

RADIOTHERAPY FOR LOCALLY ADVANCED PROSTATE CANCER: DOGMAS AND DILEMMAS

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SUMMARY

Several well documented clinical trials and retrospective studies on radiotherapy for locally advanced prostate cancer are reviewed showing that almost all conventional, 5-day-a-week, 2 Gy fraction regimes produce the "plateau effect" (further increase in total dose above some level does not improve local tumour control), although a few studies identified radiation dose as an important predictor for the treatment outcome. This suggests that conventional radiotherapy for locally advanced prostate cancer has limited efficacy. Dissimilar patient population in each of the reports under review makes conclusions uncertain because the analysis does not make it possible to separate the impact of clinical and histological predictors on the treatment outcome from the effect of the radiation dose. The advent of conformal 3D IMRT permits safe delivery of dose escalated radiotherapy. Advantages and traps of 3D-CRT-IMRT therapy are presented and discussed. Evidence of low α/β value of about 1.5 Gy for prostate cancer cases suggests that these tumours have unusual sensitivity to a change in dose per fraction which opens up a new perspective for radical hypofractionated 3D-CRT and/or 3D-high dose rate brachytherapy and various fractionation regimes. Hyperthermia combined with 3D-CRT is discussed as an interesting treatment option.

Any discussion on treatment optimization for locally advanced prostate cancer (LAPC) requires a clear definition of this entity, which at the present time is lacking. Generally, local extension of the disease is used as a major criterion for diagnosis of LAPC (stage $>T_2$, poorly differentiated histology and/or high PSA). When describing the treatment of prostate cancer and its outcome by disease burden and other prognostic factors, patients with LAPC are included in a high-risk category, which reflects both tumour burden and its aggressiveness. Therefore, LAPC encompasses patients with a stage greater than T_2 , poorly differentiated histology and/or high PSA level.

Despite that fact, there is still an active debate on the role and effectiveness of radiotherapy (RT), either as a single modality or as a part of a combined treatment programme. Review of many retrospective studies and clinical trials shows contradictory indications for RT alone, postopera-

tive RT, or RT for patients with regional lymphadenopathy. Concerning recent technological developments in radiotherapy and contemporary radiobiological studies on radiosensitivity of prostate cancer, there is a question whether conventionally fractionated dose escalation may increase therapeutic gain in terms of long-term biochemical no evidence of disease (BNED).

This paper focuses mainly on radiotherapy, although surgery is also briefly considered.

Is Conventional External Beam RT (EBRT) a dogma for prostate cancer?

A radiation oncologist has to consider multiple factors when planning treatment strategy for prostate cancer, which include: technique of irradiation, appropriate extent of the radiation portals, a possibility of dose escalation, fractionation schedule, and the need for surgery and/or hormonal therapy. Almost in all

the published studies, a conventional, 5-day-a-week, fractionation schedule with one daily fraction is used. Because prostate cancer is recognized as a slowly proliferating tumour it is not an optimal candidate for accelerated, hyperfractionated or hybrid treatment schedules. Therefore, major interest is focused on a possibility of obtaining therapeutic gain by dose escalation.

In 1985, Hanks et al. [1] reviewed 574 LAPC cases treated between 1973-1975 and found a significant dose-response effect for T_2 and T_3 but not for T_0 , T_1 and T_4 tumours. Recently, Valicenti et al. [2] pooled together 1,465 cases of the LAPC of four Radiation Therapy Oncology Group (RTOG) phase III trials and found Gleason score (GS), not the radiation dose, to be the strongest predictor of overall and disease free survival. The same study demonstrated the increase in GS from 2 to more than 10, which resulted in a significant decrease in the 10-year survival from 85% to 43%, respectively, (Fig. 1). For patients with GS from 8-10, further data analysis showed the relative risk of death from LAPC

decreased by 29% if the total radiation dose is higher than 66 Gy.

In a study of 1,127 stage T_1 - T_4 LAPC patients treated at the MD Anderson Cancer Center in Houston, Texas between 1987-1997, Pollack et al. [3] found radiation dose-response effect (Fig.2) and a substantial increase in the 4-year BNED status for moderate risk patients. These patients presented with one of the following factors: $T > 2$ or $PSA \geq 10$ ng/mL or $GS \geq 7$. Among the above four predictive factors, only total radiation dose was found as an independent predictor for BNED. In the low-risk group no gain in the BNED from dose escalation has been detected and a total dose of 67-77 Gy was proposed as an adequate treatment for patients with pretreatment $PSA < 10$ ng/mL. For the high-risk group no sustained BNED at doses lower than 80 Gy was noted. Therefore, this group of patients for optimal therapy requires a higher dose than 80 Gy, including whole pelvic irradiation, with or without androgen deprivation.

