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Methodologies in the modeling of combined chemo-radiation treatments

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Abstract
The variety of treatment options for cancer patients has increased significantly in recent years. Not only do we combine radiation with surgery and chemotherapy, new therapeutic approaches such as immunotherapy and targeted therapies are starting to play a bigger role.

Physics has made significant contributions to radiation therapy treatment planning and delivery. In particular, treatment plan optimization using inverse planning techniques has improved dose conformity considerably. Furthermore, medical physics is often the driving force behind tumor control and normal tissue complication modeling. While treatment optimization and outcome modeling does focus mainly on the effects of radiation, treatment modalities such as chemotherapy are treated independently or are even neglected entirely.

This review summarizes the published efforts to model combined modality treatments combining radiation and chemotherapy. These models will play an increasing role in optimizing cancer therapy not only from a radiation and drug dosage standpoint, but also in terms of spatial and temporal optimization of treatment schedules.

Keywords: outcome modeling, radiation therapy, chemotherapy

(Some figures may appear in colour only in the online journal)

1. Introduction
Modern medicine is developing an ever-increasing spectrum of therapies to treat cancer. In the early 20th century surgery and radiotherapy were the mainstays of treatment, joined by chemotherapy from the 1940s on and later by targeted drugs and immunotherapy in the 1990s (Devita and Chu 2008, Sudhakar 2009).
These new approaches, technical advances in existing therapies and especially the combination of different modalities have improved survival for most cancer types (Siegel et al 2012). Table 1 shows the usage of combined chemo-radiation (CRT) treatments in 8 common cancers in the United States, responsible for over half of total cancer incidence. On average 26% of the affected patients are treated with chemo-radiation, lead in total numbers by lung and breast cancer. For childhood cancers reports indicate that the proportion is even higher (Meadows et al 2009).

The paradigm of interaction between chemotherapy and radiation was conceptually described by Steel (1979) and Steel and Peckham (1979) and was summarized by Seiwert et al (2007). Generally one differentiates between two idealized modes of cooperation: spatial cooperation, which assumes no interaction between the modalities, and in-field cooperation, in which both modalities contribute to loco-regional control. In-field cooperation can further be separated into:

- Additivity: cytotoxic contributions to cell kill by chemotherapeutic agents and radiation without any modulation of effect.
- Supra-additivity (sensitization): refers to higher than additive cell kill, either through radio-sensitization through the chemotherapeutic agent or vice versa.
- Infra-additivity (protection): refers similarly to an antagonistic effect between the modalities.

These represent a qualitative, idealized classification that is rarely represented in actual treatment scenarios. Cisplatin for example, a potent platinum-based cytotoxic drug, has also radiosensitizing properties (Lawrence et al 2003). The mechanisms underlying the synergistic effects of combining chemotherapy and radiation have been well documented, as reviewed by Seiwert et al (2007), but are hard to quantify in vivo on a patient specific basis.

In the clinical setting cytotoxic agents and radiotherapy can be combined concurrently, i.e. at the same time, or adjuvant/neoadjuvant, i.e. chemotherapy following/preceding radiation.

### Table 1. Total cancer incidence in the US 2015 and the percentage treated with combined chemo- and radiotherapy for eight common cancers.

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidence US 2015 number in thousands (% of total)</th>
<th>Percentage treated with chemotherapy and radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>234 (14.1)</td>
<td>25%</td>
</tr>
<tr>
<td>Lung</td>
<td>221 (13.3)</td>
<td>29%</td>
</tr>
<tr>
<td>Colon</td>
<td>93(5.6)</td>
<td>40%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bladder</td>
<td>74(4.5)</td>
<td>30%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-hodgkin lymphoma</td>
<td>72(4.3)</td>
<td>12%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>55(3.3)</td>
<td>12%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Head and neck</td>
<td>46(2.8)</td>
<td>30%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rectal</td>
<td>40(2.4)</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Total (8 sites above)</strong></td>
<td><strong>835 (50.4)</strong></td>
<td><strong>26%</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> Estimated based on Vander Walde et al (2014).

<sup>b</sup> Numbers for combination chemo-radiation not available, estimated using number for chemotherapy with and without radiotherapy, giving the maximum number of cases where chemo-radiation can play a role in treatment.

Large clinical trials have shown that this can have clear effects on outcome, for example RTOG 9410 which showed that concurrent chemo-radiation, outperforms neo-adjuvant chemo-radiation in locally-advanced lung cancer patients (Curran et al 2011).

The dosage and scheduling of combined therapies are largely based on clinical experience and to some extent on clinical trials. There is no bio-mathematical modeling involved. This is in stark contrast to radiation-only treatments, where the optimization of delivery, fractionation and dosing has played a major role over the past decades. Further, despite the obvious importance of alterations in scheduling and dosing of radiation and chemotherapy, these modalities are usually considered separately and only heuristic attempts are made to optimize their combined application.

Gallasch et al (2013) have published a very general review of selected mathematical models without a detailed outline of the methodologies. Swierniak et al (2009) have reviewed mathematical models describing cell cycle, angiogenesis and cellular regulatory networks aimed towards optimizing therapy.

In this review we summarize the concepts that are currently used to quantitatively model the combined effect of radiation and chemotherapy, focusing on the methods and assumptions employed in the different approaches. There are at least three main ingredients necessary to model a tumor’s response to a protracted course of radiation therapy and chemotherapeutic agents: the response to a given dosage of radiation and/or drugs, and the growth of the tumor during and after treatment. Therefore we start with a brief overview of the existing models of tumor growth and the effects of radiation and chemotherapeutic agents alone, before reviewing models describing combined modality treatments.

2. Modeling tumor growth and the effects of radiation and chemotherapy alone

2.1. Tumor growth modeling

The size of a tumor and its evolution with time is one of the most basic observations to be made about cancer. The simplest model imaginable assumes that all cells in a tumor continuously divide in an unconstrained fashion, leading to exponential growth (1.1). Even though exponential growth describes the early stages of tumors and short observation periods well, it does not fit the clinically observed pattern of slowing growth with tumor size (Guiot et al 2003). Laird (1964) was the first to apply the Gompertzian growth formalism to cancer, which assumes an exponentially decreasing growth rate, and whose growth asymptotically approaches a certain capacity \( K \) (1.2). Logistic growth (1.3) was originally derived to model population growth under environmental constraints (similar capacity factor \( K \)) and fits data equally well as Gompertzian growth (Gerlee 2013). However, both of these models inhabit the same ‘phenomenological void’ (Gerlee 2013), i.e. have parameters without direct biological interpretation. The Bertalanffy model (1.4) (Bertalanffy 1957) on the other hand has parameters allowing direct biological interpretation when fitting biological data but is not very popular. The models are outlined below:

\[
\frac{dV(t)}{dt} = \rho V(t) \quad \text{Exponential} \quad \text{(1.1)}
\]

\[
\frac{dV(t)}{dt} = \rho V(t) \log \frac{K(t)}{V(t)} \quad \text{Gompertz} \quad \text{(1.2)}
\]
\[
\frac{dV(t)}{dt} = \rho V(t) \left(1 - \frac{V(t)}{K(t)}\right) \quad \text{Logistic} \quad (1.3)
\]

\[
\frac{dV(t)}{dt} = \alpha V(t)^{2+\beta} - \beta V(t) \quad \text{Bertalanffy.} \quad (1.4)
\]

Depending on the dataset under consideration, different growth laws are able to predict future tumor growth to varying degrees. For an excellent overview over growth models we refer to Gerlee (2013) and Benzekry et al (2014).

