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Radiobiology of tissue reactions

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Abstract–Tissue effects of radiation exposure are observed in virtually all normal tissues, with interactions when several organs are involved. Early reactions occur in turnover tissues, where proliferative impairment results in hypoplasia; late reactions, based on combined parenchymal, vascular, and connective tissue changes, result in loss of function within the exposed volume; consequential late effects develop through interactions between early and late effects in the same organ; and very late effects are dominated by vascular sequelae. Invariably, involvement of the immune system is observed. Importantly, latent times of late effects are inversely dependent on the biologically equieffective dose. Each tissue component and – importantly – each individual symptom/endpoint displays a specific dose–effect relationship. Equieffective doses are modulated by exposure conditions: in particular, dose-rate reduction – down to chronic levels – and dose fractionation impact on late responding tissues, while overall exposure time predominantly affects early (and consequential late) reactions. Consequences of partial organ exposure are related to tissue architecture. In 'tubular' organs (gastrointestinal tract, but also vasculature), punctual exposure affects function in downstream compartments. In 'parallel' organs, such as liver or lungs, only exposure of a significant (organ-dependent) fraction of the total volume results in clinical consequences. Forthcoming studies must address biomarkers of the individual risk for tissue reactions, and strategies to prevent/mitigate tissue effects after exposure.

Keywords: Tissue reactions; Radiopathology; Dose fractionation; Dose rate; Volume effect; Repopulation; Biomarker; Intervention

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1. INTRODUCTION

Tissue effects of ionising radiation can be observed in virtually all tissues. This article focuses on 'deterministic' tissue responses, and does not consider radiation carcinogenesis or genetic effects after germ cell exposure. One prominent attribute of 'deterministic' effects is that they only occur if a certain, albeit – for some symptoms – small, threshold dose is reached. With regard to their time course, early effects are seen within the first weeks after an acute radiation exposure, while chronic, late radiation sequelae manifest after months to many years. In some instances, the extent, i.e. severity and/or duration, of the early effects has an impact on the risk for the manifestation of late symptoms in the same tissue or organ (consequential late effects). A number of factors have been identified with regard to the exposure characteristics that significantly influence the radiation tolerance of normal tissues, summarised as the 'Rs' of radiation exposure and, particularly, radiotherapy. These include:

- intrinsic *R*adiosensitivity (Steel, 1993);
- *R*ecovery (Withers, 1975);
- *R*epopulation (Withers, 1975);
- *R*edistribution (Withers, 1975);
- *R*eoxygenation (Withers, 1975);
- i*R*radiated volume (Dörr and Van der Kogel, 2009);
- long-term *R*estoration (Dörr and Stewart, 2009); and
- molecular *R*adiopathology (Dörr, 2009c).

These parameters, besides the general pathological principles of tissue effects, will be characterised briefly in this section, as far as they apply to normal tissue effects of irradiation. Redistribution or cell cycle effects in general, based on the varying cellular radiosensitivity over the different cell cycle phases, is a phenomenon that is mainly observed in in-vitro systems. However, the relevance of this factor for tissue effects in vivo, with a variety of factors regulating cell cycle progression, must be doubted. Furthermore, reoxygenation, describing the improvement of the oxygen status of tumours during fractionated radiotherapy, is irrelevant with regard to normal tissue effects. In normal tissues, only a small and constant fraction, if any, of the radiobiologically relevant (tissue-specific target/stem) cells is subject to local hypoxia. Long-term restoration, impacting on tissue tolerance at long intervals of months to years after initial exposure, is also not the subject of the present considerations, but has been described in detail elsewhere (Dörr and Stewart, 2009).

It needs to be emphasised that these radiobiological factors that determine the biological effect of a certain radiation exposure scenario are specific for individual symptoms or endpoints of normal tissue reactions, rather than for the organs as anatomical entities. As an important consequence, these radiobiological factors may impact on different symptoms related to one organ in different ways.

2. PATHOBIOLOGICAL PRINCIPLES OF TISSUE EFFECTS

Based on their time course, early reactions in tissues are defined as those observed within weeks after the (onset of) radiation exposure, e.g. within the first 90 days after the start of radiotherapy. Any symptom that is first diagnosed at a later time is considered a late response, with typical latent times of months to many years and sometimes decades for very late effects, e.g. in the urinary bladder, or even more pronounced in the cardiovascular system. In some organs and tissues, consequential late effects develop based on the clinical manifestation, i.e. severity and/or duration of early effects in the same tissue.

