1 Biological Basis of Combined Radio- and Chemotherapy

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1.1 Introduction

1.1.1 Clinical Relevance of Combined Modality Approaches

The introduction of combined modality approaches was a highly significant step in the evolution of curative radiation treatment. Parallel to analysis of altered fractionation schedules, combined treatment has actively been investigated in recent decades in both preclinical and clinical studies around the world. When judged at this time, the most pronounced increase in therapeutic gain was probably seen by combining radiation with chemotherapy. Unfortunately, most of the recent gains in local control and also survival achieved with now accepted, more conventional combined approaches are somewhat covered by the enthusiasm created by various new and so-called targeted drugs (Nieder et al. 2003), most of which are still to demonstrate their full therapeutic potential.

Meanwhile a huge body of evidence supports the use of combined modality approaches based on the combination of ionizing radiation with cytostatic drugs. In this regard, several randomized phase-III trials for many relevant cancer sites provide a sound basis for level one evidence-based decisions. This holds true especially for glioblastoma multiforme (Stupp et al. 2005), head and neck cancers including nasopharyngeal cancer and laryngeal cancer (Brizel et al. 1998; Forasteriere et al. 2003; Budach et al. 2005), esophageal cancer (Minsky et al. 2002), colorectal- and anal cancer (Sauer et al. 2004; Bartelink et al. 1997), cervical cancer (Green et al. 2001), as well as lung cancer (Schaake-Koning et al. 1992).

The most important aim of curative cancer treatment is to eradicate all tumor cells. With regard to the amount of quantitative cell kill, it has to be emphasized that important differences exist between ionizing radiation and chemotherapy (Fig. 1.1). In principle, radiation treatment can be designed to cover the whole tumor with a homogeneously distributed full radiation dose, capable of inactivation of all tumor cells. In contrast, pharmacotherapy is limited by the fact that the dose of the active, cell killing form of the compound is variable within the tumor and its cells (Fig. 1.2). This results from problems in the delivery of drugs (perfusion, interstitial fluid pressure, tissue pH, etc.), cellular uptake, efflux, inactivation, and resistance. In many instances, the agent

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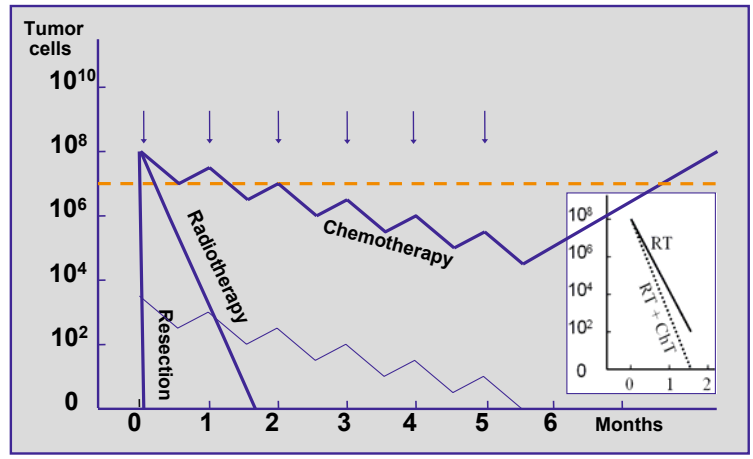

Fig 1.1. Differences in quantitative cell kill and time course. Influence of different therapeutic modalities on number of tumor cells during a course of treatment, based on the models by Tannock (1989, 1992). The *dashed line* represents the border between microscopic and macroscopic tumors, defined as a size of approximately 5 mm. Compared with surgical resection and fractionated radiotherapy, multiple courses of chemotherapy (in this case six, indicated by *arrows*) are less efficient in cell kill. While microscopic disease might be eradicated (*lower chemotherapy curve*), clinical evidence suggests that most macroscopic solid tumors (exception: more sensitive testicular cancers) will shrink temporarily but eventually regrow from surviving residues (*upper chemotherapy curve*). As shown in the inset, the strength of chemotherapy in combination with radiation treatment (besides of spatial cooperation) is the modification of the slope of the curve

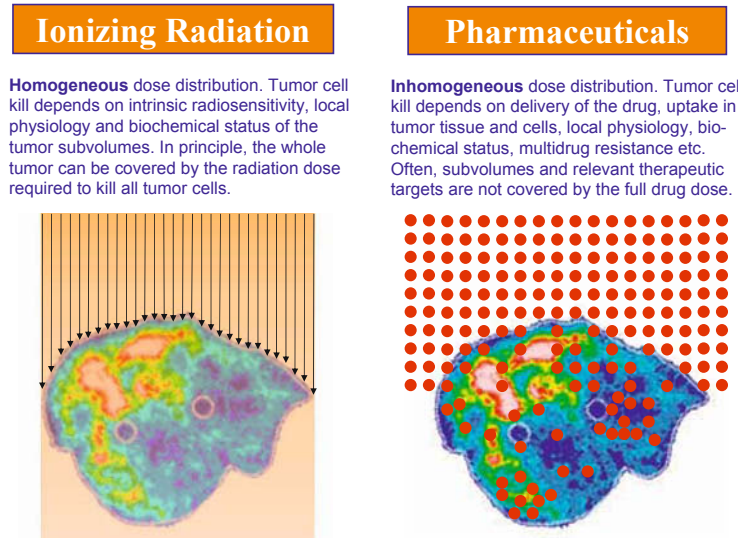

Fig. 1.2. Comparison between tumor dose distribution in radiation treatment and pharmaceutical treatment. Illustrative tumor sections from a squamous cell carcinoma demonstrate biological heterogeneity, reflected by the differently colored areas, within the tumor. Homogenous radiation dose distribution within the tumor irrespective of differences in biology, physiology, functional factors, structure, and morphology. Heterogeneous dose distribution for drug treatment, related, for example, to regional differences in perfusion, pH, metabolism, etc. Drug molecules are shown as *red circles*. (Courtesy W. Müller-Klieser, Johannes Gutenberg University, Mainz, Germany)

does not reach the relevant therapeutic targets in the required concentration and for a sufficient time period. These issues, which are addressed in the drug-specific chapters, gain complexity with simultaneous administration of two or more drugs. Such multi-agent regimens with different modes of action might be valuable when each agent kills different tumor cells, which would not become inactivated by the other agents; however, sometimes all agents might act on the same cell, causing much more damage than necessary for cell death. As illustrated in Fig. 1.1, the quantitative cell kill of ionizing radiation is significantly larger than that of chemotherapy (Tannock 1992, 1998). The magnitude of this effect might vary with cell type, culture conditions, drug, exposure time, etc. Experimental evidence suggests, however, that single radiation doses result in 1% or less cell survival compared with 10–50% with cytotoxic drugs (Epstein 1990; Kim et al. 1992; Simoens et al. 2003; Eliaz et al. 2004). Although clinically impressive remissions of solid tumors might occur after chemotherapy, the underlying cell kill is often not larger than 1–2 log and pathological examination of tissue specimens reveals residual viable tumor cells. Even with modern drug combinations, pathological complete remission (pCR) after neo-