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Review

Functional imaging early during (chemo)radiotherapy for response prediction in head and neck squamous cell carcinoma; a systematic review

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ABSTRACT

This systematic review gives an extensive overview of the current state of functional imaging during (chemo) radiotherapy to predict locoregional control (LRC) and overall survival (OS) for head and neck squamous cell carcinoma. MEDLINE and EMBASE were searched for literature until April 2018 assessing the predictive performance of functional imaging (computed tomography perfusion (CTp), MRI and positron-emission tomography (PET)) within 4 weeks after (chemo)radiotherapy initiation. Fifty-two studies (CTp: n = 4, MRI: n = 19, PET: n = 26, MRI/PET: n = 3) were included involving 1623 patients. Prognostic information was extracted according the PRISMA protocol. Pooled estimation and subgroup analyses were performed for comparable parameters and outcome. However, the heterogeneity of included studies limited the possibility for comparison. Early tumoral changes from (chemo)radiotherapy can be captured by functional MRI and ^{18}F-FDG-PET and could allow for personalized treatment adaptation. Lesions showed potentially prognostic intratreatment changes in perfusion, diffusion and metabolic activity. Intratreatment ADC_{mean} increase (decrease of diffusion restriction) and low SUV_{max} (persistent low or decrease of ^{18}F-FDG uptake) were most predictive of LRC. Intratreatment persistent high or increase of perfusion on CT/MRI (i.e. blood flow, volume, permeability) also predicted LRC. Low SUV_{max} and total lesion glycolysis (TLG) predicted favorable OS. The optimal timing to perform functional imaging to predict LRC or OS was 2–3 weeks after treatment initiation.

Introduction

Head and neck cancer (HNC) accounts for approximately 5% of cancer incidence worldwide [1]. Choice of treatment depends on factors such as primary tumor location, extension into adjacent structures and possibilities of function preservation [2]. Locally advanced tumors often require combinations of surgery, radiotherapy and/or chemotherapy [3].

Despite these treatment options, locoregional recurrence (LRF) rates in the first 2 years of 15–50% are reported in patients with advanced stage tumors [4-6]. Optimization of treatment monitoring could allow for early escalation (e.g. increasing radiation dose, addition of chemotherapy), de-escalation [7] (i.e., reducing overtreatment and unnecessary toxicity in patients with good prognosis) or switch to another treatment modality (i.e. primary surgery) [8–10].

Clinical, histopathological and anatomical imaging biomarkers are increasingly used to perform treatment selection and response assessment [3,5]. Pretreatment anatomical imaging biomarkers on computed tomography (CT) and magnetic resonance imaging (MRI), e.g. volume, are mainly morphologic tumor characteristics [11–13], while

Abbreviations: ADC, Apparent diffusion coefficient ; CT, Computed tomography; DCE, Dynamic contrast-enhanced; DWI, diffusion-weighted imaging; FLT, 3-Deoxy-3-^{18}F-fluorothymidine PET; FMISO, ^{18}F-Fluoromisonidazole; GTV, Gross tumor volume; IVIM, Intra-voxel incoherent motion; LRC, Locoregional control; LRF, Locoregional failure; OS, Overall survival; PET, Positron-emission tomography; rTBV, Tumor-blood-volume ratio; SRR-P, SUV reduction ratio in primary tumor; TLG, Total lesion glycolysis

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functional imaging can map physiological processes and capture intratumoral heterogeneity [3,14].

Change of tumor characteristics during treatment might be predictive for treatment response and long-term outcome. Changes in perfusion and metabolic activity due to cellular stress and damaged cellular membranes occur early after start of treatment and may precede changes in size [15,16]. Effects of radiation and chemotherapy start with tumoral permeability changes and reoxygenation of central hypoxic areas. Furthermore, a reduction of venous and lymphatic drainage by vascular collapse due to raised interstitial pressure [17]. This is followed by edema in the first 2 weeks, progressive thickening of the connective tissue and ends with formation of fibrosis [18,19].

These physiological changes of perfusion, diffusion and metabolic activity properties of tumor tissue may be captured by functional imaging, such as CT-perfusion, dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted (DW-) MRI, intra-voxel incoherent motion (IVIM) MRI and positron-emission tomography (PET) [20]. Imaging techniques like CT-perfusion or DCE-MRI provide information on tumor perfusion and permeability [21–25]. With DWI the mobility of water molecules can be quantified using apparent diffusion coefficients (ADC) [26,27]. Low ADC values reflect low mobility of water molecules, which is an indication of a high cellularity and is generally associated with malignancy [26]. The IVIM technique is an extension of the DWI technique [28], which separates the tissue capillary perfusion fraction from the overall diffusion signal [29]. ^{18}F-fluorodeoxyglucose (FDG)-PET assesses the metabolic, glycolytic activity of tissues [30], ^{18}F-fluoromisonidazol (FMISO) [31] measures hypoxia and 3′-Deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) assesses proliferation [32]. All these parameters could change during early stage of treatment and are therefore potential prognosticators for early LRF and overall survival (OS).

