Cell death after irradiation:

Definitions of cell death:

The successful use of radiation to treat cancer results primarily from its ability to cause the death of individual tumour cells. the biological consequences of irradiation, including cell death, are highly influenced by pathways within the DNA damage response (DDR) system. The DDR determines not only the sensitivity of cells to die following irradiation, but also the type of cell death that occurs, and the timing of cell death. Because the DDR differs among different types of normal and tumour cells (and perhaps even within different populations of tumour cells), the manifestation of cell death can also differ widely among different cell types .

Quantification is complicated by the fact that cells die at various times after irradiation, often after one or two trips around the cell cycle, and among surviving cells that continue to proliferate. Instead,of a cell to proliferate indefinitely after irradiation. This is a much more robust and relevant parameter to assess radiation effect since any cell that retains proliferative capacity can cause failure to locally control the tumour .Consequently, cell death in the context of radiobiology is generally equated with any process that leads to the permanent loss of clonogenic capacity. This is a rather wide inclusion criterion for cell death, and obviously does not have meaning when applied to terminally differentiated cell types that do not proliferate, such as nerve and muscle cells. For these types of cells, it makes more sense to consider the specific types of cell death that lead to destruction of the cell, or to evaluate how radiation alters the function of these cells. Nonetheless, loss of reproductive capacity is a widely applicable definition for cell death in radiobiology and is highly relevant for the proliferating cells, including those in tumours and in many of the normal tissues of relevance for radiotherapy.

In addition to these genetically controlled programmers , a long-recognized contributor to cell death after irradiation is mitotic catastrophe in which cells fail to complete mitosis correctly.

Apoptosis:

Apoptosis is a highly regulated form of cell death that can be initiated either as a result of conditions occurring within the cell itself (such as those after DNA damage) or from signals generated externally such as those from a surrounding tissue or immune cell . Apoptosis is an essential and normal part of many physiological processes including embryonic development, the immune system, and maintenance of tissue homeostasis. Consequently, alterations in the control of apoptosis contribute to several human diseases, including cancer. Apoptosis is both morphologically and molecularly distinct from other forms of cell death Morphologically, it is characterized by membrane blebbing, condensation, and digestion of the DNA into small fragments. During this process, cellular contents are also fragmented into many membrane-enclosed apoptotic bodies, which, in vivo, are taken up by phagocytes. This prevents leakage of potentially damaging cellular proteins and destruction of tissue architecture that is a familiar feature of necrosis.

Necrosis:

The apoptosis represents ‘death by suicide’, then necrosis is ‘death by injury’. Necrosis has historically been considered to be an inappropriate or accidental death that occurs under conditions that are extremely unfavourable, such as those incompatible with a critical normal physiological process. Examples of conditions that can activate necrosis include extreme changes in pH, energy loss and ion imbalance. Consequently, necrosis is generally thought of as an uncontrollable, irreversible and chaotic form of cell death. It is characterized by cellular swelling, membrane deformation, organelle breakdown and the release of lysosomal enzymes which attack the cell. These conditions can occur following infection, inflammation or ischaemia. Necrosis is also frequently observed in human tumours and can be induced following treatment with certain DNA-damaging agents, including radiation. More recently, a number of studies have suggested that necrosis is also a regulated process that can be modulated. For example, induction of necrosis seems to be dependent on cellular energy stores, such as NAD, and ATP. Furthermore, cell stress and cell

signalling including oxidative stress, calcium levels and p53 activation have been shown to influence lysosomal membrane permeability. Permeabilization leads to intracellular acidification and release of various enzymes that can promote necrosis.

when and why cells die after irradiation:

Multiple cell death pathways may be activated within the same cell, but because a cell can die just once, the type of cell death that is observed will be that which occurs most rapidly and not necessarily that which is most sensitive to activation. For example, just because a cell dies by apoptosis after some given dose of radiation does not imply that it would not have died by some other pathway if apoptosis had been disabled. In this regard, it is perhaps less important to consider how cells die after irradiation, but rather why cells die after irradiation. For this consideration it is possible to broadly **classify cell death mechanisms into two classes:** those that occur relatively soon after irradiation and before cell division, and those that occur comparatively late or after division.

Early cell death: pre-mitotic:

In a small minority of cell types, cell death occurs rapidly, within several hours after irradiation .This type of death, sometimes referred to as interphase death, is limited primarily to thymocytes, lymphocytes, spermatogonia, and other cells in rapidly proliferating tissues such as those in hair follicles, the small intestine, and in developing embryos. Early cell death is also observed in some types of cancers that arise from these cell types, including lymphomas, and may explain the unexpected effectiveness of radiotherapy protocols used in the treatment of this disease . In solid tumours, this type of cell death is rarely observed. Early cell death results primarily from activation of pathways in response to the initial cellular damage caused by irradiation.

Late cell death: post-mitotic:

The vast majority of proliferating normal and tumour cells die at a relatively long time after irradiation, usually after attempting mitosis one or more times.

DDR activates both cell-cycle checkpoints and DNA repair systems that aid in the survival of the irradiated cells. In these cell types, the DDR is unable to induce apoptosis despite the fact that p53 or other pro-death pathways may be induced. Instead, DNA repair is allowed to take place and can have a large influence on the outcome and radio sensitivity of the cell. Although DNA repair and checkpoint pathways play important roles in determining cell survival, cell death takes place at long times after irradiation takes place at times when the checkpoints are no longer active and when DNA repair processes have largely completed. The halftime for repair is approximately 2–4 hours for end-joining and perhaps somewhat longer from homologous recombination.

Why does irradiation cause proliferating cells to undergo mitotic catastrophe and cell death ?

This appears to result from the fact that, although DDR pathways remove much of the initial damage caused by irradiation, they are unable to prevent some cells with DNA breaks or DNA rearrangements from entering mitosis. The consequences of incomplete or improper DNA repair become readily visible as chromosomes condense in metaphase as a series of different types of chromosome aberrations. The fate of cells harbouring chromosome aberrations is largely determined by the nature of the chromosome aberration itself.