Oral Oncology 68 (2017) 81–91

Contents lists available at ScienceDirect

Oral Oncology

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

Review

Intravoxel incoherent motion magnetic resonance imaging in head and neck cancer: A systematic review of the diagnostic and prognostic value

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ARTICLE INFO

Article history:
Received 20 December 2016
Received in revised form 12 March 2017
Accepted 25 March 2017
Available online 2 April 2017

Keywords:
Head and neck neoplasms
Intravoxel incoherent motion
Diffusion-weighted Imaging
Diagnostic performance
Prognostic performance
Systematic review

ABSTRACT

Intravoxel incoherent motion (IVIM) imaging is increasingly applied in the assessment of head and neck cancer (HNC). Our purpose was to determine the diagnostic and prognostic performance of IVIM in HNC by performing a critical review of the literature. Pubmed and EMBASE were searched until May 2016. Study and patients characteristics, imaging protocol and diagnostic or prognostic outcomes were extracted by 2 independent reviewers. The studied IVIM parameters were diffusion coefficient (D), pseudodiffusion coefficient (D∗), and perfusion fraction (f). We included 10 diagnostic studies, 5 prognostic studies and 2 studies assessing both. Studies were very heterogeneous in terms of applied b-values, imaging protocols, outcome measurements and reference standards; therefore we did not perform a meta-analysis. The most commonly used sequence was "spin-echo planar imaging". A median of 10.5 b-values (range, 3–17) were used. All but three studies included at least 4 b-values below b = 200 s/mm^2. By combining IVIM-parameters squamous cell carcinomas, lymphomas, malignant salivary gland tumors, Warthin's tumors and pleomorphic adenomas could be differentiated with a sensitivity of 85–87% and specificity of 80–100%. Low pre-treatment D or f and an increase in D during treatment were associated with a favorable response to treatment. D∗ appeared to be the parameter with the lowest prognostic value. Future research should focus on finding the optimal IVIM protocol, using uniformly accepted study methods and larger patient populations.

Introduction

Head and neck cancer (HNC) accounts for approximately 4% of the cancer case worldwide, making HNC the sixth most common cancer by incidence rate [1,2]. HNC mainly consists of tumors arising in the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx and salivary glands.

Squamous cell carcinomas (SCC) account for over 90% of HNC [3]. Alcohol and tobacco use are the most important risk factors [4]. While early stage disease is usually treated by surgery or radiotherapy, advanced stage disease is generally treated by surgery and adjuvant radiotherapy with or without chemotherapy or combined chemotherapy and radiotherapy. Salvage surgery is then held in reserve for residual or recurrent disease [2,5–7]. While chemotherapy is mainly used in a concomitant setting with radiotherapy, in selected cases it can also be applied as neoadjuvant treatment [2]. There is increasing evidence that in some geographic regions up to 80% of the oropharyngeal SCC is associated with the human papillomavirus (HPV), especially in relatively young patients who do not drink or smoke [8]. HPV-associated oropharyngeal SCC has a different tumor biology and is associated with a better prognosis than HPV-negative SCC [5–7]. Therefore it is proposed to de-escalate treatment in HPV-associated oropharyngeal SCC in patients who do not smoke.

Abbreviations: ADC, apparent diffusion coefficient; CHESS, chemical shift selective; D*, pseudodiffusion coefficient; D, diffusion coefficient; DWI, diffusion-weighted imaging; f, perfusion fraction; HASTE, half-fourier acquisition single-shot turbo spin-echo; IVIM, intravoxel incoherent motion; NAC, neo-adjuvant chemotherapy; PP, perfusion-related parameter; QUADAS-2, quality assessment of studies of diagnostic accuracy included in systematic reviews; QUIPS, quality in prognostic studies; SPIR, spectral presaturation with inversion recovery; SS-SE-EPI, single-shot spin-echo echo planar imaging; STIR, short tau inversion recovery; YI, youden index.

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http://dx.doi.org/10.1016/j.oraloncology.2017.03.016
1368-8375/

Nasopharyngeal carcinoma (NPC) takes a unique place in epithelial HNC because of the very distinct geographical distribution ranging from 1:100.000 in Western Europe to >20:100.000 in parts of Southeast Asia [2,9]. Further it harbors an association with the Epstein-Barr virus (EBV) which is not seen in other HNC [9]. NPC has a different tumor biology as compared to other HNC.

Imaging is increasingly used for diagnosing and staging of HNC, monitoring the effect of treatment and in the detection of distant metastases and recurrent disease [10–12]. In this systematic review we focus on the use of intravoxel incoherent motion (IVIM) magnetic resonance imaging (MRI) for diagnosis in HNC.

In general, water diffusion is restricted in malignant tissue. With diffusion-weighted imaging (DWI) this restricted diffusion can be imaged and quantified. The main advantage of DWI compared to other functional imaging techniques (e.g. dynamic contrast-enhanced MRI and positron-emission tomography) is that it requires neither the administration of contrast medium or radioactive tracer nor the use of ionizing radiation.