The objective of this systematic review was twofold; firstly, to evaluate the prognostic value of early functional imaging during treatment of head and neck squamous cell carcinoma (HNSCC), with LRF and OS as main outcome measures; secondly, to evaluate the optimal time to perform functional imaging after start of treatment.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews was used as guidance [33].

Search strategy and study selection

PubMed (Medline) and EMBASE were searched for articles published until April 1st 2018 on functional imaging techniques in HNSCC performed early during (chemo)radiotherapy (within 4 weeks after initiation) (See Supplement A for the full search strategy), without language restrictions. Discrepancies were resolved by consensus. We used the following inclusion criteria: (1) study population consisted of at least 10 patients with HNSCC; (2) functional imaging was performed with at least one of the following techniques: CT-perfusion, DCE-/DW-MRI with or without IVIM or PET(CT/MRI); (3) imaging was performed within 4 weeks after the start of (chemo)radiotherapy and was used for predicting treatment outcome; (4) histopathology, clinical and/or imaging follow-up were reference standard. Studies were excluded if (1) nasopharyngeal tumors were the main subject, due to its unique histopathology [2]; (2) the article was a conference abstract or study with focus on an experimental treatment; (3) the study population overlapped with another study.

Data extraction

Data on study and patient characteristics, imaging protocol and prognostic parameters for LRC and OS, were extracted by 2 reviewers, independently. Discrepancies were resolved in consensus. Short-term outcome was defined as treatment response assessment with a maximum follow-up of 6 months. Locoregional control (LRC) and locoregional failure (LRF) were measures which determine LRF survival. LRF survival was defined as the interval from end of treatment with absence of pathological proven recurrence of HNSCC at the location of primary tumor or lymph node metastasis during the mean follow-up time of 2 years. Prognostic outcomes of CT-perfusion, functional MRI and PET parameters (i.e. odds ratio (OR) and hazard ratio (HR) with 95% confidence intervals (CI) and true positive [TP], false positive [FP], true negative [TN] and false negative [FN]) were extracted. In case of incomplete 2 × 2 tables, authors were contacted.

Quality assessment

We assessed the quality of and the risk for bias in the eligible studies using the QUIPS (Quality in Prognostic Studies) checklist [34].

Data synthesis

Parameters derived from imaging during treatment and delta-values (i.e. the difference between values acquired from imaging before and during treatment) were included in data synthesis [35]. The Odds-ratio (OR) and Hazard-ratio (HR) were calculated based on per patient data. Variability between individual studies was evaluated by plotting the diagnostic accuracy estimates, and the proportional hazard model was pooled and presented on forest plots with 95% confidence intervals (95%CI), using RevMan 5.3 software (Cochrane collaboration, Copenhagen, Denmark). Heterogeneity was quantified using the I^2 index, which describes the percentage of variation across studies that is due to heterogeneity rather than chance. Statistical analyses were performed using SPSS (version 22, Chicago, IL, USA).

Results

The search yielded 13,465 unique studies. The full texts of 254 studies were reviewed (Figure 1). Finally we included 52 articles in which CT-perfusion (n = 4) [17,36-38], functional MRI (n = 22) [11,39-58], and PET (n = 29) [8,16,31,32,41,53,58-80] were used (Table 1). Functional MRI techniques were studied using DCE (n = 7) and DWI (n = 17), of which 3 studies used IVIM and one study used both DWI and DCE. The used PET tracers were ^{18}F-FDG (n = 15), ^{18}F-FMISO (n = 7), ^{18}F-FLT (n = 5) and ^{18}F-Hx4 (n = 1). Thirty-two authors were contacted for additional data, 69% (22 out of 32) responded. For two studies [68,80] we suspected overlap in study populations. However, we could not verify this and because they contained complementary information we included both studies.

Baseline characteristics

Total study population consisted of 1.623 patients, of which 61–100% was male (See Supplement B and C for extended baseline and technical details, respectively). The studies mainly consisted of T2 or T3 tumors (Supplement D) and N2 nodal stage and included all sites (Supplement E1-3). AJCC stage (7th edition) of III or IV. All studies were prospective, except for 3 MRI [42,50,81] and 5 PET studies [10,67–69,73]. In one study [74] it was not specified. In 37 out of 52 studies (70%), patients received cisplatin-based chemotherapeutic regimens. Reference standard during follow-up was (histo)pathological confirmation in case of suspicion of malignancy on functional imaging (CTp, MRI or PET) and clinical examination in all studies, except for 2 PET-studies [41,70] in which the reference standard was not mentioned.

