Advanced Drug Delivery Reviews 109 (2017) 131–153

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Decision support systems for personalized and participative radiation oncology☆

Philippe Lambin *, Jaap Zindler, Ben G.L. Vanneste, Lien Van De Voorde, Daniëlle Eekers, Inge Compter, Kranthi Marella Panth, Jurgen Peerlings, Ruben T.H.M. Larue, Timo M. Deist, Arthur Jochems, Tim Lustberg, Johan van Soest, Evelyn E.C. de Jong, Aniek J.G. Even, Bart Reymen, Nicolle Rekers, Marike van Gisbergen, Erik Roelofs, Sara Carvalho, Ralph T.H. Leijenaar, Catharina M.L. Zegers, Maria Jacobs, Janita van Timmeren, Patricia Brouwers, Jonathan A. Lal, Ludwig Dubois, Ala Yaromina, Evert Jan Van Limbergen, Maaike Berbee, Wouter van Elmpt, Cary Oberije, Bram Ramaekers, Andre Dekker, Liesbeth J. Boersma, Frank Hoebers, Kim M. Smits, Adriana J. Berlanga, Sean Walsh

Department of Radiation Oncology (MAASTRO), GROW, School for Oncology and Developmental Biology, Maastricht University Medical Centre +, Maastricht, The Netherlands

ARTICLE INFO

Article history:
Received 15 September 2015
Received in revised form 8 December 2015
Accepted 6 January 2016
Available online 14 January 2016

Keywords:
Radiotherapy
Decision support systems
Prediction models
Shared decision making

ABSTRACT

A paradigm shift from current population based medicine to personalized and participative medicine is underway. This transition is being supported by the development of clinical decision support systems based on prediction models of treatment outcome. In radiation oncology, these models 'learn' using advanced and innovative information technologies (ideally in a distributed fashion — please watch the animation: http://youtu.be/ZDJFOxpwqEA) from all available/appropriate medical data (clinical, treatment, imaging, biological/genetic, etc.) to achieve the highest possible accuracy with respect to prediction of tumor response and normal tissue toxicity. In this position paper, we deliver an overview of the factors that are associated with outcome in radiation oncology and discuss the methodology behind the development of accurate prediction models, which is a multifaceted process. Subsequent to initial development/validation and clinical introduction, decision support systems should be constantly re-evaluated (through quality assurance procedures) in different patient datasets in order to refine and re-optimize the models, ensuring the continuous utility of the models. In the reasonably near future, decision support systems will be fully integrated within the clinic, with data and knowledge being shared in a standardized, dynamic, and potentially global manner enabling truly personalized and participative medicine.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Radiotherapy for Cancer: Present and Future".

* Corresponding author at: MAASTRO Clinic, Dr Tanslaan 12, PO Box 1588, 6201 BN Maastricht, The Netherlands. Tel.: +31 8844 55666; fax: +31 8844 55667.
E-mail address: philippe.lambin@maastro.nl (P. Lambin).

http://dx.doi.org/10.1016/j.addr.2016.01.006
0169-409X/

1. Introduction

Several major advances in cancer care (including radiation oncology) have been made in the last 5–10 years, with many new diagnostic techniques and treatment modalities becoming available [1]. This wealth of choice, however, has brought with it new challenges. Attaining level I evidence is increasingly difficult given the copious disease, patient and treatment parameters that exist, resulting in ever-increasing data heterogeneity [2]. This new reality is somewhat at odds with traditional evidence based medicine, whereby randomized trials are designed for large populations of homogenous patients. Consequently, new approaches are required to build evidence for clinical decision making based upon this wealth of patient, disease and treatment characteristics [3].

