



# Clinical Significance of Cell Survival Curves

# 27

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## 27.1 Introduction

Cell cycle in a dividing cell consists of two phases—the mitotic (M) phase where the cell actually divides and the S (synthetic) phase where the DNA is replicated. These are separated by two gaps, the G1 and G2 phases. The time between two successive divisions is called the cell cycle time. Of these different phases, the G2M phase is the most radiosensitive while the S phase is the least radiosensitive. Cell death of non-proliferating cells is defined as the loss of specific function and for cells capable of many divisions it is defined as the loss of reproductive integrity.

Cell death induced by radiation at conventional fractionation is primarily by creation of double strand breaks. Explaining how radiation interacts with DNA leading to cell death is beyond the scope of this chapter. At higher dose per fractionation other processes like endothelial damage and immune system stimulation play a role.

fraction is usually represented in a logarithmic scale in the cell survival curves. The shape of cell survival curves also depends on the type of radiation used. Neutrons and carbon ions which are densely ionising show an exponential curve while X-rays and gamma rays show an initial slope followed by a shoulder which again becomes straight (Fig. 27.1).

Experimental studies on cell lines and clinical data have helped us in deriving a meaningful cell survival curve. Performing studies on cell lines and collecting data from clinical studies is often cumbersome and time taking.

Mathematical models with a strong biological basis have helped us in understanding and explaining this curve. These will help in improving therapeutic ratio by creating dose fractionation schedules with equivalent or higher biological effective doses. This chapter mainly focuses on models explaining the cell survival curve of X-rays (Low LET).

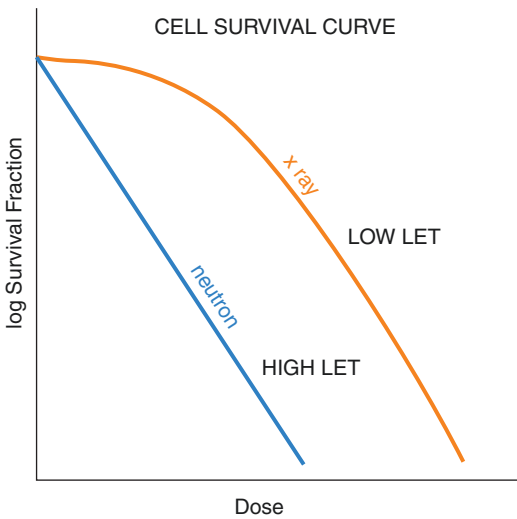
## 27.2 Cell Survival Curves

Cell survival curve is used to describe the relationship between the surviving fraction of cells to radiation and the absorbed dose. The surviving

## 27.3 Mathematical Models

Older empirical models were derived from past clinical data and could go disastrously wrong if used outside the dose fractionation they were derived from. These include the cumulative radiation effect model (CRE), nominal standard dose model (NSD), time dose fractionation model (TDF) and tumour significant dose model (TSD).

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**Fig. 27.1** Representative image of cell survival curve. Note that the cell survival curve of neutrons is a straight line while that for X-rays the survival curve has an initial slope followed by a shoulder and then becomes a straight line

The failure of these models led to creation of the linear quadratic model (LQ).

## 27.4 The Linear Quadratic Model

The LQ model is a mechanistic, biologically based model. It has sufficiently few parameters to be practical. It is reasonably well validated experimentally and theoretically. The model makes a few assumptions to work well. The assumptions include:

1. Cell killing is primarily a result of DNA damage (double strand breaks)
2. For multifractionated treatment, the fractions are well separated in time
3. Irradiation time for EBRT is short and with a constant dose rate

The *LQ model considers two types of radiation damage*:

- The first type of damage, responsible for *the linear component*, is assumed to result from a single event. This damage is *lethal* for the cell.

The probability to produce such a damage is *proportional to dose*. This is called the *alpha component*.

- The second type of damage, responsible for the *quadratic component*, is by itself not lethal for the cell. This is called *sublethal damage*. Only combination of two such lesions can yield a lethal event for the cell. *The probability to produce a single sublethal damage is again proportional to dose*. The probability to produce two of such lesions is proportional to the square of dose. This constitutes the *beta component*.