Treatment outcome was described in 45 studies (CTp (n = 4), fMRI (n = 20) and PET (n = 25) (Supplement F). Short-term outcome (treatment response evaluation with a maximum follow-up of 6 months) was described in 12 studies (CT (n = 2) [17,38], MRI (n = 7)

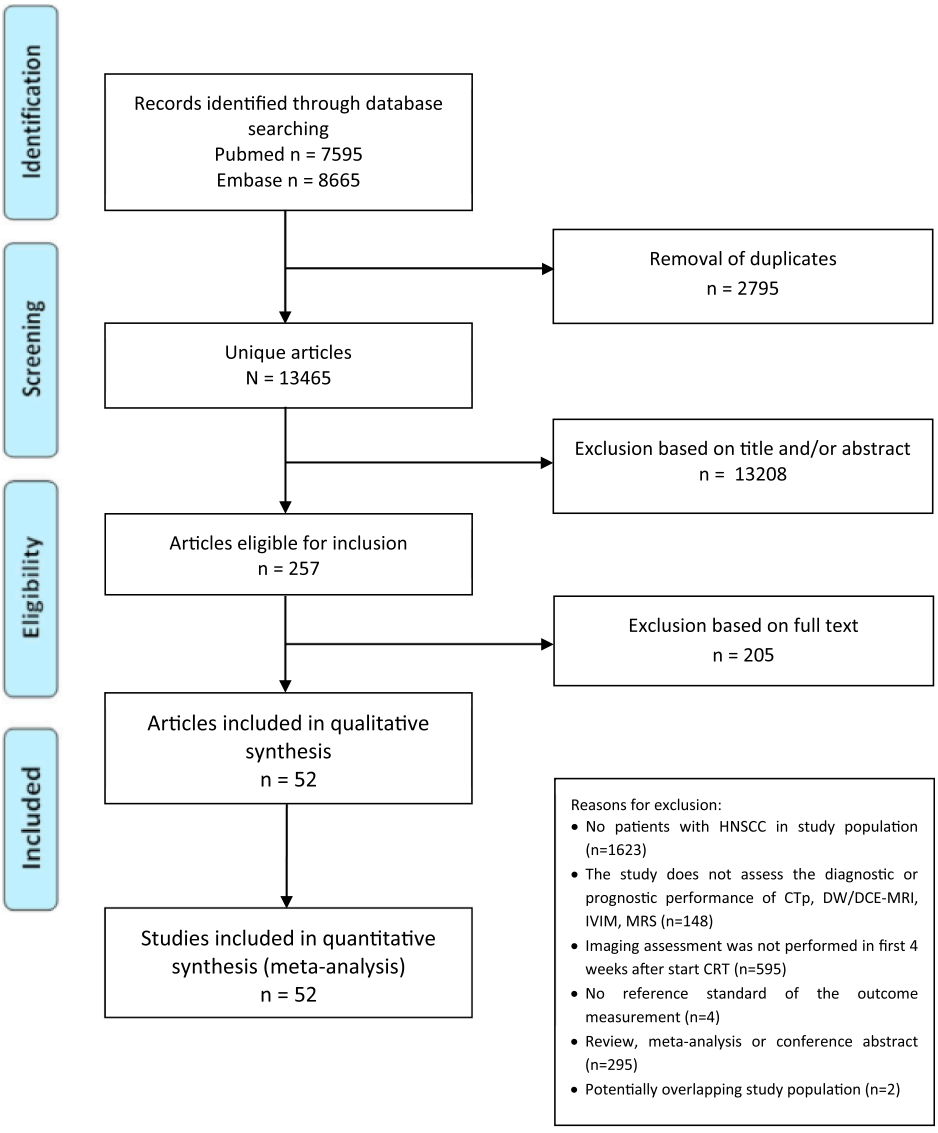

Fig. 1. PRISMA flow diagram of included studies.

[44,48,51,54,56,57], PET (n = 3) [8,63,82]). The LRC at 2 years was 87–93% of patients in CT-studies, 29–89% of patients in MRI-studies and 42–90% in PET-studies. The 2 year OS was 87–93% of patients in CT-studies, 29–91% of patients in MRI-studies and 32–97% in PET-studies.