One of the proposed methods to quantify diffusion is by considering diffusion as a mono-exponential phenomenon. In this way diffusion can be quantified in an apparent diffusion coefficient (ADC) [13]. The word "apparent" implicates that in this way true diffusion is not measured. Especially at low b-values other parameters as blood volume and blood flow also contribute to the ADC [14,15]. The ADC-concept provides a quantifiable measure with promising results in HNC, e.g. in discriminating metastatic from benign lymph nodes with an accuracy of >85% and in the detection of recurrent disease with an accuracy of >78% [16].

The signal decay after the diffusion-encoding gradients is not only caused by diffusion, but also by pseudorandom, or "incoherent", perfusion at the capillary level. To account for this, Le Bihan et al. introduced the bi-exponential IVIM model [13,1]:

$$\frac{S_b}{S_0} = (1-f)\cdot e^{(-bD)} + f\cdot e^{(-bD*)}$$

where S_b represents the signal intensity with diffusion gradient b, and S_0 represents the signal intensity without diffusion gradients. D is known as pure or slow diffusion coefficient which is related to pure molecular diffusion. D∗ is the fast or pseudodiffusion coefficient that resembles the perfusion related incoherent microcirculation and is about a factor of 10 greater than D in biological tissue [13]. Finally, f is the perfusion or (micro) vascular volume fraction which depends on capillary geometry and blood velocity [13]. In this way pure tissue diffusion may be quantified and also perfusion characteristics may be assessed without the admission of contrast-material. Commonly D is first estimated using a linear fit using only high b-values (i.e., above 200 s/mm^2 [17]) and then f and D∗ are calculated using a non-linear least-squares algorithm.

With IVIM being increasingly used in HNC, a critical systematic review of the diagnostic and prognostic value of this technique is warranted. The purpose of this study was therefore to determine the diagnostic and prognostic performance of IVIM in HNC. Histopathology, other imaging modalities or clinical follow-up were used as reference standards.

Methods and materials

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews and meta-analyses was used as a guidance [18].

Search strategy

This systematic search was conducted in Pubmed and Embase until May 2016 for original articles on the diagnostic and/or prognostic capability of IVIM in HNC. We did not apply language restrictions. We approached corresponding authors for additional data if necessary (e.g. to compute sensitivity and specificity). The only included search terms were "(IVIM OR ((intra-voxel OR intravoxel) AND incoherent AND motion))" in order to be as sensitive as possible. In the Pubmed search we used text words [tw] in the absence of MeSH-terms on this subject.

Two authors (D.P.N. and R.M.M.) independently selected relevant articles based on title and abstracts and discrepancies were resolved by consensus.

The inclusion criteria were: (1) The study population consisted of at least 10 patients with malignant lesions in the head and neck area; (2) The study assessed diagnosing malignancy, response prediction to therapy, detection of residual/recurrent disease. Or data of these subjects could be extracted from the article; (3) Histopathology, clinical follow-up or another imaging modality was used as reference standard test.

Exclusion criteria were: (1) The publication was a review, meta-analysis, only published as abstract or if it was another non-primary publication (e.g. editorial, technical note); (2) The study reported on (potentially) overlapping study populations.

Data extraction

Data on the study and patients characteristics, the imaging protocol and diagnostic outcomes were extracted by two independent reviewers (D.P.N and R.M.M.) and discrepancies were resolved by consensus. If available, source data (i.e. true positive [TP], false positive [FP], true negative [TN], and false negative [FN]) were extracted or recalculated. If unavailable, the corresponding author of the article was contacted to provide additional data.

Quality assessment

Two authors (D.P.N. and R.M.M.) independently assessed all studies for study quality and discrepancies were resolved by consensus. All included studies were assessed for quality by using the QUality Assessment of studies of Diagnostic Accuracy included in Systematic reviews (QUADAS-2) checklist [19]. The quality of prognostic studies was also assessed with the QUality In Prognostic Studies (QUIPS) checklist [20,21].

Statistical analysis

Diagnostic accuracy data is presented with 95% confidence intervals (95%CI) if presented by the authors, or when we were able to reconstruct a 2 × 2 table. Receiver operating characteristic (ROC) analysis was performed if per-patient data could be extracted using SPSS Statistics (version 20.0; Chicago, IL, USA). The Youden Index (YI) was used to determine the optimal cut-off. *P*-values were reported as NS (not statistically significant, i.e., $P \geq 0.05$), ≤ 0.05, ≤ 0.01, ≤ 0.001.

Results

The search in Pubmed and Embase retrieved 429 unique studies. After excluding 383 studies on title or abstract we reviewed the full text of 46 studies. Finally, 17 studies were included (10 diagnostic, 5 prognostic and 2 both) for qualitative analysis [22–38] (Fig. 1). Due to heterogeneity in applied b-values, imaging protocols, outcome measurements and reference standards we decided not to perform any quantitative meta-analysis.