Reports of Practical
Oncology and Radiotherapy

Continuing Maciejewski's debate on radiotherapy for locally advanced prostate cancer: I have even more dilemmas

Rafał Suwiński

Department of Radiation Oncology, Center of Oncology, Gliwice Branch, ul. Wybrzeże Armii Krajowej 15, 44-100 Gliwice

Rep Pract Oncol Radiother **2004;9:81-8, review paper in response to Maciejewski B., et al. „Radiotherapy for locally advanced prostate cancer: dogmas and dilemmas"**

Received December 11th, 2004; received in a revised form June 6th, 2004; accepted June 10th, 2004

Summary

A recent critical review of clinical trials on radiotherapy for locally advanced prostate cancer by Maciejewski et al. [1] points to a conclusion that most of conventional 5-days-a-week, 2 Gy fraction regimes produce a "plateau effect". Thus an increase in the total dose above approximately 70 Gy would not improve local tumour control, but could elevate the risk of later complications. Maciejewski et al. propose that radical hypofractionated 3D conformal or dose-intensity modulated radiotherapy with or without 3D HDR boost dose painting may improve the outcome of prostate radiotherapy. The present response describes some unforeseen challenges which may appear while implementing these new treatment strategies in clinical practice, and suggests possible solutions to solve these problems. Also, an alternative viewpoint on the data on dose-response in radiotherapy for prostate cancer is presented. It is postulated that, in addition to tumour hypoxia, distant metastases may create a quasi-plateau in dose-response, when biochemical failures and not loco-regional tumour control are used as the endpoint. Some arguments for the presence of dose response in postoperative EBRT for prostate cancer are presented. This somewhat contradictory review of the existing data on radiotherapy for prostate cancer may be considered as a stimulus for further discussion regarding optimization of local therapy. It also illustrates an urgent need for new prospective trials, which would address the clinical and radiobiological ambiguities of theoretical predictions.

Key words: dose response, relationship, therapeutic controversies, prostate cancer.

Kontynuacja debaty Maciejewskiego dotyczącej radioterapii chorych na zaawansowanego raka gruczołu krokowego: więcej wątpliwości

Streszczenie

Maciejewski i wsp. [1], w oparciu o przegląd badań klinicznych dotyczących radioterapii chorych na miejscowo zaawansowanego raka gruczołu krokowego, doszedł do wniosku, że frakcjonowanie konwencjonalne, tj. frakcje 2 Gy podawane przez 5 dni w tygodniu, może prowadzić do tzw. „efektu plateau". Oznaczałoby to, że podwyższanie całkowitej dawki promieniowania powyżej około 70 Gy nie poprawia odsetka wyleczeń miejscowych, lecz może przyczynić się do wzrostu ryzyka późnych odczynów popromiennych. Maciejewski i wsp. przedstawili przesłanki przemawiające za tym, by do radykalnej radioterapii chorych na raka gruczołu krokowego wprowadzić hypofrakcjonowanie, tj. napromienianie z zastosowaniem wysokich dawek frakcyjnych, posługując się przy tym planowaniem 3 D, modulacją intensywności dawki i wybiórczym podwyższaniem dawki w tych częściach guza, które są niedostatecznie utlenowane. W aktualnej pracy omówiono natomiast trudności, na które można napotkać próbując wprowadzić te nowe schematy leczenia do praktyki klinicznej. Przedstawiono też alternatywny punkt widzenia, dotyczący oceny zależności dawka-efekt w radioterapii chorych na raka gruczołu krokowego: przyjęto bowiem, że gdy miarą niepowodzenia leczenia jest wznowa biochemiczna to „efekt plateau" przy eskalacji dawki może być związany z ujawnieniem się przerzutów odległych. Dokonano ponownej analizy danych klinicznych dotyczących związku dawka-efekt w radioterapii pooperacyjnej. Kontrowersje przedstawione w aktualnej pracy powinny być rozumiane jako bodziec stymulujący do dalszej dyskusji dotyczącej optymalizacji leczenia chorych na raka prostaty. Ilustrują one potrzebę badań klinicznych, które pozwoliłyby rozstrzygnąć wątpliwości przewidywań opartych o przesłanki teoretyczne.

Słowa kluczowe: rak gruczołu krokowego, zależność dawka-efekt, IMRT, kontrowersje terapeutyczne.

Is there evidence of a "plateau effect" for dose escalation in conventionally fractionated radiotherapy for prostate cancer?