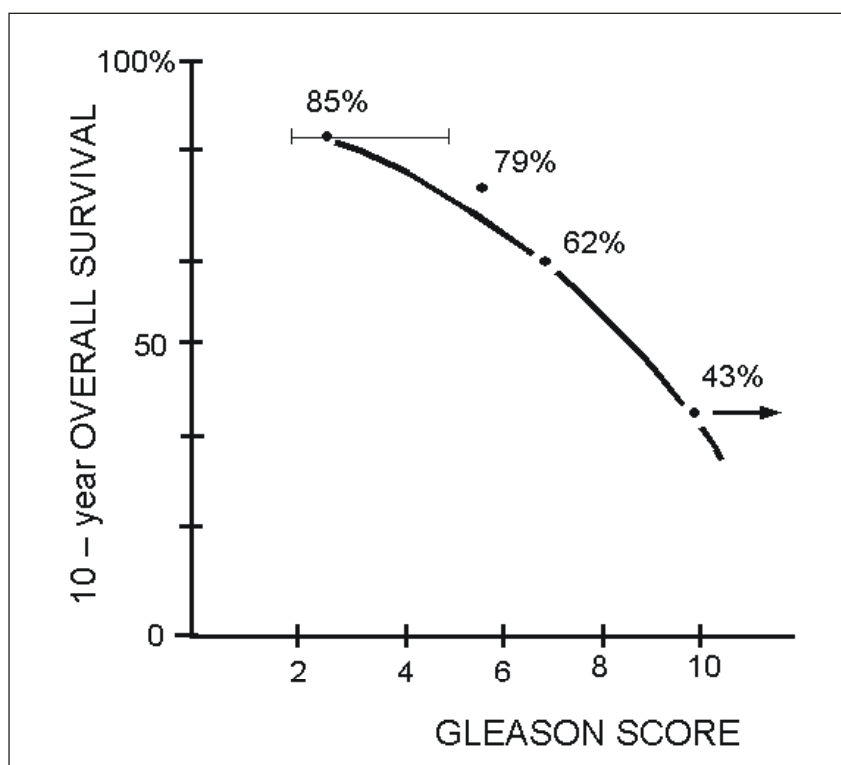


Figure 1. Correlation between Gleason score and 10-year overall survival of patients with LAPC (according to Valicenti et al., 2)

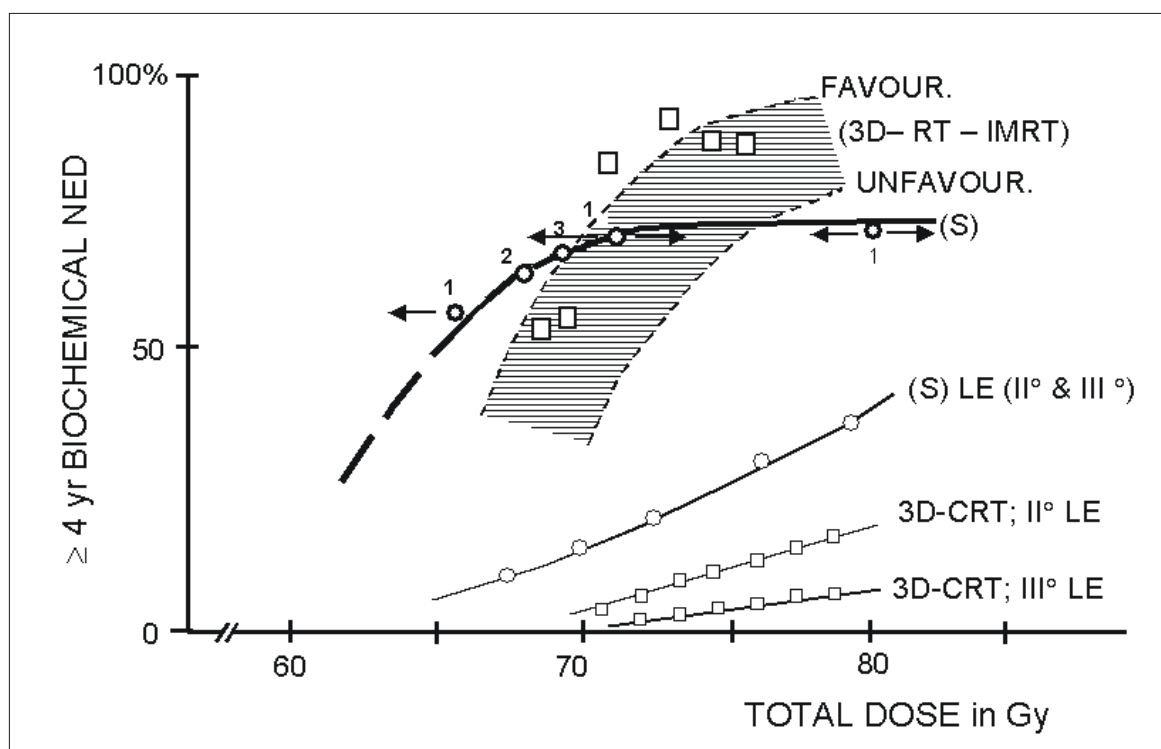


Figure 2. Dose-response relationship for locally advanced prostate cancer with conventional standard radiotherapy (S, open circle) compared with 3D-CRT, IMRT (squares). Bottom curves represent incidence of late bladder and rectal complications (LE) for respective techniques of irradiation. Dashed area reflects variations in dose and respective BNED for favourable and unfavourable LAMP.

