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Methodology

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Half-times of irradiation recovery in accelerated partialbreast irradiation: Incomplete recovery as a potentially dangerous enhancer of radiation damage

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Abstract

Purpose: To compare clinical results from accelerated partial breast irradiation with predictions from different half-times of recovery of radiation damage. *Method:* Three published results of excessive late complications led to an editorial [1] which was a "wake up call" to the possible hazards of fractions spaced close together such as two fractions of 3.85 Gy a day on five consecutive days. These results are re-examined here using linear quadratic modelling with mono-exponential and bi-exponential recovery kinetics. *Results:* Although clinical results showed rather high proportions of severe complications, only in one of the three studies discussed in reference [1] complications were severe enough to cause it to be terminated. Since then other studies with the same doses have reported acceptable results. However, none of these complication rates are predicted to be tolerable, if mono-exponential kinetics with a single T ½ of ~4 hours is assumed. *Conclusions:* Better matches to clinical results can be found by assuming bi-exponential recovery with 50%-50% components of 0.3 hand 4 h, and α/β = 3 Gy, for late complications. There is continuing need for data from more clinical results, especially concerning various tumour types.

Keywords: breast irradiation; radiation damage; mono-exponential kinetics; bi-exponential kinetics

Introduction

In 2010 a warning was published [1] that accelerated radiotherapy schedules using two fractions a day for only five days to irradiate partial breast could lead to a high risk of late complications. This warning was accompanied by a calculation of an excessively high dose, due to unrecovered dose, that assumed only a single half-time of recovery (T½) as long as 4.4 h. However a wide discrepancy from the quoted clinical results in their own editorial [1] invites a reconsideration of their specific model of T½= 4.4 h monotonic exponential recovery in accelerated partial breast irradiation.

It has been established [2] that recovery does not have unique half-times but they increase with the increase in interfraction interval. This proves the presence of more than one recovery rate. It is obvious if a shorter component of recovery of significantly less than 4.4 h is present, then the problem of incomplete recovery will be less important. This paper explores that possibility.

A recent thorough review of all aspects of radiation recovery drew attention to the bi-exponential nature of recovery in late normal-tissue complications [3]. It is obvious that the presence of a significant proportion of rapid recovery would reduce the disadvantage of incomplete recovery on schedules with two fractions a day. Some results from accelerated partial breast irradiation allow this to be demonstrated particularly clearly.

Bentzen et al. reported evidence for long half-times of recovery: 4.9 h for laryngeal oedema, 3.8 h for skin telangiectasia, and 4.4 h for subcutaneous fibrosis, so that an average T½ of four hours appeared to be a reasonable starting assumption for their warning calculations [4]. These calculations must be questioned because no shorter intervals between fractions than 6 hours were available in the CHART schedule.

Fowler et al. summarized animal and some human evidence for two different rates of repair of radiation damage (or possibly multiple rates) in their Table 1 in

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reference [5]. Ling et al. in their comprehensive review of incomplete repair accepted that two components for normal-tissue complications were most likely, but found no evidence for more than one T½ in tumour data [3].

Table 1 Clinical reports of accelerated partial breast irradiation (APBI) [1]

References	*Follow-up and 95% confidence limit (yr)*	*Reported fibrosis (moderate/severe) (%)*	*Cosmesis (poor/fair) (%)*	*Comment*
Hepel et al. [11]	1.3 (0.5-3.6)	25 (15-38)	18 (10-30)	"Remarkably high"
Jagsi et al. [12]	2.5 (1.5-3.7)	9 (2-24)	21 (9-28)	"Stopped"
Chen et al. [13]	4.2 (1.3-8.3)	9 (4-16)	13 (6-22)	"Keep volume small"

Materials and methods

Standard Linear Quadratic (LQ) formalism is used throughout [6-10] and the recovery models are either mono- or bi-exponential [5, 8].

First, not the entire dose delivered is capable of recovery in the LQ formulation. It is generally assumed that recovery from radiation damage occurs in the two-hit or multi-hit component of the damage, which is not the linear single-hit part of the damage [6-10]. The proportion of each dose fraction that is recoverable is shown in figure 1. This diagram is important because it shows how the recovery proportion rises to high values for the larger doses per fraction.