External beam radiotherapy (EBRT) alone

Following the practice of many other studies Maciejewski et al. [1] used long-term Biochemical No Evidence of Disease (BNED) as the endpoint for the analysis of therapeutic gain from radiation dose escalation in therapy for prostate cancer. The practice of using BNED instead of loco-regional tumour control has its roots in the biology of prostate cancer which regresses slowly, even if locally controlled. Thus it is difficult to distinguish a local recurrence from a persistent, but sterilized tumour. Furthermore, both sensitivity and specificity of PSA monitoring is high in the follow-up of prostate cancer making it more cost-effective compared to repeated tumour biopsies, bone scintigraphs, ultrasonography, CT and MRI imaging. This makes BNED a useful tool in determining disease-free survival. However, BNED is not a good surrogate for loco-regional tumour control, since all distant relapses also result in biochemical failure. Therefore the use of BNED for the evaluation of the effectiveness of local treatment might have limitations which will be outlined below.

The review of the data on prostate cancer by Maciejewski et al. [1] clearly shows that some studies demonstrate significant improvement in long-term BNED, while others do not. The authors conclude that the compilation of the results on BNED for locally advanced prostate cancer shows the "plateau effect" for the dose-response above 70 Gy. A careful examination of *Figure 2* from the original paper shows, however, that such a conclusion is valid mainly for a subset of older studies in which 3-D treatment planning has not been used, while flattening of a dose-response curve restricted to the trials, which utilized modern treatment techniques, is less apparent.

A new perspective can be gained when the published data on the dose-response for BNED [2-7] are stratified using prognostic factors for biochemical failure such

Table 1. The data on the significance of dose escalation effect on long-term biochemical failures in prostate cancer. The data are stratified by risk groups for biochemical relapse. Note that the data for low-risk patients consistently show that there is no significant dose escalation effect for long-term BNED when radiation doses of over 70 Gy were used. By contrast, the data for intermediate risk patients consistently show a significant effect from dose escalation irrespective of the dose level.

Study	Doses (Gy)	Significance of dose escalation effect for long-term BNED
Low risk		
Pollack et al 2002* [2]	70 vs. 78	NS
Hurvitz et al. 2002# [4]	<66.6 vs. 66.6 vs. >66.6	NS
Hanks et al. 1985# [5]	<60 vs. 60-70 vs. >70	NS
Pollack et al. 2000# [3]	67-77 vs.>77	NS
Pollack et al. 2000# [3]	<67 vs. 67-77	p<0.05
Valicenti et al 1998# [6]	<61.5 vs. >61.5	p<0.05
Lyons et al 2000# [7]	<72 vs. >72	p<0.05
Intermediate risk		
Pollack et al 2002* [2]	70 vs. 78	p<0.05
Pollack et al. 2000# [3]	67-77 vs.>77	p<0.05
Pollack et al. 2000# [3]	<67 vs. 67-77	p<0.05
Hanks et al. 1985# [5]	<60 vs. 60-70 vs. >70	p<0.05
Valicenti et al 1998# [6]	<64.8 vs. >64.8	p<0.05
High risk		
Pollack et al 2002* [2]	70 vs. 78	p<0.05
Hanks et al. 1985# [5]	<60 vs. 60-70 vs. >70	NS
Valicenti et al 1998# [6]	55.8-70.2	NS
Pollack et al. 2000# [3]	67-77 vs. >77	NS
Pollack et al. 2000# [3]	<67 vs. 67-77	p<0.05
Lyons et al 2000# [7]	<72 vs. >72	p<0.05

* randomized clinical trial

retrospective studies

NS: non significant effect of dose escalation

p<0.05: statistically significant improvement in BNED from dose escalation

as pretreatment PSA concentration, Gleason score and tumour stage. This makes possible the review of the dose-response data in low, intermediate and high-risk

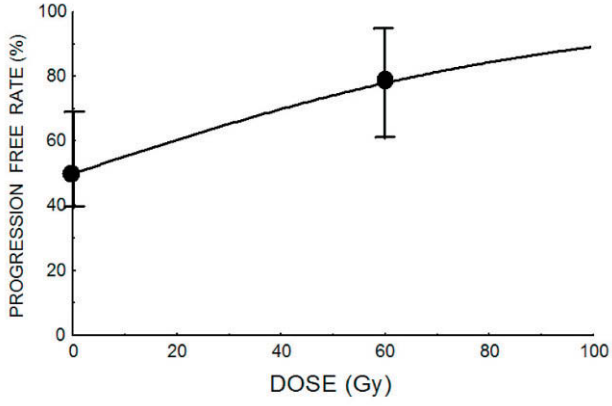

Figure 1. The proposed shape of radiation dose-response curve for biochemical progression free rates in prostate cancer. The data from 4 studies were used [11-14]. The black dots indicate the average progression free rate estimated from 4 studies and the error bars of the reported ranges. Note that the curve does not reach 100% even at high radiation doses.

