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Analysis of a large number of clinical studies for breast cancer radiotherapy: estimation of radiobiological parameters for treatment planning

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Abstract

Numerous studies of early-stage breast cancer treated with breast conserving surgery (BCS) and radiotherapy (RT) have been published in recent years. Both external beam radiotherapy (EBRT) and/or brachytherapy (BT) with different fractionation schemes are currently used. The present RT practice is largely based on empirical experience and it lacks a reliable modelling tool to compare different RT modalities or to design new treatment strategies. The purpose of this work is to derive a plausible set of radiobiological parameters that can be used for RT treatment planning. The derivation is based on existing clinical data and is consistent with the analysis of a large number of published clinical studies on early-stage breast cancer.

A large number of published clinical studies on the treatment of early breast cancer with BCS plus RT (including whole breast EBRT with or without a boost to the tumour bed, whole breast EBRT alone, brachytherapy alone) and RT alone are compiled and analysed. The linear quadratic (LQ) model is used in the analysis. Three of these clinical studies are selected to derive a plausible set of LQ parameters. The potential doubling time is set *a priori* in the derivation according to *in vitro* measurements from the literature. The impact of considering lower or higher T_{pot} is investigated. The effects of inhomogeneous dose distributions are considered using clinically representative dose volume histograms. The derived LQ parameters are used to compare a large number of clinical studies using different regimes (e.g., RT modality and/or different fractionation schemes with different prescribed dose) in order to validate their applicability. The values of the equivalent uniform dose (EUD) and biologically effective dose (BED) are used as a common metric to compare the biological effectiveness of each treatment regime.

We have obtained a plausible set of radiobiological parameters for breast cancer: $\alpha = 0.3\ \mathrm{Gy}^{-1}$, $\alpha/\beta = 10$ Gy and sub-lethal damage repair time $T_{\mathrm{rep}} = 1$ h (mono-exponential behaviour is assumed). This set of parameters

is consistent with *in vitro* experiments and with previously reported analyses. Using this set of parameters, we have found that most of the studies, using BCS plus whole breast RT and a boost to the tumour bed, have EUDs ranging from 60–70 Gy. No correlation is found between BED and the local recurrence rate. The treatments of BCS plus brachytherapy alone have a wide range of EUD (30–50 Gy), which is significantly lower than the treatments with whole breast EBRT plus a boost of the tumour bed. The studies with different fractionation schemes for whole breast EBRT also show a significant variation of EUD. Carefully designed clinical studies with large numbers of patients are required to determine clinically the relative effectiveness of these treatment variations.

The derived LQ parameter set based on clinical data is consistent with *in vitro* experiments and previous studies. As demonstrated in the present work, these radiobiological parameters can be potentially useful in radiotherapy treatment planning for early breast cancer, e.g., in comparing biological effectiveness of different radiotherapy modalities, different fractionation schemes and in designing new treatment strategies.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Breast cancer is the most common cancer in women. In the last two decades it has been demonstrated by various randomized studies that the treatment of early-stage breast cancer with BCS plus radiotherapy yields an equivalent outcome to mastectomy (Fisher *et al* 2002, Veronesi *et al* 2002, Horiguchi *et al* 2002, van Dongen *et al* 2000, Early Breast Cancer Trialists' Collaborative Group 1995). Typically, after conservative surgery, the entire breast is treated with photon EBRT of 45–50 Gy in 1.8–2 Gy fractions over 5 weeks. Frequently, interstitial brachytherapy or electron EBRT has been used to boost the tumour excision site with 10–20 Gy. Recently, brachytherapy alone using either low dose rate (LDR) or high dose rate (HDR) for selected patients was introduced in clinic (Baglan *et al* 2001, King *et al* 2000, Clarke *et al* 1994, Cionini *et al* 1993, Vicini *et al* 2001, Magee *et al* 1996, Polgar *et al* 2002, Perera *et al* 1997, Fentiman *et al* 1996, Wazer *et al* 2002). Even though it is clear that conservative surgery alone yields poorer results than BCS plus 50 Gy of radiotherapy (Fisher *et al* 2002, Holli *et al* 2001, Liljegren *et al* 2000, Clark *et al* 1996, Forrest *et al* 1996), the necessity of the boost, the delivery RT modality and radiation dose remain a subject of controversy and practices vary widely among institutions.

Brachytherapy was probably the first form of conformal therapy, and its use in cancer therapy is still increasing (Cumberlin *et al* 2002). Clinical practice has evolved empirically from the pioneering days of continuous LDR radium therapy. Dose reporting by combining the absolute doses from EBRT and BT algebraically without considering the difference in biological effects may be misleading. In addition, it is imperative to consider these biological effects in order to take full advantages of each RT modality. EBRT and BT offer distinct technical, biological and social advantages in the management of breast cancer. However, despite many decades of effort, the clinical practice of multi-modality RT as well as brachytherapy alone has been based on empirical experience and lacks scientific consistency. This inconsistency exists in part because of the current lack of appropriate biological modelling tools needed to analyse and compare the effectiveness of alternate and combined RT modalities.

The purpose of this work is to derive a plausible set of radiobiological parameters that can be used to compare different RT modalities and to design new treatment strategies for breast cancer. A large number of published clinical studies utilizing different RT modalities, different fractionation and different dose are compiled and analysed using the linear quadratic (LQ) model. We will first derive a plausible set of LQ parameters for breast cancer based on three selected clinical studies. The predictive power of the LQ model and the associated radiobiological parameters for other EBRT and brachytherapy treatment modalities are then tested using published data from other clinical studies. The biological equivalent dose (BED) and the equivalent uniform dose (EUD) are used as a common metric to compare the biological effectiveness of different RT modalities.

2. Methods

2.1. LQ model with repopulation

The analysis is done using the LQ model for cell survival probability with repopulation (Dale *et al* 1985, 1989),

$$S = \exp(-(\alpha + \beta d)D + \gamma T_t) \tag{1}$$

where D is the total dose, d is the dose per fraction for external beam, $\gamma = \ln(2)/T_{\text{pot}}$, T_t is the treatment time and T_{pot} is the potential doubling time. In general, a different expression for the exponent is needed for the case of LDR brachytherapy. However, for the particular characteristics of the temporary implants of ^{192}Ir or ^{125}I used for breast brachytherapy, some approximations are appropriate. The dose rate can be considered constant, since the implants are typically left in the patient for one or a few days, much less than the half-life of iridium-192 (72 days) and iodine-125 (60 days). Also, since the treatment time is much longer than typical repair times in tumours and normal cells, equation (1) is applicable if we define an effective dose per fraction of the form (Dale *et al* 1985)

$$d_{\text{br}} = \frac{2RT_{\text{rep}}}{\ln(2)} \tag{2}$$

where R is the dose rate and T_{rep} is the characteristic repair time of the irradiated cells. This approximation is reasonable for the purposes of the present calculation. It is important to keep in mind that the leading correction to equation (2) goes as $T_{\text{rep}}/(\ln(2)T_t)$, so for long repair times and short treatment times (high dose rates) equation (2) becomes inaccurate and the full expression of the dose protraction factor needs to be considered.

For the tumour control probability we use the Poissonian form

$$\text{TCP} = \exp(-NS) \tag{3}$$

where N is the clonogenic cell number.