Study quality

The QUIPS (Supplement G) resulted in overall low risks for bias on study participation, prognostic factor, outcome measurement and statistical analysis and reporting. However, 6 studies [8,16,42,44,53,54] scored high risk for bias on study attrition, 15 on prognostic factor measurement [8,32,39,44,46,49,50,55,61,63,65,68,72,80,83], and 7 on confounders, [8,16,39,42,48,69,84], respectively. HPV status was reported in 4 MRI-studies (18.2% of included MRI studies) [44,56,57,83] and 5 PET-studies (18.5%) [10,16,70,78,79] as possible effect-modifier. The follow-up time varied in the included studies; 2 CT-studies [17,38] and 7 DCE-MRI-studies [44,45,48,51,54,56,57] reported a limited follow-up time of 6 months, while all other included studies reported a mean follow-up time ranging from 9.7 to 64.9 months.

Locoregional control and overall survival

Prognostic effect of clinical parameters on functional parameters

The effect of tumor stage on functional biomarkers was assessed in one study [61], which reported a significant higher FDG-PET SUVmax in advanced tumor stage.

The prognostic effect of HPV-status on the functional biomarkers during treatment was assessed in 5 studies [10,44,56,57,83]. The intratreatment resolved hypoxic subvolumes in HPV-positive patients appeared to be a predictor for LRC [10]. Tumor sub-entities using a clustering method [57] and intratreatment IVIM-derived change of ADC and D [56], were identified in HPV-positive tumors with good response. Another study reported a high prevalence of resolvable hypoxic area in HPV-positive tumors using ^{18}F-FMISO-PET [10].

Perfusion (CT-perfusion and DCE-MRI)

First-pass perfusion, measured with CT-perfusion, was assessed in 4 studies [17,36-38]. High baseline blood flow (BF > 106 ml/100 g/min) and low permeability surface (≤ 47 ml/100 g/min) (PS, i.e. the product between permeability and the total surface area of the capillary endothelium in a unit mass of tissue) were predictive for LRC [17]. A persistent high or increasing BF, BV and PS at 3–4 weeks intratreatment

Table 1
Overview of included studies.

	Studies			Patients			Follow-up[2]	Treatment[3]					LRC (follow-up < 6 monhts)	LRC (follow-up > 6 months)	Overall survival
	Total	Short-term follow-up[1] (< 6 months)	Long-term outcome[1] (> 6 months)	Number of patients	Age mean (range)	Male (%)	Follow-up (months)	RT (Gy)	Plat	EGFR	VEGF	Tax	5-FU	Range (%)	Range (%)	Range (%)
CT Perfusion	4	2	2	79	56 (51-58)	80-96	26 (24-28)[2]	66-72	3	0	0	0	0	12-16 (50-65)	13-14 (87-93)	NS
MRI	22	7	18	541	54 (28-83)	100	29 (5-76)[2]	70-72[1]	17	5	2	4	3	2-40 (11-96)	5-46 (29-89)	5-32 (29-91)
DCE[5]	7	1	6													
DWI[3,4,5]	17	6	11													
- IVIM[3]	3	2	2													
PET[2]	29	3	26	1003	61 (22-118)	75-100	30 (1-83)[2]	50-78	18	6	1	0	3	6-54 (22-94)	6-75 (52-97)	7-80 (32-100)
FDG-PET[4,5]	15	3	14													
FMISO	7	0	7													
FLT	5	0	5													
FHX4	1	0	1													

Plat – Platinum-based chemotherapy EGFR – Epidermal growth factor receptor-targeting chemotherapy VEGF – Vascular endothelial growth factor-targeting chemotherapy Tax – Antineoplastic chemotherapy, 5-FU – 5-Fluoruracil NS – Not specified

[1] In 8 studies both treatment response as long term outcome was assessed.

[2] Follow-up was not specified in 1 CT, 7 PET, 3 MRI studies.

[3] Three DWI studies included IVIM assessment.

[4] In three studies, DWI was combined with FDG-PET assessment.

[5] In one study, DCE was combined with DWI and FDG-PET assessment.

were predictive for LRC [36,38]. An increase at two weeks intratreatment of BF of 27.5% [36] and capillary permeability transfer coefficient (K^{trans}) was predictive for LRC [37].

LRC was assessed in 5 studies using dynamic contrast-enhanced MRI [39,40,42–44] Two studies [40,43] showed a significantly higher tumor-blood-volume (ΔTBV) at DCE after 2 weeks after start of (chemo) radiotherapy in LRC compared to LRF (p = 0.03 and p = 0.01). A high persistent or fractional increase of K^{trans} (p = 0.012) after 2 weeks of treatment (volume transfer constant between blood plasma and extracellular extravascular space) was associated with LRC [58].