groups. Although risk criteria were not quite the same in each of the published studies, they can be regarded as reasonably similar. *Table 1* summarizes the data used by Maciejewski et al. [1], supplemented by the results from the most recent randomized trial performed in the M.D. Anderson Cancer Center by Pollack et al. [2], published after the submission of the paper by Maciejewski et al. In a new trial, 305 patients with prostate cancer were stratified by the prognostic factors for biochemical failure, and randomized to receive 70 vs. 78 Gy in 2.0 Gy fractions. The data collected in *Table 1* suggest that the results of this new randomized trial are in reasonably good accordance with retrospective data from earlier studies [3-7], and show that the BNED improvement from radiation dose escalation over 70 Gy is, for the most part, restricted to the patients with an intermediate risk of relapse and, to a smaller extent, to the patients with the highest risk. No benefit from dose escalation over 70 Gy is observed in patients with a low risk (note that the studies which show some improvement with dose escalation in low- risk patients, e.g. [6] used total doses of less than 70 Gy).

The question thus arises of why the benefit from radiation dose escalation over 70 Gy is most evident in patients with an intermediate risk of relapse? One should at this point appreciate that the incidence of distant metastases in prostate cancer is as high as 60% in high-risk tumours, and still about 15% in low risk cases [8]. Thus a likely explanation for the absence of BNED dose-response effect for low risk tumours is that almost all of them are, in fact, locally controlled, and the biochemical failures in such cases result from metastases to distant organs or to the pelvis. By contrast, patients with high-risk tumours may fail from metastases irrespectively of whether the tumours are locally controlled or not. It is therefore extremely difficult to demonstrate the existing, but obscured effect of dose-response on local tumour control when BNED is used as the endpoint.

Such an explanation of the outcome of the dose-response studies in conventionally fractionated radiotherapy for prostate cancer provides an alternative explanation for the origin of a plateau in dose-response for biochemical failure. One may thus postulate that distant metastases, and not hypoxia, are responsible for a plateau in dose-response for long-term BNED. Clearly, such a "quasi-plateau" in dose-response for biochemical failures in prostate cancer differs in its origin from the "genuine" plateaus in dose-response for local control observed in radiation therapy for head and neck cancer, and some other rapidly repopulating tumours [9, 10].

Perhaps the most likely explanation of a plateau in dose-response for prostate cancer is that both tumour hypoxia,

Table 2. Summary of the data on adjuvant EBRT for T3N0 prostate cancer compared with prostatectomy alone used by Maciejewski et al [1].

No pts.	Adjuvant EBRT (total dose)	The average progression free rate (range)	Authors
388#	0 Gy (no EBRT)	50%* (40%-64%)	Morgan [11], Stein [12], Schild [13], Valicenti [14]
137#	55-70 Gy (~60 Gy on the average)	78%* (57%-94%)	

total number of patients in 4 data sets
*the average value from 4 data sets

and distant metastases contribute to this effect. Thus the observed plateau would have, in fact, two components: a "quasi-plateau" in dose-response for BNED resulting from distant metastases, and "genuine plateau" in local control rates from tumour hypoxia, radioresistance, repopulation, and/or geographic errors.

Irrespective of the mechanisms of the plateau it is important to recognize that intermediate risk tumours appear to be the best candidates for dose escalation using conventionally fractionated external beam 3-D radiotherapy (EBRT).

At last, it has to be mentioned after Maciejewski et al [1], and after the earlier studies [9,10] that implementation of old-fashioned radiation treatment techniques may cause a "genuine" plateau to appear in a dose-response for tumour control due to systematic or occasional geographical misses, dosimetric errors, and inadequate isodose distributions. It may also result in unacceptable rates of severe normal tissue reactions.

Postoperative EBRT for prostate cancer

Using the data from the literature [11-14] Maciejewski et al concluded that generally, "there is no dose-response effect observed for the conventional EBRT given following prostatectomy". *Table 2* summarises the data used in that paper. It is apparent from these data that increase in total radiation dose from 0 Gy (no EBRT) to 55-70 Gy (~60 Gy on the average) given in conventional fractions of about 2 Gy improves biochemical progression free rate from about 50% to 78%. The data are heterogeneous, and using only two data points one can not reliably determine the shape of the dose-response curve for biochemical failures in postoperative radiotherapy for prostate cancer. Assuming, however, that the dose-response curve for biochemical failures resembles the dose-response curves for radiation treatment for subclinical cancer [15] one can attempt to plot such a curve (*Figure 1*). The postulated curve is shallow, and 20 Gy increment in radiation dose would improve progression free rate in postoperative EBRT by only 7%. Since the curve is short of reaching 100% even at high doses, one may hypothesise that approximately 15%-20% of biochemical failures after postoperative radiotherapy is due to distant metastases. Also, it would be extremely difficult to demonstrate the effect of dose escalation in postoperative EBRT for prostate cancer. A randomized trial designed to detect 7% improvement in progression free rate would have to recruit over 3500 patients to exclude the possibility of false negative conclusions. Such a trial has not been performed so far, and it is unlikely that it will ever be attempted. The lack of level I evidence for dose response effect in adjuvant EBRT for prostate cancer can not, however, be considered as evidence for the absence of the dose response.