Dose curves were estimated from the reported data sets (1 – Pollack et al.; 2 – Hanks et al.; 3 – Valicenti et al. and “squares” – Lyons et al., Hanks et al., Zelefsky et al.).

Fiveash et al. [4] reviewed outcomes of LAMP patients (T_1 - T_4) with GS 8-10, which were treated at 3 institutions. The authors found by univariate analysis, radiation dose as the only factor predictive for overall survival. In multivariate analysis, however, only T-stage was a good predictor of overall survival. A more detailed analysis of subgroups of patients showed again RT dose and pretreatment PSA level as the only independent predictors of the overall survival.

Lyons et al. [5] subdivided the data of 738 patients from the Cleveland Clinic in Cleveland, Ohio into two subgroups: 1. favorable (T_1 - T_3 , pretreatment PSA ≤ 10 ng/mL, GS ≤ 6) and 2. unfavorable (T_3 , PSA > 10 ng/mL, GS ≥ 7). There was no statistical difference in BNED among patients receiving 74 vs. 78 Gy. On the other hand, the tendency of the increase of 5-year BNED with dose escalation was observed in both groups. This gain was significant and twice as high for the unfavourable rather than the favourable group (34% vs. 17% gain in BNED).

The presented, above results are confusing and their interpretation is very difficult. Some published reports support whereas others raise relevant questions about the dose-response effect in prostate cancer [6]. This makes any conclusion concerning dose effect uncertain. The main reason for this uncertainty is a dissimilar patient population in each published report. This includes differences in T-stage, PSA level and GS. As a result, the analysis does not allow separating the impact of clinical and histological predictors on treatment outcome from the effect of the radiation dose. Therefore, the role of dose escalation for low and high-risk patients remains undefined. The Lyons et al. study [5] showed that dose escalation plays an important role for intermediate risk group patients. Whereas, for low-risk groups, PSA and GS have about twice the impact on BNED than does the increase in the total dose.

A compilation of the results in Figure 2 (solid line) shows the “effect plateau” for the dose-response above 70 Gy, which

is graphically similar to that noted for squamous cell carcinoma of the head and neck region. However, the nature and the origin of this effect for both of these tumours seem to be quite different. In contrast to squamous cell carcinoma, prostate cancer is classified as a slow proliferating tumour, and there is no convincing evidence for accelerated repopulation occurring during the course of radiotherapy. Therefore, it is hard to believe that radiation dose plateau may be the result of intensive tumour clonogen repopulation, which balances the increase in total dose accompanied by the extension of overall treatment time (OTT). There should be some other mechanism(s) involved producing the dose plateau, which will be discussed later. Irrespective of the exact mechanism explaining the dose plateau and based on the available data, there is no doubt that conventionally fractionated EBRT can produce limited benefit. However, this benefit does not increase with an additional radiation dose and only extends the duration of patient treatment course. This, in turn, may increase the risk of late toxicity without improving long-term BNED.

Postoperative EBRT – immediate or delayed

Radical prostatectomy (RP) is generally used as a primary treatment for clinically localized tumours. This treatment in a prospective randomized trial comparing RP and watchful waiting resulted in a significant reduction of the disease specific mortality but did not improve overall survival [7]. Based on this and other studies, RP has become a “gold” standard therapy for patients with localized PC. The role and timing of postoperative RT is yet to be defined and is the source of many controversies. At the present time, it is still not apparent which subset of patients may benefit from early (adjuvant) or delayed (salvage) radiotherapy [8,9].

The pretreatment PSA > 10 ng/mL and GS ≥ 7 are the factors that most consistently predict the disease recurrence. Lowe and Lieberman [10] added two more factors, i.e. positive surgical margins and/or seminal vesicle invasion to identify

pT₃N₀ patients at high risk for early PSA failure. There are a few more important factors such as: GS in pretreatment biopsy compared with GS in the surgical specimen, capsular and/or extracapsular invasion and regional lymph node involvement, which are likely to play an important prognostic role. The authors of the above study defined a low and high-risk of relapse at 5-years after RP (9.8% vs. 41.2%). Those in the high-risk group (pT_{3a,b}; GS ≥ 7, pretreatment PSA > 10 ng/mL; 2 positive margins) may benefit from adjuvant radiotherapy. Similar data was reported by other investigators [9-15].

