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Review article

Adaptive radiotherapy for head and neck cancers: Fact or fallacy to improve therapeutic ratio?

La radiothérapie adaptative des cancers de la tête et du cou peut-elle améliorer le rapport thérapeutique ?

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ABSTRACT

Modern standards of precision radiotherapy, primarily driven by the technological advances of intensity modulation and image guidance, have led to increased versatility in radiotherapy planning and delivery. The ability to shape doses around critical normal organs, while simultaneously "painting" boost doses to the tumor have translated to substantial therapeutic gains in head and neck cancer patients. Recently, dose adaptation (or adaptive radiotherapy) has been proposed as a novel concept to enhance the therapeutic ratio of head and neck radiotherapy, facilitated in part by the onset of molecular and functional imaging. These contemporary imaging techniques have enabled visualisation of the spatial molecular architecture of the tumor. Daily cone-beam imaging, besides improving treatment accuracy, offers another unique angle to explore radiomics – a novel high throughput feature extraction and selection workflow, for adapting radiotherapy based on real-time tumor changes. Here, we review the existing evidence of molecular and functional imaging in head and neck cancers, as well as the current application of adaptive radiotherapy in the treatment of this tumor type. We propose that adaptive radiotherapy can be further exploited through a systematic application of molecular and functional imaging, including radiomics, at the different phases of planning and treatment.

Mots clés :
Cancer tête et cou
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RÉSUMÉ

Les normes modernes de radiothérapie de précision, principalement motivées par les avancées technologiques de la modulation d'intensité et du guidage par l'image, ont conduit à une polyvalence accrue dans la planification et la délivrance de la radiothérapie. La capacité à conformer les doses autour des organes normaux critiques, tout en « peignant » un complément de dose dans la tumeur, s'est traduite par des gains thérapeutiques substantiels chez les patients atteints de cancer de la tête et du cou. Récemment, l'adaptation de la dose (ou radiothérapie adaptative) a été proposée comme un nouveau concept pour améliorer le rapport thérapeutique, facilitée en partie par les débuts de l'imagerie moléculaire et fonctionnelle. Ces techniques d'imagerie contemporaines ont en effet permis de visualiser l'architecture moléculaire spatiale de la tumeur. Outre l'amélioration de la précision du traitement, la tomographie conique quotidienne offre un autre angle unique d'exploration de la radiomique – un nouveau processus d'extraction et de sélection de caractéristiques à haut débit pour adapter la radiothérapie aux changements de tumeurs en temps réel. Nous avons passé en revue les preuves existantes de l'imagerie

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moléculaire et fonctionnelle dans les cancers de la tête et du cou, ainsi que l'application actuelle de la radiothérapie adaptative dans le traitement de ce type de tumeur. Nous proposons que la radiothérapie adaptative puisse être davantage exploitée par une application systématique de l'imagerie moléculaire et fonctionnelle, y compris la radiométrie, aux différentes phases de la planification et du traitement.

1. Introduction

The incidence of head and neck cancers continue to rise globally, accounting for an estimated 650,000 new cancer cases and 350,000 cancer deaths worldwide each year [1]. In the last 10 years, the epidemiological landscape of this disease has also witnessed an acute shift from the historical etiologies of smoking, alcohol abuse and ingestion of carcinogenic agents like betel nuts to the dominance of human papilloma virus (HPV)-induced squamous cell carcinoma, particularly in the oropharynx among males [1]. This has been suggested to reflect changes in behavioral and lifestyle patterns; a strong advocacy for smoking cessation coupled with a more open-minded approach to sexual intimacy [2]. Coincidentally, in Southern and Eastern parts of Asia, Northern Africa and the Arctic, another virus – the Epstein-Barr virus (EBV) is also implicated in the pathogenesis of another variant of head and neck cancers in the nasopharynx, with distinct histopathological features; the endemic form of nasopharyngeal carcinoma is often characterised as an epithelial-type cancer that is richly admixed with lymphocytes [3]. Additionally, large-scale molecular profiling using next generation sequencing platforms have also revealed genomic and expression differences between these head and neck cancers, some of which may represent candidate therapeutic targets of the specific tumor type [4]. Nonetheless, in the domain of localised disease, surgery and radiotherapy remain the only definitive therapeutic options; the choice between them often based on:

- anatomical location;
- amenability to oncological resection;
- disease extent;
- likelihood of organ preservation;
- sensitivity to radiotherapy.