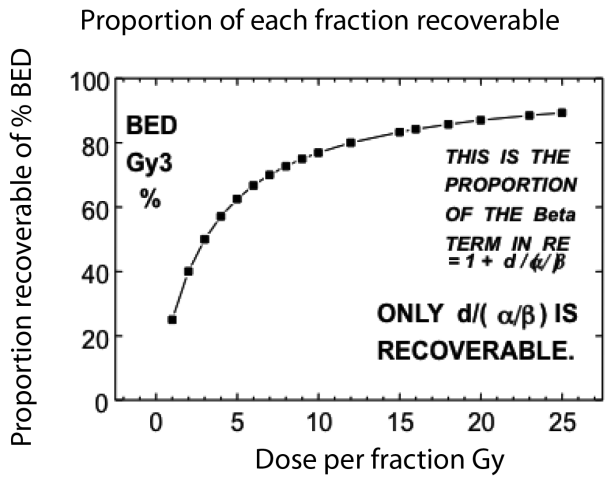

Figure 1 Barendsen-type Biologically Effective Dose (BED) is defined as Total Dose x Relative Effectiveness (RE), where RE =1 + $\frac{d}{(\alpha/\beta)}$ where d is the dose-per-fraction, and α and β are the linear and quadratic coefficients of $\log_e$ cell kill per Gy and per Gy2 respectively [8,9]. In the defining expression RE it is only the recoverable term $\frac{d}{(\alpha/\beta)}$ that can change with time; so its proportion of the whole BED is plotted in figure 1 as an index of how large is the proportion of recoverable damage as late complications in normal tissues (α/β = 3 Gy), as a function of dose-per-fraction. It rises above 50% for doses per fraction greater than 3 Gy, and as you see, it becomes very large for stereotactic body radiation therapy or ablative doses in radiotherapy.

Next, evidence is summarised for the presence of a range of short half-times of 0.1 -1 h (Figure 2), and for longer half-times of 1.5 to 7 h (Figure 3), in various animal data and one human data set. All these references are tabulated in the reference [5]. The bi-exponential half-times have often been summarised and used as 0.3 h and 4 h [5].

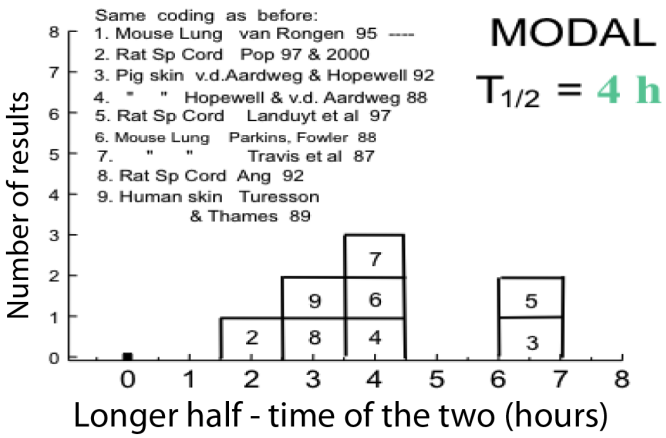

Figure 2 The longer of the two components [5]

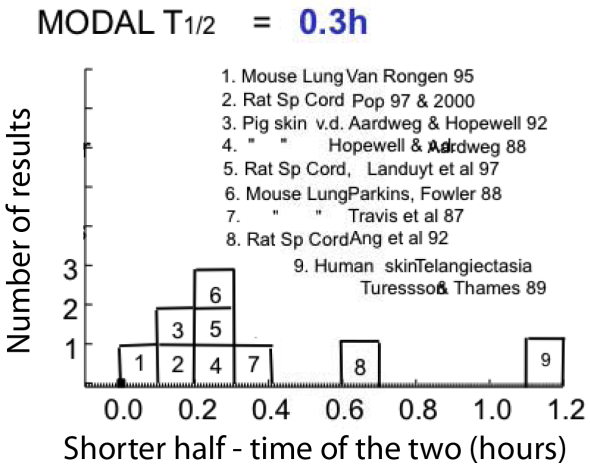

Figure 3 The shorter components of the concomitant pairs (Table 1 and reference 5).