The challenge can be exemplified as follows: For each patient, the physicians must consider biology (mutations, translations, etc.), pathology, state-of-the-art imaging (including guidance techniques), blood tests, drugs/hormones, improved radiotherapy planning systems, dose, fractionation, radiation type, and, in the near future, radiogenomic data [4]. Medical decisions should balance cure rate, median survival, toxicity, comorbidity, quality of life, patient preferences (inform and involve the patient) and (in most healthcare systems) cost effectiveness [5]. This myriad of factors renders clinical decision making a dauntingly complex, and perhaps inhuman, task as human cognitive capacity is limited to roughly five factors per decision [2]. Furthermore, dramatic genetic [6], epigenetic [7], transcriptomic [8], histological [9] and microenvironmental [10] heterogeneity exists within individual tumors, and even greater heterogeneity exists between patients [11]. In radiation oncology there is heterogeneity in dose prescription, treatment margins and plan quality (i.e., 3DCRT, IMRT, VMAT, etc.). Moreover, there is a growing availability of targeted agents and immunotherapy which also may affect outcome. Despite these enormous complexities, individualized cancer therapy is realizable. Indeed, intra- and inter-tumoral variability can be potentially exploited advantageously to maximize the therapeutic ratio, i.e. increasing the effects of therapy upon the tumor while decreasing those effects on healthy tissues [12–14].

The principal challenge is how best to collect and integrate diverse multimodal data sources (clinical, treatment, imaging, biological/genetic, etc.) in a quantitative fashion that can provide specific clinical predictions that accurately and robustly estimate outcomes as a function of the possible decisions [15,16]. Presently, numerous published prediction models are available that account for factors related to both disease and treatment, but lack standardized evaluation of their robustness, reproducibility and/or clinical utility [17]. Consequently, these models may not be suitable (let alone optimal) for clinical decision support systems.

In this position paper we highlight the recent advances in decision support systems (DSS) for personalized radiation oncology, with a focus on the methodological aspects of prediction model development/validation as well as the sophisticated and innovative information technologies which are fundamental to the implementation and success of DSS. The benefits and accompanying challenges of DSS are also discussed as well as the steps required for the continued progression and wide spread acceptance of DSS within the clinic.

2. Rapid learning healthcare

2.1. The four phases of rapid learning healthcare

Rapid learning health care (RLHC) [2] (also known as: knowledge-driven medicine, computer assisted theragnostics, intelligent medical networks, etc.) is the (re)use of medical data (from both standard clinical practice and clinical trials) to aid in decision making with respect to new patients and/or to investigate novel hypotheses [18–22] (Fig. 1a). RLHC is comprised of four sequential infinitely reiterated phases [2] (Fig. 1b) that culminates in model development/validation which can be clinically implemented through DSS [23] (Fig. 1c). The Data phase handles the attainment and mining of prior data (e.g., patient, disease, treatment, outcome, etc.). The Knowledge phase utilizes sophisticated analytical methods, (e.g., machine learning), to harness knowledge from the aggregated data. The Application phase exploits this knowledge to improve clinical practice. The Evaluation phase assesses DSS performance with respect to outcomes, subsequently the initial phase commences once more. For each phase, current best practice coupled with the latest scientific understanding is used to optimize the process. The sections below describe each phase in detail.

2.2. The '4 Vs' of 'Big Data'

Perfect RLHC demands the '4 Vs' of 'Big Data'; veracity, velocity, variety, and volume of data (http://www.ibmbigdatahub.com/infographic/four-vs-big-data). The veracity of data is critical to the amount of trust that can be placed in the knowledge acquired. The velocity of data is essential to guarantee that knowledge is gathered as continuously and constantly as practicable. The variety of data (predominantly with respect to treatment modalities as well as patient and disease characteristics) is fundamental to ultimately conclude which treatment is optimal for an individual patient. The volume of data is key: A) to obtain enhanced knowledge (the fidelity of knowledge is directly related to the number of patients upon which that knowledge is founded); and B) to gain knowledge regarding rarer, less heterogeneous patient cohorts and/or to increase the number of variables in the knowledge phase.

Accessing data with adequate fidelity in relation to the '4 Vs' is the largest obstacle in RLHC. It is recognized that both the clinical and research communities need to embrace a data sharing ethos [24], traversing institutional and national boundaries, so as to realize this goal [25]. One initiative to accomplish this goal is CancerLinQ [26] (http://cancerlinq.org/), of the American Society of Clinical Oncology (ASCO). It is a RLHC system designed to monitor, coordinate, and improve the quality of care provided to patients with cancer through the collection, aggregation, and analysis of data extracted from the electronic health records (EHRs) and practice management systems at