Apart from these very generic models researchers have also developed very specific growth models for certain sites. For example Swanson et al (2008) used a diffusion-reaction type differential equation to model the growth and spread of glioblastoma in the brain.

Over the past decades the focus has shifted from these macroscopic growth models to the microscopic mechanisms of cancer genesis, differentiation and progression, together with our formidable gains in knowledge about the genetic and molecular underpinnings of cancer (Bozic et al 2010). Even though our understanding about the different sub-populations of cancer has increased vastly in the past decade (Baumann et al 2008, Durrett et al 2011), the different compartments used in the various approaches still need a growth model themselves. Clinically, tumor size is still one of the main observables and underpins the definitions of staging, regression and progression of disease. Thus, the models mentioned above can be used to calculate optimal time periods between screening images (Hart et al 1998) or the time to regression after therapy (Clare et al 2000).

2.2. Radiation effect modeling

Radiation effect models have been in widespread use to interpret clinical data for decades (Fowler 2010), their main purpose is to calculate the iso-effect of different dose fractionation schedules applying the BED (biologically equivalent dose) concept.

They evolved from basic radiobiology research and the description of cell survival curves, i.e. the relationship between the surviving fraction of cells in vitro to the dose they were exposed to. The earlier theories were single/multi-target theory models that provided a phenomenological description without proper biological basis, before more mechanistically motivated descriptions were developed (Rossi and Zaider 1992, Joiner and Van der Kogel 2016).

The most widely used is the linear-quadratic model, which describes cell survival as a term linear and one quadratic in dose \(D\), shown in its general formulation in (2.1). \(G\) is the generalized Lea–Catcheside time-factor (2.2) for any arbitrary Dose rate function \(\bar{D}(t)\), which accounts for fractionation effects (Lea and Catcheside 1942)

\[
\text{cell survival} = \exp\left[-(\alpha D + \beta GD^2)\right] \quad (2.1)
\]

\[
G = \frac{(2/D^2)}{\int_{-\infty}^{\infty} \bar{D}(t)dt \int_{-\infty}^{t'} e^{-\lambda t' - \mu t'}\bar{D}(t')dt'} \quad (2.2)
\]

The linear quadratic model was initially motivated as a fit to in vivo iso-effect curves (Fowler 1989). Generally speaking, two classes of mechanistic radiation effect models stand out at this point in time: the binary-repair/lesion-interaction models on one hand, to which the linear-quadratic model can be counted, and the saturable repair models on the other. Popular exponents of the former include the lethal-potentially-lethal (LPL) (Curtis 1986) and the repair-misrepair (RMR) models and their variations (Tobias 1985). They usually have a binary misrepair term.
in common, which conceptually leads to an interaction of sub-lesions and describes the more-than exponential decrease of cell survival with dose (Tobias 1985, Curtis 1986). Additionally, repair is assumed to be independent of dose or initial damage, which sets them apart from the saturable repair models, in which repair capacity decreases with dose (Brenner et al 1998). It has been shown (Brenner et al 1998) that these models lead to similar predictions of time-dose relationships for all but the highest fraction sizes, which can be reduced to the formulation in the commonly used linear-quadratic model. It can therefore be concluded that the LQ model is a surprisingly robust tool to calculate the iso-effect of various dose and fractionation regimes.

The radiation effect models solely describe the cell kill through radiation and the repair dynamics thereafter. To simulate a protracted course of radiation therapy they have to be combined with the tumor growth models (2.1) to include the effects of normal or accelerated growth (repopulation) during and after therapy. Excellent examples for the application of such radiation-only models combined with specialized growth models can be found in the optimization of radiotherapy regimen for glioblastoma, a highly invasive brain tumor with poor prognosis (Corwin et al 2013, Badoual et al 2014, Rockne et al 2015).

2.3. Chemo effect modeling

For a long time the prevailing theory of chemotherapy cell kill was the ‘log kill’ hypothesis, which states that a given dose of chemotherapeutic agent kills a certain fraction of existing cancer cells, regardless of tumor size (Skipper et al 1964). This was based on observations in experimental mouse models of leukemia, which showed exponential growth. Observations in other model systems lead to the Norton–Simons hypothesis (Traina et al 2010), predicting that the rate of tumor regression due to chemotherapy is proportional to the rate of growth of the unperturbed tumor of that size. This has led to the emergence of ‘dose-dense’ treatment schedules, for example for the treatment of metastatic breast cancer with Capecitabene (Norton et al 2005, Traina et al 2008).

Kohandel et al (2006) has investigated the difference between the predictions of these different chemotherapy cell kill models for ovarian cancer. Others have incorporated the relatively simple log cell kill model into complex multi-scale models including different cell populations and spatio-temporal discretization (Stamatakos et al 2010).

Lately the focus has shifted to the modeling of resistance, as this continues to be the main obstacle in the successful treatment of late-stage disease with targeted agents (Foo et al 2012). The theory behind the emergence of resistance is usually based on variations of the work of Luria and Delbrück in the field of bacteriology (Luria and Delbrück 1943). These fundamental concepts were applied to chemotherapy resistance by Goldie and Coldman in a series of seminal papers (Goldie and Coldman 1984, Goldie et al 1988a, Goldie 2001). Their work has led to two main conclusions, which have since been widely applied in the design of treatment schedules and became known as the Goldie–Coldman hypothesis.

I. Chemotherapy should be started as early as possible, as the probability of cure is inversely related to tumor size, as the size of the cell population is related to the probability that a resistant phenotype has occurred.

II. Multiple chemotherapeutic agents should be used concurrently whenever possible, otherwise in an alternating manner. This should exert a maximal effectiveness against heterogeneous cell populations.