Can hypofractionation for prostate cancer appear deleterious?

Is there reliable evidence for low α/β value for prostate cancer?

Recent analysis of the existing data on dose fractionation in EBRT and brachytherapy for prostate cancer performed by Fowler et al [16] gave the estimate of a very low α/β ratio of 1.49 Gy. Such a low α/β value for prostate cancer provides theoretical rationale for the use of large doses per fraction (hypofractionation) in curative radiotherapy for these tumours.

Shortly afterwards, however, the data used by Fowler were re-analyzed by Nahum et al. [17]. When tumour hypoxia and/or high intrinsic radioresistance of subpopulations of tumour cells were incorporated into the model, the estimated α/β values for prostate cancer were 8.5 Gy and 15.5 Gy for well-oxygenated and hypoxic clonogens, respectively. This strongly contradicted the results obtained by Fowler, and indicated that hypofractionation for prostate cancer would have theoretical disadvantage over conventional fractionation.

Clinical arguments against hypofractionation for prostate cancer

One of the highlights of the most recent 2003 ASTRO meeting was the report from a randomized trial, which compared two fractionation schedules for patients with T1 and T2 prostate cancer [18]. Patients were randomized to 66 Gy in 33 fractions over 6.5 weeks (conventional arm) vs. 52.5 Gy in 20 fractions of 2.625 over 4 weeks (hypofractionation). Both arms were well balanced with regard to stage, Gleason score and pretreatment PSA level. The total number of patients in the trial was 936. There were 460 failures: 216/470 (45.9%) in conventional arm vs. 244/466 (52.3%) in hypofractionation, a statistically significant difference favouring the conventional arm. The acute grade 3 or 4 toxicity was higher in hypofractionation (13.5% vs. 8.1%), while grade 3 or 4 late toxicity was similar, and low in both arms.

The results of the trial are consistent with the hypothesis that the α/β value for prostate cancer is likely to be low, even though hypofractionation did not improve local control. It illustrates that it is difficult to design a hypofractionation schedule which would appear superior to conventional fractionation in prostate cancer. Also, it does not resolve the questioned whether hypofractionation with doses higher than 52.5 Gy will appear tolerable. The criticism to the design of this study raised at the ASTRO 2003 is that the failure rates were high in both trial arms, and that currently, the conventionally fractionated dose of 66 Gy is considered to be inappropriately low in conventional

radiotherapy for prostate cancer. Likewise, the total dose (52.5 Gy) and the dose per fraction (2.625 Gy) in the experimental arm were low, which makes it impossible, to fully exploit the theoretical advantage of hypofractionation in prostate cancer. Assuming that α/β value for prostate is 1.5 Gy the total dose of 52.5 Gy is equivalent to only 61.9 Gy administered in 2.0 Gy fractions.

Irrespective of the results of the randomized trial on dose fractionation in T1 and T2 tumours one would have even greater dilemmas with hypofractionated therapy of more advancer, high-risk tumours. This is because cure rates in such patients are improved when elective pelvic irradiation is used [19]. Is it, thus, rationally justified to use hypofractionation for elective pelvic irradiation in prostate cancer? Is the low α/β value a unique feature of primary prostate cancer, or can analogous feature be attributed to pelvic micro-metastases? There is no good answer to these questions, and the designers of future clinical trials would have to confront serious new dilemmas.

Unforeseen traps of high-tech radiation techniques, and the possible solutions

Numerous studies, including Maciejewski et al. [1], discuss the advantages of 3D conformal and IMRT therapy for prostate cancer. While the superiority of high-tech radiation techniques emerges as a new dogma of radiotherapy, much less attention is addressed to some potential challenges which may appear while implementing these new treatments into clinical practice. In this paragraph some unforeseen traps of high-tech radiation techniques, and the possible solutions will be discussed.

Local tumour control

It is too often postulated that technical improvement in tumour imaging and dose delivery will quickly be transformed into improvement in cure rates of cancer. Strict avoidance of normal tissues surrounding the tumour is increasingly common in high-tech radiotherapy. Such practice raises, however, great concern that even minimal inter- or intra- fraction movement of the target organ would exclude a part of the tumour from the irradiated volume. Also there is reason to be concerned that subclinical extensions of the primary cancer and/or metastases will be excluded. Thus sparing of the normal tissues would be achieved at the expense of tumour control. While the mobility of the prostate is relatively low compared to e.g. lungs it is obviously not negligible. The topography of the pelvis changes considerably during and between the fractions of radiotherapy depending on urinary bladder continence and large bowel movements. Furthermore, there are considerable discrepancies in delineating GTV and CTV from one physician to an other and even greater diversity between the cancer centres (e.g. lack of consensus on indications for irradiation of seminal vessels, or prophylactic pelvic irradiation).

