

# Radiobiology of Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

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## Abstract

In recent years, increasing number of cancer patients are treated with stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT), which deliver hypofractionated irradiation with high-dose per fraction. It is highly likely that the radiobiological principles such as 4 Rs (Reoxygenation, Repair, Redistribution, Repopulation) for the conventional fractionated radiotherapy with small-dose per fractions do not apply for SRS and SBRT. Reoxygenation: When tumors are exposed to high-dose per fraction, e.g. >10 Gy, significant vascular damage will occur. Consequently, intratumor environment becomes hypoxic and acidic, which not only will prevent reoxygenation of hypoxic cells but also will cause indirect cell death. Repair: delivery of SRS or SBRT lasts considerable lengths of time, which may allow repair of sub-lethal radiation damage during the irradiation exposure. Redistribution: high-dose irradiation prevents cell cycle progression and cells undergo interphase death in the cell cycle phases where they are irradiated. Repopulation: Since SRS or SBRT treatment is completed within 1-2 weeks, repopulation of tumor cells during the course of treatment may be negligible. The linear-quadratic (LQ) model, which is used to calculate isoeffect doses for different hyperfractionated irradiation schemes, may be applied for hypofractionated SRS or SBRT, provided that indirect cell death due to vascular damage is negligible.

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## 1 Introduction

In the early era of radiotherapy which began soon after X-rays were discovered in 1895, tumors were irradiated with high-doses of X-rays in a single fraction. However, by the 1930s, it was realized that irradiation with multiple fractions of small doses is more effective than irradiation with a large single dose for causing cancer control and sparing normal tissue late damage (Coutard 1932). Relevant to such clinical observations, irradiation of the scrotum of rams with fractionated daily irradiation was found to be more effective than a single large dose irradiation to sterilize the rams without causing severe skin damage (Hall 2006). These early clinical and radiobiological observations led to the development of current practice of fractionated radiotherapy, where tumors are irradiated 30–70 times with small fractionated doses, e.g. 1.2–2.0 Gy, over several weeks. Further clinical and radiobiology research revealed that tumor response and normal tissue damage caused by fractionated radiotherapy are governed by 4 radiobiological principles at cellular and tissue levels, which are commonly referred to as 4 Rs, that is, Reoxygenation, Repair of sublethal damage, Redistribution of cells in the cell cycle and Repopulation of cells (Withers 1975; Hall 2006). The introduction of the linear-quadratic model (LQ model) in 1980s based on radiobiological observations with tumor cells or experimental tumors and normal tissues made it possible to calculate cell killing by different total dose, size of fraction and fraction number in radiotherapy (Fowler 1989). With the support of these radiobiological principles, fractionated radiotherapy with small dose per fraction has been the major regimen of radiotherapy for treating divergent cancers in the past.

However, interest in hypofractionated radiotherapy with high-dose per fraction has resurged in recent years mainly influenced by the rather encouraging clinical outcomes of stereotactic radiosurgery (SRS) of brain tumors, which delivers high-doses of radiation, e.g. 15–25 Gy, to brain lesions in 1–2 fractions. This unique technique was developed in 1950–1960 initially to deliver a large dose of radiation to non-malignant vascular lesions in brains using a  $^{60}\text{Co}$  unit (gamma knife) (Leksell 1951), but it is now used to treat brain tumors, mainly inoperable intracranial

metastases (Leksell 1983). The concept and technique of SRS have then been adapted to irradiate extracranial tumors, which is generally referred to as stereotactic body radiation therapy (SBRT). The recent remarkable improvements in tumor imaging technique and radiation delivery system now make it possible to accurately and precisely deliver high-dose radiation to target tumors (Potters et al. 2004; Levitt et al. 2008). Numerous clinical trials conducted throughout the world clearly demonstrated that SBRT with doses up to 60–70 Gy in 1–5 fractions is often effective to eradicate various malignant tumors in lung, breast, liver, prostate and spine with generally acceptable levels of normal tissue damage (Timmerman et al. 2007; Timmerman 2008; Yamada et al. 2008; Kavanagh 2008; Dolinsky and Glatstein 2008; Milano et al. 2008; Whelan et al. 2008; Ritter 2008; Nedzi 2008; Timmerman et al. 2010).

In the mean time, a legitimate question arose as to whether or not the radiobiological principles such as 4 Rs play any role in the response of tumors to SRT and SBRT (Hall and Brenner 1993; Dolinsky and Glatstein 2008; Milano et al. 2008; Story et al. 2008). Another important question is whether the LQ model which is widely used to calculate the effect of total dose and dose per fraction in conventional fractionated radiotherapy can be applied for SRS and SBRT (Brenner et al. 1995; Fowler et al. 2004a, b; Brenner 2008; Kirkpatrick et al. 2008; Ritter 2008; Park et al. 2008).