This has lead to the emergence of evolutionary cancer modeling, which contributes to a better understanding how drug resistance arises and the development of improved dosing schedules. For an excellent review on these issues we refer to Foo and Michor (2014).
These two central hypotheses in chemotherapeutic effect modeling are sometimes termed *kinetic resistance* (Norton–Simons) and *mutation-driven* resistance (Goldie–Coldman) and can lead to different conclusions about optimal drug combinations and dosing strategies (Bonadonna *et al* 2004, Lavi *et al* 2012).

3. Models describing combined chemotherapy and radiation

The models under review cover a wide range of approaches. Section 3.1 reviews models employing very general methodologies, which are not tailored towards a specific disease site or clinical hypothesis. Section 3.2 covers models that use phenomenological approaches to fit outcome data, usually based on clinical data for a specific site. Section 3.3 contains specialized, site-specific models that employ methods specifically tailored to the site or hypothesis. They cannot be easily translated to other sites and consist mostly of glioblastoma treatment models.

In each section we first review the methodologies by grouping models employing similar approaches, highlighting the differences between them. Subsequently we turn towards the results and conclusions drawn.

3.1. Generic models

3.1.1. Methodologies. Goldie and Coldman, mentioned above for their pioneering work on mutation induction and chemotherapy treatment schedules, also published a model of alternating chemotherapy and radiation (Goldie *et al* 1988b). Their stochastic model constitutes the earliest approach to the modeling of combination therapy, using a three compartment model (stem, differentiating and end cells) to model tumor growth. The therapeutic effects are parameterized as log-cell kill similar to their earlier work, though here employed to model cell kill by chemotherapy as well as by radiation. The interesting feature in their model is the inclusion of multiple sub-populations resistant to therapy, chemo-resistant as well as radio-resistant, and an extra parameter that measures the overlap of the populations, i.e. cells exhibiting joint resistance. This early innovative concept of varying chemo- and radio-resistant sub-populations and their overlap has surprisingly not been adopted by other chemo-radiation modeling approaches.

Beil and Wein (2001, 2002) formulate the sequencing of radiotherapy, chemotherapy and surgery as a control problem, using a set of differential equations to model the primary tumor and its metastases (assuming identical behavior of primary and metastatic tumor). The effects of therapy are modeled by local exponential cell kill through radiotherapy (i.e. no quadratic term in dose), systemic log-cell kill through chemotherapy and removal of a fixed fraction of primary tumor by surgery, with exponential growth assumed during therapy. They do not model the exact time course of the treatment or any interaction between chemo- and radiotherapy to keep the problem analytically tractable. However, they do model metastases that originate from dormant cells and angiogenesis in their equations, leading to an interaction of the primary tumor and metastatic compartments and to the emergence of optimal modality sequences. Their model is distinctive in its explicit treatment of metastasis and angiogenesis. However, the model’s 14 parameters are difficult to deduce from clinical data. Therefore, the model is based on a set of parameter ranges formulated as biological or clinical observations, such as ‘the kill rate of radiotherapy is greater than or equal to the kill rate of chemotherapy’.

A similar control theory approach was used by Ergun *et al* (2003) to determine the optimal scheduling and doses of angiogenic inhibitors and radiotherapy, though adapting a more mechanistic model of vascularized tumor growth (Hahnfeldt *et al* 1999). The two compartments
modeled represent tumor and endothelial cells, and while radiation is modeled as linear-quadratic cell kill acting on all cells, log-cell kill by angiogenic inhibitors only acts on endothelial cells. The tumor compartments Gompertzian growth is limited by the carrying capacity, i.e. the size of the endothelial compartment.

Salarí et al (2013) extend the biologically-effective dose (BED) model with a term linear in chemotherapy dose (independent cell kill), and a multiplicative term linear in chemo- and radiotherapy dose (radiosensitization). The main difference to the models above is therefore that the radiosensitizing effect of chemotherapy only acts on the linear term of survival, not on the quadratic one.

In a series of papers, Powathil et al (2012) develop a multiscale model based on cellular automata to investigate the spatial distribution and microenvironment of a cell population during treatment. The spatial domain consists of a 2D grid with randomly distributed blood vessels, each point representing either a cancer cell, a blood vessel or extracellular matrix. Cell-cycle dynamics, as well as oxygen and drug diffusion dynamics are explicitly modeled through differential equations. Chemotherapy effect is estimated through a modified log cell-kill model, which only kills cells above a certain drug concentration threshold. For radiation effect, the linear-quadratic model is modified with two separate factors: an oxygen modification factor to take into account the impact of a cell’s oxygenation status on its radiation sensitivity, and a cell cycle factor to modify its sensitivity according to its current cell cycle.

Although the following two publications do focus on specific sites (glioblastoma, head and neck), their methods are presented in this section because they can be applied to other sites as well.

Barazzuol et al (2010) model radiotherapy in the treatment of Glioblastoma using the linear quadratic model and investigate the additional effect of temozolomide in two simplified scenarios. Either the drugs effect can be characterized as only cytotoxic, modeled as independent log cell kill, or as modification of the radiosensitivity parameters of the linear-quadratic model.

Marcu et al (2006) use a stochastic approach, representing the tumor by a stem cell, a proliferating and a quiescent cell compartment. The cell cycle is explicitly modeled with varying radiosensitivity in the different phases, a recruitment factor brings quiescent cells back to the proliferating population after radiotherapy, and chemotherapy arrests cells in the more radiosensitive G2 phase for a set time. Through these indirect mechanisms an interaction between chemotherapy and radiotherapy arises. They do not explicitly model radiotherapy fractionation, instead they assume a fixed survival fraction, depending on cell cycle, after each 2 Gy fraction. Daily and weekly doses of chemotherapy are similarly modeled as inducing a fixed fraction of G2 arrest and cell kill.

These two last studies (Barazzuol et al 2010) illustrate two very different model approaches as shown in figure 1. The model used by Marcu and co-authors can be described as a bottom-up approach, using cell cycle and radiosensitivity parameters taken from in vitro studies to inform their model. Barrazuol et al on the other hand start out with the survival curves from a clinical trial, and work their way backward to derive in vivo parameters from patients in a top-down procedure. Which approach is advisable depends on the research question and available data at hand, but generally it is assumed that top-down approaches yield parameters that are closer to the in vivo situation, while bottom-up models allow for more extrapolation outside of current clinical experience.

3.1.2. Results and discussion. The described models differ widely in their approach. Table 2 gives an overview over their assumptions and the conclusions that can be drawn from them. This section summarizes the main findings.
The conclusions Goldie and Coldman (1988b) draw from their work are primarily focused on therapy sequencing and its impact on resistance development (the stem-cell compartment), in line with their earlier work on multi-agent chemotherapy (Goldie and Coldman 1984). They show that a regimen consisting of three doses of chemotherapy and radiation in an alternating fashion is superior to sequential treatment to the same doses in the same period, because it leads to a better suppression of the resistant subpopulation causing treatment failure. This confirms animal studies carried out in rats using hepatoma cell lines. The model does not include host response and can thus not quantify absolute survival, only predict qualitative relationships between the regimen.

