21 Early and Late Treatment-Induced Toxicity

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CONTENTS

21.1 Introduction

Malignant tumors, by definition, infiltrate the surrounding normal tissue structures; therefore, it is inevitable that the target volume of curative radiotherapy of solid tumors includes a significant volume of normal tissues, which are exposed to toxicity-inducing radiation doses. In addition, areas of suspected microscopic spread and safety margins accounting for organ- and patient motion are to be included. In principle, normal tissues refers to non-malignant structures within the tumor, such as blood vessels or connective tissues, areas at the tumor margins, and also organs and structures traversed by the radiation beams. The volume of normal tissues receiving radiation doses that may eventually result in clinically manifest morbidity hence can be substantially larger than the tumor volume. These normal tissue responses are based mainly on the cytotoxic effects of ionizing radiation resulting in clonogenic cell death. This, however, does not only include cell kill by mitotic death, but also induction of differentiation, e.g., in fibroblasts, or induction of apoptotic processes, e.g., in endothelial cells.

As already defined in 1936 by Holthusen, the optimum radiation dose is the dose associated with a small, generally accepted incidence of severe side effects in cured patients (Fig. 21.1); therefore, manifestation of severe side effects per se must

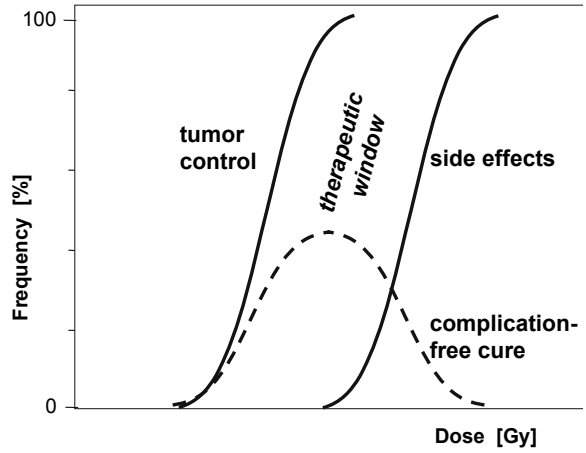

Fig. 21.1. Dose dependence of tumor control and side effects. Tumor control probability (TCP) and side effects (normal tissue complication probability, NTCP) of cancer therapy are represented by sigmoid dose–effect curves. The overlay of both curves results in the dose–effect relationship for complication-free tumor cures, which initially increases, but subsequently decreases, when the side effects become a dominating factor. This results in a therapeutic window with a width that depends on the position of the TCP- and NTCP curve at the abscissa. (Adapted and modified from Holthusen 1936)

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not be considered a consequence of a wrong treatment strategy but is the price to pay for a maximum chance of tumor cure. Radiation-induced side effects in general, besides a possible systemic inflammatory response, only occur within the irradiated volume. In contrast, systemic treatment with cytotoxic drugs will eventually affect entire organs if accumulation of the drug occurs, or the entire body through widespread distribution. This results in a reduction of the residual compensatory capacity of the individual organs and tissues. It must be emphasized that such a reduction has to be taken into account if the volume effect, which is well known for radiotherapy (Hopewell and Trott 2000; Hopewell 1997), is to be exploited during the treatment, e.g., for lung, liver, or kidneys. With modern delivery techniques, volume-sparing high-dose treatment of, for example, early-stage lung cancer results in very low complication rates (Zimmermann et al. 2005).

Table 21.1. Examples of recently published acute esophageal toxicity studies

Reference	Patients and treatment	No. of patients	Study end point	Results
Kim et al. (2005)	Lung cancer, with or without CTx, all cRT	124	≥ Grade 3 toxicity (RTOG)	Significant risk factors: concurrent CTx; V60 >30% (risk 6% without concurrent CTx and 11% with concurrent CTx when V60 ≤30%)
Belderbos et al. (2005)	Lung cancer, with or without CTx, dose per fraction 2.25–2.75 Gy	156	≥ Grade 2 toxicity (RTOG)	Significant risk factors: concurrent CTx; volume receiving >35 Gy
Patel et al. (2004)	Lung cancer, concurrent CTx, hyperfractionated RT	36	≥ Grade 2 toxicity (RTOG)	Significant risk factors: volume receiving >50 Gy; low pretreatment body mass index

Table 21.2. Examples of recent lung toxicity studies

Reference	Patients and treatment	No. of patients	Study details	Results
Tsujino et al. (2003)	SCLC and NSCLC, concurrent CTx	71	Paired organ analysis[a]	V20 significant risk factor for RP, mean V20 in patients without RP was 20%
Claude et al. (2004)	NSCLC (also post-operative), 64% had previous CTx	90	Paired organ analysis[a]	V20, V30, and MLD sign. risk factors for RP and V20 in patients without RP was 12% (MLD 10 vs 13 Gy with RP)
Hernando et al. (2001)	SCLC and NSCLC, most patients had previous CTx, some concurrent	201	Paired organ analysis[a]	V20, V30, and MLD sign. risk factors for RP and RP rate was 16% for MLD 11–20 Gy and 27% for 21–30 Gy
Graham et al. (1999)	NSCLC, 42% had some type of CTx	99	Paired organ analysis[a]	V20 significant risk factor for RP, V20 <22% caused <10% RP, RP rate was 9% for MLD 11–20 Gy and 24% for 21–30 Gy
Willner et al. (2003)	SCLC and NSCLC, concurrent CTx in all but 1 patient	49	Both paired and separate organ analysis	RP correlated to high dose volume, V10–40, and MLD of ipsilateral lung; less pronounced effects were seen for the whole lung
Lee et al. (2003)	Esophageal cancer, preoperative RCT	61	Paired organ analysis[a]	V20 significant risk factor for RP, unfavorable results when V20 ≥20%

SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; CTx, chemotherapy; RCT; combined radio- and chemotherapy; V20, lung volume receiving at least 20 Gy; RP, radiation pneumonitis; MLD, mean lung dose.
[a]Both lungs were considered as a single organ. Note that the gross tumor volume is usually excluded. Differences exist between planning algorithms and dose calculation, e.g., inhomogeneity correction.