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Overview

Biomarkers of Tumour Radiosensitivity and Predicting Benefit from Radiotherapy

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Abstract

Radiotherapy is an essential component of treatment for more than half of newly diagnosed cancer patients. The response to radiotherapy varies widely between individuals and although advances in technology have allowed the adaptation of radiotherapy fields to tumour anatomy, it is still not possible to tailor radiotherapy based on tumour biology. A biomarker of intrinsic radiosensitivity would be extremely valuable for individual dosing, aiding decision making between radical treatment options and avoiding toxicity of neoadjuvant or adjuvant radiotherapy in those unlikely to benefit. This systematic review summarises the current evidence for biomarkers under investigation as predictors of radiotherapy benefit. Only 10 biomarkers were identified as having been evaluated for their radiotherapy-specific predictive value in over 100 patients in a clinical setting, highlighting that despite a rich literature there were few high-quality studies for inclusion. The most extensively studied radiotherapy predictive biomarkers were the radiosensitivity index and MRE11; however, neither has been evaluated in a randomised controlled trial. Although these biomarkers show promise, there is not enough evidence to justify their use in routine practice. Further validation is needed before biomarkers can fulfil their potential and predict treatment outcomes for large numbers of patients.

Key words: DNA damage response; molecular signature; predictive biomarker; radiosensitivity; radiotherapy

Statement of Search Strategies Used and Sources of Information

A literature search of PubMed for molecular signatures predictive of radiotherapy benefit was conducted using the terms (predict OR prediction OR predictive OR predictor OR predicts) AND (radiotherapy OR radiosensitivity OR chemoradiotherapy) AND ('radiosensitivity index' OR gene signature OR molecular signature OR gene expression profile) and yielded 122 results. A second literature search of PubMed for biomarkers related to DNA damage response predictive of radiotherapy benefit using the terms (predict OR prediction OR predictive OR predictor OR predicts) AND (radiotherapy OR radiosensitivity OR chemoradiotherapy) AND (biomarker OR molecular OR signature) AND (DNA repair OR DNA damage OR DNA OR 'DNA damage response') found 476 results. Searches were supplemented by hand searching of reference lists of relevant studies and reviews. Abstracts were reviewed for all relevant titles and full papers obtained if necessary. Citations were excluded if they were not original research articles or not relevant to cancer biomarker research. Biomarkers predicting benefit from chemotherapy, hypoxia modifying therapy, targeted agents and endocrine therapy were excluded, as were those concerning diagnostic or prognostic markers and those predictive of normal tissue toxicity. Citations relating to imaging markers were excluded. Pre-clinical work, studies with small patient numbers (<100) and studies with no control population were also excluded. Only reports published in English up to January 2015 week 1 were included.

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Introduction

Radiotherapy in Cancer Treatment

In 2012 there were 14.1 million new cancer diagnoses worldwide, the most common being lung (13%), breast (11.9%), colorectal (9.7%) and prostate (7.9%) [1]. Radiotherapy is recommended as a key component of curative management of these cancers, as either neoadjuvant, definitive or adjuvant treatment [2–5] and is essential in palliative oncology care [6]. Overall more than half of newly diagnosed cancer patients will require radiotherapy [7]. Although recent technological advances in radiotherapy planning and delivery techniques have led to more individualised radiotherapy based on the anatomy of the tumour with subsequent improved therapeutic ratio [8], the adaptation of radiotherapy with respect to tumour biology has significant potential to contribute to further therapeutic gain.

Predictive Cancer Biomarkers

Cancer is characterised by considerable genetic and epigenetic heterogeneity driven by genomic instability [9,10]. It is therefore not surprising that even patients diagnosed with the same cancer type vary widely in the natural progression of their disease and response to treatment. An era of personalised cancer medicine in which biomarkers can be used to tailor treatment to each specific patient is a major goal in oncology.

Prognostic biomarkers provide information regarding disease outcome regardless of the treatment received and predictive biomarkers determine which patients will probably derive benefit from a specific therapy [11,12]. Examples of the few predictive biomarkers that have successfully transitioned to routine clinical use are those predicting response to targeted drugs, such as HER-2 in selecting breast cancer patients for HER-2 targeted therapies [13–15] and EGFR and ALK mutations in predicting response to tyrosine kinase inhibitors in non-small cell lung cancer [16–19]. These biomarkers have had a dramatic effect on current practice for selected populations of cancer patients.

Radiosensitivity Biomarkers

Potential applications of a radiosensitivity biomarker include tailoring of the dose depending on tumour biology, aiding decision making between radical radiotherapy and radical surgery where both are viable options and avoiding delay of definitive surgery for those unlikely to benefit from neoadjuvant radiotherapy or chemoradiotherapy. Radiosensitivity biomarkers may also be useful in predicting normal tissue toxicity, but this will be discussed in another review.

Many factors are known to influence tumour response to irradiation, including total dose, fractionation, tumour potential doubling time, hypoxia and intrinsic radiosensitivity. Fractionation and hypoxia will be discussed in separate reviews. Traditional laboratory tests to determine intrinsic radiosensitivity, such as measuring *ex vivo* surviving fraction at 2 Gy (SF2) by clonogenic survival assay, have been correlated with clinical outcome [20], but are not practical for routine use. Therefore alternative strategies must be sought.

The development of high throughput molecular profiling techniques has led to the identification of gene expression signatures in tumours. Signatures such as Oncotype Dx® and MammaPrint® have been successful in stratification for recurrence risk and aiding decision making regarding adjuvant chemotherapy in breast cancer [21,22] and a hypoxia signature has been shown to predict benefit from concurrent hypoxia modification with radiotherapy in laryngeal cancer [23]. This may also be an attractive approach for the development of a biomarker of intrinsic radiosensitivity. Additionally molecules involved in DNA damage response (DDR) signalling pathways (Figure 1), which sense and repair DNA damage [24], are excellent candidates for evaluation as radiosensitivity biomarkers, as cells with a defective DDR have less ability to repair lethal radiation-induced DNA double-strand breaks (DSBs) and are therefore more sensitive to irradiation, as seen in radiosensitivity syndromes such as ataxia telangiectasia [25].

Aims of Review

Cancer biomarker research is an ever-expanding field with large numbers of publications, including numerous pre-clinical studies. In order to focus on the most promising radiosensitivity biomarkers, this review will concentrate on molecular signatures and DDR-related biomarkers that have been evaluated for their ability to predict benefit from radiotherapy in a clinical setting.

Materials and Methods

Literature Searches

A literature search of PubMed for molecular signatures predictive of radiotherapy benefit was conducted using the terms (predict OR prediction OR predictive OR predictor OR predicts) AND (radiotherapy OR radiosensitivity OR chemoradiotherapy) AND ('radiosensitivity index' OR gene signature OR molecular signature OR gene expression profile) and yielded 122 results. A second literature search of PubMed for biomarkers related to DDR predictive of radiotherapy benefit using the terms (predict OR prediction OR predictive OR predictor OR predicts) AND (radiotherapy OR radiosensitivity OR chemoradiotherapy) AND (biomarker OR molecular OR signature) AND (DNA repair OR DNA damage OR DNA OR 'DNA damage response') found 476 results. Searches were supplemented by hand searching of reference lists of relevant studies and reviews. Abstracts were reviewed for all relevant titles and full papers obtained if necessary.

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