The model of Beil and Wein (2001, 2002) is above all concerned with the sequencing of surgery (S), chemotherapy (C) and radiotherapy (R). The large set of parameters used in their model makes their recommendations qualitative in nature, but the use of ranges of parameters formulated as clinical observations elegantly circumvents the question of exact parameter estimation and increases the robustness of the predictions. They conclude that SCR is preferable to SRC, if the metastatic tumor load is large relative to the primary tumor. They also propose a new schedule (SRCR) with a split radiotherapy regimen, which maximizes tumor control probability under certain assumptions for vascular growth.

Ergun et al (2003) makes more quantitative predictions, not only about the sequencing of the biologic agent and radiation, but also about the dosing schedule. The optimal combination regimen occurs when antiangiogenic therapy is constantly escalated to maintain an optimal tumor-to-vasculature ratio, while radiation fraction sizes change over therapy to maximize tumor control probability.

Salari et al (2013) investigate how the addition of a chemotherapeutic agent and its mode of action change the optimal fractionation regimen for concurrent chemo-radiotherapy. They conclude that the addition of chemotherapeutic agents with only additive cytotoxic effect does...
Table 2. Overview of the methodologies used in different models and the conclusions drawn.

<table>
<thead>
<tr>
<th>Model properties</th>
<th>Radiation modeling</th>
<th>Linear-linear-quadratic</th>
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<td>Oxygen/drug diffusion</td>
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<td>Specific site</td>
<td>GBM</td>
<td>H&amp;N</td>
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**Note.** Models are ordered as they appear in the text. Abbreviations/symbols used: ordinary differential equation (ODE), partial differential equation (PDE), glioblastoma multiforme (GBM), head and neck (H&N),

* = generalized.

* = modified.

* = diffusion included.
not alter the optimal fractionation regimen present without concurrent chemotherapy, while a radiosensitizing agent may alter the optimal choice of fraction size. Depending on the ratio of radiosensitization in normal compared to target tissue, the optimal regimen changes from hypo- to standard-fractionation. They also demonstrate that if a drug is both independently cytotoxic as well as radiosensitizing, it can lead to the emergence of optimal non-uniform fractionation protocols. This study is very comprehensive in the sense that they explicitly include the drug and radiation effects in the normal tissue, drawing conclusions not only about higher tumor cell kill, but also about a higher therapeutic index of varying fractionation schedules.

Powathil et al analyze the efficiency of various sequences of cell-cycle specific chemotherapeutic agents, either active in G1 or in G2-M-S phase, on total cell-kill and the cell cycle distribution among surviving cancer cells (Powathil et al 2012). Moreover they simulate experimentally measured cell cycle re-distribution after radiotherapy and the varying combinations of cell-cycle specific drugs with radiotherapy (Powathil et al 2013). To show a clinical application they apply their model to two known and one hypothetical treatment regimen for esophageal cancer, concluding their proposed alternative regimen to be more effective.

Barazzuol et al (2010) investigate the interaction of temozolomide and radiotherapy in the treatment of Glioblastoma, adjusting their model parameters to the outcome data of the EORTC-NCIC trial (Stupp et al 2005). Their main goal is to answer the question if the benefit of temozolomide comes from its radiosensitizing properties in the concurrent phase or from the additional cell kill of the adjuvant phase. They conclude that the model assuming only radiosensitization matches the observed survival curves more closely than assuming independent cytotoxicity. Notable in their approach is the efficient use of the available outcome data, fitting their model not only to specific points of the survival curve, i.e. 1 year or 2 years overall survival, but to the entire curve.

Marcu et al (2006) investigate different time courses of cisplatin and radiotherapy for advanced head and neck cancer. The amount of cell recruitment after radiotherapy increases the interaction of cisplatin and RT and therefore the cell kill of the combined therapy schedules significantly. They conclude that to observe the true synergistic effect between cisplatin and RT reported in the literature, they would have to include a proper radiosensitizing term. They demonstrate that weekly administration of cisplatin leads to lower tumor control than daily doses, and that the combined effect is maximal if cisplatin is given close in time to the radiation fractions.

3.2. Phenomenological models based on outcome data

3.2.1. Methodologies. In the following paragraphs we describe a group of models that fit a function, usually logistic, to clinical data (following a ‘top-down approach’ as shown in figure 1). As outcome data is the foundation of these models, the derived parameters apply typically only to one specific site, and often do not allow a specific mechanistic biological interpretation. They do allow broad inferences about the mode of action of chemotherapy in combination with radiation (independent cell kill versus sensitization), and have the advantage that they are derived directly from clinical outcome data.

Jones and Dale investigate the chemo-radiation problem in two publications (Jones and Dale 1999, 2005). In the earlier paper they modify the linear quadratic model to study radiation sensitizers by including a sensitizing factor $s$ that acts as a multiplying factor on the dose. Furthermore the effect of repopulation is modeled, as well as the complete suppression of repopulation by cytostatic drugs. In their second paper they also include independent cell kill due to chemotherapy, defining the effect of cytotoxic chemotherapy as radiation equivalent biologically-effective dose (CBED) (Jones and Dale 2005). The same CBED formalism is
used in an investigation studying the contribution of independent cell kill by chemotherapy to local tumor control in cervical cancer by Plataniotis and Dale (2008). Later the model was expanded to investigate also a radiosensitization-only mode of action similar to Jones and Dale (1999), without independent cell kill, in an analysis of bladder cancer outcomes (Plataniotis and Dale 2014). The authors do discuss the combination of both effects, though in their case a simultaneous fit does not provide a better match to their noisy outcome dataset.

The additive effect of chemotherapy in head and neck cancer was investigated using a simple BED model by Kasibhatla et al (2007) and later improved by Fowler (2008).

Arvidson et al (2009) included repopulation and incomplete repair of sublethal damage to model accelerated schedules in their dose-response model of limited-stage small-cell lung cancer. Chemotherapy was modeled in a slightly different way compared to the approaches above, treating the progression-free survival for chemotherapy-only as baseline for the response curve of the chemo-radiation model, as described in equation (3.3).

Two papers explore clinical outcomes for pancreatic cancer, which is usually treated with chemo-radiation for locally advanced disease. Moraru et al (2014) model response using a modified linear-quadratic model that accounts for initial tumor size and repopulation, and incorporates chemotherapy as sensitization-only process. Durante et al (2015) on the other hand investigate chemotherapy as a purely additive effect, but study x-rays and charged particles separately.