Diffusion (DWI and IVIM)

Twenty-two studies [39-58,83,85] assessed the prognostic accuracy of DWI, of which 3 used IVIM [56,57,83]. An optimal cut-off of percentage increase of ADC_{mean} was determined per study, above which patients were prognostic for LRC (Figure 2, see Supplement H for patient data). Firstly, the percentage ADC_{mean} change was assessed, which showed that an percentage ADC_{mean} increase at 2 weeks intratreatment higher than the optimal cut-off of 10.8–15.5% was predictive for LRC during 2 years of follow-up (pooled OR of 19.34 (95%CI 6.28–59.51, I^2 = 0%)). A higher percentage ADCmean increase than the optimal cut-off of 15.5%[83] or 24%[85] (Figure 2) at 3 weeks predicted LRC (n = 34, n = 35, respectively) resulting in a pooled odds ratio of 19.79 (95%CI 1.06–369.52, I2: 68%).

An ADCmean increase after 1 week of treatment was reported higher in LRC than in LRF patients [47]. At 2–3 weeks two studies did not find significant differences in ΔADC_{mean} between LRC and LRF patients [52,53], whereas three other studies showed an overall trend towards a higher ADC_{mean} increase at 3 weeks intratreatment in LRC (22%[45], > 25%[54], 100% increase [56]) compared with LRF (7%[45], not specified [54], 38% increase [56]). An ADC_{mean} increase of 25% at 4 weeks was reported in LRC [55]. A high (> 1.12) value or an increase (52%) of IVIM parameter D at 3 weeks intratreatment, was found predictive for LRC [56,57,83] No study used ADC_{mean} to predict OS.

Positron-emission tomography

^{18}F-FDG-PET SUV_{max} was measured in 17 studies [8,41,53,58,60,61,63-69,71-73,80,82]. A lower metabolic rate than 16 (in μmol/min/100 g of tissue) at 3 weeks intratreatment (p = 0.007) was associated with LRC in three studies within a short follow-up time of 6 months [8,63,82].

An absolute SUV_{max} higher than the optimal cut-off defined in each study, ranging from 4.25 to 5.05, at 3–4 weeks intratreatment, was found to be predictive for LRF in 4 studies [68,71,72,80], with a pooled HR of 2.32 (95%CI 1.39–3.87; I^2: 0%) (Figure 3a). Although the patient population, the image system and acquisition protocols differed in the pooled studies, the patient population and outcome were homogeneous (I^2 = 0; Figure 3). Lower absolute SUV_{max} after 3 weeks of (chemo) radiotherapy (i.e. absolute SUV_{max} < 4.25 g/mL) was predictive for LRC (p = 0.002) [68,80].

The accuracy of predicting OS with (Δ)SUV_{max} intratreatment is shown in Figure 3b. An absolute SUV_{max} higher than the optimal cut-off value defined in each study was predictive for a better OS (pooled HR of 2.59; 95%CI, 1.62–4.12, I^2:0%)).

Three studies [68,72,80] reported that a lower total lesion glycolysis (TLG) at 3 weeks intratreatment was moderately predictive for LRC and OS (Figure 4a and 4b, respectively). The pooled HR for TLG higher than the optimal cut-off of 9.4–14.0 was found 5.68 (95%CI 2.86–11.31; I^2:0%) for LRC and 3.04 (95%CI 1.70–5.42; I^2:0%) for OS. The prognostic value of TLG was directly compared to the SUVmax reduction in one study [68], shown that TLG was the best prognostic indicator of oncological outcomes. One study [73] showed that a TLG reduction of > 5% per week was associated with improved LRC (p = 0.04; HR = 0.37; 95%CI = 0.15–0.95). Three studies [68,72,80] reported that an absolute TLG value lower than the ≤ 9.4 or < 14.0