Table 1 summarizes some of the reported clinical studies and shows that adjuvant EBRT provides a higher BNED rate than RP alone. In contrast, Anscher et al. [16] found no difference in the 10-year actuarial survival (52%) for both RP alone and adjuvant EBRT. The reason for this lack of difference is very likely due to the patient selection for adjuvant EBRT. These patients almost certainly had a more advanced disease at diagnosis than those treated with RP alone. Studies presented in Table 1 and many other published reports showed no dose-response effect similar to that of EBRT alone. This effect is irrespective of the conventional radiotherapy technique and radiation dose levels used with or without a boost. Valicenti et al [17] and Leibovich et al. [18] using matched-pair analysis detected for adjuvant EBRT about 20% overall improvement in recurrence-free survival across all patient categories.

Some investigators suggested that the higher incidence of local tumour control after adjuvant EBRT did not correlate well with a decreased incidence of distant metastasis. This was presumed to be due to the presence in some patients of micrometastasis at the time of initial therapy. More recent published reports, however, [8,19] showed an improvement in biochemical control rates disproving the hypothesis of micrometastasis. These reports also recommended the need for a longer follow-up to demonstrate a reduction in the incidence of distant metastasis.

Table 1. Selected results of adjuvant EBRT for T₃N₀ prostate cancer compared with prostatectomy alone (> 3 yr. BNED) (according to Valicenti et al. 8)

No pts.	Adjuvant EBRD (total dose)	Progression free rate BNED	Author
33	no	64 %*	Morgan (13)
17	yes (60 – 66 Gy)	94 %*	
91	no	43 %	Stein (14)
24	yes (55 – 60 Gy)	75 %	
228	no	40 %	Schild (15)
60	yes (57 – 68 Gy)	57 %	
36	no	55 %	Valicenti (8)
36	yes (59.4 – 70.2 Gy)	88 %	

* follow-up of 11 months

The most important problem facing urologists and radiation oncologists when evaluating patients with pT₃N₀ tumours is the difficulty in making the two key decisions. These decisions relate to whether a patient should receive adjuvant EBRT and what should be its timing following RP [20]. In other words, should a patient receive immediate adjuvant EBRT or should a wait and watch policy be adopted. The latter approach seems justifiable in low-risk group patients with PSA < 10 ng/mL, GS ≤ 6 and negative surgical margins. A recent report presenting long-term results, however, does not support the wait and watch approach due to a relatively poor treatment response (20%) obtained with salvage EBRT in this group of patients [20]. Many studies on delayed EBRT as a salvage therapy show that such a policy might be useful in patients without seminal vesicle involvement, and in those with PSA lower than 1.1 ng/mL at initiation of irradiation.

Generally, there is no dose-response effect observed for the conventional EBRT alone or RT given following prostatectomy, although a few studies identified pre-treatment PSA and radiation dose as independent predictors of the BNED. Majority of the published reports consist of retrospective studies and include heterogeneous groups of patients, making an attempt to identify a dose response effect a very difficult task. Among com-

pleted randomized trials only one seems to support the dose-effect relationship [3]. It is apparent to radiation oncologists that radiation dose is an important parameter. Otherwise, there will be no good reason to plan the patient for a course of irradiation. However, despite a few decades of clinical experience and many studies performed, there is no convincing evidence of dose escalation effect. It appears that any meta-analysis studies may not be useful to attempt and the interpretation of already published studies would be difficult and uncertain due to a simple basic fact. To date, there is no consensus on the definition of the end-point for biochemical complete response after completing the treatment and there is a wide range of definitions of biochemical progression. For a complete biochemical regression PSA level as the end-point is used in the range of 0.0 – 0.4 ng/mL. Many authors suggest that the most important factor in defining biochemical regression is the magnitude of the decrease in the PSA level. As an example, it should make a difference whether PSA decreases from >20 ng/mL to zero compared with a decrease from <10 ng/mL to 0.4 ng/mL [17]. The end-point for biochemical progression is even more difficult to define because it differs from study to study. It ranges from a low of >0.05 to a high of 2.0 ng/mL or it is used in a nonparametric scale, requiring from two to three rises in the PSA level,

or it is based on so-called panel consensus [11,14-16]. If we agree that PSA elevation predicts treatment failure and disease progression, it does not, however, indicate whether the recurrence is strictly localized or involves subclinical metastasis.

An interesting study of Zagars and Pollack [21] presented modified prognostic groups based on biochemical relapse hazard (Table 2). This proposed model

may become a useful guideline for treatment strategy, but uncertainty immediately arises concerning the potential for tumour grading errors. Roberts and Roach [22], who performed careful analysis of biopsy and pathological staging data, found about 50% of low-grade tumours undergraded, a 15% chance of under- and a 10% chance of overgrading for intermediate grade tumours and about 25% of high-grade tumours being undergraded.