A set of studies explore outcome and mucosal toxicity in head and neck cancer (Hartley et al 2010, Meade et al 2013a, 2013b), using a chemo-equivalent BED for tumor and mucosal toxicity. They include repopulation effects, though Meade and co-authors use three different methods to integrate chemotherapy: additional chemo-equivalent BED added with, without or with variable repopulation (by varying the doubling time during accelerated repopulation).

Pettit et al (2013) extend the work of Hartley et al, using the same model and chemo-equivalent BED concept. They investigate if the parameters derived from head and neck squamous cell carcinoma can be used to predict outcomes for anal squamous cell carcinoma and separate the clinical studies into subgroups according to differing chemotherapy schedules.

The equations (3.1)–(3.3) illustrate the different approaches used to integrate chemotherapy into the BED concept by the phenomenological models discussed in this section. Equation (3.1) describes the probability of response, here taken to be overall survival (OS), as simply the additive effects of radiation-only (RS) and chemotherapy-only survival (CS), similar to Durante et al (2015). Equation (3.2) shows RS modeled as logistic curve with an optional radiosensitization parameter s, conceptually similar to the formulations employed by Jones and Dale (1999), Moraru et al (2014) and Plataniotis and Dale (2014). Equation (3.3) shows an approach that also assumes independent modes of action, but incorporates chemotherapy as ‘baseline-response’, i.e. as the survival at zero radiation dose (Arvidson et al 2009)

\[
\text{OS} = \text{RS} + \text{CS} (1 - \text{RS})
\]  
\[
\text{RS} = \frac{1}{1 + \exp \left[ 4s_0 \left( 1 - \frac{s \times \text{BED}}{D_{50}} \right) \right]}
\]  
\[
\text{OS} = \text{CS} + \frac{1 - \text{CS}}{2} \left[ 1 + \text{erf} \left( \frac{\text{BED} - D_{50}}{\sqrt{2}s_0} \right) \right]
\]

All of the models above use the linear-quadratic formalism to account for different fractionations, though the methods to include additional parameters (repopulation, initial tumor size) vary.
3.2.2. Results and discussion. Jones and Dale study how cytostatic, i.e. preventing proliferation, and radiosensitizing chemotherapies can be combined with radiotherapy, and how they are affected by accelerated repopulation and perfusion changes (Jones and Dale 1999). One of their main conclusions is that delayed application of chemotherapy is preferential, especially in the presence of accelerated repopulation. The same authors (Jones and Dale 2005) include the scenario of independent cytotoxicity and show which degree of radiosensitization or cell kill needs to be present for a specific increase in tumor control probability. In another publication (Plataniotis and Dale 2008), this approach of independent cell kill is applied to clinical data from cervical cancer trials, deriving the chemo-equivalent BED of concurrent chemotherapy for this setting.

Arvidson et al (2009) have tailored their model to small cell lung cancer with the aim to optimize the treatment time for a fixed late complication rate. They conclude 3 weeks to be an optimal overall treatment time and that a BID (twice daily) schedule would be advantageous at that treatment length, even though the clinical differences at longer schedules are not significant.

Hartley et al (2010) explore the trade-off between tumor control and mucositis in head and neck cancer. They infer that concurrent chemotherapy adds more to local control (9.3 Gy_{10}) than to mucosal toxicity (6.4 Gy_{10}). If only radiation dose-escalation, instead of chemotherapy, would have been used to increase the dose to the same BED, mucosal dose would have been risen by 11.6 Gy_{10}. Thus, chemo-radiation is sparing the mucosa the equivalent of 4.3 Gy in 2 Gy fractions compared to pure radiation dose escalation. In two later studies, Meade et al (2013a, 2013b) investigate three different approaches to model the addition of chemotherapy. All assign a chemo-equivalent BED to chemotherapy, but repopulation is either neglected, modeled the same as in radiation-only, or assumes varying values for the doubling time during accelerated repopulation. Even though all models correlate with the clinical data, the assumption of accelerated repopulation with a doubling time of 5–10 d leads to the strongest correlation.

All models above describe repopulation as a kind of accelerated growth phase that cells enter during treatment, sometimes with a delay. The validity of this description depends on the site and is controversial (Yom 2015) as it might not always represent the biological findings (Duru et al 2014).

Pettit et al (2013) derive a chemotherapy BED from published data for head and neck squamous cell carcinoma, similar to Hartley’s work (Hartley et al 2010). They separate various chemotherapy regimens, deriving chemotherapy equivalent BED values from 3 Gy for mitomycin C to 12.7 Gy for platinum/5-fluorouracil doublets. Then they apply the global average of 9.3 Gy that synchronous chemotherapy adds for head and neck squamous cell carcinoma, also derived earlier by Hartley et al (2010), to anal squamous cell carcinoma. They predict a theoretical improvement in local control of 24.6%, compared to an observed value of 21.4% in clinical trials. They also predict outcome improvement for trials with a differing chemotherapy schedule, and demonstrate that adjusting the BED value according to the schedule differences improves outcome predictions. Even though their paper is about anal squamous cell carcinoma, their re-analysis of the head and neck data is an interesting result and generates hypotheses to be clinically tested.

Table 3 shows a compilation of the quantifiable results of chemotherapy effects for the models presented here, showing a significant range in calculated effectiveness from <1 to 94 Gy chemotherapy effect equivalent. It has to be kept in mind that these values are relative to the effectiveness of radiation as a single modality in a given site. For example the unusually large chemo-therapy equivalent dose derived by Durante et al (2015) is mainly caused by the low 1 year survival probability with radiation alone, which is rarely performed these days and had to be fit using older clinical data.
Table 3. Quantified chemotherapy contributions either as chemo-equivalent radiation dose or as radiosensitization factor.

