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Late side-effects after curative intent radiotherapy: Identification of hypersensitive patients for personalized strategy

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Abstract

Radiation therapy undeniably enhances local control and thus improves overall survival in cancer patients. However, some long-term cancer survivors (less than 10%) develop severe late radio-induced toxicities altering their quality of life. Therefore, there is a need to identify patients

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who are sensitive to those toxicities and who could benefit from adapted care. In this review, we address all available techniques aiming to detect patients' hyper-radiosensitivity and present the scientific rationales these techniques are based on.

Keywords: Radiotherapy outcome; Predictive markers

1. Introduction

Radiation therapy belongs to anticancer therapies and is offered to more than two-third of patients in curative intent. Even though its role is incontestable as main anticancer treatment, some patients develop severe late radio-induced toxicities (SLRIT) which alter their quality of life. Classically, early toxicities are defined as radio-induced side effects occurring either during radiotherapy course or within the two months following radiotherapy completion. In contrast, late toxicities occur at least six months after radiotherapy completion.

Although only a small proportion of long-term cancer survivors will be concerned by SLRIT (less than 10%), there is a need to identify such patients as those toxicities impair their quality of life.

2. The development of biomarkers

By definition, a biomarker can be measured objectively with a precise and reproducible method. The biomarkers studied here are used to predict the risk of SLRIT. Guidelines for cancer biomarkers are well established by the National Cancer Institute through the Early Detection Research Network [1] and could be translated for normal tissue biomarkers. At an early stage, the latter would detect patients at high risk of SLRIT. These screening tools should be non-invasive and inexpensive to allow a widespread application. Moreover, they should have a high sensitivity (i.e. ability to identify patients at risk) and a high specificity (i.e. ability to exclude patients without any risk of developing SLRIT). For a comprehensive reading of this review, it is fundamental to keep in mind that five steps are needed to develop predictive biomarkers. The step 1 only encompasses preclinical exploratory studies aiming to identify characteristics unique to the disease (i.e. severe fibrosis in our case). Different techniques could be used such as immunohistochemistry, western blots, gene expression profiling based on microarrays or protein expression profiling based on mass spectroscopy. When a biomarker seems adequate, one needs to ascertain its ability to distinguish between case and control subjects (i.e. with or without severe fibrosis). Therefore, sensitivity and specificity are usually determined, as well as receiver operating characteristic (ROC) curve and area under the ROC curve that are mostly used for providing true- and false-positive rates (TPR and FPR). The second step consists in developing a clinical trial in patients with the specific disease (severe fibrosis). However, as the biomarker is found when the disease is already established, it is not yet possible to know whether the biomarker is able to predict the disease at an early stage. The sample size needed for the clinical trial is determined using estimations of TPR, FPR and ROC stated in statistical hypotheses. The step 3 includes retrospective longitudinal repository studies to measure the biomarker of interest before the development of the disease in both case and control subjects. Indeed, this type of study provides evidence regarding the biomarker capacity to predict the disease occurrence. Here, the studied cohort comprised apparently healthy subjects monitored for severe fibrosis and from which clinical specimens were collected and stored. This study cohort should reflect the target population in terms of disease screening and biomarker metabolism. The sample size is determined based on the following items: number of case subjects, number of control subjects and number of clinical specimens per subject. In addition, criteria for a positive screening test are defined to prepare the next step. Indeed, the step 4 is a prospective screening study aiming to determine, in a relevant population, the operating characteristics of the biomarker screening test including the detection rate and the false referral rate. Finally, the fifth step comprises control studies assessing the overall benefit of the screening biomarker for the screened population.

3. Risk factors of normal tissue radiosensitivity

Risk factors related to patient and those related to treatment should be distinguished [2]. It is well established that severe fibrosis mostly occurs in patients with the following conditions: diseases related to micro-vascularization (e.g. mellitus diabetes, hypertension, etc.), diseases related to excess deposit of collagen (e.g. scleroderma, etc.), and syndromes related to DNA repair defect (e.g. ataxia telangiectasia, etc.). Besides intrinsic radiosensitivity risk factors, other risk factors have been described and are related to radiotherapy modalities (e.g. high total dose, high dose per fraction, large irradiated volume) or related to treatment combination (e.g. endocrine therapy, chemotherapy, history of surgery).

However, even though all these characteristics are linked to a risk of developing SLRIT, none of them can precisely predict severe fibrosis. Therefore, biomarkers predictive of normal tissue late toxicities are needed as well as adapted measurement methods.