Results

Referring to figure 1,3.85 Gy given twice a day, gives a proportion of 0.56 in the recovery "beta" term, so that each day's treatment of 2F × 3.85 Gy at six hours apart leads to a nominal overdose of 36% × 0.56 = 20.2% of the delivered dose. That is, 10.1% for each of the two fractions and therefore a nominal overdose of 10.1% for the whole prescribed dose, because the same dose is administered for every day of treatment.

But there is overnight decay occurring too, not falling to a negligible dose until the weekend (two days of no irradiation). Each 24 h interval leads to 2.52% nominal overdose, plus 0.91% for the 18h interval from the second fraction per day, giving 3.43% nominal overdose for each treatment day. These overnight increments accumulate on successive nights, giving $(1.0343)^4$ from Monday night to Friday morning, when the week's cycle is terminated by the Friday afternoon dose. A total of 14.4% nominal overdose has to be added to the 10.1% daytime overdose described above for the whole week.

Together, these two parts of the day yield 1.101 × 1.144 = 1.2595 x prescribed dose; a nominal overdose of 26%, assuming T½ = 4 h only. How does this compare with the clinical observations reported from accelerated partial breast irradiation by Bentzen and Yarnold [1]? This 26% extra predicted dose causes the biologically equivalent total dose in 2-Gy fractions (EQD) of the 38.5 Gy treatments to be increased from a modest 52 Gy (in 2 Gy equivalent fractions) to a much greater 65 Gy. In reference [1] T½ of 4.4 h was used, predicting an even higher EQD of 68 Gy, so we agree with the estimate in reported [1]. This gave a predicted incidence of moderate-to-severe skin reactions of 75-82% [1], which is certainly excessive. Fortunately the clinical results observed were nowhere near this level (Table 1 in reference 1), and that is the point of this paper.

Although the last two reports [11, 12] cited by Bentzen and Yarnold [1] had shorter follow-up, that was the opposite of reassuring, but moderate-to-severe reactions were nowhere near the 75-82% stated in reference [1], when the T½ was assumed to be ~ 4 h only. It is not simply a coincidence that real 13% result in the third study [13] cited by Bentzen and Yarnold [1] is half that of the modelled, when T½ was similarly assumed to be ~4 h 26% nominal overdose described above; it is what we would expect if the real T½ was half of the assumed T½ of ~4 h, that is, bi-exponential with the other component much smaller than ~4 h.

The trend is to support the concept from the many *in situ* experiments in Table 1 of reference [4] that approximately half of recovery does indeed have a T½ of ~4h, and the remainder has much shorter T½. This is illustrated in the following block diagrams where the modal value of each experimental *in situ* recovery result reported is plotted from the Table 1 in reference [4]: the longer of the two components in the present figure 2 and the shorter ones in figure 3. The two distributions of modal values at 4 h and 0.3 h are more clearly shown here than in the referenced tabulation [5]. It is the presence of the shorter ones too that the present paper is all about.

The concept of the two distributions with modal half-times of 4 h and 0.3 h, possibly approximating more complex spectra of many half-times [13, 14], is then obvious. It is clear from Figure 2 that a long component of recovery is present in all the animal tissues tested and one human tissue, as indeed reported by Bentzen et al. [4]. Figure 3 shows the simultaneous shorter component in each tissue, plotted from the experimental results cited in reference [4]. The proportions of long versus short half-times were between 40% to 60% (or 60% to 40%) of each component, which we approximate here by assuming 50% to 50%.

It is a logical step to propose that a similar pair of T½ values is present in other normal tissues and this assumption brings the dangers of late damage into much closer correspondence with the clinical observations than assuming that the only T½ is the long one of about 4 h in the 2F/day schedules made in [1]. Wang et al. [16] have proposed many times that the only T½ present is ~0.3 h – 0.8 h, and this is equally incorrect. The statements made in [1] that "changes in skin appearance would be expected to be 75%-82% compared with 31% after 50 Gy in 2-Gy fractions" were obtained by the assumption of a single T½ of ~4 h only. We simply find that the inclusion of the shorter vales of T½ in both the daily pair of doses, and to a less extent the overnight pair, decrease the 26% overdose predicted by Bentzen and Yarnold [1], to just 13%. It is unlikely to be a coincidence that a 13% incidence of poor-to-fair cosmesis is the clinical result reported for the only set of patients that has adequate follow-up of 4.2 years (Table 1, in reference 1).

