Is the α/β Ratio for Prostate Tumours Really Low and Does It Vary with the Level of Risk at Diagnosis?

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Abstract. *Aim: To answer the questions: Is the α/β ratio (radiosensitivity to size of dose-per-fraction) really low enough to justify using a few large dose fractions instead of the traditional many small doses? Does this parameter vary with prognostic risk factors? Methods and Materials: Three large statistical overviews are critiqued, with results for 5,000, 6,000 and 14,000 patients with prostate carcinoma, respectively. Results: These major analyses agree in finding the average α/β ratio to be less than 2 Gy: 1.55, (95% confidence interval=0.46-4.52), 1.4 (0.9-2.2), and the third analysis 1.7 (1.4-2.2) by the ASTRO and 1.6 (1.2-2.2) by Phoenix criteria. All agree that α/β values do not vary significantly with the low, intermediate, high and "all- included" risk factors. Conclusion: The high sensitivity to dose-per-fraction is an intrinsic property of prostate carcinomas and this supports the use of hypo-fractionation to increase the therapeutic gain for these tumours with dose-volume modelling to reduce the risk of late complications in rectum and bladder.*

Radiation therapy for prostate cancer has been facing a potential paradigm shift since 1999. That is when Brenner and Hall (1) pointed-out that the biological properties of prostate tumours were more like those of very slowly-proliferating late-responding normal tissues (that lead to late complications in normal tissues), than they were to the much more rapidly re-populating carcinomas of most other types of human tumours. This unusual reversal of the relative sensitivities to dose-fraction size, of tumours *versus* late-responding normal tissues at-risk in conventional radiotherapy, suggested that a few large fractions – hypo-fractionation – might be advantageous for these specific types of tumour (with very low α/β ratios). This is a totally different strategy from the hard-learnt "many-and-small-fractions" strategies that were successful for other types of tumours (which had higher α/β ratios near 10 Gy). Such a great change of perspective was so opposite to conventional habits and instincts of safe practice in radiotherapy that instead of welcoming the opportunity to investigate hypo-fractionation, as a possible opportunity to give more biological damage to prostate tumours (only) and less damage to the normal tissues at-risk by using slightly lower total doses and many fewer fractions, almost 15 years of controversy have arisen.

Although many individual datasets, including some well-conducted randomized clinical trials, have brought in arguments into the debate, these were generally small and consequently a different strategic thinking has been slow to be adopted. This is because the traditional 2-Gy fractionation has also been gradually improved by restricting the volumes of normal rectum and bladder irradiated. "If it ain't broke, don't mend it" went the refrain to stay with 2-Gy fractions-only, although the costs of achieving such high-tech treatments like intensity-modulated radiation therapy (IMRT) for conventional fractionation have risen greatly. But even the best 2-Gy fractions schedules have been found to stop at a total dose of about 80-82 Gy. The higher dose claimed for one schedule totalling 86 Gy was for doses per fraction of 1.8 Gy instead of 2 Gy, and was therefore reduced in iso-effect by 4%, compared with 2 Gy fractions, assuming a low α/β ratio of 2 or 3 Gy. The search for how to safely give a greater biological damage to tumours with higher degrees of risk continues.

This short article aims to review recent clinical data and answer two central questions in the debate on the radiosensitivity to size of dose-per-fraction of prostate tumours: Is the α/β ratio really low enough to justify using a few large dose fractions instead of the traditional many small doses? Does this parameter vary with prognostic risk factors?

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Materials and Methods

The real biological variations between individual patients and tumours have meant that wide confidence intervals have prevented conclusions drawn from clinical trials with only a hundred or two hundred patients being statistically significant. That is why large clinical analyses of many thousands of patients are essential before we can obtain reasonable precision for the biological coefficients representing radiosensitivity, alpha and beta, and their ratio α/β which represents the sensitivity to the size of individual dose fractions. Standardized queries in the literature and the personal reference database of the Authors have identified three large reviews published within the past three years reporting on the results from 5,000, 6,000 and 14,000 patients respectively (2-4). The analyses have been carried out assuming standard linear quadratic (LQ) modelling following the usual Barendsen (5) and Fowler (6) rationisations of the LQ modelling. These reviews will be discussed from the perspective of the two central questions in the debate on the relevant α/β ratio of prostate tumours.