The concept of biologically effective dose (BED) is used to compare treatment modalities (Fowler *et al* 1989):

$$\text{BED} = D(1 + d/(\alpha/\beta)) - \gamma T_t/\alpha. \tag{4}$$

2.2. Derivation of a plausible LQ parameter set

We select three studies from the literature to derive a plausible set of LQ parameters for breast cancer. Even though none of these individual studies is sufficient to rigorously derive the LQ parameters, the information can be combined to derive a plausible set of α, $r \equiv \alpha/\beta$, and the repair time T_{rep}. Clinical studies indicate that repopulation effects can impact on treatment

outcome. A higher risk of recurrence has been reported in several studies (Clarke *et al* 1985, Dubray *et al* 1992, Van Limbergen *et al* 1990) when the treatment time is increased. Clarke *et al* (1985) found a significant increase in the relative risk (RR) of local recurrence when the interval between the excisional biopsy and the initiation of RT was larger than 7 weeks. Dubray *et al* (1992) found that the probability of recurrence increased with longer intervals between external irradiation and brachytherapy. Van Limbergen *et al* (1990) also found a lower local control for longer treatment times. In the current work, the repopulation rate is set *a priori* to a value consistent with results reported by Haustermans *et al* (1998), who measured the potential doubling time T_{pot} for 35 breast tumours and found a median of 15 days (range 4–74). A similar value of $T_{\mathrm{pot}} = 14$ days is recommended by Hall (2000) for breast tumours. The impact of considering lower or higher T_{pot} is investigated.

The first study selected for analysis is a randomized trial reported by Fourquet *et al* (1995). They compared two different modalities for delivery of a boost to the tumour after whole breast irradiation of 58 Gy in 1.8 Gy fractions: an iridium-192 implant of 0.64 Gy h^{-1} median dose rate and a cobalt-60 external irradiation boost. The prescribed boost dose was $D_{\mathrm{boost}} = 20$ Gy for both trial arms. The Paris system was used for the dose prescription of the iridium implants. The 255 patients had breast tumours ranging from 3 to 7 cm in diameter treated with radiotherapy only and were selected on the basis of partial or total response to the initial whole breast irradiation. After a median follow up of 8 years they found that the iridium boost was more effective with local control $\mathrm{TCP_{Ir}} = 0.76$ versus $\mathrm{TCP_{Co}} = 0.61$ for the ^{60}Co boost. We apply equation (3) for the TCP of iridium and ^{60}Co, and we take the natural logarithm. The ratio of the logarithms of TCP is the same as the ratio of surviving fractions (the parameter N cancels out). Taking the natural logarithm of this ratio, we obtain

$$-\ln\left(\frac{\ln \mathrm{TCP_{Ir}}}{\ln \mathrm{TCP_{Co}}}\right) = D_{\mathrm{boost}}[(\alpha + \beta d_{\mathrm{br}}) - (\alpha + \beta 1.8\ \mathrm{Gy})] + \frac{\ln(2)\Delta T_t}{T_{\mathrm{pot}}} \tag{5}$$

where ΔT_t is the difference in treatment time between the iridium and the cobalt boost. Since there is no specific information about the treatment times in Fourquet *et al* (1995), we estimated this difference to be 12 days, since typically the Co boost in 1.8–2 Gy fractions takes 12–15 days and the Ir boost can last 1–2 days. Setting $T_{\mathrm{pot}} = 15$ days (Haustermans *et al* 1998) we get

$$0.59 = \beta D_{\mathrm{boost}}(d_{\mathrm{br}} - 1.8\ \mathrm{Gy}) + 0.55. \tag{6}$$

The left-hand side of equation (6) is a measure of the increased TCP in the iridium arm of the trial (it would be zero if both arms had the same local control) and its numerical value is almost equal to the repopulation term on the right-hand side. With these considerations, equation (6) implies that the increased local control in the iridium arm can be almost completely accounted for by the gain in treatment time with the LDR implants versus the external beam.

The second study, by Mazeron *et al* (1991), considered the influence of dose rate on local control for patients with breast carcinoma treated also with radiotherapy alone. The patients received 45 Gy of external beam radiation in the whole breast plus a tumour boost of 37 Gy from the ^{192}Ir implant. The 340 tumours were divided retrospectively into three groups according to dose rate: 0.32–0.49 Gy h^{-1} (I), 0.5–0.59 Gy h^{-1} (II) and 0.6–0.9 Gy h^{-1} (III). The actuarial local control rates at 15 years were 60%, 72% and 84% respectively (estimated by the Kaplan Meier method after 7.7 years of median follow up). Using equations (1)–(3) and neglecting the repopulation effect (the difference in treatment times is much smaller than T_{pot}) we find

$$\ln\left(\frac{\ln \mathrm{TCP}_i}{\ln \mathrm{TCP}_j}\right) = \beta(d_i - d_j)D_{\mathrm{boost}}. \tag{7}$$

where d_i are the effective doses per fraction for each dose rate group. Two independent equations for the product βT_{rep} can be obtained with the data of Mazeron *et al* (1991) by selecting the dose rate in the middle of each interval to calculate d_i and using $D_{\mathrm{boost}} = 37$ Gy ($i = \mathrm{I}$, $j = \mathrm{II}$ and $i = \mathrm{II}, j = \mathrm{III}$):

$$0.0297\ \mathrm{Gy}^{-2}\ \mathrm{h} = \beta T_{\mathrm{rep}} \tag{8a}$$

$$0.0295\ \mathrm{Gy}^{-2}\ \mathrm{h} = \beta T_{\mathrm{rep}}. \tag{8b}$$

The fact that both numbers are so similar implies that the data of Mazeron *et al* (1991) are consistent with the LQ model with Poissonian tumour control probability.

In the LQ model, the variation in TCP due to the different delivery methods (brachytherapy versus teletherapy or brachytherapy with different dose rates) is manifested in the quadratic (β) term, as is evident from equations (5) and (7). Using these equations it is possible to determine the values of β and T_{rep}. To obtain the value of α another piece of information is needed.

The third dataset we consider is a recent retrospective study by Resch *et al* (2002) of 410 patients treated with BCS with whole breast radiotherapy plus an ^{192}Ir boost to the tumour bed. Two different brachytherapy modalities were used: an LDR boost of 20 Gy with 0.7 Gy h^{-1} median dose rate and an HDR single fraction boost of 9.7 Gy. The LDR group had a whole breast mean dose of 48.4 Gy and the HDR group received a mean dose of 52.3 Gy. The true recurrences (TR) rates were the same in both modalities after a median follow up of 8.7 years, and therefore we consider the corresponding BEDs as equivalent (the term with the difference in treatment time is neglected since 1–2 days time is much smaller than the potential doubling time T_{pot} of 15 days),

$$48.4(\alpha + \beta 1.8) + 20(\alpha + \beta d_{\mathrm{br}}) = 52.3(\alpha + \beta 1.8) + 9.7(\alpha + \beta 9.7) \tag{9}$$

where d_{br} is the effective dose per fraction defined in equation (2). Using this definition and rearranging we get

$$6.4\ \mathrm{Gy}\,\alpha + 40.4\ \frac{\mathrm{Gy}^2}{\mathrm{h}}\,\beta T_{\mathrm{rep}} = 6.4\ \mathrm{Gy}\,\alpha + 1.2 = 101.1\ \mathrm{Gy}^2\beta \tag{10}$$

where we have used $\beta T_{\mathrm{rep}} \approx 0.03\ \mathrm{Gy}^{-2}$ h from equation (8). Equation (10) implies that $0 < T_{\mathrm{rep}} < 2.5$ h and $0 < r < 16$ Gy, in order for r and T_{rep} to be positive. A set of LQ parameters that is consistent with the selected clinical data was then derived based on equations (5)–(10). The details of how these equations were used to obtain the resulting parameters appear in section 3.