It must be emphasised that tissue effects in many instances are not based on the consequences of radiation exposure of an individual organ, but on the interaction of radiation effects in physiologically 'connected' organs, such as the lung and the heart after thoracic exposure, or the systemic contribution of the immune system to individual organ effects.

2.1. Early radiation effects

Typical early radiation effects are found in turnover tissues (Dörr, 2009a; Dörr and Schmidt, 2014), where physiologically permanent cell loss from the differentiated, post-mitotic compartments of the tissue is well balanced by proliferation in the germinal parts of the tissue. Typical examples are the haematopoietic system, with cell production in the bone marrow, or the epidermis and epithelia of the upper and lower gastrointestinal tract. Radiation exposure of such tissue systems impacts on the cell production rate, while the normal cell loss rate remains unchanged, at least over a wide range of doses. As a consequence of the proliferative impairment, the reduced cellular supply to the differentiated tissue layers results in progressive hypoplasia and, eventually, in complete cell depletion. Regeneration, based on surviving proliferative cells within the exposed volume, or migrating proliferative cells from unexposed tissue or even the circulation, is usually complete. The tissue 'parenchymal', hypoplastic-regenerative response is regularly accompanied, or even preceded, by local vasculoconnective (e.g. vasodilation, vascular leakage, erythema) and immunological reactions, such as macrophage activation (Dörr, 2009a; Dörr and Schmidt, 2014), which also represent the basis of related pain. The interaction between the latter with the parenchymal effects, at molecular level, is subject to current radiobiological investigations.

2.2. Late radiation effects

The pathogenesis of late (chronic) radiation effects is more complex and includes the organ parenchyma, the vasculature and connective tissue components, and, in many instances, a major contribution of the local immune system, mainly macrophages (Dörr et al., 2009b). The response of parenchymal cells is organ specific. Exposure of a certain fraction of these cells may cause cell loss and (slowly progressing) parenchymal hypoplasia, which can occur in slow-turnover parenchymal tissues such as airway epithelia or urothelium, according to the mechanisms described

above. Cell loss may also cause recruitment of non-proliferating cells into the cell cycle, and consequent loss of these cells via mitotic death or through other cell death pathways.

Radiation exposure of mitotic fibroblasts triggers their early differentiation into post-mitotic fibrocytes. The consequence is a substantial increase in the synthesis and deposition of collagens, as a basis for the development of tissue fibrosis (Rodemann and Bamberg, 1995; Yarnold and Brotons, 2010).

In the vasculature, radiation exposure results in changes in, or loss of, endothelial cell function, and thus 'leaky' vessels, which progresses into thrombi formation and vascular occlusion, loss of capillaries, or pathological dilation of small vessels, depicted as telangiectasia (Fajardo et al., 2001; Dörr, 2009b). All these changes markedly impact on the blood supply within the exposed volume, as well as downstream tissue compartments, which further promotes the development of progressive loss of tissue function. For very late radiation effects, e.g. in the cardiovascular system, the vascular component appears to be the dominating pathophysiological factor.

Macrophages, present at the time of exposure or recruited into the exposed volume, contribute to the tissue changes by chronic production of reactive oxygen species, and synthesis and release of a number of signalling molecules, with transforming growth factor ß as a promoter of tissue fibroses being one of the most prominent (Hakenjos et al., 2000). They also significantly trigger the chronic inflammatory changes regularly found in association with late radiation sequelae (Rubin et al., 1995; Bentzen, 2006; Yarnold and Brotons, 2010).

2.3. Consequential late effects

Consequential late effects develop in situations where the early radiation responses are associated with breakdown and loss of a physiological protective barrier against mechanical or physical stress (Dörr and Hendry, 2001; Dörr, 2009b). This is, in particular, found for surface epithelia of the upper and lower digestive tract (oral cavity, oesophagus, small and large intestine, rectum) with a combination of mechanical and chemical influences, the epithelium of the urinary bladder (chemical stress), the epidermis at localisations with major mechanical wear and tear, and also in the lung. With regard to time course and clinical manifestation, consequential late effects are similar to generic chronic radiation reactions. Their radiobiological behaviour, however, corresponds to that of the early responding tissue component, e.g. with a less pronounced fractionation effect and a pronounced effect of the overall treatment time (see below).