Blood vessels are important components of tumors, which directly control the intratumor microenvironment and thus the survival and proliferation of tumor cells. Therefore, changes or damage in tumor blood vessels by radiation will markedly impact the outcome of radiotherapy by altering intratumor environment such as oxygenation status or acidity. It is therefore important to elucidate the effects of high-dose irradiation on tumor vasculatures for effective use of SRS or SBRT. Most of the previous studies on the radiation-induced vascular changes in human tumors have been aimed at gaining insights into the vascular changes caused by fractionated irradiation with low-dose per fraction. In this chapter, we will first address the vascular damages in tumors caused by high-dose fraction irradiation, and its potential implication for the treatment outcome of SRS or SBRT, and will discuss the role of 4 Rs in the response of tumors to SRS or SBRT. Finally we will

discuss whether LQ model is applicable for modeling SRS and SBRT.

## **2 Vascular Factors in SRS and SBRT**

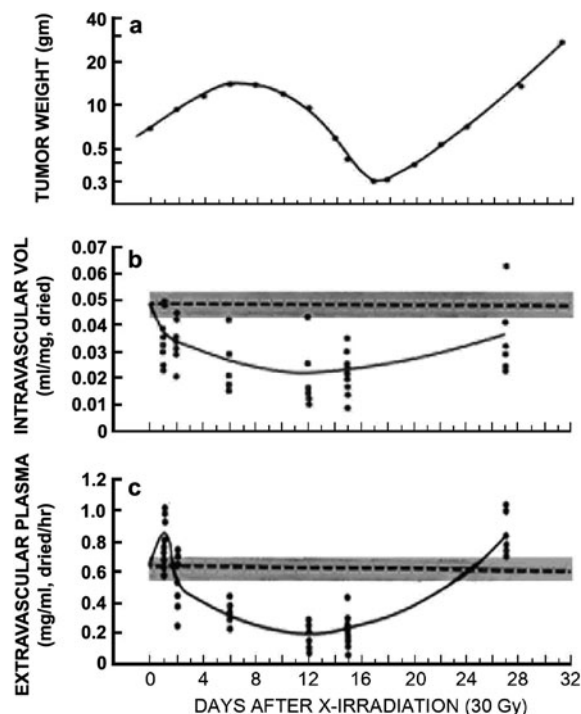
### **2.1 Vascular Changes in Tumor by Radiation**

The tumor blood vessels are formed by angiogenesis through sprouting or intus-susceptive microvascular growth, vasculogenesis by progenitor and other stem-like cells from the blood and bone marrow and co-option of neighboring vessels in normal tissues (Folkman 1985; Hammersen et al. 1985; Konerding et al. 1998; Dewhirst et al. 1996; Yancopoulos et al. 1998; Jain 2003). The structure and physiological aspects of vascular bed in tumors are markedly different from those in normal tissues (Jain 1989; Vaupel et al. 1989; Konerding et al. 1998; Endrich and Vaupel 1998; Song 1998; Dewhirst et al. 1996) and thus the hastily formed immature capillary-like tumor blood vessels are composed of single-layer endothelial cells often separated by gaps between the endothelial cells occupied by tumor cells without underlying basement membrane. As such, tumor vessels are highly leaky as compared with normal tissue blood vessels (Song and Levitt 1971a, b). Furthermore, tumor vessels are frequently devoid of innervations and thus they are unable to autoregulate in response to external stresses such as ionizing radiation. Unlike the well-organized web-like network of capillaries in normal tissues, tumor blood vessels are irregular in diameter, often sharply bent, tortuous, sinusoidal and branched with multiple dead ends. Consequently, the blood perfusion through such disorganized and rough tumor vascular networks is sluggish, and intermittently stationary. Furthermore, fractions of tumor perfusion are shifted often to arteriole-venous shunts. Because of the lack of adequate draining through the lymphatic system in vascular networks in combination with elevated leakiness of blood vessels, the interstitial pressure of tumors is significantly elevated leading to collapse of small capillary-like tumor blood vessels intermittently or permanently. However, the structural and functional features of the vascular bed in slowly-growing human tumors are less pathologic than those in fast-growing animal tumors or human tumors growing in window

chambers. Nevertheless, the abnormal features of tumor vasculatures probably account for the hypoxic, nutritionally deprived and acidic intratumor micro-environment, and also the differential response of tumor and normal tissue to ionizing radiation (Lee et al. 1997; Song 1998; Vaupel 1996; Endrich and Vaupel 1998; Park et al. 2000; Dewhirst et al. 1996).