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>Site</th>
<th>Effect type</th>
<th>Effect of chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plataniotis and Dale (2008)</td>
<td>Cervix</td>
<td>Independent action</td>
<td>Equivalent to 0.4–8 Gy in 2 Gy fractions, depending on tumor radiosensitivity</td>
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<tr>
<td>Kasibhatla et al (2007) and Fowler (2008)</td>
<td>Head and neck</td>
<td>Independent action</td>
<td>Equivalent to 8.8 Gy or 7.6 Gy in 2 Gy fractions</td>
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<tr>
<td>Moraru et al (2014)</td>
<td>Pancreas</td>
<td>Sensitization only</td>
<td>Radiosensitization factor 1.18–1.35</td>
</tr>
<tr>
<td>Plataniotis and Dale (2014)</td>
<td>Bladder</td>
<td>Independent action or sensitization</td>
<td>Equivalent to 36.3 Gy in 2 Gy fractions or radiosensitization factor of 1.3</td>
</tr>
<tr>
<td>Durante et al (2015)</td>
<td>Pancreas</td>
<td>Independent action</td>
<td>Equivalent to 94 Gy or 67 Gy</td>
</tr>
<tr>
<td>Pettit et al (2013)</td>
<td>Head and neck</td>
<td>Independent action</td>
<td>Equivalent to 3–12.7 Gy, depending on chemotherapy regimen</td>
</tr>
<tr>
<td>Pettit et al (2013)</td>
<td>Anal</td>
<td>Independent action</td>
<td>Equivalent to 4.1 Gy for 5-FU and 9.1 Gy for MMC/5-FU</td>
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</table>
This reveals a frequently neglected weakness when using generalized dose-response curves over a wide range of data. The main approaches in use are the Poisson, the logistic and the probit models. And even though these models can give similar results, especially with data points in the 30–70% response range, they can differ substantially at the tails of the distribution. Given an underlying logistic dose-response pattern, fitting a Poisson model could severely underestimate the steepness of the response. This can have a disproportional impact when radiation-only, at the low response end of the distribution, and chemo-radiation data are fitted on the same response curve, as with many of the studies above. For further reading on this topic we refer to Bentzen and Tucker (1997).

Furthermore the dose-response model used above rest on certain assumptions, e.g. the Poisson model assumes a Poisson distribution of surviving clonogens after treatment. Presenting results as chemo-equivalent radiation dose (in Gy) neglects potential differences in mechanism between radiation and chemotherapy and implicitly applies radiotherapy mechanisms also to chemotherapy.

### 3.3. Site-specific models

#### 3.3.1. Methodologies

Vogelius et al (2011a, 2011b) model chemotherapy as an independent cytotoxic process. It is quantified in terms of chemotherapy equivalent radiation dose (CERD), uniformly distributed across the patient, similar in concept to the more general approach of chemo-equivalent BED used in many of the phenomenological models in the previous section. What sets it apart is the combination of this homogenous chemo-equivalent dose background with the actual spatial dose distribution in the patient. They use a critical volume model, where each functional subunit has a tolerance of 20 Gy, to estimate the risk of radiation pneumonitis. This causes the chemo-equivalent background to interact differently with the dose distribution, leading to a varying normal tissue complication probability of 3D-conformal compared to intensity-modulated radiotherapy. We classified this approach as site specific since it is very tailored to lung as organ at risk, where the dose bath characterized by $V_{20}$ and $V_{10}$ plays a dominant role in toxicity, a situation not arbitrarily transferable to other organs.

The following paragraphs describe a suite of models tailored to high-grade glioma, a common and aggressive type of primary brain cancer characterized by low survival and high rates of recurrence. Its highly invasive behavior complicates surgical resection and makes specialized volumetric growth formulations a key component of all models. The relative large interest of modelers in this site can be explained by the low median survival, which has seen its only increase in decades through the addition of temozolomide to radiation (Stupp et al 2009). This indicates that on one hand beneficial modifications of therapy can be easily detected, on the other that the clinical community is more inclined to embrace alternative treatment regimens to improve dismal outcomes.

Powathil et al (2007) combine a diffusion-reaction type glioma growth model (Swanson et al 2008) with logistic local growth, enabling them to simulate the spread of glioma cells along white fiber tracks in the brain and therefore the variable cancer cell density throughout the volume. They describe radiation effects with a generalized linear-quadratic model including repair to describe accelerated schedules (multiple fractions per day), and temozolomide effect by log cell kill.

A similar model simulating glioblastoma growth, proliferation and treatment has been developed by Eikenberry et al (2009). The main difference is the division of the cell population in two classes, proliferating cells and migrating cells, with stochastic transitions between them. In contrast to Powathil et al (2007), radiation and chemotherapy are modeled in the
same fashion, both as killing a fixed fraction of cells, though acting differently on the proliferating and migrating cell compartments.

3.3.2. Results and conclusions Vogelius et al (2011a, 2011b) compare the risk of radiation pneumonitis for lung cancer patients treated with different radiation modalities, i.e. dose distributions. They conclude that above a certain dose of chemotherapy, less conformal radiation techniques, such as 3D-conformal radiotherapy, could lead to less radiation pneumonitis than more conformal techniques such as IMRT and tomotherapy. Their results can be explained by the interplay between the critical volume model used and the way they incorporate chemotherapy, as homogeneous chemo-equivalent background of radiation dose. As intensity-modulated techniques spread the dose more over a larger lung volume, an increase of this background above a certain value leads to more functional subunits being pushed over their 20 Gy tolerance threshold than with 3D-conformal techniques, which focus higher radiation doses in smaller volumes.

Powathil et al (2007) model the treatment of glioblastoma patients with radiotherapy with and without temozolomide after surgery. They first study different fractionation schedules of radiotherapy only, concluding that hyperfractionated treatments (1.2 Gy twice per day) to the same total dose do not significantly improve survival, in agreement with published clinical trial data. They further deduce the temozolomide cell-kill parameters from published survival data and compare different sequencing combinations with the same dose of chemotherapy and radiotherapy. Their modeling suggests that a hypothetical neo-adjuvant + adjuvant chemotherapy combination is slightly superior to the conventional concurrent + adjuvant temozolomide/RT combination.

Eikenberry et al (2009) demonstrate that their glioblastoma model can reproduce clinically observed behaviour and show a non-linear relationship between resection margins and time to regrowth. They deduce from their model that to delay recurrence, it is necessary to increase resection margins in combination with aggressive post-surgery chemo-radiation.

4. Discussion and conclusion

4.1. Sites

The sites most prominently featured are glioblastoma, head and neck, and lung, indications where combination therapy plays an important role in clinical management. Noteworthy is the small amount of attention that breast cancer receives (with the exception of Beil and Wein (2002)) despite its high incidence (see table 1), which might be due to the role of surgery in this setting. We have not specifically included surgery, the third standard modality in cancer care, as it usually presents a binary decision (surgery yes/no) and does not lend itself easily to treatment adaptation or optimization. In the few publications that include surgery, it is usually represented as a simple bulk removal of tumor cells (Beil and Wein 2001, 2002).

Examining table 1, colon, bladder and non-Hodgkin lymphoma stand out as high incidence sites where combined CRT plays a crucial role. Childhood cancer also features a high fraction of combined CRT treatments and good prospects for modeling.