3. INTRINSIC RADIOSENSITIVITY – TISSUE TOLERANCE

The radiobiological target/stem cell concept postulates that the radiation tolerance of any organ or tissue is defined by the number and intrinsic sensitivity of the tissue-specific target cells (Dörr and Schmidt, 2014; Dörr, 2009b). Specific target cell markers, however, are lacking for the vast majority of normal tissues; hence, this

concept must be considered as hypothetical but valid. Detailed information on the tolerance of the major organs to radiation exposure was reviewed in Dörr (2009b), and Dörr and Schmidt (2014). Again, it needs to be emphasised that 'tolerance' applies to individual symptoms or endpoints within an organ, rather than an organ per se. In this context, the tolerance dose is defined as the maximum radiation dose that is associated with a minimum probability (usually of a few percent) of the specific endpoint under consideration (Dörr and Schmidt, 2014).

4. RECOVERY – FRACTIONATION/DOSE-RATE EFFECT

Recovery describes the observation that administration of a certain total radiation dose in separate fractions rather than a single acute exposure decreases the incidence of tissue effects. The same phenomenon is observed when a tissue is exposed to a given total dose at a significantly reduced dose rate, starting from below approximately 1 Gy min^{-1} (Van der Kogel, 2009) down to chronic levels. In turn, the total dose required to induce a certain tissue effect (i.e. the tolerance dose) increases if the exposure occurs in smaller dose fractions or at smaller dose rates. One underlying mechanism is the restoration of the cellular integrity of the target cells during the overall exposure time. This is frequently termed 'repair', which, however, indicates the involvement of DNA repair. Although it is undoubted that DNA repair has a significant role, other mechanisms contribute to the phenomenon of recovery in tissues, e.g. the continued, potentially altered metabolic activity of lethally damaged cells (Dörr and Schmidt, 2014).

Recovery has been quantitated for numerous endpoints in preclinical investigations and clinical studies over the last decades (Bentzen and Joiner, 2009; Dörr, 2009b; Joiner and Bentzen, 2009). In general, the fractionation effect is low, but still significant, for early normal tissue reactions, and pronounced for late tissue endpoints. The linear-quadratic model is currently accepted to describe the relationship between total equieffective doses and dose per fraction or dose rate, respectively, in radiotherapy and other exposure scenarios (Bentzen et al., 2012). It is applied to estimate the toxicity of a given exposure after changes in dose per fraction or dose rate and total dose (Thames and Hendry, 1987; Bentzen and Joiner, 2009; Joiner and Bentzen, 2009; Dörr and Schmidt, 2014). This formalism was initially based on cell survival concepts, but must today just be considered as the most appropriate mathematical formula to fit fractionation/dose-rate data at the tissue level without any biological background (Bentzen et al., 2012). In this formalism, an α/β-value describes the shift of dose–effect curves to higher equieffective doses with a decrease in dose per fraction/dose rate. The lower the α/β-value, the more pronounced the effect of dose fractionation/dose rate, i.e. the increase in tolerance with a reduction in dose per fraction/dose rate. In general, late responding tissues are sensitive to changes in dose per fraction (low α/β-value, <6 Gy), while early responding tissues display a minor, but still significant, fractionation effect (Thames and Hendry, 1987; Bentzen and Joiner, 2009; Joiner and Bentzen, 2009; Dörr and Schmidt, 2014). The consequential component of late

effects (see above), however, may not significantly benefit from reduced doses per fraction/dose rates.

The linear-quadratic formalism may underestimate the biological effect of a certain total dose at doses per fraction <1.0 Gy, due to 'low-dose hyper-radiosensitivity' (Marples et al., 1997; Joiner et al., 2001), as well as overestimate the effect of high doses per fraction >10 Gy (Joiner, 2009; Bentzen et al., 2012).

5. REPOPULATION – THE TIME FACTOR

Repopulation in normal tissues, generally defined as an increase in radiation tolerance with increasing overall treatment time (Dörr, 2009a; Dörr and Schmidt, 2014), is observed for typical early radiation effects that occur in turnover tissues (see above). This phenomenon is based on a tissue regeneration response that appears to be initiated by the tissue changes induced during protracted radiation exposure. The complex biological mechanisms include a profound reorganisation of the proliferative structure, both at the stem/target cell and the total tissue level. Clinical and experimental observations of normal tissue effects regarding variations in overall treatment time (Dörr, 1997, 2003, 2009a; Dörr and Schmidt, 2014) consistently illustrate that:

- the exposure effect is compensated with increasing overall treatment time, once the repopulation processes have become effective;
- the rate at which this compensation occurs is in the range of up to 5×2 Gy week^{-1} (e.g. in human oral mucosa); and
- the rate at which tissue cell depletion is observed decreases substantially after the onset of repopulation.