The important role of tumor blood perfusion in the response of tumors to radiotherapy was reported as early as in 1936 by Mottram (1936), who observed that the regions in tumors with good blood supply were more vulnerable to radiation than those lacking adequate blood supply. The subsequent demonstrations that oxygen supply through blood perfusion greatly impacts the radiosensitivity of tumor cells prompted many investigators to elucidate the effects of radiation on tumor vasculatures. Although a variety of tumors were studied and different methods were used for assessing the radiation-induced vascular changes, the conclusions of the studies were similar: when human tumors are treated with conventional fractionated radiotherapy with 1.5–2.0 Gy per fraction, the blood perfusion tends to increase during the early period of treatment, but returns to the pre-irradiation levels or declines to the levels lower than that before the treatment toward the end of treatment (Mäntylä et al. 1982; Pirhonen et al. 1995; Marry et al. 1996). In a recent study by Ng et al. (2007), vascular changes in human non-small-cell lung cancer were determined after irradiation with 9, 18 and 27 Gy in 4.5 Gy per fraction. The functional vascularity significantly increased in the tumor rim while it increased only slightly in the tumor center. It was possible that the blood vessels in the tumor rim were of normal tissue origin and thus dilated upon irradiation, similar to the blood vessels in other normal tissues.

Much of present knowledge on the effects of high-dose fraction radiation on tumor blood vessels are obtained using animal tumor models or human tumor xenografts. It has been shown that an irradiation with high-doses, i.e. 10 Gy or higher, in a single fraction causes severe vascular damage in human tumor xenografts (Bruberg et al. 2006; Kioi et al. 2010) or animal tumors (Song and Levitt 1971a, b; Song et al. 1972, 1974; Wong et al. 1973; Clement et al. 1976, 1978; Chen et al. 2009; Fenton et al. 2001). Figure 1 shows the changes in tumor volume, intravascular volume (vascularity) and the rate of extravasation of



**Fig. 1** Effects of 30 Gy irradiation in single dose on the tumor weight (as an indication of tumor size) (a), intravascular volume (b) and extravasation rate of plasma protein (c) in Walker 256 carcinoma grown subcutaneously in the leg of Sprague–Dawley rats. The solid lines in a, b and c indicate the means of 6–10 tumors used at the different time points indicated. The dotted lines in b and c are the mean values of 15 control tumors weighing 0.3–2.0 g; the shaded areas show the range of standard error of the mean

plasma protein (vascular permeability) in the Walker 256 carcinoma of rats after irradiation with 30 Gy in a single dose. The tumor weight or size continuously increased for 7–8 days after irradiation and then markedly decreased until 15 days after irradiation. The vascular volume significantly decreased within one day after irradiation and further decreased for about 12 days and then began to recover. The extravasation rate of plasma or vascular permeability significantly increased soon after irradiation, declined thereafter until 12 days post-irradiation and then began to recover. The continuous increase in tumor size for several days after irradiation with 30 Gy may be ascribed to delayed disintegration of dead cells and induction of edema as a result of increased vascular permeability. Although the tumor size began to increase from about 15 days post-irradiation, it is possible that proliferation of tumor cells began before