Such a perspective may be quite disturbing bearing in mind that only a small number of randomized clinical trials have so far been designed to compare control rates obtained using conventional 2D vs. "standard" 3D radiotherapy, and, to the best of my knowledge, none of them has compared local control in "standard" 3D conformal RT with IMRT. Excellent isodose distributions on the paper may not necessarily convert into improved clinical results, because they show physical and not biological doses. Furthermore, it has already been pointed out in this paper that complete local eradication of the tumour does not always result in the cure of cancer. Had the radiation oncologist a "supremnac" - a hypothetical therapeutic machine, which would allow complete eradication of 100% of the malignant primary prostate tumours without any dose delivered to normal tissue, he would find himself in the same position as the surgeon after successful prostatectomy. Unfortunately, distant metastases are the most common cause of treatment failure in prostate cancer in spite of early detection. Since effective adjuvant hormonal therapies for prostate cancer exist, combination of high-tech radiotherapy and hormonal treatment offer a solution of this obvious problem.

A reasonable solution to the difficulties associated with topographical location of a tumour, delineation of GTV, and/or micrometastases, in spite of access to high-tech diagnostics equipment, is the use elective irradiation. This is because the doses, which are used to control subclinical cancer, not only contribute to the reduction in subclinical metastases, but also provide a "safety margin" for uncertainties in the delineation of a primary tumour. Remarkably, a dose to sterilize clonogens in a minute portion of a primary cancer, which would remain beyond high-dose volume, is much lower than the dose to sterilize a whole tumour. This is because the number of clonogens in the microscopic portion of a tumour is much smaller than that in a gross tumour. The results of a recent clinical trial on a whole-pelvis versus prostate-only radiotherapy [19] shows a clear benefit of elective pelvic irradiation in high-risk prostate patients. The question of whether elective field or shrinking-field technique is justified in low-risk patients remains to be solved in future trials.

Subclinical disease

One of the potential traps of IMRT is the ability to construct non-homogeneous dose-distribution inside the PTV (planning target volume) so that GTV (a tumour) is treated with a higher dose per fraction, and a higher total dose than CTV (subclinical disease). Such technique would allow delivery of e.g. 76 Gy given in 38 fractions of 2.0 Gy in the overall treatment time of 53 days to the primary tumour, while subclinical cancer (the electively treated part

of the pelvis) would be irradiated in the same overall treatment time to the total dose of 50 Gy. Thus the electively treated volume would be treated with 1.32 Gy/fraction, i.e. the average rate of dose accumulation in the pelvis would be 6.6 Gy/week. The advocates of such intensity modulated technique believe that a low dose per fraction in the pelvis would decrease the rate of acute and late normal tissue reactions without compromising local control in the pelvis. This could be predicted since prostate cancer is on average a slowly growing tumour, and there would be little, if any, repopulation during 7-8 weeks of the therapy. The problem however is, that the estimates of Tpot for a considerable proportion of prostate tumours indicate that they may repopulate rapidly. Furthermore, virtually nothing is known about repopulation of micrometastases in the pelvis, because all of the available data on repopulation and dose-time effect in radiotherapy for prostate cancer come from the data on primary cancer. However, the existing data on other types of cancer suggest that the repopulation rate of a subclinical tumour deposits may be much faster than that of a primary cancer. Another problem previously discussed of low doses per fraction in prostate cancer is its unusual radiobiological characteristics with respect to the fraction size. Assuming that α/β for prostate cancer is 1.5 Gy, 50 Gy given in 38 fractions would be biologically equivalent to only 40.2 Gy given in 2.0 Gy fractions.

It can thus be postulated that unnecessary protraction of the overall treatment time in elective pelvic irradiation for prostate cancer should be avoided. Perhaps future developments in molecular biology and imaging will allow the identification of individuals who may actually benefit from treatment protraction.