Table 2. Biochemical relapse hazard groups of the LAPC according to Zagars and Pollack (21)

Hazard group	T stage	Pretreatment PSA in ng/mL	Gleason Score
I	T ₁ – T ₂	≤ 4	2 – 6
II	T ₁ – T ₂	≤ 4	7 – 10
III	T ₁ – T ₂	4 < - ≤ 10	2 – 7
		4 < - ≤ 10	8 – 10
IV	T ₃	10 < - ≤ 20	2 – 7
		≤ 4 - ≤ 10	2 – 10
UNFAVOURABLE	T ₁ – T ₃	10 < - ≤ 20	2 – 7
		10 < - ≤ 20	8 – 10
		> 20	2 – 10

Based on the published data, there is convincing evidence of the “plateau effect” for the conventional EBRT alone or for adjuvant radiotherapy following prostatectomy. As discussed, there is, however, no clear definition of the end-point for biochemical complete regression or biochemical progression. For the past few decades, in conventional EBRT, clinicians favoured a uniform dose distribution within the designated target volume and for dose escalation protocols in patients with LAPC. In fact, prostate cancer is a clinically heterogeneous tumour even within the same TNM stage. Histologically, there is a good recognition of tumours having different cell patterns and cell density. Therefore, at the present time we are confronted in LAPC with more dilemmas than dogmas.

Pathologic uncertainties

It is extremely difficult to evaluate the results of single or combined treatment

modalities if precision of predictive power of PSA and Gleason Score is uncertain. In the era of genetic, molecular markers and some very specific and sensitive tests, i.e. RT-PCR, there is a question whether the most frequently used factors predicting prognosis such as PSA and GS still remain useful in the clinic. This question becomes of particular relevance because of the fact that needle biopsy is the preferred diagnostic method in patients suspected of having PC. The difficulty not only stems from the small amount of tissue available for examination through a needle biopsy but also because of the histological signs of malignant disease can be subtle, increasing the risk of imprecise diagnosis. Many histological pictures seen in benign disease may mimic cancer leading to an erroneous diagnosis of malignancy with all its implications. There is evidence that positive staining of α -methylacyl-CoA racemase (AMACR) may increase confidence in the diagnosis of prostate cancer [23]. The degree of diagnostic uncertainty

increases with the knowledge that from 33 to 45% of Gleason scores are underestimated, while in 4 to 32% of patients GS is overestimated based on biopsy material comparing with Gleason score, which is based on the surgical specimen [24]. The assessment of GS is difficult because histological pattern of the tumour is to a large extent heterogeneous. A tumour that is mostly GS 3 with less amount of pattern 4 has GS 7, as does a tumour that is mostly pattern 4 with a lesser amount of GS 3. The latter is associated with a worse prognosis than the former one and it probably requires a more aggressive treatment. Because GS grading is subjective and difficult to establish based on a limited amount of tissue obtained via a biopsy, there may be a need to obtain more than one biopsy. Typically, biopsy samples are obtained with at least 6 cores, with the length of a core at about 15 mm. In addition, a second pathological review of GS may also be very useful.

Kranz et al [25] stated that the experience of a pathologist is a major determinant of an accurate tumour grading. Otherwise, since the diagnosis is not certain, treatment becomes problematic and it may be another source of a dilemma when the treatment results are being evaluated. The use of special instructions in prostate cancer diagnosis for 916 pathologists increased the precision of Gleason scoring by about 12% [25]. However, despite all of these doubts and uncertainties predictive and prognostic value of PSA and GS have not been questioned in any of the published studies.

Advantages of conformal (3DCRT) and dose intensity modulated (IMRT) radiotherapy

During recent years, technological innovations in computers and in imaging modalities helped to develop precise three-dimensional treatment planning, beam's eye view displays, computing and displaying reconstructed radiographs from digital CT data sets, dose-volume histograms (DVHs) and multileaf collimators (MLC) allowing for the individual conformal

beam shaping. The advantage offered by 3DCRT and IMRT over conventional RT is an improvement of target coverage, avoidance of critical normal tissues, individual field shaping, decrease in positioning errors and translation of DVH(s) into biologically normalized DVH (BNDVH) and probability of tumour cure (TCP) and of normal tissue complications (NTCP). Actually, the IMRT is the most precise method of individually modified dose intensity and heterogenous dose delivery within the designated target.

There is still not enough outcome data with sufficiently long follow-up, which would allow to precisely and objectively evaluate the effectiveness of 3DCRT and IMRT. Results of the published studies by Lyons et al. [5], Hanks et al. [1] and Pollack et al. [3] show that compared with conventional RT about 10-15% gain in BNED can be expected (*Fig. 2: dashed line*). The other two large RTOG and Medical Research Council (MRC) phase III trials are still ongoing. On the other hand, Dearnaley et al. [26], Koper et al. [27] and Zelefsky et al. [28] found that 3DCRT/IMRT significantly (10–15%) reduced grade II and III gastrointestinal and genitourinary late toxicity. Zelefsky et al. [28], using IMRT with dynamic MLC, noted a significant (16%) decrease in the incidence of treatment related acute rectal toxicity. This incidence decreased from 61% for conventional EBRT to 45% in patients treated with IMRT. It is even more important to note that late grade II/III rectal bleeding decreased from 13% for conventional RT to 0.5% for those treated with IMRT (*Fig. 2 - bottom curves*).