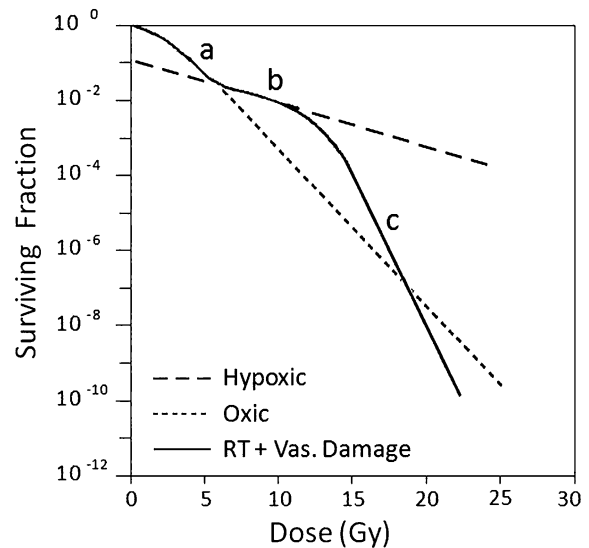
the recovery of tumor size became visible (Hermens and Barendsen 1969). In this connection, it was of interest that the tumor vasculature began to recover 2–3 days prior to the recovery of tumor size suggesting that proliferation of tumor cells and recovery of vasculatures are closely related. It has been reported that the recovery of tumor vascularity after irradiation is due to vasculogenesis using stem-like cells in the blood circulation (Kioi et al. 2010). As shown in Fig. 1 and also reported elsewhere (Wong et al. 1973; Song et al. 1974), the functional vascularity in tumors decreases within several hours after irradiation with doses higher than 10–15 Gy. Such a rapid decline in functional vascularity after high-dose irradiation may be due to death of endothelial cells and also, at least in part, due to collapse of the fragile tumor vessels as a result of an increase in the interstitial fluid pressure caused by extravasation of plasma protein (Fig. 1) (Wong et al. 1973; Song et al. 1972, 1974). The endothelial cells in tumors have been reported to undergo ceramide-mediated apoptosis soon after irradiation of the tumors with doses higher than 8–10 Gy leading to indirect tumor cell death (Garcia-Barrps et al. 2003; Fuks and Kolesnick 2003). The late decrease in functional vascularity in irradiated tumors may be attributed not only to the direct effect of radiation on the tumor vasculatures but also to the disorganization in vascular networks resulting from the shrinkage of tumor volume (Song et al. 1974). It has been demonstrated that the blood vasculatures in the inner regions of tumors are preferentially destroyed as compared with those in the tumor periphery (Ng et al. 2007; Fenton et al. 2001), and that the blood vessels in smaller tumors are more radiosensitive than those in larger tumors (Song and Levitt 1971b). Parts of vascular networks in the tumor periphery are normal tissue blood vessels that are incorporated into the tumor mass, and thus they might be relatively resistant to radiation as compared to the newly formed tumor blood vessels.

## 2.2 Implication of Vascular Damage for SRS and SBRT

The survival and proliferation of tumor cells are directly dependent on the blood supply. Therefore, it would be reasonable to anticipate that vascular damage by irradiation will cause indirect death in tumor

cells. Denekamp (1984) pointed out that one endothelial cell subtends a segment of a tumor cord containing as many as 2000 tumor cells. Since the blood vessels are serial tissues, injury even at a single focal point of vessels may obstruct or completely halt the down-stream blood flow, thereby causing an avalanche of tumor cell death along the defunct vessels.

The recent clinical studies conducted at a numerous institutes have demonstrated that SRS of cranial tumors with about 20 Gy in 1–2 fractions or SBRT of extracranial tumors with 20–60 Gy in 1–5 fractions are highly effective in achieving local tumor control. For example, SRS with 20–24 Gy in a single exposure produced local control in more than 80% of brain metastases (Shiau et al. 1997; Vogelbaum et al. 2006; Kim et al. 2010). Similarly, 90% local control could be achieved when metastatic spinal lesions were treated with 18–24 Gy in a single dose (Yamada et al. 2008). In a phase II study for stage 1 non-small-cell lung cancer, the local control rate was 95% after treating the tumors with 3 fractions of 20 Gy (total 60 Gy) (Timmerman et al. 2010). Importantly, these rather high-tumor responses occurred despite the fact that significant fractions of clonogenic cells in human tumors are hypoxic. In an effort to reveal the biological mechanisms underlying the response of tumors to SBRT, Brown et al. (2010) evaluated the expected level of cell killing by different regimens of SBRT. The mathematical calculation showed that irradiation with 25 Gy in a single exposure will reduce the cell survival by 3.3 logs and 20 Gy  $\times$  3 irradiation will reduce cell survival by 7.7 logs assuming that the  $\alpha/\beta$  ratio of the tumor cells is 10, and 20% of the tumor cells are hypoxic. It was concluded that even the 60 Gy/3-fraction regimes is barely sufficient to control a small tumor. Fowler et al. (2004b) concluded that, for the control of 1–10 gm tumors with SBRT, three fractions of at least 23 Gy ( $3 \times 23$  Gy) is needed to reduce viable hypoxic tumor burden to  $10^{-10}$ – $10^{-11}$  if it is assumed that 20% of tumor cells are hypoxic, oxygen enhancement ratio is 3, no reoxygenation occurs and no repopulation of tumor cells occurs during the course of treatment. One may then wonder how the impressive clinical results could be obtained as indicated above by SRS or SBRT overcoming the hypoxic protection with such insufficient radiation doses. It seems imperative to conclude that extreme hypofractionated radiotherapy is capable of overcoming hypoxic