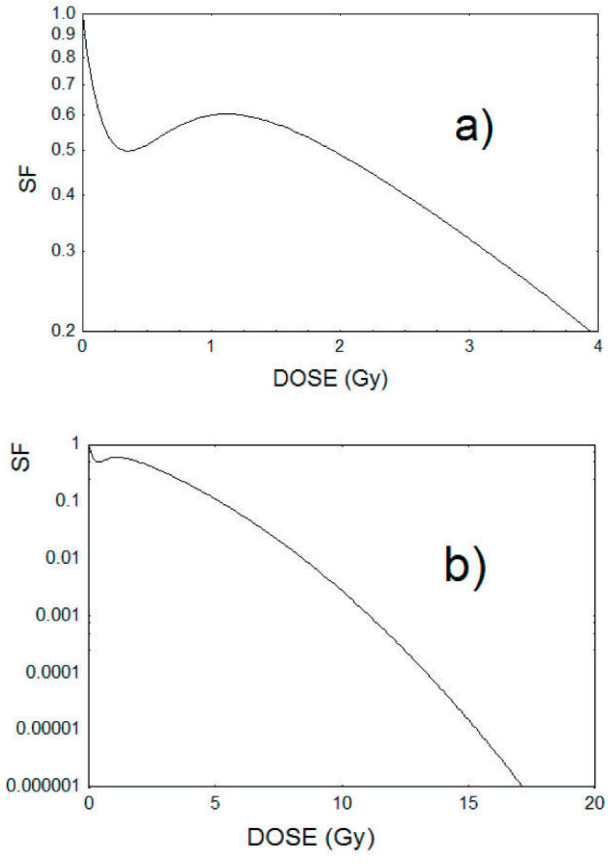

Figure 2. The model cell survival-curves which incorporate the effect of hypersensitivity of normal tissues to low doses per fraction.
a) an initial portion of cell-survival curve shows that within the range of doses per fraction of about 0.1-1.0 Gy there is much more cell kill than that predicted from a linear-quadratic model,
b) at higher doses per fraction the shape of the cell-survival curve is analogous to that predicted by a linear-quadratic model.

Late responding tissues

A troublesome dogma regarding 3-D conformal radiotherapy and IMRT is that such techniques will decrease the rate of normal tissue complications because the total dose and doses per fraction given to such tissues are low. This can be achieved by using multiple beams, which would almost-perfectly focus on the target volume. This conclusion apparently ignores growing evidence of hypersensitivity of normal tissues to low doses per fraction. Several pre-clinical studies show that there is little, if any, DNA repair if fraction doses of about 0.3-0.6 Gy are used [20]. A likely explanation of such unexpected phenomenon is that low doses per fraction are not high enough to trigger molecular mechanisms of repair (*Figure 2*). Unfortunately, large volumes of normal tissues are often exposed to low doses per fraction when multiple beams are used (*Figure 3a*). The double trouble is that low radiation doses have a known potential for induction of a second cancer, and that the relationship between the risk of such induction and the total dose is non-linear with a highest risk for leukemia at about 1.0 Gy.

How high would be a dose given in 0.5 Gy per fraction to risk necrosis of subcutaneous tissues? Assuming that no repair occurs at such fraction doses the total dose to induce severe late effect would have to be similar to the doses which are historically known to cause necrosis with a single dose irradiation, i.e. about 24-26 Gy. Considering a situation described in *Figure 3* 80 Gy given to the tumour would result in the accumulation of 20 Gy in 0.5 Gy per fraction in large volumes of normal tissues. Luckily, this is much less than the hypothetical dose-threshold for severe late complications in the absence of DNA repair. However, if the total radiation dose for the tumour were escalated to 100 Gy the dose accumulated in 0.5 Gy per fractions would be 25 Gy. This may result in unexpected problems.

The postulated solution of the problems associated with low-dose hypersensitivity and risk of a second cancer is avoidance of low radiation doses distributed over large volumes of normal tissues. This can easily be avoided when the number of beams is reasonably reduced (*Figure 3b*).

