed within 2 days. Preliminary results of more 95% 5-years biochemical no evidence of disease are very encouraging. For the last 3 years, the *Oncentra Prostate* boost of 10 Gy after 54 Gy in 25 fractions has also been used at the Institute of Oncology in Gliwice and the results are similar to that achieved by Gonzales. It appears that a new sunrise has arrived for brachytherapy.

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