The results of the recent studies discussed above showed that LAPC patients with the intermediate risk factors are most likely expected to benefit from 3DCRT/IMRT dose escalation. Patients with low risk factors and early stage of the disease may have target volume small enough that conventional RT is adequate to eradicate the tumour. For the high-risk group the role of the 3DCRT/IMRT is yet to be defined. An interesting observation may be obtained from *Figure 2*. Although, dose-response curves (dashed lines) for 3DCRT/IMRT are indirectly drawn from the recently published data they are steeper than

those for conventional RT and the plateau is reduced. This factor seems to be one of the promising advantages of the CRT/IMRT. The dashed area suggests a range of doses instead of a single dose for a given TCP and it reflects variation in PSA, GS and T stage. Simultaneously, NTCP curves for late effects became flattened for the IMRT as theoretically predicted. It clearly illustrates a larger "safely window" offered by the IMRT (delivery of a higher dose with a lower risk of late effects).

However, geographical miss, even small, during contouring the target is a major potential problem for the IMRT, and it may erase the expected benefit. A decrease in the radiation dose in 1% of the target's volume decreases TCP even to zero. This justifies the 3DCRT/IMRT requirement for utmost precision and careful step-by-step treatment planning including double-checks, quality assurance process and careful treatment delivery.

Radiobiological Advantages

Bladder and rectum are the organs, which always need to be identified in the process of treatment planning. It is of critical importance to exclude from the therapeutic dose of radiation as much volume of these organs as it is viewed safe. Because these two organs are characterized by a threshold, dose-volume curve much higher dose than the "conventional" 60 Gy tolerance dose can be safely given to a smaller volume. This represents the key benefit of IMRT. However, it should be remembered that different parts of an organ may have very different local functional radiosensitivity and, therefore, such mini-volumes should be avoided by more precise IMRT planning. At the present time, without functional PET and dose-function histograms (DFV) this goal may not be realistic.

Optimization of radiotherapy for carcinoma of the prostate is mainly discussed through the dose escalation (simple increase in the total dose) and/or new methods of irradiation such as 3DCRT or IMRT. Until recently, little attention has been paid to the potential benefit of altering fractionation schedules because PC

has been recognized as a slowly growing tumour with a low potential for accelerated repopulation. Although TCP curves for head and neck cancer and those for prostate cancer show similar "effect plateau", their nature and origin are likely to be quite different. For the former tumours it is intensive repopulation of the surviving clonogens, which almost entirely compensates for cell kill effect of daily doses delivered beyond week 5-6 of treatment. For prostate cancer it is unlikely that accelerated repopulation may influence the TCP plateau. Recent analysis of a large body of clinical data by Fowler et al. [29] gave an overall estimate of a very low $\alpha\beta$ ratio of 1.49 Gy (95% CI of 1.35–1.63 Gy) for prostate cancer (patients with "intermediate risk" with a PSA 10-20 ng/mL, GS > 6). This very low value for $\alpha\beta$ may result from intrinsically resistant and/or persistent hypoxic fraction of tumour cells. It may also explain why LAPC is less responsive to the conventional fractionation with 1.8 – 2.0 Gy daily, and why above 70–75 Gy the "effect plateau" occurs (surviving hypoxic cells poorly respond to 2 Gy fractions). This, in turn, suggests that prostate cancer has unusual sensitivity to a change in dose per fraction favouring the use of hypofractionation to improve the therapeutic ratio.

For $\alpha\beta$ of 10 Gy which is usually accepted for carcinomas, dose-fractionation escalation would not produce significant improvement in local control (Fig. 3), whereas, an $\alpha\beta$ of 1.5 Gy, as suggested by several studies, would predict significant and large local benefit. Among a few dose-per-fraction escalation schemes designed by Fowler et al. [29] (Fig. 4) the schedule of 10 x 4.68 Gy seems most promising because of the predicted increase in TCP but also a 14% decrease in the incidence of late effects. However, some caution should be applied since a decrease in the overall treatment time and the increase in dose accumulation per week could likely result in a significant increase in acute toxicity. Therefore, clinical testing of such hypofractionated schedules requires a careful monitoring of acute effects and late effects to assure that clinical results meet the expectations. It is apparent that there

is a need for long-term follow-up and a clear definition of end-point of tumour control and tumour progression. What is also particularly attractive is that 3D-real time high-dose rate brachytherapy (3D-CHDRBT) can effectively be used alone as a treatment for PC or be used as a boost.