We are then ready to look harder at the problem of extra radiation damage that may occur in other schedules that have been proposed and used for other cancer sites. Table 2 summarises the present author's results for two fractions per day from accelerated partial breast irradiation schedules and for other bi-exponential schedules used to treat head and neck cancers. The bottom line of Table 2 contain my best estimates, which might be tested until any better results for T½ values are obtained. Better T½ values should be sought but are challenging to obtain.

Table 2 Incomplete recovery with two fractions a day (2F/day) of various doses per fraction: Two doses delivered daily with an interval of 6 h between fractions, assumed bi-exponential recovery with 50% recoverable damage with a halftime (T½) of 0.3 h and the remaining 50% with a halftime of 4 h.

Dose/ fraction	*3.85 Gy*	*2 Gy*	*1.6 Gy*	*1.2 Gy*
Predicted overdose from incomplete recovery for 2F/d and a/b = 3 Gy	13%	9%	7.9%	6.4%

Discussion

Berrang et al. [16] from Canada reported 3-year results of their multicentre trial with a range of doses per fraction from 3.5 Gy to 3.85 Gy twice a day in 5 days for ductal carcinoma *in situ* or node-negative margins, less than 3 cm in diameter. They reported grade-1 toxicities in most normal tissues at 3 years follow-up.

Even more convincing is the report of Bourgier et al. [17] who treated between October 2007 and September 2008 25 breast cancer patients in an IMRT conformal trial, using 10 hypofractionated doses of 4 Gy each fraction, given twice daily in 5 days. They delivered an "en face" electron field plus two mini-tangents. Toxicities were assessed at 1, 2 and 6 months and then at 6 months intervals. After a median follow-up of 12 months, only 1 patient had a significant moderate field contracture (grade 2). They limited the clinical target volumes (CTV) to a mean of 13.9 cc and median of 15.1 cc, and the planning treatment volume (PTV) to 117-113 cc. (CTV includes the tumour volume and margins round it. PTV includes margins around CTV to allow for patient's movement, setup error, and organ movement). Bourgier et al. [17] delivered mean doses of 41.8 Gy (range 41-42.4 Gy) to PTV. The arithmetic for the single T½ of 4 h with 40 Gy instead of 38.5 Gy shows an incomplete recovery prediction of 1.271, instead of 1.259 as here, which is not a clinically significantly different conclusion from that in the present paper.

Conclusion

The conclusion was that this level of dose was acceptable, and that no patients had yet failed. Later results, as they mature, might comment on the relative frequency of the shorter versus longer components in either normal tissues or the tumours. Table 2 lists the present accelerated partial breast irradiation schedule and three commonly used 2F/day head and neck radiotherapy schedules together with the estimations of the excess percentage-dose assuming bi-exponential recovery of 50% with T½= 4 h and 50% with T½= 0.3 h. It is not surprising that several attempts to use 2F x 2 Gy per day have been tried and all have been given up as too damaging for clinical late effects from Jackson et al. in Vancouver [19] to Bourhis et al. in Paris [20]: they reported 9% extra dose -- larger dose errors than many protocols would allow anyway. In contrast the prediction of 7.6% extra dose for 2F × 1.6 Gy per day did not result in complaints from Fu et al. [21], Trotti et al. [22], Leborgne et al. [23], or the originator of the 2F × 1.6 Gy per day schedules, Wang [24]. It is unlikely that 2F/d schedules employing doses per fraction less than 1.6 per fraction would present problems of excess late complications due to incomplete recovery, but the large doses used in stereotactic body radiation therapy should indeed be checked, using the two half-times described here until any more definitive values for T½ can beobtained.

Acknowledgement

I should like to thank Dr. Soeren Bentzen for originally doing the calculation of the discrepant doses in the 2 ×3.85 Gy/d schedules of APBI that made this demonstration possible of the better matching to clinical results that bi-exponential T½ can provide.

Conflict of interest

The author wish to express that he has no conflict of interest.

References

[1] Bentzen SM, Yarnold JR (2010) Reports of unexpected late side effects of accelerated partial breast irradiation--radiobiological considerations. Int J Radiat Oncol Biol Phys 77:969–973.

