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Overview

Is the α/β Value for Prostate Tumours Low Enough to be Safely Used in Clinical Trials?

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ABSTRACT:
There has been an intense debate over the past several years on the relevant α/β value that could be used to describe the fractionation response of prostate tumours. Previously it has been assumed that prostate tumours have high α/β values, similar to most other tumours and the early reacting normal tissues. However, the proliferation behaviour of the prostate tumours is more like that of the late reacting tissues, with slow doubling times and low α/β values. The analyses of clinical results carried out in the past few years have indeed suggested that the α/β value that characterises the fractionation response of the prostate is low, possibly even below the 3 Gy commonly assumed for most late complications, and hence that hypofractionation of the radiation treatment might improve the therapeutic ratio (better control at the same or lower complication rate). However, hypofractionation might also increase the complication rates in the surrounding late responding tissues and if their α/β value is not larger that of prostate tumours it could even lead to a decrease in the therapeutic ratio. Therefore, the important question is whether the α/β value for the prostate is lower than the α/β values of the surrounding late responding tissues at risk. This paper reviews the clinical and experimental data regarding the radiobiological differential that might exist between prostate tumours and the late normal tissues around them. Several prospective hypofractionated trials that have been initiated recently in order to determine the α/β value or the range of values that describe the fractionation response of prostate tumours are also reviewed. In spite of several confounding factors that interfere with the derivation of a precise value, it seems that most data support a trend towards lower α/β values for prostate tumours than for rectum or bladder. Daşu, A. (2007). *Clinical Oncology* 19, 289–301

Key words: Alpha/beta, clinical trials, hypofractionation, normal tissue, prostate, radiobiological analysis

Introduction

There is increased interest in the clinically relevant α/β value for prostate tumours in light of the potential advantages of hypofractionated treatments. Such treatment, with a few large radiation fractions, will lead to fewer treatment sessions, which might be convenient from the point of view of both the patient (who will face a shorter treatment) and the economy of the radiotherapy department (which might be able to treat more patients in the same time period and therefore shorten the waiting lists). Furthermore, hypofractionated treatments of prostate carcinomas might also have the potential of an increased therapeutic ratio if it is confirmed that these tumours do have a smaller α/β value than the late responding normal tissues at risk. This paper will critically review the published clinical and experimental data regarding the radiobiological differential that might or might not exist between prostate tumours and the late normal tissues around them. Relevant publications reporting the derivation of the α/β value for prostate tumours or the outcome of radiotherapy in patients with prostate carcinoma were retrieved using standardised queries (e.g. 'prostate alpha/beta', 'prostate radiotherapy', 'prostate hypofractionation', etc.). These were supplemented with references from the relevant papers, as well as by additional papers identified in the personal database of the author.

Radiobiological Analysis of Clinical and Experimental Data

An α/β value as low as 1.5 Gy (95% confidence interval 0.8–2.2 Gy) was first presented in detail by Brenner and Hall [1], based on a review of 367 patients from two centres, some being treated at a low dose rate with I-125 and the others with high dose rate external beams at 1.8 or 2.0 Gy per fraction. This first report was disputed [2,3] and was the starting point for many discussions about the prospects of hypofractionation for the treatment of prostate tumours [4–17]. The proposals of various groups are summarised in Table 1 and in Fig. 1.

A radiobiological analysis carried out by Fowler *et al.* [6] on data from 1471 patients from 10 centres treated with low

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Table 1 — Radiobiological analysis of clinical data

Reference	α/β value (Gy)	95% confidence interval	Patient number	Conditions	Assumptions
[1]	1.5	0.8—2.2 Gy	367 patients from two centres	Comparison between high dose rate external beam radiotherapy at 1.8 or 2.0 Gy per fraction and low dose rate brachytherapy with permanent I-125 implants	No proliferation, no parameter heterogeneity, unity relative biological effectiveness for the brachytherapy radiation
[2]	4.96	4.1—5.6 Gy	367 patients from two centres	Reanalysis of the data used in [1]	Partial heterogeneity, no proliferation, unity relative biological effectiveness for the brachytherapy radiation
[3]	2.1		367 patients from two centres	Reanalysis of the data used in [1]	Full heterogeneity, no proliferation, unity relative biological effectiveness for the brachytherapy radiation
[6]	1.49	1.25—1.76 Gy	1471 patients from 10 centres	Comparison between high dose rate external beam radiotherapy and low dose rate brachytherapy with permanent I-125 and P-103 implants	No proliferation, no parameter heterogeneity, unity relative biological effectiveness for the brachytherapy radiation
[8]	0.97—27				Non-unity relative biological effectiveness for the brachytherapy radiation, no proliferation, no parameter heterogeneity
[36]	0.52				1.75 relative biological effectiveness for the brachytherapy radiation, no proliferation, no parameter heterogeneity
[37]	0.89—1.1				Ranges of values for the relative biological effectiveness for the brachytherapy radiation, no proliferation, no parameter heterogeneity
[10]	1.2	0.03—4.1 Gy	192 patients from one centre	Comparison between high dose rate external beam radiotherapy and high dose rate brachytherapy	No proliferation, no parameter heterogeneity, unity relative biological effectiveness for the brachytherapy radiation
[23]	3.1	1.7—4.5 Gy	1471 patients from 10 centres	Comparison between high dose rate external beam radiotherapy and low dose rate brachytherapy with permanent I-125 and P-103 implants	Very fast onset of accelerated proliferation, no parameter heterogeneity, unity relative biological effectiveness for the brachytherapy radiation
[25]	3.1—3.9		1471 patients from 10 centres	Comparison between high dose rate external beam radiotherapy and low dose rate brachytherapy with permanent I-125 and P-103 implants	Very fast onset of accelerated proliferation, no parameter heterogeneity, unity relative biological effectiveness for the brachytherapy radiation
[38]	8.4	1.2—15.5 Gy		*In vitro* irradiation of cells	
[47]	1.33		705 patients from one centre	Comparison between hypofractionated and conventional treatments with external beam irradiation	
[35]	1.1—6.3			*In vitro* irradiation of cells	