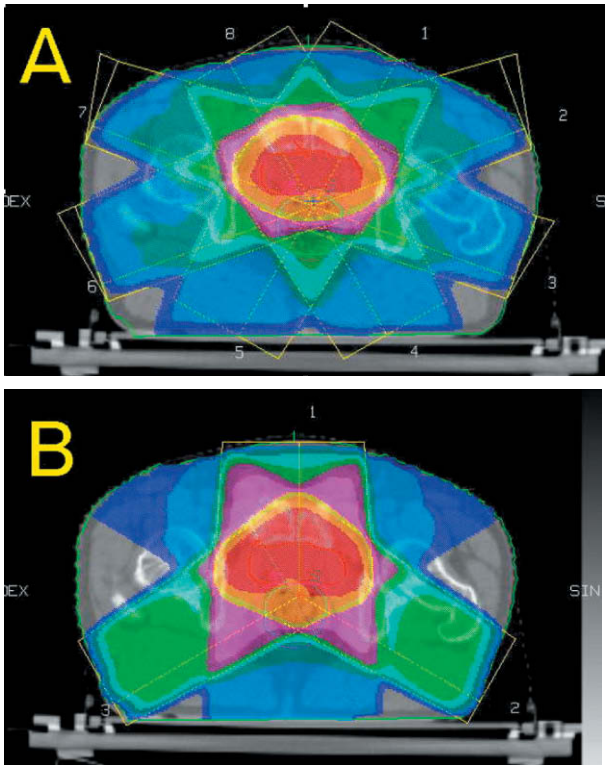

Figure 3. Suppose that a dose per fraction prescribed to GTV is 2.0 Gy and that 8 beams are used. The weights of the beams are equal, that is 0.25 Gy is given from each beam. Since there are 4 pairs of the opposed beams large volumes of normal pelvic tissue surrounding the tumour will be irradiated with about 0.5 Gy per fraction (*Figure 3A*). Much smaller volumes of normal tissues are irradiated with low doses when only 3 beams are used, but critical organs may receive a higher total dose (*Figure 3B*). It is not easy to resolve which treatment plan is better if the phenomenon of hypersensitivity of low doses to radiation is taken into account.
Colours (dose per fraction): red: 2.0 Gy, yellow:1.9-2.0 Gy, purple:1.5-1.9 Gy, green: 0.6-1.5 Gy, blue: 0.2-0.6 Gy

In each individual case the potential gain from the reduction of the beam number must be, however, carefully weighed against the risk of overdosing critical organs.

IMRT vs. fractionation vs. radio-protectors in prostate cancer

Some grumpy people translate the acronym "IMRT" as "I M Really Tired", because they think there is too much work to do. It is because this procedure is considerably more time-consuming than the does it "standard" 3-D radiotherapy. Not only take longer to prepare a treatment plan, but it takes much more time on the treatment machine to deliver a defined radiation dose to the target in a dynamic way. Also, in-vivo dosimetric procedures are far more complicated in IMRT than in "standard" 3-D radiotherapy. It is not possible to double-check the calculations using standard treatment planning units. It is postulated that using unconventional fractionation schedules and/or radio-protectors of normal tissues, it may be possible to get a similar sparing effect for normal tissues as from the implementation of IMRT.

The trouble is that unconventional fractionation schemes, which have the potential for sparing of normal tissue (e.g. CHART), are, theoretically at least, inappropriate for prostate cancer because of their unique characteristics with respect to fractionation sensitivity (postulated low α/β value). Radio-protectors have the theoretical potential for sparing normal tissue, but their clinical feasibility is still the subject of critical discussion, and they have, so far, a lofty prices. This shows that high-tech radiotherapy will, most likely, play a major role in routine treatments for prostate cancer. One should, however, bear in mind the limitations and traps of this technique when trying ensure the appropriate use of this new tool.

Can hypoxia by be overcome by "dose painting" to become useful in the clinic?

If hypoxic spots exist in a tumour how high should the dose be to sterilize the hypoxic clonogens in such a place? Suppose that SF2Gy for well oxygenated prostate cancer cells is 0.55, and that an early stage tumour contains 108 clonogens, than a Poison model of tumour control would predict 65 Gy as the dose to achieve 80% probability of tumour control, which is reasonably-well consistent with clinical data. If, however all clonogens in a tumour containing 10^8 cells were hypoxic, the dose to achieve 80% probability of hypoxic tumour would be 3x65=195 Gy, because the oxygen enhancement ratio for most of human cells is about 3.0. If, by contrast, only 10^4 clonogens were in a hypoxic spot than the dose to control such a spot would be 97.5 Gy (i.e. 50% of the dose to control 108 cells), and 146 Gy for a spot containing 10^6 hypoxic clonogens (i.e 75% of the dose to control 10^8 cells).

Is it technically possible to deliver such a dose to hypoxic spots without risking severe overdosing of normal tissues in the proximity of the tumour? With high-tech brachyterapy it seems likely that such doses may be safely achieved in the near future. However, the question arises of whether the use of hypoxic cell sensitizers would better do the task than "dose-painted" radiation therapy alone, or whether tumours containing hypoxic spots are, perhaps, the best candidates for surgery. Does re-oxygenation play a role in fractionated radiotherapy for prostate cancer? Only future trials can solve these questions.

Summary

The present review challenges the viewpoint presented by Maciejewski et al. that conventional 5-days-a-week, 2 Gy fraction regimes produce a "plateau effect" in therapy for prostate cancer, and that an increase in the total dose above 70 Gy would not improve local tumour control in this tumour site. It is suggested that not only tumour hypoxia, but also distant metastases may create

a quasi-plateau in dose-response for prostate cancer, when biochemical failures and not loco-regional tumour control are used as the endpoint. A conclusion that intermediate-risk prostate cancers are good candidates for dose escalation in conventionally fractionated radiotherapy is presented. Also, some unforeseen challenges, which may appear while implementing new radiation treatment strategies in the treatment for prostate cancer, are discussed, and possible solutions to solve these problems are proposed. Furthermore, some arguments are given against hypofractionation for prostate cancer. Such openly controversial opinions are aimed to stimulate a broader discussion regarding the optimization of local therapies for prostate cancer. The conclusions presented illustrate an urgent need for new prospective trials, which would address clinical and radiobiological ambiguities of theoretical predictions.