Results

The first large-scale review was analyzed in Australia by Proust-Lima and the team led by Scott Williams (2). They found α/β=1.55 Gy [95% confidence interval (CI)=0.46-4.52 Gy], from an individual re-analysis of 5,093 patients from six internationally well-known institutions. Their conclusion was that this confirms a low and more precise α/β ratio than any other published before, "robust to adjustment of the linear mixed model". It may be noted however that their upper confidence limit was still not below the value of 3 Gy, which is usually taken as being the lowest value to represent the slowly-repopulating normal tissues at risk. Does this mean that it is not quite safe to recommend hypo-fractionation for treatments of prostate radiotherapy?

Scott Williams *et al*. had previously suggested that α/β increased with the diagnostic risk level (7), and this suggestion had disturbed many scientists working on this topic because it was a biologically rational concept, but no such changes in α/β ratio were found in the review by Proust-Lima *et al*. (2). Their change of opinion on this point is clearly stated but qualified in the usual way: "these results should be interpreted with caution, as with any modelling exercise... Prospective studies continue to be highly anticipated in this regard."

The second large review was by the well-known team led by Jolyon Hendry at Manchester, UK (3), who has also carried-out pioneering analyses on head and neck data, and was largely responsible for the recommendations in 1996 from the UK Royal College of Radiology to correct for "days missed" in standard treatments, before the use of prostate specific antigen (PSA) and the new thinking about prostate radiotherapy began in 1999. This analysis of outcome in 5,969 patients in seven international institutional datasets, analyzed as individual patients (3), gave a low result for α/β of 1.8 Gy (95% CI=0.9-2.4 Gy), in their preliminary calculation published as an abstract (8) at the 2009 Annual Meeting of the American Society for Radiation Oncology (ASTRO) (8). In this case, the upper 95% confidence limit was clearly below 3 Gy. Some hypo-fractionated results were included in this analysis but no brachytherapy schedules were included, which should improve resolution when done. The α/β ratio was found to be slightly, but not significantly, higher for high-risk patients than for low risk ones, thus contradicting Scott Williams' first suggestion that it was significant. This abstract was then updated by a subsequent full article (3) reporting α/β=1.4 Gy (95% CI=0.9-2.2 Gy), accepted December 2010 by the International Journal of Radiation Oncology Biology Physics, but not published until January 2012. It was still found that α/β does not significantly change with the diagnostic risk level. The article states the conclusion that "The overall α/β value was consistently low, unaffected by AD deprivation [androgen deprivation], and lower than the appropriate values for late normal-tissue morbidity. Hence the fractionation sensitivity differential (tumour/normal tissue) favours the use of hypo-fractionated radiotherapy schedules for all risk groups, which is also very beneficial logistically in limited-resource settings." It can hardly be stated more clearly than that!

The third large review summarized here (4) is a solid confirmation of the previous statement, by two of the three present authors. It is a major update of the review which was published 5 years ago (9) and has been well-referred to. In this large review 11,330 patients were treated conventionally and 2,838 with hypo-fractionated schedules. Five-year biochemical recurrence-free survival results were used, with separate calculations for both the ASTRO and the Phoenix criteria, as published by the original authors. The clinically reported results were-reanalyzed by a standard LQ logistic equation to examine which α/β ratio predicted the clinical result recorded, for each arm of each dataset respectively. Calculations were performed for low, intermediate, high and mixed (all) risk patients. For these four groups of risk patients, the derived α/β values were 0.6, 1.2, 1.1 and 1.7 Gy for ASTRO and 1.0, 1.3, 1.7 and 1.6 Gy for Phoenix, respectively. They were all low and not significantly different from each other. The analysis also yielded differences between the positions of the dose-response curves corresponding to the ASTRO and Phoenix data, suggesting that biochemical failure criteria should not be mixed in analyses. Furthermore, there seems to be an inverse relationship between the gamma slope of the curves and the size of the analysed populations – in agreement with a previously-identified correlation between slope and interpatient heterogeneity (10) – indicating that it is unlikely that a single curve slope would be applicable to all studies, in contrast with other proposals (11).

The conclusion of this analysis, which now answers the question being asked five years ago (9), was that high fractionation sensitivity is an intrinsic property of prostate carcinomas and this supports the development – with appropriate care by modelling for complications, including the avoidance of too short overall times (12) – of hypo-fractionation to increase the therapeutic gain for these tumours, with dose-volume modelling to reduce the risk of late complications in rectum and bladder, as described in recent publications (12,13).

Conflicts of Interest

All the Authors declare they have no conflict of interests.

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