Effective cancer treatment necessitates both high efficacy of local treatment and combating sub-clinical systemic disease. Consequently, cancer therapy today involves various combinations of local and systemic treatment modalities. Of those, combining drugs and radiation has been attracting particular attention both in terms of its biological rationale and its potential of increasing the therapeutic outcome.

Besides surgery, radiotherapy and systemic therapy constitute two main anticancer treatment modalities. The main aim of combining thereof is to optimise the therapeutic ratio, i.e. the ratio between tumour control probability and normal tissue complication probability. In practical terms, the goal of combining radiation with drugs is to increase disease-specific or overall survival by virtue of increasing local control and decreasing the risk of distant metastasis. Obviously this can only be achieved if the increase of combined treatment efficacy outweighs the increase of treatment toxicity.

Drugs and radiation may be administered sequentially (induction, adjuvant) or concurrently. The former is mainly hoped to decrease the risk of distant metastasis, whereas the latter - to increase local control. The mechanisms of drug-radiation combinations include spatial cooperation, cytotoxic enhancement, biological cooperation, temporal modulation and normal tissue protection. Several cytotoxic agents have been combined with radiotherapy. For sequential therapy usually the least toxic drugs with proven independent activities are used, whereas compounds for concurrent therapy are selected considering their interaction mechanisms.

The effects of drug-radiation therapy may be assessed in vitro (e.g. by clonogenic assay, apoptosis, cell viability assay) or in vivo (e.g. by regrowth delay assay, tumour control assay). In vitro studies aim at demonstrating the radiosensitisation of tumours or tumor cells and the lack of radiosensitisation in normal tissues or cells. Phase I clinical studies allows for establishing maximal tolerated dose (MTD) and recommending the dose of drug and radiation for phase II studies. The later assess efficacy of novel therapeutic strategy that warrants further development in phase III comparative trials, and collect additional toxicity data. The final verification of novel treatment against established standard of care is performed in phase III studies in which unbiased comparison between study groups is achieved through randomisation.

Apart from classical cytotoxic compounds, radiotherapy may be combined with non-cytotoxic agents (e.g. EGFR inhibitors, antiangiogenic agents or hypoxic cell radiosensitisers). Of those, particularly promising to date seems to be monoclonal anti-EGFR antibody cetuximab, which was proven to increase the efficacy of radiotherapy in locally advanced head and neck cancer. Cytoprotective agents, which are commonly used in combination with chemotherapy, should be combined with radiotherapy cautiously, as they may seriously compromise its efficacy. Examples of compounds inducing such negative interactions include recombinant erythropoietins and colony-stimulating growth factors.

There are currently several clinical applications of drug-radiation strategies. For example, chemotherapy and radiation (used concurrently or sequentially) has been proven to be more effective than radiotherapy alone and is routinely used in non-small and small cell lung cancer, cancer of the head and neck, cervix, stomach, breast, rectum and anus, as
well as in glioblastoma. Endocrine therapy is routinely combined with radiation in breast cancer and prostate cancer. Yet, there is an apparent room for further improvements for combined modality strategies. This may be achieved by better staging classification, better imaging techniques, optimization of both modalities, strategies aimed at reducing toxicities and developing predictive markers for both efficacy and toxicity.

**Key references**


