ORIGINAL PAPER

Biologically adapted radiation therapy

Daniela Thorwarth *

Sektion Biomedizinische Physik, Universitätsklinikum für Radioonkologie, Eberhard Karls Universität Tübingen, Germany

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Abstract

The aim of biologically adapted radiotherapy (RT) is to shape or paint the prescribed radiation dose according to biological properties of the tumor in order to increase local control rates in the future. Human tumors are known to present with an extremely heterogeneous tissue architecture leading to highly variable local cell densities and chaotic vascular structures leading to tumor hypoxia and regions of increased radiation resistance. The goal of biologically adapted RT or dose painting is to individually adapt the radiation dose to biological features of the tumor as non-invasively assessed with functional imaging in order to overcome increased radiation resistance.
This article discusses the whole development chain of biologically adapted RT from radio-biologically relevant processes, functional imaging techniques to visualize tumor biology non-invasively and radiation prescription functions to the implementation of biologically adapted RT in clinical practice.

Keywords: Biologically adapted radiotherapy, Dose painting, Functional imaging, Hybrid imaging, PET, MRI

Biologisch adaptierte Strahlentherapie

Zusammenfassung

Ziel der biologisch adaptierten Radiotherapie (RT) ist es, die verschriebene Strahlendosis individuell an die biologischen Eigenschaften eines Tumors anzupassen, um in der Zukunft bessere Kontrollraten zu ermöglichen. Menschliche Tumoren zeigen eine extrem heterogene Gewebearchitektur, bedingt durch lokal stark variierende Tumorzelldichten und chaotische Blutgefäßstrukturen was zu lokaler Tumorhypoxie führt. Als Folge daraus ergeben sich Bereiche innerhalb eines Tumors, die stark erhöhte Strahlenresistenz aufweisen. Daher ist das maßgebliche Ziel der biologisch adaptierten RT bzw. des Dose Paintings eine individuelle Anpassung der Strahlendosis an die mittels funktioneller Bildgebung gemessene lokale Strahlenresistenz um eine bessere Tumorkontrolle zu erreichen.
In diesem Artikel werden Aspekte der biologisch adaptierten RT diskutiert, die die gesamte Entwicklungskette dieses Therapiekonzepts betreffen – von strahlenbiologisch relevanten Prozessen über die Identifikation geeigneter funktioneller Bildgebungstechniken, dedizierten Dosisverschreibungsfunktionen bis hin zur klinischen Umsetzung der biologisch adaptierten RT.

Schlüsselwörter: Biologisch individualisierte Strahlentherapie, Dose Painting, Funktionelle Bildgebung, Hybridbildgebung, PET, MRT

* Corresponding author: Daniela Thorwarth, Sektion Biomedizinische Physik, Universitätsklinikum für Radioonkologie, Eberhard Karls Universität Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany. Tel.: +49 07071/29 86055.
E-mail: daniela.thorwarth@med.uni-tuebingen.de

Introduction

In the last decades, radiotherapy (RT) treatment equipment including machinery as well as treatment planning concepts has experienced a number of technological innovations and developments [1–3]. Today, RT treatment is extremely fast, highly precise and benefits from a large number of degrees of freedom in terms of hard- and software options [4–6]. Thus, precise application of high radiation doses in challenging clinical scenarios such as moving target volumes and continuous anatomy changes leading to adaptation requirements for the treatment plan can be handled in clinical practice [7–9].

However, patients treated with modern, evidence based combination therapies consisting of RT, chemotherapy and eventually surgery still present with limited cure rates. For example, in locally advanced primary head and neck cancer (HNC) of patients with human papilloma virus (HPV) negative tumors control rates of only approximately 50% are reported [10,11].

Recent studies hypothesize that the major cause of the clinically observed radiation resistance lies in the biological heterogeneity of tumor tissues [12,13]. The chaotic nature of tumor growth, cell division and irregularity of vessel architecture in tumors lead to tumor hypoxia as well as varying cellular density and metabolism [12,14,15]. These phenomena and their expression levels can vary strongly throughout the volume of one single macroscopic tumor mass and thus cause different levels of radiation sensitivity inside one single tumor, varying on length scales of only millimeters in addition to temporal fluctuations [16–19]. Furthermore, it has been shown that tumors of the same histological type may present with varying gene expression patterns leading to different levels of radiation resistance [20].

Consequently, there is evidence that the biological nature of individual tumors strongly impacts the radiation sensitivity of those tumors. Thus, targeting radiation resistant regions of the tumor using escalated radiation doses may be beneficial in terms of increasing local control rates after RT. Today's RT equipment is extremely flexible and can therefore realize local dose escalations to tumor sub-volumes without increasing the dose to organs at risk (OAR) or healthy surrounding tissue. However, before such RT dose painting (DP) concepts can be clinically implemented, meaningful radiobiological targets have to be defined which can be visualized non-invasively using functional imaging techniques.

Functional imaging using positron emission tomography (PET) and magnet resonance imaging (MRI) has been shown to enable for non-invasive measurement of biological and functional processes of the tumor [21–27]. Therefore, those imaging techniques seem to be a powerful tool to base biologically adapted RT on [28–30].

Fig. 1 illustrates all steps which are necessary for a clinical implementation of biologically adaptive RT including radiobiology, functional imaging, selection of relevant imaging biomarkers, definition of a prescription function as well as the technical realization of dose painting treatment planning.

Radiobiological rationale for functional dose adaptation

The selection of the radiobiological effect to be targeted by dose painting RT concepts is one of the main challenges. In order to have a high likelihood for improved outcome, biological processes which have a strong impact on the efficiency of radiation treatments have to be targeted. Radiobiological studies have identified a few potential effects, which are relevant for the success of RT and can furthermore be visualized non-invasively.

The efficacy of radiation treatments in terms of cellular survival or tumor control probability (TCP) can be modeled in its most simple and pragmatic way using the Poisson model [31] with

$$-\ln(TCP) = n\rho\ \exp(-\alpha D)$$

where ρ is the number of cells per voxel, n the number of voxels, α the radiation sensitivity and D the applied radiation dose. In conventional RT ρ, n, and α are assumed to be constant throughout the whole tumor. Consequently, the prescribed radiation dose D is also requested to be homogeneous in the whole tumor volume in order to reach a similar cell kill

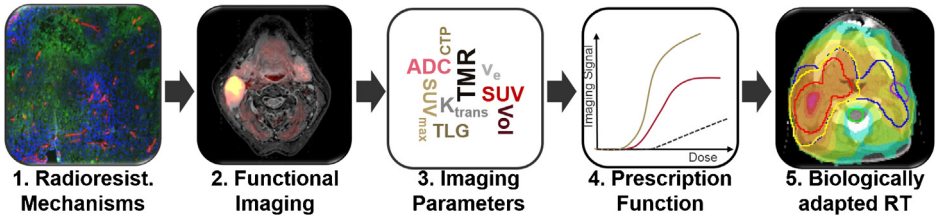

Figure 1. Schematic illustration of all steps, which have to be taken into consideration for clinical realization of biologically adapted radiotherapy. (1) Radioresistance mechanisms, here: immunohistochemical staining of a human tumor section (approx. 1 mm × 1 mm; blue: proliferation, red: vessels, green: hypoxia). (2) Functional imaging, here: [^{18}F]-FMISO PET/MR of a head and neck cancer before RT. (3) Selection of relevant imaging parameters. (4) Definition of an appropriate prescription function relating the imaging signal to a local dose prescription. (5) Planning and application of biologically adapted RT plans, here: hypoxia dose painting in head and neck cancer using photon radiotherapy.