The survival at a given radiation dose is due to a combination of alpha and beta killing and can be represented by the following formula:

$$S(D) = e^{-\alpha D - \beta D^2}$$

$S$ : Surviving fraction at dose  $D$ ;  $D$ : Dose

The above formula works well for single fraction treatments. When the treatment is fractionated and protracted, a time factor has to be included in the formula to account for *dose rate* and also *the rate of damage repair* during this time. This modification called the generalised time factor ( $G$ ) was provided by Lea and Catcheside.

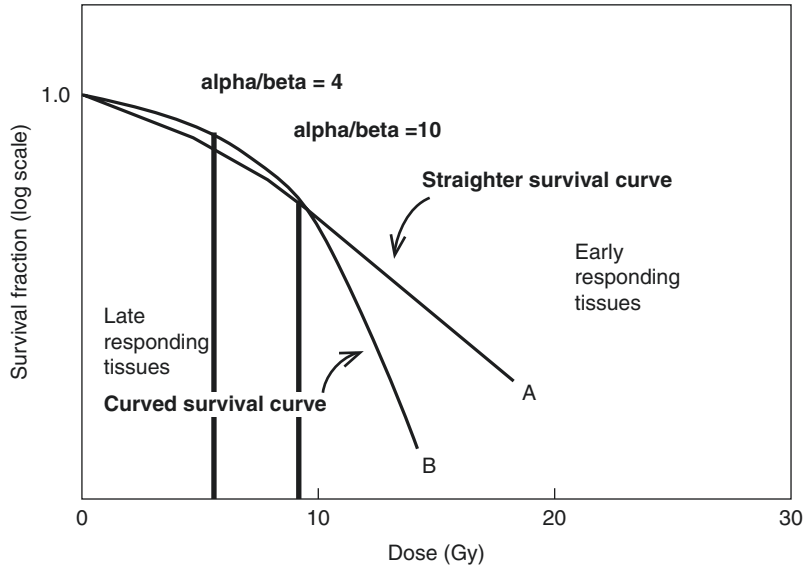
$$S = \exp\left[-(\alpha D + G\beta D^2)\right].$$

$G$ : Generalised time factor

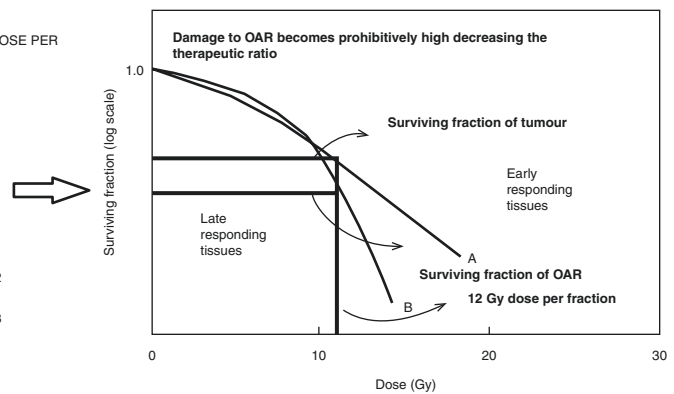
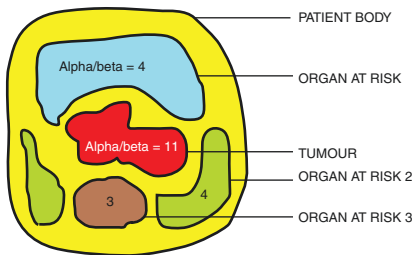
### 27.4.1 The Alpha by Beta Ratio and Its Implication in Radiation Oncology

The radiation dose at which the alpha killing (lethal) is equal to beta killing (combinations of sublethal killing leading to lethal killing) is called the *alpha by beta ratio*. Its unit is *Gray*. Cells with poor repair capability (e.g. tumours) tend to develop more lethal damage than cells with good repair capability (e.g.: Late responding normal tissue). This leads to a higher alpha/beta ratio for tumours with a straighter cell survival curve than late responding tissue

**Fig. 27.2** Difference in cell survival curve between early (tumour) and late responding tissue as explained by LQ model



AS TUMOUR HAS ALPHA BY BETA OF 11, ASSUME THE DOSE PER FRACTION AS 12 Gy



**Fig. 27.3** Effect of different tissues with different alpha/beta ratios as explained on cell survival curves

(Fig. 27.2). This difference in cell survival curves provides rationale for fractionated radiation therapy treatment.