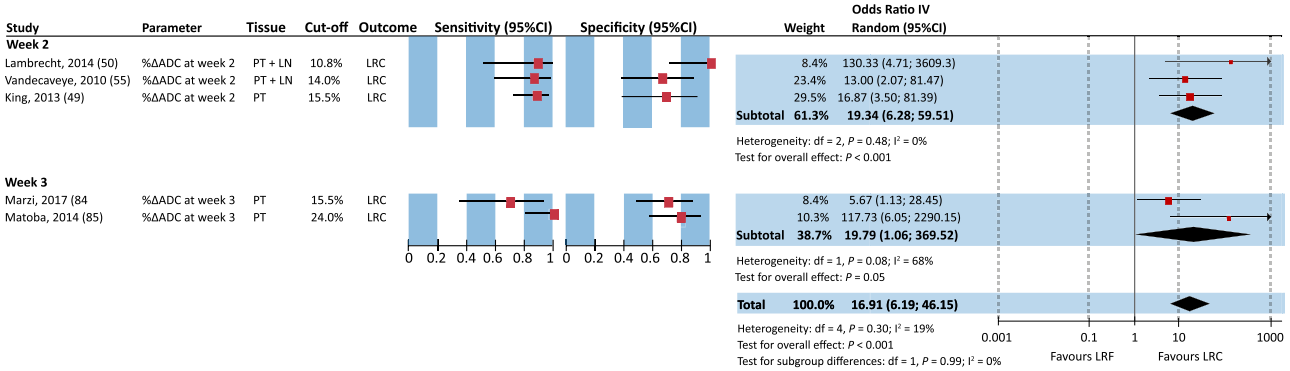

Fig. 2. The accuracy of DWI studies to predict locoregional control sorted by imaging time point; at 2 and 3 weeks after treatment initiation. Sensitivity and specificity are reported with 95% confidence interval as horizontal lines. On the right, a pooled odds ratio of %ADC increase to predict locoregional failure (recurrence). A higher %ADC increase than the optimal cut-off value (OC) resulted in a higher odds for locoregional control (LRC). *Abbreviations:* ADC = apparent diffusion coefficient, PT = primary tumor, LN = lymph node, LRC = locoregional control, LRF = locoregional failure, I^2 = I-square, df = degrees of freedom, IV = instrumental variable, CI = confidence interval.

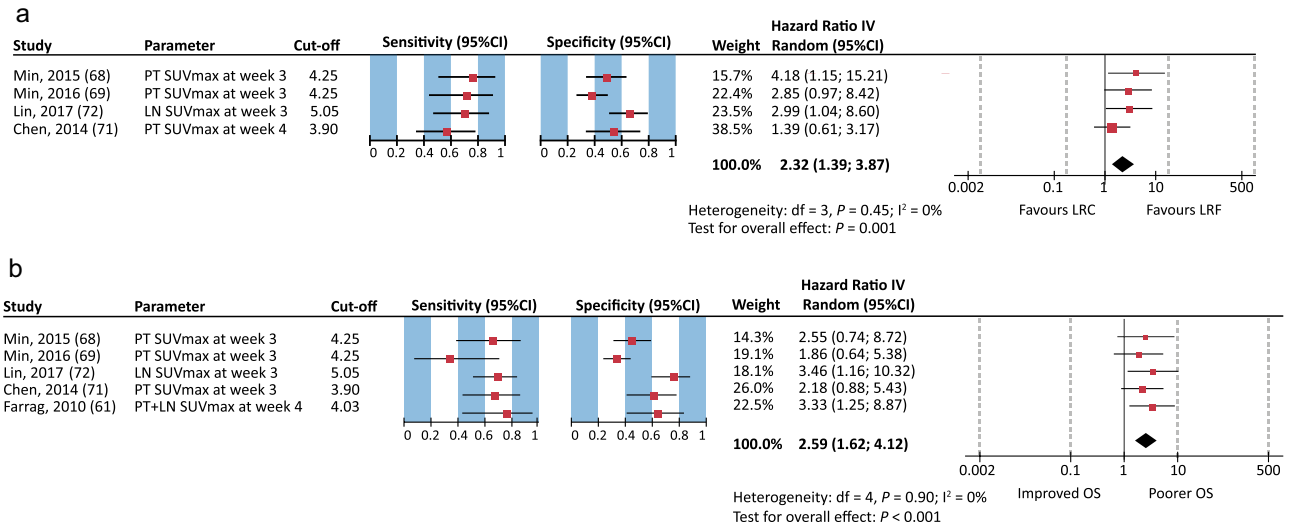

Fig. 3. (A) The accuracy and hazard ratio of SUV_{max} for the prediction of DFS. Low to moderate accuracy is shown for the week 3–4 assessment of SUV_{max}. (B) The accuracy and hazard ratio of SUV_{max} for prediction OS. Higher SUV_{max} than the optimal cut-off resulted in a higher hazard for death. *Abbreviations:* df = degrees of freedom, IV = instrumental variable, LN = lymph node, LRC = locoregional control, LRF = locoregional failure, OS = overall survival, SE = standard error, SUV = standard uptake value, PT = primary tumor.