Figure 2, which classifies the reviewed models based on their approach and application, shows the relationship between site-specificity and modeling approaches. Site-specific models, studying lung and glioblastoma, are all based on clinical data and tend to be more phenomenological in nature than their more mechanistic counterparts based on in vitro data. The phenomenological models on the other hand employ very general methods, though are based on such indication-specific data that they form their own category in the lower left of the figure.
4.2. Normal tissue modeling

Normal tissue toxicities play only a minor role in modeling studies. Only four models include a normal tissue aspect in their investigations (Vogelius et al. 2011a), even though a main feature of clinical practice is the trade off between normal tissue complications and tumor control, i.e. exploiting/increasing the therapeutic window. A possible explanation is that the exact mechanisms that lead to toxicity from chemotherapy are not well understood, even less in combination with radiation.

This will become even more important in the future, as targeted therapeutics often result in off-target effects, for example the cardiac toxicity seen with anti-ERBB2 agents or tyrosine-kinase inhibitors (Force and Kolaja 2011, Zambelli et al. 2011). As the exact role of radiation in cardiac toxicity is only taking shape clinically and is still an area of active research (Lenihan et al. 2013), formulating models that explain combined effects remains elusive for now.

Given the high long-term survival rates that chemo-radiation has achieved in pediatric cancer, it is conceivable that especially in this setting chemo-radiation modeling will focus on toxicities while maintaining the high tumor control probabilities of current regimen.

4.3. Radiotherapy effect modeling within chemo-radiation models

The linear-quadratic model seems to be the clear preference to model radiation therapy, though there are a few significant variations how it is employed in detail. In models using multiple cell compartments, it is used with compartment dependent parameters, modifying for example the cell cycle distribution (Marcu et al. 2006) or the ratio of proliferating to migrating cells...
While being applied for this purpose frequently in radiation therapy, the linear-quadratic formalism is utilized for assessing varying fraction sizes and dose schedules in chemo-radiation treatments only rarely (e.g., Ergun et al. (2003), Powathil et al. (2007)).

4.4. Chemotherapy effect modeling within chemo-radiation models

The log-cell kill model, i.e. killing a fixed fraction of cancer cells, is the standard choice to model chemotherapy. No model under review employs the Norton–Simons model (Traina et al. 2010) described in section 2.3, in which the effect is proportional to the growth rate, i.e. the proliferating fraction. Some authors modify the log-cell kill model, letting it act differentially on proliferating cells (Marcu et al. 2006, Eikenberry et al. 2009), which makes these models behave according to the Norton–Simons hypothesis.

Changing the doses and treatment schedules of chemotherapy is rarely modeled. Only two publications (Ergun et al. 2003, Marcu et al. 2006) are quantifying differences between chemotherapy schedules.

A possible reason is that chemotherapy dosing is complex to model quantitatively, as the delivery of drugs involves a multitude of processes, such as interstitial transport and cellular uptake, and includes many patient specific factors (Kim et al. 2013). Drug delivery spans a multitude of spatial and temporal scales, to a greater extent than radiotherapy, from the organism over the tissue and cell to the intracellular level. While radiation effects differ among cells and cellular radiosensitivity varies, at least the amount of radiation ‘seen’ by each cell is well known, even in a patient.

Drug uptake heterogeneity is an important factor in the response of tumors to therapy, and efforts are under way to investigate this in vivo (Saggar et al. 2013, Thurber et al. 2013). Such quantitative models and imaging techniques that allow to image and predict the spatio-temporal distribution of drugs in tumors will enhance our quantitative understanding of biological agents and enable more accurate models of their effect, alone and in combination with radiation. However, the constantly expanding variety of biological agents in clinical use also impedes their quantitative description, while radiation has been a mainstay of treatment for many decades.

4.5. Modeling radiosensitization through chemotherapy

Table 3 illustrates the different ways that the interaction between chemotherapy and radiation can be expressed. The models using the LQ-model for radiation modeling express this factor usually either in a dose-modifying fashion, i.e. applying a factor to the radiation dose \( d \), or in a parameter-modifying fashion, i.e. modifying the radiosensitivity parameters \( \alpha \) and \( \beta \). Figure 3 demonstrates the main difference between these two approaches: dose-modifying approaches, pictured on the left, can only modify the entire curve evenly and lead to enormous changes already in the 3–5 Gy range. Parameter-modifying approaches however can change the shape of the survival curve, for example increasing the \( \alpha \) more than the \( \beta \) parameter, leading to a straightening of the curve and affecting lower doses over-proportionately. This behavior, a change in shape of the survival curve, is often found in in vitro studies (Franken et al. 2013) and has consequences for the optimization of the fractionation scheme.

Another popular way to model the interaction between chemotherapy and radiation is in an indirect way, by a compartmentalization of the cell population in combination with a variable radiosensitivity. This classification of cells can be via the cell cycle, as often employed by multi-scale approaches that model all cells and their states explicitly (Marcu et al. 2006,
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Powathil et al. (2013). Usually the chemotherapy agent leads to temporary cell cycle arrest in a phase more sensitive to radiation, increasing cell kill through radiation. Other approaches (Eikenberry et al. 2009) divide the cells in proliferating and migrating populations with different radiosensitivity. All of the indirect approaches share the same principle: the existence of different cell states with different radiosensitivity, combined with chemotherapy acting as a modifier of transition probabilities between states, results in an interaction of drug and radiation.

All of these approaches involve a varying number of parameters, sometimes taken from in vitro or animal studies, exposing a significant weakness of most of the studies described above: the uncertainty inherent in most model parameters and the sensitivity of the model predictions to their assigned values.

This partly explains the limited clinical application of the models and represents the main challenge that needs to be addressed to demonstrate the clinical utility of biophysical modeling and anchor it in clinical practice. There are two main approaches to address this challenge, either through models yielding robust conclusions, insensitive to parameter variations, or through ones incorporating feedback loops from patient-specific response assessment to update their predictions, as discussed below.

4.6. Models yielding robust conclusions

Although it is clear that most of the models described above contain many assumptions and uncertain parameters, some interesting conclusions can still be drawn. This is especially the case if the results are robust towards the exact parameter choices of the models in use. Ergun et al. (2003) for example deduce an optimal scheduling of radiation and antiangiogenic inhibitors maximizing tumor control probability. The key insight is that the drug schedule has to escalate to maintain an optimal tumor to vasculature ratio, which seems to be robust towards the exact parameters chosen. Salari et al. (2013) present an approach including normal tissue and tumor, hence allowing statements about the therapeutic ratio of a schedule. They infer that
adding a radiosensitizer to a separately optimal radiotherapy regimen can change the choice of optimal fraction size, and even lead to non-stationary fractionation schemes being optimal. Even though the exact range of parameter ranges for which the statements above hold might be uncertain, they represent important insights and challenge current paradigms regarding how we should combine biological agents and radiotherapy.