2.3. Consideration of inhomogeneous dose distributions

It is well known that the dose distributions for external beam treatments are very different from those for brachytherapy. In order to study the impact of the volume effect in the derivation of the LQ parameters it is necessary to consider the dose distributions for the patients in the studies that we selected. Alternatively, a representative dose volume histogram averaged over a large number of patients should be used. Since this information is not available, we consider a dose–volume histogram (DVH) representative of each treatment modality (figure 1) available in the literature. The DVH for external beam boost is a typical external beam DVH with the dose in the target volume being the prescribed dose plus or minus 10%. The brachytherapy DVH is taken from Vicini *et al* (2001), in a study of brachytherapy boost after BCS. Vicini *et al* (2001) performed a CT scan after the iridium implant placement and

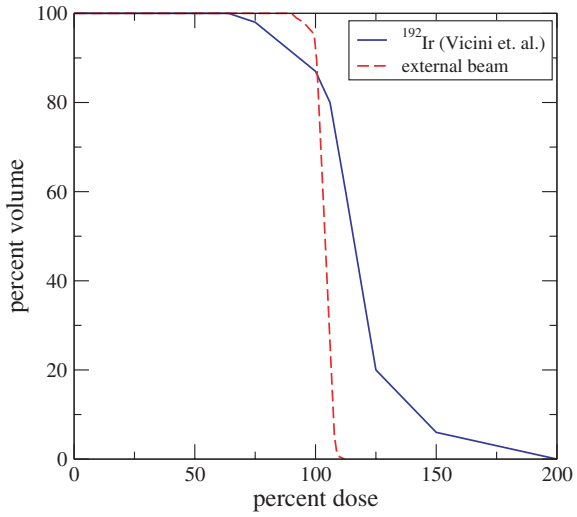

Figure 1. Cumulative DVHs for external beam and brachytherapy implants with ^{192}Ir wires from Vicini *et al* (2001). EUD is calculated based on these two DVHs.

analysed the coverage of the lumpectomy cavity, the target volume (lumpectomy cavity plus 1 cm margin) and the entire breast for patients treated with BCS and radiotherapy. The DVH we selected is the median (of five patients) cumulative DVH for the lumpectomy cavity, taken from figure 3 of Vicini *et al* (2001), where significant interpatient variation of the DVH is apparent. Even though we selected a DVH from an implant of the tumour bed after BCS, it is also representative of a DVH for the tumour volume in the case where radiotherapy is the only treatment.

The volume analysis depends dramatically on the choice of the DVH for brachytherapy, in particular, on the size of the cold spot. Therefore we have chosen to provide a qualitative description of the impact that volume effects can have in the calculation. For a quantitative analysis, the individual patients DVH for the particular studies that we are using would be necessary.

Several efforts have been reported to account for the volume effects in the tumour and normal tissue control probabilities. The concept of equivalent uniform dose (EUD) (Niemierko 1997) was introduced to reduce the dose distribution to a single dose level that produces the same biological effect. A more general concept, the biologically effective uniform dose (Mavroidis *et al* 2001) allows us to consider different radiobiological models and multiple target volumes and critical structures. We use the concept of EUD and follow Wang *et al* to define

$$\mathrm{EUD} = \frac{-\ln\left\{\sum_i v_i \exp[-(\alpha + \beta d_i)D_i + \gamma T_t]\right\}}{\alpha + \beta 1.8 - \gamma 1.4/1.8} \tag{11}$$

where v_i is the fraction of the target volume irradiated with dose D_i and d_i is the dose per fraction for external beam or the effective dose per fraction for brachytherapy as defined in equation (2). The dose per fraction in each dose bin d_i can be calculated for an external beam as $d_i = D_i d/D$ and for the temporary brachytherapy implants using equation (2) with dose rate $R_i = RD_i/D$. With this definition EUD is expressed in terms of the uniform dose delivered in 1.8 Gy daily fractions that yields the same TCP as the given dose distribution.

Treatment times for external beam with 1.8 Gy fractions were set to $T_t = D \times 1.4/1.8$ (days) and for brachytherapy implants they were calculated as the ratio of the prescribed dose to the median dose rate $T_t = D/R$.

Including the effect of non-homogeneous dose distributions in the analysis of Fourquet *et al* (1995) data, equation (6) becomes

$$0.59 = (\alpha + \beta 1.8 - \gamma 1.4/1.8)(\mathrm{EUD_{Ir}} - \mathrm{EUD_{Co}}). \tag{12}$$

The impact of volume effects for Resch *et al* data can be considered by changing equation (9) to

$$\mathrm{EUD}^{\mathrm{eb}}_{\mathrm{LDR}} + \mathrm{EUD}^{\mathrm{boost}}_{\mathrm{LDR}} - \mathrm{EUD}^{\mathrm{eb}}_{\mathrm{HDR}} - \mathrm{EUD}^{\mathrm{boost}}_{\mathrm{HDR}} \equiv \Delta\mathrm{EUD} = 0 \tag{13}$$

where the superscript eb stands for external beam.

Similarly, equations (8a) and (8b) considering the effect of the DVH for brachytherapy in the Mazeron *et al* study can be rewritten as

$$0.63 = (\alpha + \beta 1.8 - \gamma 1.4/1.8)[\mathrm{EUD}(R_{\mathrm{I}}) - \mathrm{EUD}(R_{\mathrm{II}})] \tag{14a}$$

$$0.44 = (\alpha + \beta 1.8 - \gamma 1.4/1.8)[\mathrm{EUD}(R_{\mathrm{II}}) - \mathrm{EUD}(R_{\mathrm{III}})] \tag{14b}$$

In general, EUD depends on the LQ parameters as well as on the DVH in a complicated way, so it is difficult to find an analytic solution. In this work, we considered the impacts of dose inhomogeneity and volume effects graphically, that is in a qualitative way, based on equations (11)–(14).

2.4. Analysis of multi-institutional clinical results

To validate the applicability of the derived LQ parameters, we have analysed a large number of published clinical results that employ single and/or multi-mode radiotherapy for early-stage breast cancer after BCS. The LQ parameters derived presently were used to compare the biological effectiveness of these treatments. These selected studies are analysed and summarized in three tables. Table 1 compiles the studies using BCS plus whole breast RT and a boost to the tumour bed. Table 2 summarizes current experimental radiotherapy for the tumour bed alone (not whole breast) after BCS. Table 3 deals with the use of alternative fractionation schemes in the RT treatment of the whole breast after BCS. The values of BED and EUD were used to measure the biological effectiveness of these treatments.