**Fig. 2** Contribution of direct death and indirect death due to vascular damage to total clonogenic death of cells in tumors irradiated with various doses of radiation in a single fraction. In the tumors, 10% of tumor cells are assumed to be hypoxic cells. The dotted lines indicate the response of oxic (---) and hypoxic (---) tumor cells in the tumors. The response at doses 0–5 Gy is dominated by oxic cells (a), while that at 5–12 Gy is dominated by hypoxic cells (b). As radiation dose is increased above 12 Gy, indirect cell death due to vascular damage prevails (c)

radioprotection through mechanisms other than directly killing tumor cells via DNA damage such as immune response and damage to vasculature (Brown and Boong 2008; Brown et al. 2010). In support of this conclusion, Kirkpatrick et al. (2008) and Kocher et al. (2000) reported that the total cell death in the tumors receiving SRS or SBRT is the product of cell death directly caused by radiation and the cell death indirectly caused by radiation-induced vascular/stromal damage. Relevant to this contention, Clement et al. (1978) reported that irradiation of rodent tumors with 10–20 Gy in a single dose caused vascular damage, which then killed a substantial proportion of hypoxic tumor cells. Figure 2 illustrates a possible contribution of direct death of tumor cells and indirect tumor cell death caused by vascular damage to the total clonogenic cell death after irradiation of tumors with various doses. In this calculation, 10% of the tumor cells were assumed to be hypoxic. The initial steep decline in the cell survival by irradiation with doses lower than 5 Gy corresponds to the direct killing of oxic cells by radiation while the subsequent



shallow phase of the survival curve between 5 and 12 Gy irradiation relates to the death of hypoxic cells by direct effect. When tumors are exposed to doses higher than 10–12 Gy, indirect cell death due to vascular damage becomes predominant, which is demonstrated by the second sharp decline in cell survival. The relative importance of direct death versus indirect death to the total death of tumor cells after SRS or SBRT will depend on the size of fraction.

A recent development in cancer biology is the realization that small fractions of tumor cells in human tumors are self-renewing cancer stem cells which are radioresistant and thus give rise to relapse after the bulk of non-stem cancer cells are killed by radiotherapy (Dean 2006; Baumann et al. 2008). Interestingly, tumor perivascular niche has been identified as the home of cancer stem cells and that the tumor endothelial cells supply factors that maintain the cancer stem cells in a self-renewing and undifferentiated state (Calabrese et al 2006; Charles and Holland 2010). It is therefore conceivable that eradication of cancer stem cells as a result of death of endothelial cells and destruction of vasculatures might be an additional explanation why extreme hypofractionated radiotherapy with relatively small total doses, e.g. 20 Gy, are capable of inducing tumor control.

It should be noted that SBRT or SRS are not always given with extremely high-dose fractions. For instance, human prostate tumors were treated with 36.15 Gy in 5 fractions of 7.23 Gy (Pawlicki et al. 2007). Treating brain metastases with 36 Gy in 6 fractions or 20 Gy in a single exposure exhibited similar survival time while the fractionated irradiation was less toxic to patients (Kim et al. 2010). When tumors are treated with such fractions, indirect cell death due to vascular damage may be negligible particularly in tumor periphery regions in which most of blood vessels are of normal tissue origin. In fact, irradiation of non-small-cell lung cancer with 4.5 Gy per fraction up to total dose of 27 Gy was reported to increase blood perfusion in tumor rim (Ng et al. 2007).

### 3 Role of 4 Rs in SRS and SBRT

It is well-known that the effectiveness of fractionated radiotherapy with multiple small doses is directly influenced by the following four radiobiological principles which are referred to as 4 Rs: Reoxygenation of

hypoxic tumor cells, Repair of sub-lethal radiation damage, Redistribution of cells in cell cycle phases and Repopulation of cells (Withers 1975; Hall 2006). In this section, the possible role of 4 Rs in the response of tumors to SRS or SBRT is discussed.