References

1. Maciejewski B, Petrovich Z, Lange D, Borówka A. Radiotherapy for locally advanced prostate cancer: dogmas and dilemmas. Rep Pract Oncol Radiother. 2003;8:97-110.
2. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys. 2002;53:1097-105.
3. Pollack A, Smith LG, van Eschenbach AC. External beam radiotherapy dose response characteristics of 1127 men with prostate cancer treated in the PSA era. Int J Radiat Oncol Biol Phys. 2000;48:507-12.
4. Hurwitz MD, Schnieder L, Manola J, Beard CJ, Kaplan ID, D'Amico AV. Lack of radiation dose response for patients with low-risk clinically localized prostate cancer: a retrospective analysis. Int J Radiat Oncol Biol Phys. 2002;53:1106-10.
5. Hanks GE, Leibel SA, Krall JM. Pattern of case studies: Dose-response observations for local control of adenocarcinoma of the prostate. Int J Radiat Oncol Biol Phys. 1985;11:153-57.
6. Valicenti RK, Lu J, Pilepich M. Survival advantage from higher dose radiation therapy for clinically localized prostate cancer treated on the radiation therapy oncology group trials. J Clin Oncol. 2000;18:2740-46.
7. Lyons JA, Kapelian PA, Mohan DS. Importance of high radiation doses (72 Gy or greater) in the treatment of stage T1-T3 adenocarcinoma of the prostate. Adult Urol. 2000;55:85-90.
8. Eastham JA, Kattan MW, Groshen S, Scardino PT, Rogers E, Carlton CE Jr, et al. Fifteen-year survival and recurrence rates after radiotherapy for localized prostate cancer. J Clin Oncol. 1997;15:3214-22.
9. Suwinski R, Taylor JMG, Withers HR. The effect of heterogeneity in tumor cell kinetics on radiation dose-response. An exploratory investigation of a plateau effect. Radiother Oncol. 1999;50:57-66.
10. Suwiński R, Taylor JMG, Withers HR, Maciejewski B. „Efekt plateau" w radioterapii. Nowotwory 1999;49:682-8.
11. Morgan WR, Zincke H, Rainwater LM, Myers RP, Klee GG. Prostate specific antigen values after radical retropubic prostatectomy for adenocarcinoma of the prostate: impact of adjuvant treatment (hormonal and radiation) J Urol.1991;145:319-23.
12 Stein A, de Kernion JB, Dorey F, Smith RB. Adjuvant radiotherapy in patients post-radical prostatectomy with tumour extending through capsule or positive seminal resides. Urol. 1992;39:59-62.
13. Schild SE, Wong WW, Grado GL, Buskirk SJ, Robinow JS, Frick LM, et al. Radiotherapy for isolated increases in serum prostate-specyfic antigen levels after radical prostatectomy. Mayo Clin Proc. 1994;69:613-19.
14. Valicenti RK, Gomella LG, Perez CA. Radiation therapy after radical prostatectomy: a review of the issues and options. Semin Radiat Oncol. 2003;13:130-40.
15. Withers HR, Peters LJ, Taylor JMG. Dose-response relationship for radiation therapy of subclinical disease. Int J Radiat Oncol Biol Phys. 1995;31:353-9.
16. Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumours really low? Int J Radiat Oncol Biol Phys. 2001;50:1021-31.
17. Nahum AE, Movsas B, Horwitz EM, Stobbe CC, Chapman JD. Incorporating clinical measurements of hypoxia into tumor local control modeling of prostate cancer: implications for the alpha/beta ratio. Int J Radiat Oncol Biol Phys. 2003;57:391-401.
18. Lukka H, Hayter C, Warde P, Morris J, Julian J, Gospodarowicz M, et al. A randomized trial comparing two fractionation schedules for patients with localized prostate cancer. Int J Radiat Oncol Biol Phys. 2003;57:S126.
19. Roach M, DeSilvio M, Lawton C, Uhl V, Machtay M, Seider MJ, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppresion: Radiation Therapy Oncology Group 9413. J Clin Oncol. 2003;21:1904-11.
20. Joiner MC, Lambin P, Malaise EP, Robson T, Arrand JE, Skov KA, et al. Hypersensitivity to very-low single radiation doses: its relationship to the adaptive response and induced radioresistance. Mutation Research 1996;358:171-183.
21. EJ Hall. Late effects of radiation: carcinogenesis and nonspecific life shortening. In: Radiobiology for the radiologist. JB Lippincott Company, Philadelphia 1988, 385-409.