Conformal high dose rate (HDR) RT provides an accurate increase in the dose delivered to the prostate without significantly affecting adjacent normal tissues. Real-time guidance makes it possible

to generate a steep dose gradient between the target and critical organs that may become unaffected by organ motion or setup uncertainties. Experience of the Sloan Kettering Memorial Cancer Center in New York [28] and a similar experience of a few European Centers suggest that in the near future hypofractionated IMRT and/or 3D-C HDR BT can be selectively used with PET guided hypoxic (or intrinsically resistant) parts of the tumour. This will be the beginning of real “**dose painting**”.

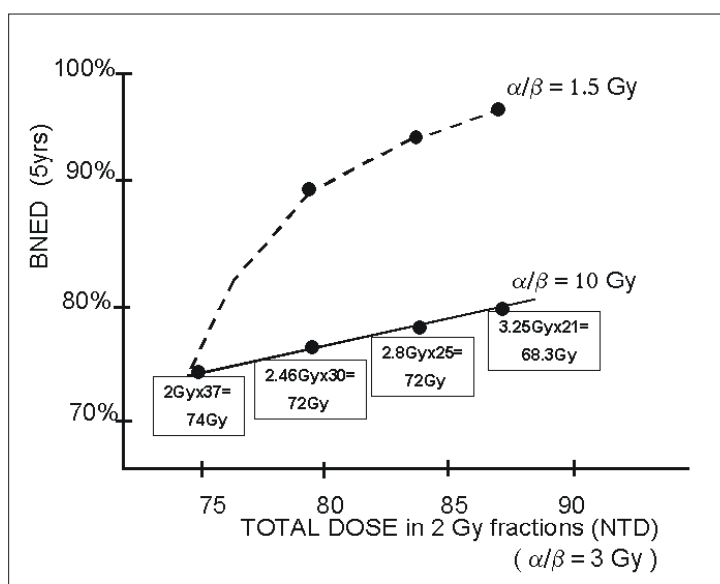


Figure 3. Predicted biochemical no evidence of disease (at 5 yrs.) in relation to dose escalation (NTD) calculated for $\alpha/\beta = 3$ Gy (representing late responding tissues). Note that if the α/β for prostate cancer would be as high as 10 Gy the schemes do not predict significant increase in tumour control, whereas, for $\alpha/\beta = 1.5$ Gy local control benefit is pronounced (according to Fowler, 29).

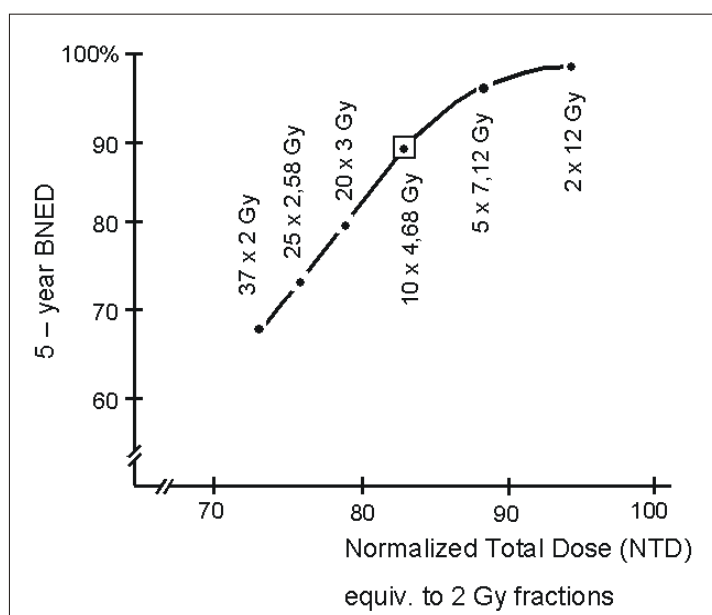


Figure 4. Example of dose-fractionation escalation schemes increasing tumour control while maintaining a-constant late effects. Square shows clinically feasible scheme (Fowler, 29).

Hyperthermia perspectives

Hyperthermia (HT) is a treatment, which increases the temperature of the designated tumour bearing volume to 41-43°C. The anti-tumour effects of HT have been known since the antiquity, but modern applications of this therapy date back to the 1970s. There is a strong and very well documented biological rationale for the use of HT in combination with RT and/or chemotherapy (CT) [30,31]. The exact biological mechanism of HT action as a part of multidisciplinary treatment approach in cancer is beyond the scope of this paper. It needs to be stated, however, that for the optimal effectiveness HT-RT and/or CT need to be given in an appropriate sequence and duration [32]. HT is usually given as a part of combined management in patients with locally advanced and/or recurrent tumours [30,31]. Multiple randomized trials conducted over the past decade have clearly demonstrated the effectiveness of HT-RT combination over that of RT alone in terms of significant improvement in the incidence of local tumour control rates and survival [30,31,33-36]. Over the past quarter of a century clinical HT suffered as a result of technical problems relevant to a precise energy deposition in the designated tumour bearing area. A related problem was due to a frequently imperfect methodology of temperature measurements. It is apparent that the existing HT technology is primarily capable of heating optimally small volumes of tissue in superficial tumours. Deep regional HT requires much work to optimize this important treatment. Improved temperature distribution was reported with the use of a more advanced BSD-2000 deep HT system [37,38].