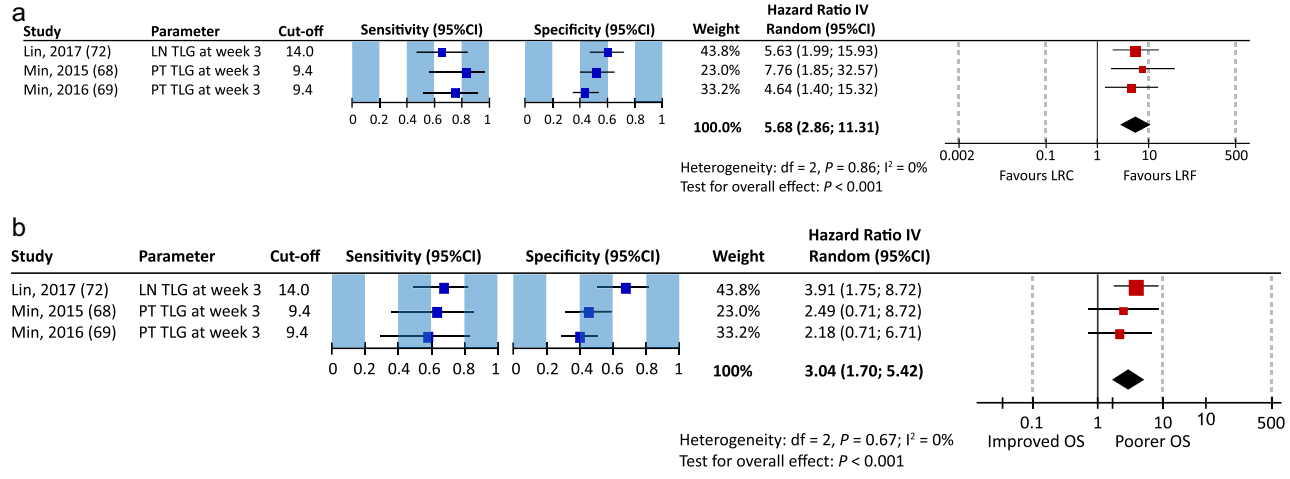

Fig. 4. (A) The accuracy and hazard ratio of FDG-PET TLG was low to moderate for prediction of DFS. (B) The accuracy and hazard ratio of TLG for predicting OS is shown, which resulted in a moderate accuracy. *Abbreviations:* df = degrees of freedom, IV = instrumental variable, LN = lymph node, LRC = locoregional control, LRF = locoregional failure, PT = primary tumor, SE = standard error, TLG = total lesion glycolysis.

cut-off values at week 1–3 intratreatment resulted in a LRC of 72% and 78% compared to 35% and 41%, respectively (p = 0.012, p = 0.005, HR 4.36–7.76; 95%CI = 1.40–32.6). One study found that a total of all lymph node metastases intratreatment TLG (SUV_{mean} × metabolic tumor volume (MTV)) and MTV reduction of > 50%, was a biomarker, which significantly correlated with LRC and OS [72].

FMISO-PET uptake with tumor-to-background-ratio (TBR) (gradation of hypoxia) during treatment < 1.26 or < 1.93 at 2 weeks or < 1.17 at 3 weeks intratreatment, was associated with a better 2-year LRC (p = 0.001, p = 0.016, p = 0.02, respectively) [31,75,41]. TBRpeak (SUVpeak divided by the SUVmean of the background) at 1 or 2 weeks intratreatment was predictive for LRC (p = 0.019, p = 0.012, respectively) [79]. Delta TBR was significantly predictive for LRC (p < 0.01) [78].

An FLT-PET SUV_{max} decrease of ≥ 45% at 2 weeks (chemo)radiotherapy was associated with a better 3-year LRC (88% vs. 63%, p = 0.035) [32].

Recommendations for clinical practice

Included studies described associations between functional imaging parameters and patient outcome, based on which limited data was reported on recommendations for clinical practice (Supplement I).

Suggestions for treatment de-escalation was reported in one CTp [37], 3 DCE studies [39,43,44], one DWI study [57], one FDG-PET, [72], one FMISO [78] and one FLT-PET study [32].

The identification of candidates for escalation of treatment was described in 2 DCE [41,44], FDG-PET [61,69,71,75,80] FMISO-PET [31,76], FLT-PET-study [32,62]. A change to surgery was reported in one CTp [38] and one PET-study [63].

Discussion

This systematic review provides an extensive overview of the prognostic value of performing early intratreatment functional imaging regarding the effect of tumoral perfusion and permeability, diffusion and metabolic rate on locoregional control (LRC) and overall survival (OS).

Summary of findings

The included studies showed that functional MRI parameters (i.e. increase of ADC_{mean} and K^{trans}) acquired during treatment, were able to predict LRC [17,36-38,40,43,45,49,50,54,55,57,85]. Similarly, ^{18}F-FDG-PET studies showed that SUV_{max} reduction was also prognostic for LRC [68,71,72,80].