3. Results and discussion

3.1. Derivation of LQ parameters

Based on the combined results (equations (6)–(8)) from the three selected clinical studies Fourquet *et al* (1995), Mazeron *et al* (1991) and Resch *et al* (2002), we have derived a plausible set of LQ parameters. Cancelling the numerical factors in equation (6) and using equation (2) we obtain

$$d_{\mathrm{br}} \approx 1.8\ \mathrm{Gy} \Rightarrow T_{\mathrm{rep}} \approx 1\ \mathrm{h}. \tag{15}$$

That is, from the study by Fourquet *et al* (1995), assuming a doubling time of 15 days, a repair time of 1 h is implied. Replacing the value of T_{rep} in equations (8) and (10) we get $\beta \approx 0.03\ \mathrm{Gy}^{-2}$ and $\alpha \approx 0.3\ \mathrm{Gy}^{-1}$. Thus, $r = \alpha/\beta \approx 10$ Gy. These LQ parameters are consistent with previously reported results. For example, the value of $\alpha \approx 0.3\ \mathrm{Gy}^{-1}$ agrees with *in vitro* experiments by Ruiz de Almodóvar *et al* (1994). For five different

breast cancer cell lines they reported α values ranging from 0.1 to 0.6 Gy^{-1}. Brenner (1993) obtained $\alpha = 0.06$ Gy^{-1} when analysing clinical data for breast cancer from Arriagada *et al* (1985). In this analysis, $\alpha/\beta = 10$ Gy was used along with other assumptions. Brenner (1993) speculated that if the analysis was performed using a distribution of α values for the population of patients, a larger value would be obtained. Webb (1994) verified this speculation by doing the analysis assuming a Gaussian distribution. Webb (1994) obtained $\alpha = 0.27 - 0.325$ Gy^{-1} as the average of the distribution with clonogenic cell densities 10^7–10^9 cells/cm^3. Using the currently derived parameters ($\alpha = 0.3$ Gy^{-1}, $r = 10$ Gy, $T_{rep} = 1$ h) in equations (1) and (3), a mean tumour volume of 100 cm^3 (derived from the tumour sizes reported by Fourquet *et al* (1995)), and a treatment time of 7 weeks, we get a clonogenic cell density $\rho \approx 4 \times 10^8$ cells/cm^3. In addition, using the same mean tumour volume with the currently derived parameters for the data reported by Mazeron *et al* (1995) (treatment time of 11 weeks), we get $\rho \approx 3 \times 10^8$ cells/cm^3. These clonogenic cell densities are consistent with Webb's (1994) analysis.

To study the variation of the parameters if a different potential doubling time is selected, we considered the wide range of T_{pot} (4 to 74 days as reported by Haustermans *et al* (1998)) and calculated the LQ parameters for the extreme values of T_{pot}. The repair time, which is the least sensitive to variations of T_{pot}, was found to range from 0.4 h to 1.7 h. The α/β ratio varies from 13 Gy to 5 Gy. The largest variation is seen in the individual values of α and β: α varies a whole order of magnitude, from 0.98 to 0.08 Gy^{-1}, while β ranges fourfold from 0.075 to 0.017 Gy^{-2}. Interestingly, the ratio $\gamma/\alpha = \ln(2)/\alpha T_{pot}$, which represents the increase in the dose to compensate one day's extension of the treatment time if β was zero, is almost constant for all the possible values of doubling time, going from 0.18 to 0.12 Gy/day. This value is quite a bit smaller than that found for head and neck cancers of 0.5–0.7 Gy/day, which are more rapidly growing tumours with T_{pot} of about 4 days.

It is important to keep in mind that several factors can affect treatment outcome that are not considered in this derivation, like the presence of hypoxic cells, intra-tumour and inter-tumour variations of the parameters, inhomogeneous density of clonogens, etc. The present estimation of the parameters should be viewed as a guideline to estimate tumour response and compare the effectiveness of different treatment strategies. It is also useful for the design of new treatment modalities, although any new schedule or treatment scheme should be properly tested in appropriate clinical trials.

3.2. Effects of dose inhomogeneity

In this section we present the impact of dose inhomogeneity and volume effects in the derivation of the LQ parameters based on the EUD calculation. It is found that EUD depends both on the LQ parameters and DVH. For an external beam treatment, the numerical value of EUD is very close to the prescribed dose if it has the same fraction size. For example, for the 20 Gy boost delivered in 1.8 Gy fractions, EUD varies from 20.5 to 20.6 Gy for α/β ranging from 4 to 12 Gy and α values from 0.1 to 0.5 Gy^{-1}. For brachytherapy, EUD also depends on the repair time T_{rep}. The results reported by Fourquet *et al* (1995), Mazeron *et al* (1991) and Resch *et al* (2002), are represented by equations (12) to (14) using the concept of EUD. As described below, these equations (equations (12)–(14)) can be solved graphically and a set of LQ parameters can be obtained. As before, we set the doubling time *a priori* to be 15 days (Haustermans *et al* 1998).

In figure 2, the right-hand side of equation (12) is plotted as a function of α for different values of the r and T_{rep}. The intersection with the horizontal line at 0.59 represents a solution to the equation. For example, for a repair time of 0.5 h an α value from 0.125 to 0.175 Gy^{-1}

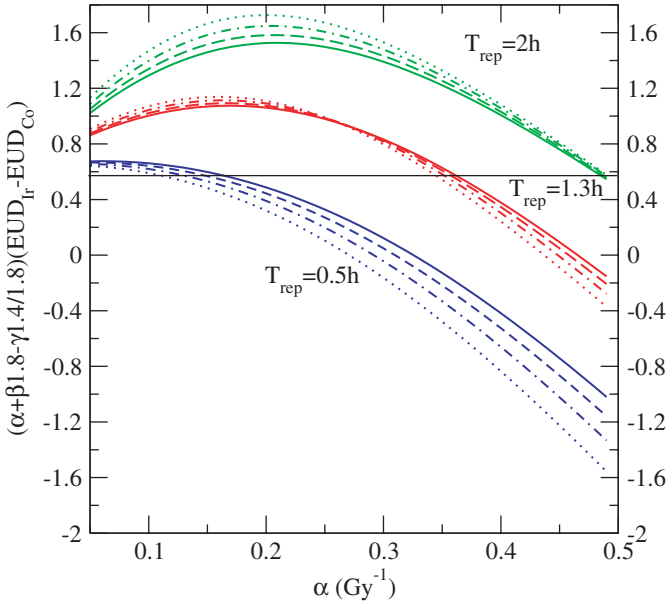

Figure 2. Graphic solution of equation (12) as a function of α. The intersection of the curves with the horizontal line at 0.59 represents a solution for different values of repair time and α/β ratio. Solid line: $\alpha/\beta = 10$ Gy, dashed line: $\alpha/\beta = 9$ Gy, dotted-dashed line: $\alpha/\beta = 8$ Gy, dotted line: $\alpha/\beta = 7$ Gy.