The use of adjuvant HT in addition to RT for PC has infrequently been reported. This was due to the above noted difficulty of heating deep-seated tumours such that of the prostate. A report on the use of deep regional HT was published as a part of multi-center phase I-II trials of 352 patients, which included 20 PC [39,40]. All of these 20 PC patients presented with locally advanced recurrent and/or persistent tumours following definitive RT. It is of interest to note that

patients with PC had greater probability of complete and partial response than those with other diagnoses. The above reports clearly demonstrated the difficulty with the use of HT instrumentation designed in the 1980s for deep regional treatments [41].

Intracavitary HT using the transrectal route has been under study to improve temperature deposition in the prostate and decrease the incidence of HT related acute morbidity related to the use of deep regional HT [42,43,44]. Of a considerable interest is an unexpected effect of HT on cell-mediated immunity [42,44]. This effect, if proven in other studies, could be utilized in designs of future HT trials in patients with PC. Recently published reports suggest HT regulated and enhanced gene therapy, which may also be of major interest for designing future clinical trials [45,46].

The work at The University of Southern California (USC) in Los Angeles, California and The University of Leuven in Leuven, Belgium demonstrated good prostate heating with the use of transrectal and transurethral microwave HT [47-49]. It is apparent that major effort needs to be undertaken to design prospective randomized trials comparing radiotherapy alone with RT-HT combination in locally advanced adenocarcinoma of the prostate. The outcomes of these future trials will define the role of HT in the management of patients with this tumour.

Molecular and genetic prediction

Currently more studies concentrate on the predictive value of oncogene expression and on molecular markers [23]. Because prostate cancer is a relatively slowly growing tumour it appears that genes controlling tumour redistribution and proliferation may not be of primary interest. We should concentrate more on tumour hypoxia, tumour metastatic potential (E-Cadherin, CD44, nm23), chronic inflammation (Cox2) and apoptosis (TP 53, Rb1, bax/bcl2). Wider application of hyperthermia in the clinic may lead to increasing interest in heat shock proteins (hsp 70). Most of the recent studies show, however, that there is not a single

genetic or molecular predictor. It is most likely that complex configuration of a few of these parameters may reveal an important predictive value. All genetic and molecular studies show that prostate cancer is composed of heterogeneous cell population, which differs significantly even within the same clinical stage, GS or PSA level. Although gatekeeper genes have not yet been identified, they may represent a new and exciting frontier in our knowledge. The search for these genes is expected to be difficult and require considerable resources to process numerous serum and tissue samples.

Summary

Diagnosis of prostate cancer is a very complex process. Many benign histological patterns may mimic the histological appearance of prostate cancer, which in turn may result in serious implications. Despite all the discussed uncertainties, PSA, GS and tumour stage remain widely used and reliable predictors of treatment outcomes. Except for cases in the early stage of the disease with "low-risk" factors, conventional EBRT has limited efficacy because of the "plateau effect", which probably represents tumour persistent hypoxia and resistance. Because prostate cancer is a heterogeneous tumour with important differences in its characteristics (even within the same stage, GS and PSA level) regarding cell density, hypoxia, apoptosis potential, and local inflammation the treatment of this entity needs to be highly individualized. Radiotherapy treatment planning should be designed for each patient with heterogeneous dose distribution. The major dilemma is our limited understanding of the pattern of heterogeneous cell distribution. It seems likely that PET and molecular mapping may be of help to resolve this problem in the near future. The main lesson we learned from over two decades of conducting clinical studies is the dose escalation above 70-75 Gy using conventional 2 Gy daily fractions does not produce a significant benefit. On the contrary, it may increase the risk of development of severe late complications. Evidence of low α/β value of about 1.5 Gy for pro-

state cancer suggests that these tumours have unusual sensitivity to a change in dose per fraction and therefore hypofractionated EBRT and/or 3D-high dose rate brachytherapy could be more effective than the conventional irradiation. Despite the diagnostic and tumour biology uncertainties prostate cancer patients are excellent candidates to consider for 3D-conformal and dose intensity modulated radiotherapy with or without 3D-HDR boost dose painting. These are attempts to escalate the dose selectively to the tumour and to spare critical neighbouring normal tissue. Hyperthermia with radiotherapy may become an interesting treatment option for selected patients with PC when PET-hypoxia mapping will become available in the clinic.

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