The alpha by beta ratio for most tumours is 10 or higher with prostate and breast cancers being the exceptions (<3). The alpha by beta ratio is the dose at which the survival curve bends and killing tends towards exponential. Therefore, adopting a dose per fraction more than the alpha by beta ratio will kill more cells than when dose per fraction is less than the alpha by beta ratio for the same given total dose. This seems practically feasible only in tumours with a low alpha by beta ratio as normal late responding tissue around the tumour

with a lower alpha by beta ratio tends to get damaged more. This phenomenon is pictorially depicted in Fig. 27.3 for better understanding. Alpha/beta ratio of different tissues is summarised in Fig. 27.4.

The classical LQ model described above has the following limitations:

1. It does not include the effect of redistribution and reoxygenation in a protracted treatment course
2. The cell survival curve predicted by the LQ model is continuously bending but in reality, the cell survival curve becomes linear at higher doses

Early-Responding Tissues	$\alpha/\beta$	Late-Responding Tissues	$\alpha/\beta^b$
Jejunal mucosa	13	Spinal cord (110, 166, 245, 284, 285, 322)	1.6–5
Colonic mucosa	7	Kidney (44, 127, 291, 305)	0.5–5
Skin epithelium	10	Lung (90, 211, 214, 275, 289, 295)	1.6–4.5
Spermatogenic cells	13	Liver (91)	1.4–3.5
Bone marrow	9	Human skin (32, 211, 279, 280)	1.6–4.5
Melanocytes (302)	6.5	Cartilage and submucosa (171, 329)	1.0–4.9
Tumors			
Mouse fibrosarcoma metastases (173)	10	Dermis (106)	2.5 ± 1.0
Human tumors (169, 171, 195, 258)	6–25	Bladder (252, 265)	5.0–10.0
Experimental tumors (306)	10–35	Bone (212)	1.8–2.5

**Fig. 27.4** Alpha/beta ratio of different tissues

3. Robust clinical data is missing for LQ model validity at high dose per fraction (>10 Gy)

The solutions to the above limitations are explained in brief in the next section.

proposed to circumvent problems in the era of SRS and SBRT:

1. Universal survival curve
2. LQL model

## 27.5 The LQR Model

The LQR model is an extension of LQ model to account for redistribution and reoxygenation. It regards both the processes by a single term called re-sensitisation. This model adds two parameters to the LQ formalism—re-sensitisation magnitude and re-sensitisation time. It assumes that the re-sensitisation is monotonic i.e. it always increases the radiosensitivity of tissues. Explaining the LQR model in detail is beyond the scope of this chapter and readers are requested to refer to the original article by Brenner et al. on LQR model [1].

## 27.6 Models for High Dose per Fraction

The LQ model fails at high dose fractionation and due to continuously bending curve predicted by it, the model overestimates the killing at higher doses. The following models have been

## 27.7 Universal Survival Curve (USC) Model

The USC model combines the LQ model and multitarget model. The multitarget model states that multiple targets are hit for cell killing after radiation. As there is no clear biological basis for the above statement at low doses (DNA is the target), the multitarget model was not universally accepted. But at higher doses, with endothelium and immune cells also becoming targets for tumour cell kill, the multitarget model started getting importance. The USC model uses the LQ model for survival prediction at low dose per fractions and the multitarget model for higher dose per fraction. By combining the two models, the curve predicted at higher doses is straighter and more in line of experimental data. The model introduced two terms i.e. surviving fraction equivalent dose (*SFED*) and standard effective dose (*SED*). Explaining the USC model in detail is beyond the scope of this chapter and readers are requested to refer to the original article by Park et al on USC model [2].

As all processes involved in cell killing at higher doses have not been completely elucidated, it is difficult to decide on the most suitable model to be used in doses used in SBRT and SRS.

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## 27.8 Conclusion

Understanding the cell survival curve and the basics of *mathematical models* predicting cell survival is of utmost importance for radiation oncologists. This chapter provides only insights into various mathematical models without

venturing into formulae and technical terms. We encourage the readers to go through the original articles of LQ, LQR and USC models.

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## References

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