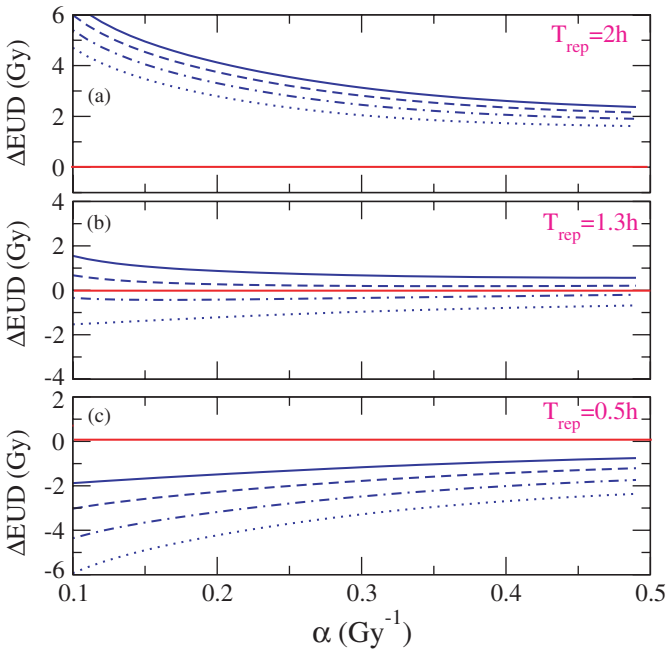

Figure 3. Graphic solution of equation (13) as a function of α. The intersection with the horizontal line at zero represents a solution. When the repair time is 1.3 h the solution is approximately independent of α and indicates an α/β ratio close to 8.5 Gy. Line convention as in figure 2.

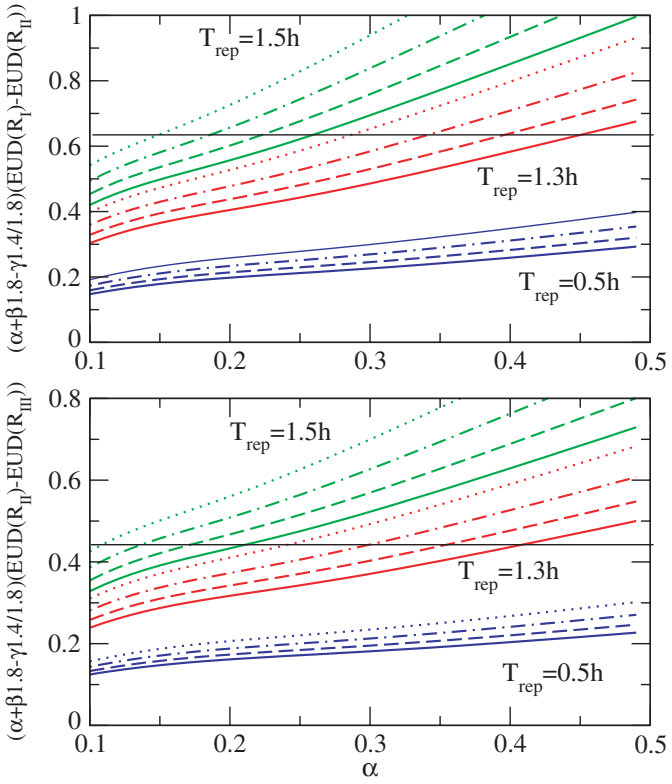

Figure 4. Graphic solution of equations (14a) (top) and (14b) (bottom). Line convention as in figure 2. For an α/β ratio of 8.5 Gy and a repair time of 1.3 h, a value of $\alpha \approx 0.3$ Gy^{-1} is obtained.

is obtained for r in the range 7–10 Gy. For longer repair times, larger values of α with little dependence on r are obtained.

The graphic solution of equation (13) is presented in figure 3 where we plot the left-hand side versus α for different values of the ratio r. The intersection with the x-axis gives the solution of $\Delta\text{EUD} = 0$. It is evident from figure 3(a) that for longer repair times only values of r smaller than 7 will intersect the zero line, while for smaller values of T_{rep}, large values of r are needed to find a solution. For $T_{\text{rep}} = 1.3$ h, the solution is nearly independent of α and it implies $r \approx 8.5$ Gy.

In figure 4 the solution of equations (14a) and (14b) is presented. Both equations give similar solutions, again showing that the data are consistent with the model.

From figures 2, 3 and 4 we find that if we select $T_{\text{rep}} = 1.3$ h, from figure 3 we get $r \approx 8.5$ Gy and a value of $\alpha \approx 0.35$ Gy^{-1} consistent with figures 2 and 4. Larger values of T_{rep} imply larger values of α in figure 2 but smaller in figure 4 and the opposite is true for smaller values of T_{rep}. Therefore, there is no global solution for other repair times.

In summary, $T_{\text{rep}} = 1.3$ h and $\alpha = 0.35$ Gy^{-1}, $r = 8.5$ Gy is a solution consistent with the volume analysis of all three datasets. These values are very similar to those obtained using the prescribed doses, with no consideration of the dose distribution. We conclude that a representative DVH for brachytherapy treatments has a small impact in the value of the parameters obtained from the analysis of these three studies. The repair time and α come out a little larger, while the α/β ratio is a little smaller.

Because the qualitative consideration of dose inhomogeneity and volume effects does not significantly alter the LQ parameters, we have used the LQ parameter set derived based on the prescribed dose in the following analyses.

3.3. Comparison of multi-institutional and multi-mode radiotherapy

In the last couple of decades it has been demonstrated by various studies (Fisher *et al* 2002, Veronesi *et al* 2002, Horiguchi *et al* 2002, van Dongen *et al* 2000, Early Breast Cancer Trialists' Collaborative Group 1995) that the treatment of early-stage breast cancer with BCS plus radiotherapy yields equivalent results to mastectomy. As early detection increases, more cancers are diagnosed in the early stage and BCS treatments play a central role in the management of breast cancer. In this section we summarize the information of a representative group of clinical studies for early breast cancer treated with BCS plus whole breast irradiation and a boost to the tumour bed (we consider studies published within the last 10 years). We use the LQ parameter set derived in section 3.1, $r \approx 10$ Gy, $\alpha \approx 0.3$ Gy^{-1}, $T_{\mathrm{rep}} \approx 1$ h to compare the different modalities. The result is presented in table 1, where we list the reference, the number of tumours treated, median follow up, whole breast radiation dose, boost dose and RT modality, actuarial rates of local recurrences, EUD and BED (calculated neglecting the repopulation effect, see below). For the whole breast and boost, the dose listed is the mean or median dose if available or the average between the maximum and minimum values if only the range is reported. The actuarial recurrence rates are presented for each modality separately whenever possible, otherwise the overall rates are listed. When T1 and T2 rates are reported the average weighted by the number of patients is listed.

Frazier *et al* (2001) reports a slightly lower recurrence rate for external beam (the average of photons and electrons is 7%) than for brachytherapy (the average of ^{192}Ir and ^{125}I is 9%) while Perez *et al* (1996), Mansfield *et al* (1995) and Deore *et al* (1993) find that the recurrence rate for electrons is slightly higher. Touboul *et al* (1999) only report the overall rates and find after a univariate analysis that boost type did not influence the recurrence rates. In all cases the authors report no statistically significant difference in the local control between different boost modalities.

The fact that the external beam and brachytherapy boosts appear equivalent in these studies seems contrary to the result of Fourquet *et al* (1995), where the brachytherapy boost was more effective. However, in the study by Fourquet *et al* (1995) the tumours were treated with radiation only and the control rates were in the 0.6–0.75 range. In the case of BCS plus radiotherapy treatments, the control rates are very high because the surgery removes most of the tumour burden, making differences in local control very hard to detect. Furthermore, if the gain in local control in the Fourquet *et al* (1995) study can indeed be attributed to the reduction in treatment time as we have postulated, such effect can be washed out in studies for early breast cancer because the treatment times and schedules vary wildly at different institutions. For example, Touboul *et al* (1999) report a median interval from external beam to iridium boost of 25 days while the median interval to the electron boost was 5 days. On the other hand, Mansfield *et al* (1995) who pioneered the perioperative iridium implants, delivered the brachytherapy boost 4–6 h after surgery and the whole breast irradiation started 10–14 days after that. In their case the electron boost was delivered after the whole breast irradiation which started 10–14 days after surgery. Deo *et al* (2001) had a similar schedule to Mansfield *et al* (1995). However, in Perez *et al* (1996), 29 patients had the brachytherapy boost perioperative while 90 patients had it after the external beam treatment. Resch *et al* (2002) delivered the boost before EBRT for some patients, during or after EBRT for others. Other studies, like Moreno *et al* (2000), do not mention the schedule at all. The BED and EUD

Table 1. Summary of radiotherapy treatments with whole breast irradiation plus a boost to the tumour bed after BCS.