The biological mechanisms underlying normal tissue repopulation have been summarised as the '3As' (Dörr, 1997, 2003, 2009a; Dörr and Schmidt, 2014): **A**symmetry loss; **A**cceleration of stem/target cell divisions; and **A**bortive divisions of doomed cells.

The target/stem cell hypothesis postulates that the radiation tolerance of (turnover) tissues is defined by the number of tissue-specific target cells. Therefore, compensation of the expected decrease in radiation tolerance expected from continued exposure, that is observed once repopulation has started, must be based on generation of new target cells to replace those sterilised by irradiation. Physiologically, target cells, on average, divide asymmetrically, i.e. into one new stem and one transit/differentiating daughter cell, thus maintaining the stem cell number. Additional production of new target cells, in contrast, requires symmetrical divisions into two stem cell daughters (asymmetrical loss).

The rate of dose compensation during repopulation in oral mucosa has been found to be in the range of 5×0.5 to 5×1 2 Gy-fractions week^{-1} (Dörr, 1997, 2003, 2009a). Based on a 2-Gy-surviving fraction of the stem cells of approximately 0.5, this requires five symmetrical divisions within 7 days, corresponding to a cell

cycle time of 1.4 days, which is substantially shorter than the physiological cell cycle time (acceleration of stem cell divisions).

Effective repopulation is associated with a constant, or only a slight reduction of, overall cell number (Dörr and Kummermehr, 1990; Dörr, 2003, 2009a), although differentiation and cell loss continue at their physiological rate (Dörr et al., 1996). Moreover, assessment of overall cell production revealed a largely unchanged activity (Dörr et al., 1994; Dörr, 1997). However, the vast majority of stem cells are sterilised before repopulation becomes effective. In consequence, generation of the original number of (overall) cells to counteract the cell loss would require the remaining stem cells to proliferate with an unlikely short cycle time of only a few hours (Dörr et al., 1994; Dörr, 1997, 2009a). Hence, cells must be generated from other sources than the surviving stem cells. 'Doomed' (or 'sterilised') stem cells do have a residual proliferative capacity in the form of abortive divisions, which result in daughter cells that can undergo near normal differentiation (Dörr et al., 1996). This mechanism significantly contributes to the compensation of the ongoing physiological cell loss (Dörr et al., 1994; Dörr, 1997, 2009a).

6. EFFECT OF THE EXPOSED VOLUME

In radiotherapy, major advances in radiation physics during the last decades have resulted in a progressive conformation of high-dose volume to the macro- and microscopic tumour tissue. In consequence, the volumes of normal tissues exposed to significant doses were significantly reduced, and dose distribution within these volumes became inhomogeneous. This implies that the effect of exposure of the fractional volume of a normal tissue to certain doses, rather than the dose to the entire tissue or organ, needs to be considered. Moreover, accidental radiation exposures most frequently occur in a localised form. Consequently, the irradiated volume of an organ must be taken into account as an important parameter that determines the clinical consequences of tissue exposures (Dörr and Van der Kogel, 2009; Dörr and Schmidt, 2014).

The exposed volume can affect the quality and consequences of the clinical manifestation of tissue effects, even if the tissue sensitivity and the pathological changes per unit volume are identical, e.g. in the case of skin ulceration. In contrast, the pathological changes underlying identical clinical symptoms and consequences can be dependent on different dose-volume parameters and mechanisms, as has been demonstrated for the lung (Novakova-Jiresova et al., 2007). With regard to detailed conclusions on the volume effect in individual normal tissues, recent reviews by Dörr and Van der Kogel (2009) or the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) initiative (Marks et al., 2010) are recommended.

6.1. Volume effects and tissue architecture

The concept of functional subunits (FSUs), proposed by Withers et al. (1988), defines an FSU as the largest tissue sub-volume that can be restored from a single surviving stem/clonogenic cell. The number of FSUs sterilised by a certain exposure

is hence dependent on the parameters influencing clonogenic cell survival. While structural damage is related to the individual FSU, the clinical manifestation is a consequence of the 'anatomical' arrangement of the FSUs, which can be either in parallel or in a series. In tissues with parallel structure, the FSUs are functioning independently of each other. Thus, clinical consequences of the exposure only become manifest if the number of eliminated FSUs, i.e. the fractional tissue volume, reaches a (tissue-specific) threshold. Here, the exposure constraints should refer to a threshold organ fractional volume, which is not to be exceeded (Dörr and Van der Kogel, 2009; Dörr and Schmidt, 2014). Examples for (predominantly) parallel organs are lung, kidney, and liver.

