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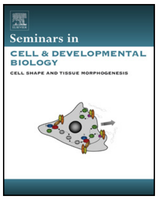

Review

Cancer heterogeneity and imaging

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ABSTRACT

There is interest in identifying and quantifying tumor heterogeneity at the genomic, tissue pathology and clinical imaging scales, as this may help better understand tumor biology and may yield useful biomarkers for guiding therapy-based decision making. This review focuses on the role and value of using x-ray, CT, MRI and PET based imaging methods that identify, measure and map tumor heterogeneity. In particular we highlight the potential value of these techniques and the key challenges required to validate and qualify these biomarkers for clinical use.

Contents

1. Introduction

Tumors are biologically heterogeneous [1,2]. This fact has been the subject of much interest following recent high profile studies that have begun to map and track the presence of genetic variation in tumors. The relevance that these findings may have for the treatment of patients with cancer is beginning to be investigated by numerous research groups worldwide [3]. Spatial variation in cell genetic profiles leads to altered microenvironments. This regional variation is visible through analysis of tissue pathology images [4]. The current understanding of cancer heterogeneity from the perspectives of genomics and tissue pathology are covered elsewhere in this special issue.

In this article, we focus on the role and value of using imaging methods to identify, measure and map the tumor heterogeneity

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that arises from genetic and tissue pathology variation. Particular emphasis is placed on clinically available imaging techniques such as x-ray computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) that are readily available and enable the non-invasive whole-lesion sampling of tumor structure and function [5,6].

2. Terminology

Different research studies have different understandings of the meaning of 'tumor spatial heterogeneity'. The variation in structure and function found between different tumors in individual patients is termed intertumor heterogeneity. In distinction, the spatial variation seen within individual lesions is termed intratumor heterogeneity. Finally, some studies compare the differences in lesions between different patients, termed interpatient heterogeneity. Imaging methods can be used to study all three of these scenarios. In this article, we focus on intratumor heterogeneity, assessed by regarding tumors as 3D structures composed of individual 3D pixels known as voxels.

While much of the terminology used in imaging studies of tumor heterogeneity are similar or identical to the terms used in genomic and tissue pathology research, it is important to appreciate that clinical imaging is performed on a different scale. This has important sequelae, and there is considerable need for investigators to determine how these different insights into tumor biology, from multiscalar data, can be combined into models that best describe tumor growth, response to therapy, resistance to therapy, relapse and progression. Although several genomic studies of heterogeneity have achieved high profile status, it is important to remember that extensive genomic profiling of tumors is still only performed on a sub-set of patients' tumors, whereas image-based whole tumor sampling is performed repeatedly during diagnosis, staging and response assessment in nearly all patients with solid tumors [7].

3. Current clinical use of imaging data

Clinical imaging has been recognised as one of the great advances in modern medicine [8]. It has revolutionized how oncologists diagnose and stage solid tumors, by detecting the presence of a cancer and by mapping the locations of the primary lesion and its metastases [9]. Imaging is also central to assessing response to therapy and in detecting disease recurrence, by measuring change in lesion size [10] and (sometimes) lesion function [11]. Imaging is used to identify patients at risk of toxicity (for example, cardiotoxicity may preclude use of some chemotherapy agents) [12]. Finally, imaging can detect complications from the cancer (for example urinary tract obstruction) and the treatments (for example, presence of lung consolidation due to pneumonia) [13].

For the above applications, tumor heterogeneity is not generally considered a key consideration. However, for some indications, radiologists interpret spatial heterogeneity in clinical images on a daily basis. The fact that many breast lesions are spiculated has been recognised for many decades, and this feature forms part of the BI-RADS classification for evaluating risk of malignancy [14,15], with spiculation indicating a very high risk of a mass being malignant (Fig. 1a). In another example, tumors are composed often of different regions including highly vascular and avidly enhancing regions, enhancing soft tissue and relatively non-enhancing regions, which include areas of necrosis within the tumor as well as hemorrhage. Some tumors, for example high grade glioma, also have areas of surrounding edema. These features can be appreciated readily using sequences that identify tumor anatomy and morphology, along with some functional information (here, enhancement due to administration of intravenous contrast agents; Fig. 1b) and help radiologists diagnose, assess therapy and detect relapse. In addition, other imaging techniques, such as ^{18}F FDG PET-CT provide functional information, such as metabolic activity, and these techniques can also be used to identify regional variation in tumor function in solid tumors (Fig. 1c) [11]. It is important to appreciate that in these examples, spatial heterogeneity tends to be reported using qualitative description (e.g. 'enhancing rim versus non-enhancing core', or 'focal region of intense tracer avidity'), rather than be quantified.

There has been considerable effort over the last decade to covert these qualitative observations of heterogeneity into quantitative *biomarkers* for clinical use. A biomarker is a "defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions" [16,17]. An imaging biomarker is a measurement derived from one or more medical images [18]. This idea represents an important paradigm shift, where images are regarded as being composed of arrays of data, arranged spatially in individual 3D voxels [7]. Here, each individual voxel is a cube (or cuboid) of data which summarizes a particular morphologic, metabolic or physiologic signal over a volume of around (0.25–5) millimetres [3], depending on modality and subject (animal or human).

4. Considerations for voxel–wise analysis of clinical images

Several important factors must be considered when analyzing images on a voxel-wise basis. Firstly, some voxels suffer partial volume averaging (typically at interface with non-tumor tissue), so may only partially represent tumor tissue. Secondly, there is inevitable compromise between having sufficient numbers of voxels to perform the analysis versus sufficiently large voxels to overcome noise and keep patient scan times practical [19]. Most analysis methods require hundreds to thousands of voxels for robust application.

Thirdly, many clinical studies of tumor spatial heterogeneity have used imaging protocols determined by healthcare considerations, rather than optimizing research needs; for example, portions of tumor will be omitted when non-contiguous tumor sampling is used [20] which confounds 3D spatial analyses [21]. Fourthly, some calculated voxel values, such as apparent diffusion coefficient (ADC), contrast transfer coefficient (K^{trans}) and blood flow are derived from multiple images obtained over time. Optimal estimation of the errors associated with motion will vary for different parameters and for different voxels. This issue is seldom considered when assessing intratumor heterogeneity [22].

5. Strategies for imaging intratumor spatial heterogeneity

Nearly all malignant tumors show intratumor heterogeneity on imaging, although the extent varies between pre-clinical cancer models and between patients [23]. Spatial variation is dynamic, for example, variations in tumor pO_2 can be mapped and have been shown to fluctuate over minutes to hours using a range of imaging techniques [24,25]. Furthermore, the degree of intratumor heterogeneity tends to increase as tumors grow [26,27].

There is considerable research interest in identifying and measuring both the overall degree of spatial tumor heterogeneity and also which sub-populations within tumors are responsible for mediating response to therapy and resistance [28]. The clinical significance of established spatial heterogeneity is discussed in detail elsewhere in this special issue, but in general, greater heterogeneity tends to indicate a relatively poor clinical outcome [29]. This is considered, in part to result from resistant subpopulations of cells driving resistance to therapy [5,30]. However, it is important to