Reference	Number of tumours	EBRT (Gy)	Boost (Gy)	Modality	Local recurrences (%)	Follow up (years)	EUD (Gy)	BED ($Gy_{10,1h}$)
LDR and electrons								
Frazier *et al* (2001)	122	47.5 (45–50)	12.5 (10–15)	^{125}I 0.625 Gy h^{-1}	5% (13 y)	9.7	62	71
	194	47.5 (45–50)	12.5 (10–15)	^{192}Ir 0.625 Gy h^{-1}	15% (13 y)	9.7	62	71
	232	47.5 (45–50)	12.5 (10–15)	el	6.0% (13 y)	9.7	61	71
	15	47.5 (45–50)	12.5 (10–15)	ph	17% (13 y)	9.7	61	71
Touboul *et al* (1999)	298	45 (45–50)	15 (15–25)	^{192}Ir 0.52 Gy h^{-1}	7% (5 y), 14% (10 y)	7	64	73
	225	45 (40–50)	15 (5–20)	el @ 2.5 Gy/fr	same	7	63	75
Perez *et al* (1996)	119	49 (48–50)	15 (10–20)	^{192}Ir 0.45 Gy h^{-1}	7% (10 y)	5.6	65	75
	493	49 (48–50)	15 (10–20)	el	10% (10 y)	5.6	65	76
	89	49 (48–50)	0	–	13% (10 y)	5.6	50	58
Mansfield *et al* (1995)	654	45	20	^{192}Ir 0.45 Gy h^{-1}	7% (5y), 12% (10 y)	3.3	65	76
	416	45	20	el	8% (5 y), 19% (10 y)	3.3	66	77
Deore *et al* (1993)	15	45	22.5 (15–30)	el @ 2.5 Gy/fr	27%	4.6	71	81
	17	45	22.5 (15–30)	^{192}Ir 0.2–0.29 Gy h^{-1}	24%	4.7	67	77
	144	45	22.5 (15–30)	^{192}Ir 0.3–0.49 Gy h^{-1}	5%	4.7	68	78
	69	45	22.5 (15–30)	^{192}Ir 0.5–0.69 Gy h^{-1}	9%	4.7	69	79
	27	45	22.5 (15–30)	^{192}Ir 0.7–0.99 Gy h^{-1}	7%	4.7	70	81
	13	45	22.5 (15–30)	^{192}Ir 1–1.6 Gy h^{-1}	8%	4.7	72	84
LDR and HDR								
Resch *et al* (2002)	136 (HR)*	48.4	20	LDR 0.7 Gy h^{-1}	2% (5 y), 4% (10 y)	8.7	70	81
	274 (HR)*	52.3	9.7	HDR	same	8.7	70	81
LDR								
Deo *et al* (2001)	51	45	17.5 (15–20)	^{192}Ir 0.550 Gy h^{-1} (0.5–0.6)	0% (<2%)	3.5	64	73
Moreno *et al* (2000)	530	48.7 (42–52)	16.8 (10–27)	^{192}Ir 0.655 Gy h^{-1} (0.3–1.2)	5% (5 y) 8% (7 y)	3.3	68	78
Formenti *et al* (1995)	100	47.5 (45–50)	>20	^{192}Ir 0.47 Gy h^{-1} (0.2–0.8)	5% (5 y), 7% (10 y)	7	69	79
Krishnan *et al* (1993)	250	47.5 (45–50)	17.5 (15–20)	^{192}Ir 0.4 Gy h^{-1}	7% (11 y)	5.75	66	76
Boyages *et al* (1992)	131	50	30	^{192}Ir 0.45 Gy h^{-1} (0.4–0.5)	4% (5 y), 13% (10 y)	6.9	79	94
HDR								
Reitsaner *et al* (2002)	160	53.5 (51–56)	9	Intraop,ph	0%	1.2	70	80
Manning *et al* (2000)	18 (HR)*	50	15	^{192}Ir 6 × 2.5 Gy	0% (<5%)	4.17	68	79
Hammer *et al* (1994)	190	47.5 (45–50)	10	^{192}Ir HDR 85 Gy h^{-1}	4.3% (5 y) 7% (8 y)	5.1	66	76
	22	47.5 (45–50)	10	^{192}Ir 2 × 5 Gy	4% (5 y)	5.1	62	71
Hennequin *et al* (1999)	108	45	10	^{192}Ir 2 × 5 Gy	5% (5 y)	3.75	60	68
Boost versus no boost								
Bartelink *et al* (2001)	2661	50 (2)	16	el, ph or ^{192}Ir 0.42 Gy h^{-1}	4.3% (5 y)	5.1	68	78–79
	2657	50 (2)	0	–	7.3% (5 y)	5.1	52	60
Romestaing *et al* (1997)	521	50 (2.5)	10	el @ 2.5 Gy/fr	3.6% (5 y)	5	66	75
	503	50 (2.5)	0	–	4.5% (5 y)	5	54	63

* HR = High risk.

listed in table 1 are calculated by setting $\gamma = 0$, since we do not have accurate information about treatment times and they vary widely among studies. The EUDs in table 1 are very close to the prescribed doses. The studies that compare brachytherapy versus external beam boost all have very similar EUDs for both arms, which is consistent with the statistically equivalent local recurrence rates. In figure 5 we present a plot of the actuarial rates of local recurrence at 5 and 10 years versus BED.

Most of the BEDs lie between 70 and 80 $Gy_{10,1h}$ and the recurrence rates between 7 and 14 per cent at 10 years and 2 and 8 per cent at 5 years. At first sight, there is no obvious correlation between BED and the recurrence rates. Kendall's τ test indicates a weak

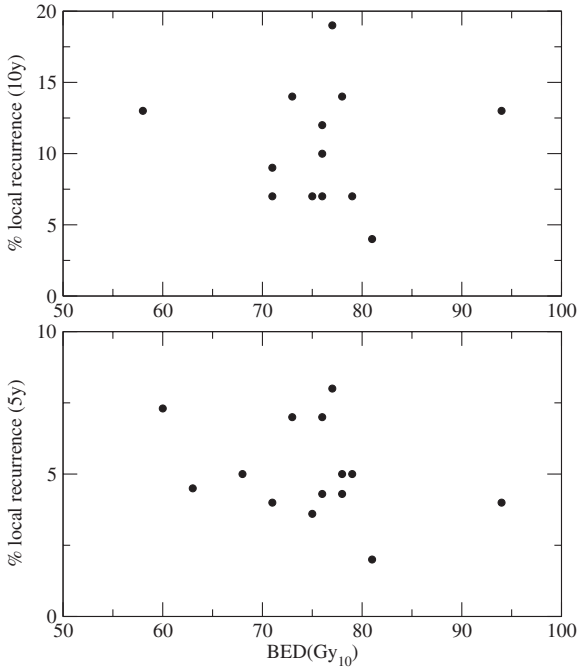

Figure 5. Local recurrence rates at 10 and 5 years respectively versus BED from table 1. There is very poor correlation between the BED and the local recurrence rates.