In organs with a serial ('tubular') organisation, e.g. spinal cord, intestine, or oesophagus, inactivation of one single FSU results in clinically manifest effects in the downstream tissue compartments in a binary response pattern (Dörr and Van der Kogel, 2009; Dörr and Schmidt, 2014). However, the FSUs are not simply arranged as a bunch or in a chain in any real organs. The vasculature in any organ, for example, represents a serial tissue component.

6.2. Normal tissue effect models and the QUANTEC initiative

Mathematical models describing normal tissue effect probabilities (in radiation oncology: normal tissue complication probabilities) include estimates of tissue-specific tolerance doses and fractionation parameters, such as the α/β-values and halftimes of recovery. For tolerance doses, the compilation by Emami et al. (1991) has frequently been applied in the past. More recently, the results of the QUANTEC analyses, reported in the *International Journal of Radiation Oncology Biology Physics*, summarised the available information on dose-volume-effect relationships for a variety of organs and tissues (Bentzen et al., 2010b, Marks et al., 2010), including the clinical significance of various endpoints, dose-volume tolerance data, and risk factors. For further analyses of specific tissue and organ tolerances, the reader is strongly recommended to screen the current literature.

7. MOLECULAR RADIOPATHOLOGY – BIOMARKERS AND INTERVENTIONAL STRATEGIES

7.1. Molecular and 'tissular' radiopathology

After radiation exposure of tissues, a whole orchestra of events, which may be summarised as 'damage processing' (Dörr, 2009c; Dörr and Schmidt, 2014), is seen way before any clinical changes become manifest. The cascades are initiated by the induction of free radicals and acute oxidative stress. These result in changes in the activity of transcription factors, and thus in the modification of various intracellular and extracellular signalling pathways. Such changes can be demonstrated in all tissue components (parenchyma, fibroblasts, vasculature) and also in activated – directly by exposure or due to the abovementioned changes – macrophages and other immune cells. The combination of all these events induces unspecific as well as

tissue-specific changes at the cellular/histological level (e.g. cell death, differentiation or proliferation, DNA damage response, chronic oxidative stress, and many others). The integrated response eventually results in the known, pathological changes described earlier. Detailed knowledge of the molecular/tissular radiopathology processes is a major prerequisite for the identification of early biomarkers of the risk for the development of subsequent macroscopic tissue effects, and also for the development of biology-based interventional strategies for the modification of such effects.

7.2. Tissue effect biomarkers

Early radiopathology-based indicators of exposure-related tissue effects (effect biomarkers) can facilitate the stratification of individuals, already timely after their radiation exposure according to their individual risk for the manifestation of (severe) clinical consequences. Major activities in this field, particularly in relation to radiation dose/dose distributions, have only recently been initiated (Bentzen et al., 2010a). Such biomarkers need to be identified according to a precise and detailed knowledge of the individual molecular and cellular process cascades involved in the eventual clinical manifestation of specific exposure endpoints. Some promising examples are inflammatory and immune response markers, e.g. in the urinary bladder and the intestine (Hille et al., 2009; Varela et al., 2009; Gibson and Bowen, 2011; Henson and Ang, 2012).

7.3. Interventional strategies

Any interventions in the manifestation of normal tissue effects may be described as recommended at a National Cancer Institute workshop on normal tissue protection (Stone et al., 2004) according to their timing in relation to the radiation exposure as:

- prophylaxis/protection: pre-exposure;
- mitigation: during or shortly after exposure, before clinically manifest symptoms occur (i.e. during the latent time); and
- treatment/management: in the symptomatic phase.

Interventions in the damage processing pathways can, in principle, be performed at each of the levels of the event cascade described above. Some prominent principles and examples have been systematically summarised by Dörr (2009c), and Dörr and Schmidt (2014). In general, although a variety of such interventional strategies have been suggested, most of these approaches are highly experimental, and few have entered advanced preclinical studies. Very few approaches have been translated into clinical studies to date.

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