#### 3.1 Reoxygenation

Varying fractions of clonogenic cells in tumors are radio-resistant hypoxic cells. However, when tumors are treated with conventional fractionated radiation with small dose per fraction, proportions of hypoxic cells are reoxygenated during the interval of fractions (Van Putten 1968; Howes 1969; Kallman 1972; Clement et al. 1978; Hall 2006). It is believed that such reoxygenation of hypoxic cells and resultant restoration of radiosensitivity is the major benefit gained by treating tumors with multi-fractionated radiotherapy. The reoxygenation of hypoxic cells is believed to occur as a result of death of oxic tumor cells and resultant decline in oxygen demand enabling oxygen to diffuse from blood vessels to previously hypoxic regions (Clement et al. 1976, 1978). Therefore, vascular damage by radiation will prohibit reoxygenation of hypoxic tumor cells. This implies that reoxygenation of hypoxic cells may not occur after tumors are treated with high-dose fraction SRS and SBRT because of vascular damage. Instead, it is likely that, as discussed in the previous section, varying proportions of hypoxic cells as well as oxic cells may undergo secondary death following treatment with high-dose fraction SRS or SBR. It should be emphasized that the extent of vascular damages by irradiation are usually heterogeneous throughout the tumor volume. It is therefore likely that some regions in tumors may remain oxic and some hypoxic cells may even undergo reoxygenation although the overall oxygen supply to tumor will be markedly diminished when tumors are treated with high-dose fraction SRS or SBRT. Contrarily, certain extent of reoxygenation may be expected to occur in the tumors treated with mildly fractionated SRS or SBRT, e.g. 3–8 Gy per fraction, because vascular damage will be insignificant in such tumors.

There have been interesting discussions in recent years as to whether SRS or SBRT should be applied in a single fraction or multi-fractions (Hall and Brenner 1993; Ling et al. 2006; Fowler 2007; Dolinsky and Glatstein 2008; Story et al. 2008). Hall and Brenner

(1993) concluded that SRS of brain tumors should be given in 5 or 6 fractions instead of a single fraction to take advantage of reoxygenation of hypoxic cells and also to reduce the late complication of normal tissues. Fowler (2007) also strongly argued that SBRT should be fractionated with several doses, even two or three, in order to allow hypoxic cells to undergo reoxygenation so that the tumors become sensitive to subsequent irradiation. It must be emphasized that the fraction size should be small enough to avoid significant vascular damage when SRS or SBRT are fractionated in order to induce reoxygenation of hypoxic cells.

In summary, when tumors are treated with a single fraction or extremely high-dose fraction SRS or SBRT, the intratumor environment will become hypoxic leading to secondary cell death due to vascular damage. However, reoxygenation of hypoxic cells may occur in the tumors treated with hypofractionated irradiation with relatively low-dose per fraction, i.e. <10 Gy.

### 3.2 Repair of sub-lethal Radiation Damage

The extent of repair of sub-lethal damage in irradiated cells greatly influences the fate of the cells (Elkind and Sutton 1960; Belli et al. 1966). It has been shown that the repair rate of radiation damage is related to various factors such as dose per fraction, dose rate and the nature of the tissue or cells (Ang et al. 1987; Hall and Brenner 1991; Fowler et al. 2004a, b). In treating tumors with conventional fractionated irradiation, the delivery of 1.2–2.0 Gy is completed in a short period. Therefore, repair of sub-lethal damage during the radiation exposure is negligible. On the other hand, the delivery of large doses of radiation in treating tumors with SRS or SBRT usually lasts considerably long times, and thus substantial repair of sub-lethal radiation damage may occur during the radiation exposure (Fowler et al. 2004a; Ling et al. 2010). It has been known that the repair kinetics of sub-lethal radiation damage in irradiated cells is biphasic. It was reported that the median half-time of the faster components is about 0.3 h while that of subsequent slow components is about 4 h (Fowler et al. 2004a). Therefore, at least 10% of biological effectiveness is lost due to the repair of damage when irradiation exposure lasts longer than half an hour such is the

case in treating tumors with SRS or SBRT. The loss of biological effectiveness due to repair of sub-lethal radiation damage is expected to be greater for late complications in certain normal tissue than tumors because the  $\alpha/\beta$  ratio for normal tissues is usually lower than that for tumors. Additionally, the vascular injury and ensuing chaotic intratumor environment such as hypoxic, acidic and nutritionally-deprived environment caused by high-dose fraction SRS and SBRT, may significantly hinder the repair of radiation damage. Needless to mention, no repair would occur after treatment with an ablative radiation dose.

In summary, when tumors are treated with SRS or SBRT, considerable repair of sub-lethal radiation damage may take place during the prolonged radiation exposure. The estimated loss of radiation effect due to repair of radiation damage is greater than 10% when the irradiation of tumors lasts longer than 30 min.