correlation for the 5-year data ($\tau = -0.24$, $p = 0.23$) and even weaker for the 10-year data ($\tau = -0.028$, $p = 0.89$). The absence of correlation is not surprising at this high level of control, very large numbers of patients are needed to detect small differences in local control. For example, to determine the value of boost of the tumour bed after whole breast irradiation, Bartelink *et al* (2001) used more than five thousand patients to detect a difference of 4% in local control between two arms, one with boost (BED = 69 Gy_{10}) and one without boost (BED = 51 Gy_{10}). In Romestaing *et al* (1997) with 1024 patients a difference of less than 1% was detected in the control rates at 5 years for a 12 Gy_{10} difference in BED. The other studies in table 1 have a much smaller variation of BED and number of patients. Furthermore, even though we have used estimates of actuarial rates of local control, the follow up time is different among these studies and this may have an impact on the estimated rates.

A variety of factors can also influence the treatment outcome, such as volume of tumour and nodal involvement, radiation of axilla, supraclavicular nodes and intermammary chain, age, menopausal status, type of surgery, excision margins, hormone response, adjuvant chemo and hormone therapy and the presence of extensive intraductal component. These important factors that are not considered in the present calculations may have great impact on the recurrence rate and may vary in the patient populations of different studies.

Regarding the dose-rate effect, Deore *et al* (1993) calculated local control rates for groups of patients with different dose rates in the iridium implant. They found an increase in recurrences for the group with the lowest dose rate (0.2–0.3 Gy h^{-1}) but no significant difference in local control among the other groups. This seems to contradict the result of Mazeron *et al* (1991) where clear differences were found among groups with different dose rates. However, the difference in EUD for Deore *et al* (1993) is 5 Gy from the lowest to the highest dose rate. At such a high level of control, 5 Gy may be too small to generate any

difference in control rates, as explained above, particularly since there are very few patients in each group. Mazeron *et al* (1991) treated patients with radiotherapy only (no surgery). Their control rates were in the range of 0.6–0.8 and the corresponding EUDs were between 78 and 82 Gy. In the steep part of the TCP sigmoidal curve, such small differences in EUD can have a significant impact on the TCP. Even though the differences in control rates for dose-rate variations are small, it is important to keep in mind that they do exist and have a radiobiological effect for both tumour and normal tissue. From equations (1) and (2), it can be seen that a change in dose rate from 0.2 Gy h^{-1} to 1.6 Gy h^{-1} is roughly equivalent to changing the effective dose per fraction by a factor of 8 (from 0.6 Gy to 4.6 Gy). Such changes may have their biggest impact in normal tissue response. Deore *et al* (1993) did detect a significant increase in complications in the highest dose-rate groups.

Regardless of some controversial issues such as whether the boost after whole breast irradiation is needed or under what circumstances it is needed, it is clear that BCS plus radiotherapy treatments yield high control rates with acceptable levels of complications. However, the long schedule (5–7 weeks) of radiotherapy after surgery can discourage some women from choosing BCS. Additionally, a reduction in treatment time could yield a better radiobiological effect and lower costs. Currently, there are studies being conducted to determine alternative schedules of radiotherapy after BCS that may yield equivalent results to conventional treatment. One option is the use of radiation to the tumour bed only, as opposed to the whole breast. Another option is the search for an alternative whole breast irradiation scheme, with higher dose per fraction and shorter treatment time. The analysis of these studies is presented in the next two sections.

3.4. Analysis of brachytherapy-alone treatments

Since a good number of the local recurrences occur at or near the site of the original tumour, it has been speculated that only a local radiation treatment (as opposed to whole breast irradiation) may be sufficient to control the tumour (e.g. Kuske 1999). At present, local treatment only is the subject of several trials for LDR and HDR brachytherapy, external beam and intraoperative techniques. These studies are presented in table 2, which is an updated version of the one reported by Baglan *et al* (2001). The values of EUD and BED calculated presently for these studies vary widely. Because follow up times for most of these studies are still short, it is difficult to arrive at any definite conclusions. The two studies with the longest follow up times have rather large recurrence rates although their corresponding BEDs are the largest. However, these studies have been criticized for their patient selection criteria (Baglan 2001, Kuske 1999) The Hungarian group (Polgar *et al* 2002) has a 4.4% recurrence rate in almost 5 years of median follow up.

The BEDs from table 2 are significantly smaller than those of table 1 (most of them range from 40 to 60 $Gy_{10,0.1}$, as was pointed out in a comment by Dale *et al* (1996)). However, in this case it is also important to take into account the time factor for a more meaningful comparison. The studies in table 2 have short total treatment times. For example, LDR treatments are less than 1 week and so are the HDR treatments since they often deliver two fractions per day, sometimes a single fraction and sometimes two fractions separated by a week. For treatment times of a week or less, the time factor is negligible and BED and EUD with the repopulation term included will be essentially the same as those listed in table 2. In table 1, however, the treatment times are much longer. Even though, as we stated before, the treatment times in the studies listed in table 1 vary widely, they have a minimum of 7–8 weeks when the boost is given by external beam. To estimate a time factor, we take a treatment time of 7 weeks for all the studies of whole breast treatment plus a boost. With $T_{pot} = 15$ days and

Table 2. Summary of BCS treatments with radiotherapy of the tumour bed only.

Institution reference	Number of tumours	Boost (Gy)	Modality	Follow up (years)	Local recurrences	EUD (Gy)	BED ($Gy_{10,1h}$)
HDR Series							
Oshner Clinic (King *et al* 2000)	26	32	4 Gy × 8	1.7	0%	35	45
Royal Devon/Exeter Hospital (Clarke *et al* 1994)	45	20	10 Gy × 2	1.5	8.8%	32	40
		28	7 Gy × 4			37	48
		36	6 Gy × 6			43	58
Budapest, Hungary (Polgar *et al* 2002)	37	36.4	5.2 Gy × 7	4.75	4.4%	42	55
	8	30.3	4.33 Gy × 7	4.75		34	43
London Regional Center (Perera *et al* 1997)	39	37.2	3.72 Gy × 10	1.7	2.6% (7 y)	39	51
William Beaumont Hospital (Baglan *et al* 2001)	38	32	4 Gy × 8	2.6	2.6%	35	45
Wazer *et al* (2002)	33	34	3.4 Gy × 10	2.75	3% (4 y)	36	46
LDR series							
Lawenda *et al* (2003)	19	50–60	0.5 Gy h^{-1}	1.9	0%	43–50	57
Krishnan *et al* (2001)	24	20–25	0.5–0.8 Gy h^{-1}	4	0%	21–25	24–30
Oshner Clinic (King *et al* 2000)	26	45	0.4 Gy h^{-1}	1.7	0%	39	50
Guy's Hospital (Fentiman *et al* 1996)	27	55	0.4 Gy h^{-1}	6	37%	45	61
Cionini *et al* (1993)	90	50–60	0.4 Gy h^{-1}	2.25	4.4% (7 y)	42–49	56–67
William Beaumont Hospital (Vicini *et al* 2001)	50	49.92	0.52 Gy h^{-1}	3.9	0%	43	57
External beam series							
Christie Hospital (Magee *et al* 1996)	353	40	5 Gy × 8	8	19.6% (7 y)	52	60
Intraoperative							
Vaidya *et al* (2001)	25	5–20	1 fraction	–	–	–	7.5–60
Veronesi *et al* (2001)	86	17–21	1 fraction	0.67	–	–	46–65