[2] van den Aardweg GJ, Hopewell JW (1992) The kinetics of repair for sublethal radiation-induced damage in the pig epidermis: an interpretation based on a fast and a slow component of repair. Radiother Oncol 23:94–104.

[3] Ling CC, Gerweck LE, Zaider M, Yorke E (2010) Dose-rate effects in external beam radiotherapy redux. Radiother Oncol 95:261–268.

[4] Bentzen SM, Saunders MI, Dische S (1999) Repair halftimes estimated from observations of treatment-related morbidity after CHART or conventional radiotherapy in head and neck cancer. Radiother Oncol 53:219–26.

[5] Fowler JF, Welsh JS, Howard SP (2004) Loss of biological effect in prolonged fraction delivery. Int J Radiat Oncol Biol Phys 59:242–249.

[6] Lea DE, Catcheside DG (1942) The mechanism of the induction by radiation of chromosome aberrations in Tradescantia. J Genet 44:216–245.

[7] Curtis SB (1986) Lethal and potentially lethal lesions induced by radiation--a unified repair model. Radiat Res 106:252–270.

[8] Dale RG (1986) The application of the linear-quadratic model to fractionated radiotherapy when there is incomplete normal tissue recovery between fractions, and possible implications for treatments involving multiple fractions per day. Br J Radiol 59:919–927.

[9] Fowler JF (1989) The linear–quadratic formula and progress in fractionated radiotherapy. Review Article. Br J Radiol 62:679–694.

[10] Barendsen GW (1982) Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys 8:1981–1997.

[11] Hepel JT, Tokita M, MacAusland SG, Evans SB, Hiatt JR, et al. (2009) Toxicity of three-dimensional conformal radiotherapy for accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 75:1290–1296.

[12] Jagsi R, Ben-David MA, Moran JM, Marsh RB, Griffith KA, et al. (2010) Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial-breast irradiation. Int J Radiat Oncol Biol Phys 76:71–78.

[13] Chen PY, Wallace M, Mitchell C, Grills I, Kestin L, et al. (2010) Four-year efficacy, cosmesis, and toxicity using three-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 76:991–997.

[14] Dale RG, Fowler JF, Jones B (1999) A new incomplete-repair model based on a 'reciprocal-time' pattern of sublethal damage repair. Acta Oncol 38:919–929.

[15] Fowler JF (2002) Repair between dose fractions: a simpler method of analyzing and reporting apparently biexponential repair. Radiat Res 158:141–151.

[16] Wang JZ, Huang Z, Lo SS, Yuh WT, Mayr NA (2010) A generalized linear-quadratic model for radiosurgery, stereotactic body radiation therapy, and high-dose rate brachytherapy. Sci Transl Med 2:39ra48.

[17] Berrang TS, Olivotto I, Kim DH, Nichol A, Cho BC, et al. (2011) Three–year outcomes of a Canadian multicenter study of accelerated partial breast irradiation using conformal radiation therapy. Int J Radiat Oncol Biol Phys 81:1220–1227.

[18] Bourgier C, Pichenot C, Verstraet R, El Nemr M, Heymann S, et al. (2011) Early side effects of three-dimensional conformal external

beam accelerated partial breast irradiation to a total dose of 40 Gy in one week (a phase II trial). Int J Radiat Oncol Biol Phys 81:1228–1235.

[19] Jackson SM, Weir LM, Hay JH, Tsang VH, Durham JS (1997) A randomised trial of accelerated versus conventional radiotherapy in head and neck cancer. Radiother Oncol 43:39–46.

[20] Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, et al. (2006) Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 368:843–854.

[21] Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, et al. (2000) A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 48:7–16.

[22] Trotti A, Fu KK, Pajak TF, Jones CU, Spencer SA, et al. (2005) Long term outcomes of RTOG 90-03: A comparison of hyperfractionation radiotherapy for head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 63(Suppl 1): S70–S71.

[23] Leborgne F, Leborgne JH, Fowler J, Zubizarreta E, Mezzera J (2001) Accelerated hyperfractionated irradiation for advanced head and neck cancer: effect of shortening the median treatment duration by 13 days. Head Neck 23:661–668.

[24] Wang CC (1988) Local control of oropharyngeal carcinoma after two accelerated hyperfractionation radiation therapy schemes. Int J Radiat Oncol Biol Phys 14:1143–1146.