### 3.3 Redistribution

Ionizing radiation delays cell cycle progression by causing dose-dependent arrest of cells in the cell cycle phases. The extent and kinetics of cell cycle arrests by irradiation vary depending on phase of the cell cycle, cell type and microenvironment. The G1 arrest is absent or negligible in many cell types after irradiation with doses lower than several Gy, and the S-phase delay usually occurs after irradiation with relatively low radiation doses, i.e. 1–5 Gy. The G2 arrest occurs after irradiation with doses as low as 1 Gy in practically all types of mammalian cells. Therefore, G2 arrest is far more pronounced than G1 arrest or S-phase delay. The transient arrests of cells in different phases of the cell cycle are caused by activation of cell cycle checkpoints, which are to prevent the progression of cells into next cell cycle phase before the radiation-induced damage is repaired. For example, G1/S checkpoint inhibits the progression of G1 cells with damaged DNA into S-phase. This process allows cells to repair DNA damage and prevents the duplication of damaged DNA if the cells with the damaged DNA progress into S-phase. Likewise, during G2 arrest that is caused by G2/M checkpoints, damages in DNA are repaired before cells enter mitosis. If cells enter mitosis with incompletely repaired DNA, they may be unable to complete the complicated mitosis and die, which is termed mitotic death or post-G2 apoptosis. When cells

are irradiated with moderate doses of radiation, the cell cycle arrest eventually disappears and the distribution of cells through the cell cycle phases is restored to pre-irradiation state, which is referred to as redistribution of cell cycle. However, after an exposure to rather high-doses of radiation, cells tend to be arrested indefinitely in the cell cycle phases in which they are irradiated, and undergo apoptosis or necrosis, that is, cells die in the G1 phase, S-phase or G2 phase wherever they were at the time of irradiation. As shown in Fig. 3, a pronounced G2 arrest occurred in HL-60 cells after irradiation with 4 Gy. Thereafter, small fractions of cells progressed into G1 phase while the majority of the cells died of apoptosis. On the other hand, after irradiation with 20 Gy, there was no change in cell cycle distribution and cells died from the cell cycle phases in which they were irradiated. These observations imply that interphase death of tumor cells will prevail when tumors are treated with high-dose fraction SRS or SBRT.

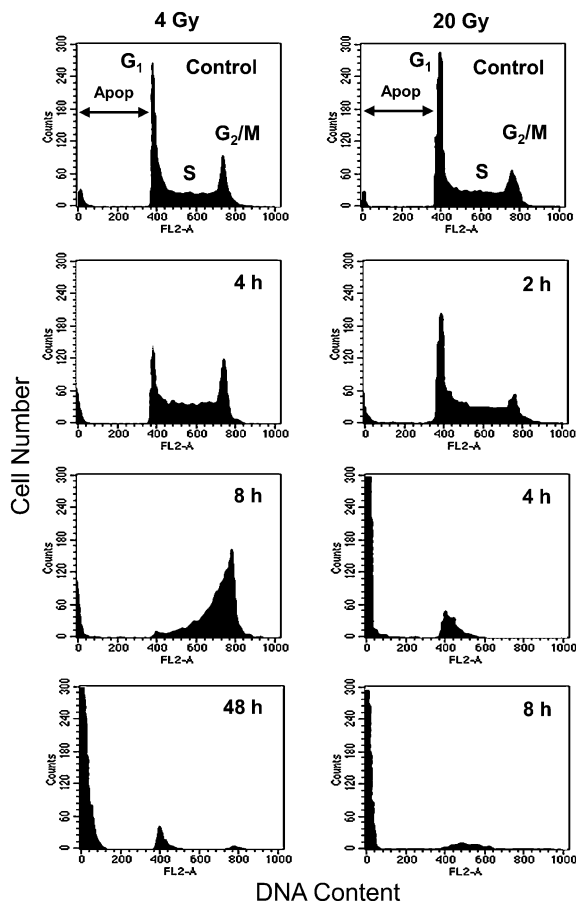
In summary, irradiation with moderate doses causes transient cell cycle arrest predominantly in G2 phase and induces mitotic cell death. However, after irradiation with extremely high-doses of irradiation, i.e. >15–20 Gy, in a single fraction, cells are indefinitely arrested in the phases of cell cycle where they were irradiated and undergo interphase death.

### 3.4 Repopulation

During the course of fractionated radiotherapy for an extended period, tumor cells or normal cells that survive the radiation exposure begin to proliferate. Therefore, the number of tumor cells that must be sterilized increases when tumors are treated with conventional fractionated irradiation. Such compensatory repopulation of tumor cells is evoked usually 3–4 weeks after initiation of radiotherapy. Since SRS or SBRT treatment lasts for a short period, at most 2 weeks, repopulation of tumor cells will not be substantial during the course of SRS or SBRT.