For example, radiotherapy is often preferred for head and neck cancers in the naso- and oropharynx, as it achieves optimal tumor control rates without the necessity for extensive debilitating surgeries. In the same vein, concurrent chemoradiotherapy can be an effective option for voice and function preservation in carefully selected patients with advanced cancers of the larynx [5,6]. However, surgery is favored in the management of oral cavity and sinus cancers, with further adjuvant radiotherapy reserved for patients with adverse pathologies.

Given the dominant role of radiotherapy in the treatment of head and neck cancers, it is therefore intuitive that dramatic technological advancements such as intensity-modulated radiotherapy and image guidance have led to substantial gains in radiotherapy therapeutic ratio for this disease. Intensity-modulated radiotherapy exploits the advantage of targeted dose escalation to the tumor by creating steep dose gradients at the border between the target and adjacent normal tissues; this has translated to improved disease control like in nasopharyngeal carcinoma and reduction of radiotherapy-induced toxicities such as xerostomia with sparing of the parotid glands [7]. With image-guided radiotherapy, high quality daily cone beam computed tomography (CBCT), apart from ensuring interfraction accuracy, also offers spatial and temporal assessment of radiotherapy-induced tumor responses and normal tissue changes [8,9]. Such data could potentially inform on clinical management; for example, geometrical and anatomical variations in the neck due to substantial nodal response mid-treatment could result in critical dosimetric effects within the nodal tumor and adjacent normal tissues, thereby necessitating a replanning of radiotherapy [10]. In support, plan simulation on CBCT datasets has also revealed compromisation of tumor coverage with volumetric reduction and isocentre shifts [11]. These examples highlight the clinical importance of incorporating a workflow that allows for rapid adaption of the original radiotherapy plan that is based on CBCT-derived features.

The concept of adaptive radiotherapy, whereby radiation doses to the tumor and normal tissue are modulated "real-time" in response to geometrical and biological changes to both targets, is attractive. At present, the clinical value of adaptive radiotherapy has mostly been examined in the setting of replanning mandated by substantial variation to the body contours due to tumor shrinkage or weight loss; evidence has shown that replanning compared to no action reduces the incidence of severe acute toxicities [9]. However, there remains much untapped potential with adaptive radiotherapy, particularly with regard to exploiting the tumor biological response to design novel dose escalation and de-escalation strategies [12]. This idea comes on the backbone of advances in radiological modalities, including molecular positron emission tomography (PET), functional magnetic resonance imaging (MRI), etc., which have broadened the capacity of imaging to capture biological surrogates of the tumour/normal tissue [13]. Recent enthusiasm in exploring a "genomics"-type approach (radiomics) to glean large amounts of radiological information that are not permissible by the human eye adds another layer of information [14]. The sudden influx of large radiomics and molecular imaging datasets thus prompts a review of the current approach of adaptive radiotherapy and if existing technologies can be utilised to implement more thorough and innovative methods of adaptive radiotherapy than merely adapting a plan in response to volumetric changes for the sole purpose of reducing toxicities.

2. Search strategy

We searched the Pubmed and Medline databases for articles published in English from 1 January 2000 to 30 June 2016 with the keywords "head neck cancer", "nasopharynx cancer", "squamous cell carcinoma", "adaptive radiotherapy", "image-guided radiotherapy", "cone beam", "computed tomography", "molecular imaging", "positron emission tomography", "FDG-PET", "hypoxia", "functional imaging", "magnetic resonance imaging", "diffusion weighted", "ADC", "radiomics" and "genomics". Articles were selected based on relevance, with priority given to highly-cited articles and articles written in English. Conference abstracts were also reviewed and considered if they reported statistical methods and hazard ratios (HR), with corresponding confidence intervals (CI) and *P*-values. Articles that proceeded the search time-frame were also included if they were highly regarded seminal work.

3. Clinical advantages of adaptive radiotherapy for head and neck cancers

As aforementioned, significant anatomic changes related to tumor response and on-treatment weight loss are common in

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