$\alpha = 0.3$ Gy^{-1}, using equation (4a), the BEDs in table 1 are reduced by 8 $Gy_{10,1h,0.3}$, which would put most of them in the range of 62–72 $Gy_{10,1h,0.3}$ (if a delay in the onset of repopulation was included in the model, the BEDs in table 1 would be reduced even less). The BEDs in table 2 (local treatment only) are about 10–30% lower than this estimate (they are equivalent to or a little higher than those with whole breast irradiation with no boost). Given the fact that the patients selected for these studies are low risk (see, for example, Kuske *et al* (1999)) and that the dose response effect is small, it may be acceptable to use a lower dose. More studies with larger numbers of patients are needed to search for the appropriate dose regime and delivery method. The ABS has recommended (Nag *et al* 2001) for brachytherapy as a sole radiation treatment modality a dose of 45–50 Gy delivered at 0.42 Gy h^{-1}. For HDR, the ABS recommended 34 Gy in 10 fractions separated by at least 6 h. These two schemes have a significant difference in the BED ($BED_{LDR} = 50$–56 $Gy_{10,1h}$ versus $BED_{HDR} = 46$ $Gy_{10,1h}$). Of course normal tissue tolerance must also be taken into account when designing a treatment protocol, but it is important to keep in mind such a difference in the BEDs for the tumour.

We have included in table 2 two new studies radiotherapy of the tumour bed by intraoperative techniques, (Veronesi *et al* 2001, Vaidya *et al* 2001) even though the local

Table 3. Breast radiotherapy treatments with different fractionation for whole breast irradiation after BCS.

Reference	Number of tumours	EBRT (Gy), number of fractions and time	Local recurrences (%)	Follow up (years)	EUD (Gy)	BED ($Gy_{10,0.3}$)
Whelan *et al* (2002)	612	50 in 25 fr, 35 d	3.2% (5 y)	6	53	55
	622	42.5 in 16 fr, 22 d	2.8% (5 y)	6	49	51
Shelley *et al* (2000)	294	40 in 16 fr, 22 d	3.5% (5 y)	5.5	45	47
Olivotto *et al* (1996)	186	44 in 16 fr, 22 d	6% (5 y)	6.7	51	53
Yarnold *et al* (1994)	719	50 in 25 fr, 35 d			53	55
		42.9 in 13 fr, 35 d			50	52
		39 in 13 fr, 35 d			44	46
Yarnold *et al* (1995)		50 in 25 fr, 35 d			53	55
		45 in 20 fr, 28 d			49	51
		40 in 15 fr, 21 d			46	47
START Trial	Trial A	50 in 25 fr, 35 d			53	55
Management Group		41.6 in 13 fr, 35 d			48	50
(1999)		39 in 13 fr, 35 d			44	45
	Trial B	50 in 25 fr, 35 d			53	55
		40 in 15 fr, 21 d			46	47

recurrence rates are not available yet and we do not have a reliable way to calculate EUD. However, the availability of portable devices that are easy to use in a standard operating room may offer an interesting alternative for the treatment of breast cancer with BCS either by local treatment only or as a boost to the tumour bed complementing whole breast irradiation.

3.5. Comparison of different fractionation schemes

There have been studies using accelerated fractionation regimes without boost (Whelan *et al* 2002, Shelley *et al* 2000, Olivotto *et al* 1996) for low risk patients. These studies produce similar recurrence rates as the standard 45–50 Gy in 1.8–2 Gy fractions over 35 days. A summary of these studies is tabulated in table 3. The most recent study is by Wheelan *et al* (2002), a randomized trial of the standard 50 Gy in 25 fractions over 35 days versus 42.5 Gy in 16 fractions over 22 days. Similar recurrence rates were found in both arms. The BED difference between the two fractionations, obtained using $r = 10$ Gy, $\alpha = 0.3$ Gy^{-1} and $T_{pot} = 15$ days, is 4 $Gy_{10,0.3}$. As discussed before, this is a rather small difference and a very large number of patients may be needed to detect a dose response effect. For example, Romestaing *et al* (1997) only saw a 0.8% difference in recurrence rates for a difference in BED of 12 Gy_{10}.

In general, as shown in table 3, the different fractionation schemes used have significantly different BED (up to 10 Gy_{10} with the present LQ parameters). However, it has not been proved yet that all these schemes are equivalent in terms of local control. The studies done up to present have too few patients to detect small differences in local recurrence rates at such high levels of tumour control. As pointed out by Yarnold *et al* (1994), large numbers of patients are needed for a meaningful comparison.

Yarnold *et al* (1994) surveyed different institutions in the UK about their radiotherapy treatment schedules after BCS. In table 3 under Yarnold *et al* (1995) we list the most utilized schedules according to the survey. Based on the information from the survey, the START trial (START Trial Management Group 1999) has been designed to determine the optimal schedule for breast cancer radiotherapy. The different regimes being investigated are listed

in table 3. Trial A compares different fractionation schemes over the same period of time (35 days). The results of this trial should, in turn, determine the α/β ratio for breast cancer cells. Trial B compares two fractionation regimes with different treatment times. The result of this trial should give quantitative information about the time factor in a clinical setting. Accrual was scheduled to complete by the end of 2001 so it will take a few years to know the results. For the moment, the plausible parameter set that we have derived provides a tool to compare treatment strategies based on a quantitative analysis of previous clinical studies.

4. Summary and conclusions

We have derived a plausible set of LQ parameters ($\alpha = 0.3$ Gy^{-1}, $r = \alpha/\beta = 10$ Gy and $T_{\text{rep}} = 1$ h) for breast cancer based on three published clinical studies. This set of parameters is consistent with *in vitro* experiments and with previously reported analyses. To validate their applicability, these parameters have been used to analyse and compare a large number of published clinical studies using different RT modalities (other fractionation schedules and prescribed doses). Considering influence from many other factors, the present calculated results are found to be generally consistent with the published clinical findings. This indicates that the estimated radiobiological parameter sets for breast cancer may be useful for the intercomparison and design of alternate and refined treatment plans for early-stage breast cancer.

A large number of published clinical studies has been compiled and summarized in three tables for three main RT regimes currently used or investigated in clinic. Table 1 lists studies with standard treatments for early breast cancer using whole breast RT plus a boost to the tumour bed after BCS. The EUDs calculated using the present LQ parameters range from 60 to 70 Gy. Table 2 summarizes experimental studies with local treatment of the tumour bed only (no whole breast RT) after BCS. The presently calculated BEDs and EUDs are found to be lower than the values in table 1. These values are roughly equivalent to the dose for whole breast irradiation only (without boost).

There is a wide range of EUDs and BEDs in the studies of table 2. Table 3 reviews studies of different fractionation schemes, designed with the aim of reducing the treatment time. Significant difference in the BED was found among these studies. In summary, the three tables are comprehensive and provide a good picture for the current status of breast cancer RT.

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