## 4 Linear-Quadratic Model in SRS or SBRT

The LQ model, is widely used for calculating radiotherapeutic isoeffect doses for different fractionated radiotherapy schemes (Fowler 1989). The LQ model



**Fig. 3** Cell cycle progression of HL-60 cells after irradiation. Cells were irradiated with 4 or 20 Gy and the cell cycle progression (DNA histograms) was measured with flow cytometry. Most of the cells were in late S and G2 phases 4 h after 4 Gy irradiation, and then died of apoptosis as indicated by the large increase in the sub-G1 fraction. When irradiated with 20 Gy, no cell cycle progression occurred and the cells died of interphase death in the cell cycle phases, where the cells were at the time of irradiation (Park et al. 2000)

encompasses two components,  $\alpha$  and  $\beta$ , which represents non-repairable and repairable damage, respectively. This model assumes that the biological outcome of irradiation is directly proportional to total dose and fraction size and that the ratio of  $\alpha$  and  $\beta$  ( $\alpha/\beta$ ) indicates the sensitivity of tissues to different fraction size. The radiation-induced cell death and sub-lethal damage repair are incorporated in the LQ model. Brenner et al. (1995) proposed to include cell cycle redistribution and reoxygenation into the LQ model, which is termed LQR model, in order to improve the usefulness of LQ model. Although the



LQ model has been proven to be very useful for comparing the effectiveness of different fractionated radiotherapy protocols, there have been considerable discussions in recent years as to whether or not LQ model is applicable for SRS or SBRT (Brenner 2008; Kirkpatrick et al. 2008; Fowler et al. 2004b; Park et al. 2008). The primary concern has been that the radiation dose–response survival curve calculated by LQ model bends downward at high-radiation doses whereas the experimental radiation dose–response curves are linear. It was therefore argued that LQ model overestimates cell death or underestimate cell survival at high-radiation doses, and thus the model cannot be used for SRS or SBRT. It should be noted, however, that there is no much experimental data that supports the assertion that dose–response curves remains linear at  $10^{-10}$ – $10^{-11}$  survival range, clinically relevant levels, because it is technically difficult to determine the clonogenic survival at such low levels. Furthermore, in vitro studies are carried out using growth media which select cells that proliferate fast in culture, unlike the cells in tumors in animals or human patients which are influenced by hormonal and microenvironmental factors. It is conceivable that the  $\alpha/\beta$  ratio of cells in such environment may be unnaturally high rendering the survival curve remain linear at high-radiation doses. Brenner (2008) reported that LQ model is still acceptable for doses per fraction of 15–18 Gy although the model becomes progressively less accurate at doses above 10 Gy. An important fact that must be addressed here is that irradiation with doses higher than 10–12 Gy in a single exposure is likely to cause significant vascular damage followed by indirect cell death. Therefore, the LQ model may become increasing inaccurate for hypofractionated irradiation with fraction size larger than 10–12 Gy. However, it should also be noted that SRS or SBRT is often given with fractions smaller than 10 Gy. When tumors are treated with mildly-fractionated irradiation, i.e. <10 Gy per fraction, the conventional LQ model will be a useful model to calculate the radio-therapeutic isoeffect doses for SRS and SBRT.

Guerrero and Li (2004) proposed to modify the LQ model to more accurately describe radiation response for high fraction/acute doses by adding a new parameter to the LQ model and reported that the modified LQ model (MLQ model) produced a better fit to the iso-effect data than the LQ model. Park et al.

(2008) constructed an alternative model termed USC (universal survival curve) by hybridizing the LQ model and the classical multi-target model, and concluded that USC provides an empirically and clinically well-justified rationale for SBRT while preserving the strengths of the LQ model for the conventional fractionated radiotherapy. More recently, Wang et al. (2010) proposed a generalized LQ (gLQ) model that encompasses the entire range of possible dose delivery patterns. The authors concluded that gLQ model could derive the traditional LQ model for low-dose and low-dose rate irradiation and the target model for high-dose irradiation. A recent study suggested that the value of  $\beta$  parameter in the LQ model might impact the calculation of clinical relative biological effectiveness (RBE) of high-LET radiation such as proton especially when the radiation exposure is hypofractionated (Carabe-Fernandez et al. 2010). Unfortunately, it is apparent that all these modified LQ models will not be applicable for high-dose fraction radiotherapy because the indirect cell death caused by vascular damage is not incorporated into the models.

In summary, the indirect tumor cell death due to vascular damage render the LQ model inapplicable when tumors are treated with extremely high-dose fraction radiotherapy. However, the LQ model should be applicable for hypofractionated radiotherapy with fraction size smaller than approximately 10 Gy.

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