4.7. Response imaging as input for chemo-radiation modeling

In order to develop and apply models predicting patient-specific tumor response for treatment planning or treatment adaptation, parameters used in modeling need to be measurable. The expansion of molecular imaging in the clinic is advancing our knowledge of tumor status and development during and directly after treatment, allowing for quantitative estimation of tumor parameters in vivo. The advent of new molecular imaging markers, for example FLT (\textsuperscript{18}F-fluorothymidine) as response marker to targeted therapy (Sohn et al 2008) and NaF (\textsuperscript{18}F-sodium fluoride) in castrate resistant metastatic prostate cancer (Simoncic et al 2015), provides more information to be used in biophysical models of tumor development and response to therapy (Merchant et al 2014). Magnetic resonance imaging (MRI) and optical techniques are also increasingly being investigated (Matsuo et al 2014, Ueda et al 2014, Lambregts et al 2016). Especially diffusion-weighted MRI, which gives quantitative information reflecting tumor cellularity changes yet is clinically practical, is yielding enhanced information to characterize tumor tissue and predict response (Koh and Collins 2007).

The methodologies presented in this review do not employ imaging input to inform the model and update its predictions on a patient-specific basis. In case clinical data is used, for example overall survival, it is usually employed to derive population-averaged parameters for the whole patient population.

There are some successful examples that demonstrate how to integrate patient-specific imaging information into modeling, though not directly in the field of chemo-radiation modeling. Ellingson et al (2011) use diffusion MRI as input to update a glioma growth and invasion model, estimating cell diffusion and proliferation rates based on serial images of 53 patients. Resulting proliferation rate maps were then compared to independent magnetic resonance spectroscopy results measuring the choline-to-N-acetylaspartate ratio, showing good spatial correspondence.

Weis et al (2015) use diffusion weighted MRI to inform a patient-specific response model for breast cancer. They use the images before and after the first cycle of neo-adjuvant therapy to calibrate a tumor growth model incorporating restricted cell diffusion due to mechanical stiffness, and show that the improved model vastly outperforms the standard model in the prediction of patient outcome. Diffusion-weighted MRI has also been applied in animal studies to test the validity of the underlying tumor growth models in a controlled environment (Hormuth et al 2015).

There are also efforts to incorporate multi-parametric images into models to forecast tumor development (Padhani and Miles 2010, Yankeelov 2012, Yankeelov et al 2013, 2015, Wong et al 2015).

4.8. Mechanistic models of interaction and their importance for particle therapy

None of the models reviewed has the ability to differentiate between different types of radiation, i.e. if the interaction with biologic agents differs for x-rays compared to protons or carbon ions. This would necessitate taking into account the different types of damage that
radiation inflicts, like the different number of double strand breaks or varying repair kinetics for more complex damage. Protons, for example, differ in how they inflict biological damage on the molecular, cell and tissue level, and their relative biological effect can vary based on the endpoint studied (Girdhani et al. 2013). This applies even more to heavier particles (Takahashi et al. 2003, Oonishi et al. 2012).

Durante et al. (2015) show a significant difference in clinical results for chemotherapy in combination with particle therapy in comparison to the same doses of conventional x-rays. The possible reasons for this effect are manifold, from a different oxygen enhancement ratio (Loeffler and Durante 2013), a stronger immune response (Durante et al. 2013), or a different interaction with chemotherapy. To enable modeling of different interaction effects based on radiation quality, the approach must include an explicit description of lesions and their repair, both in the radiation as well as in the chemotherapy model. Taleei and Nikjoo (2013) developed a very explicit description of double strand break repair that could be used as foundation for such an approach.

Clinical trials in particle therapy have up to now focused on the physical advantages compared to conventional radiotherapy. Modeling the different interaction of particle with chemotherapy could help identify indications and drugs as likely candidates for early phase trials.

4.9. Data mining and predictive modeling

All of the models discussed above, if based on patient data, have one aspect in common: they rely on relatively small, well-curated datasets, and are underpinned by some form of biological rationale or underlying hypothesis. They focus on one specific question, e.g. the importance of repopulation in a specific site, and they usually neglect other clinical knowledge about the patient.

In recent years other techniques have made their way into healthcare research that take a different approach: taking in as much data as possible and learning without underlying hypothesis or biological rationale. Whatever the exact term used, from ‘data mining’ to ‘machine/rapid learning’, their common aim is to aid clinical decision making by integrating data from various sources and they can be grouped under the wider term clinical decision support systems (CDSS) (Lambin et al. 2016).

For example, Dekker et al. (2014) investigated if a CDSS based on a cohort of lung cancer patients from the Netherlands can be used to predict the overall survival of a test cohort automatically extracted from the oncology information system of a clinic in Australia. They achieve a surprisingly good predictive performance and were able to reach interesting conclusions due to the differences in clinical practice inherent in the training and test datasets.

Models that arise from these data mining approaches are in general very ‘phenomenological’ in nature, but they can still give clues to biological or clinical differences among populations, that can then be further described by some of the specialized approaches described above. For a more detailed overview on the development and validation of such models in the clinic we refer to Lambin et al. (2013, 2016) and Trifiletti and Showalter (2015).

4.10. Outlook

Modeling is expected to lead to exploration of the trade-off between radiation and drug dosage. Currently both are standardized and not patient specific. A faster growing tumor that is more probable to metastasize might require more systemic agents, with a simultaneous de-escalation of radiation to achieve the same level of toxicity. Similarly different extents of vascularization or a varying proliferating fraction might make require changes in optimal drug
dosage and/or radiotherapy fractionation. Salari et al (2013) demonstrate how the addition of a drug can change the optimal fractionation regimen, a notion that is not commonplace in clinical practice and trial design. Thus, modeling is expected to guide clinical trials and decisions when new biological agents are combined with radiotherapy. As demonstrated in some of the studies discussed here, many effects can change the optimal combination regimen. An agent whose primary property is cell kill has to be combined differently with radiation than a radiosensitizer or an antiangiogenic agent. Planning a schedule employing multiple different drugs and radiation opens such a wide spectrum of possibilities that modeling will be essential to guide clinical trial design.

The main missing element for this to become reality are patient and tumor specific inputs for modeling. We still know far too little about a tumor’s state at a specific point during therapy. In the future, well-calibrated molecular imaging techniques and advanced blood analyses (circulating tumor cells, circulating tumor DNA) might fill that knowledge gap, and even be complemented by pathology and genomic data. We need to incorporate part of this enormous amount of available information into predictive tumor models, whose projections get iteratively compared to the patient’s follow-up. This will enable us to constantly refine and re-adjust our approaches and parameters, transforming modeling into an essential cornerstone of oncology practice far beyond radiotherapy.

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