The most accurate prognosticators for OS with ^{18}F-FDG-PET imaging were SUV_{max} and total lesion glycolysis (TLG) reduction, whereas prognostic functional MRI parameters were not reported. Overall, reproducible prognosticators were found early during treatment, which can be used to stratify patients for early personalized treatment modifications (e.g. early treatment (de)escalation or switch to another treatment) to increase effectivity and reduce unnecessary toxicity in patients with good prognosis.

Biological characteristics captured by functional imaging during treatment

Knowledge about the biological tumor characteristics such as vascularization, cellularity, and metabolic activity can determine (chemo) radio-sensitivity of a lesion and can change during treatment.

Perfusion and permeability describe the vascularization properties of tumors, which are different compared to normal tissue [36]. Tumors easily become hypoxic and necrotic, because of altered vascular architecture, rapid proliferation and insufficient blood supply as the tumor rapidly grows. Another contributor to this disturbed vascularization and decreased perfusion is a reduction of venous/lymphatic drainage due to vascular collapse due to raised interstitial pressure [17,37]. Intratumoral inflammation, mainly due to radiotherapy, leads to an increase of blood flow and permeability surface by the upregulation of vascular endothelial growth factor (VEGF) in tumor and stromal cells and to the expression of endothelial nitric oxide, that may result in opening up previously non-perfused vessels and in neoangiogenesis [86]. In this study, patients with LRC showed a high persistent or intratreatment increased blood flow (BF), volume (BV), permeability surface (PS) and capillary permeability (K^{trans}). These parameters might reflect in patients with LRC the net imbalance of pro-angiogenic factors (e.g. VEGF) by chemo-/radiotherapy over anti-angiogenic factors; increasing the blood supply and permeability of tumor microvessels as a local supply of oxygen. Early cell degradation results in expansion of interstitial space (i.e. increase of Ve) and increased vascular permeability (i.e. increase of K^{trans}), which is also associated with LRC [58]. Reoxygenation of hypoxic tumor areas might help restore radiosensitivity [2,39–43,87]. In contrast, an imbalance of anti-angiogenic factors over angiogenic factors may have caused a low baseline perfusion characteristics, representing a more aggressive phenotype [36]. During treatment, the (chemo)radiotherapeutic cytotoxic effect may have manifested on endothelial cells of vessels, which have led to thrombosis and secondary small vessel occlusion [37]. Low persistent perfusion could also lead to a compensational induction of VEGF and its receptors in residual tumor cells, resulting in an anti-apoptotic factor for endothelial cells. [37] In this study, this was reflected by an intratreatment persistent low perfusion and the absence of intratreatment increase of perfusion BF, BV and K^{trans} in LRF [36,37,44,58].

Diffusion characteristics of the tumor reflect micro-structural cellular tissue organization, including cellular density [52] and heterogeneity [45]. Tumors with high cellularity are reflected by a high diffusion restriction (i.e. low ADC) and are associated with LRC. Early intratreatment increase of ADC is attributed to an increase in molecular diffusion in the extracellular space that occurs with cell shrinkage and death, and movement of water from the intracellular to extracellular space as a result of cell membrane destruction [51,54]. In contrast, heterogeneous tumors are associated with small hypoxic areas of necrosis (i.e. high ADC) with insufficient blood supply resulting in LRF [52,57]. The LRF might be explained by an intratreatment persistent impairment of delivery of sufficient chemotherapeutic agents and/or oxygen (hypoxia), which decreases radiosensitivity [17,83]. The absence of an ADC increase after treatment initiation was correlated with the dens microstructure of persistent HNC [55]. Perfusion-free diffusion coefficient D (from IVIM-analysis) or DWI histogram analysis seemed more sensitive to variation in the cellular microstructure caused by early radiation effects, than ΔADC_{mean} [56,57,83].

Tumoral metabolic activity was mainly assessed by FDG-PET studies [61,64,65,68,69]. Intrinsically aggressive tumors are likely to have high baseline proliferation rates, which will remain high during (chemo) radiotherapy [80]. However, infiltration of inflammatory macrophages with overexpression of GLUT-1 transporters will contribute to the FDG-PET signal. Accumulation of FDG in peritumoral tissue could be caused by radiation-induced inflammation after 2–3 weeks [61]. A strong decrease of total lesion glycolysis (TLG) was a better reflector of the metabolic burden compared to SUV_{max}, which is based on the highest single-voxel intensity [68]. Smaller hypoxic areas (i.e. reduction of TBR_{max} on FMISO-PET) early during (chemo)radiotherapy were associated with LRC due to an improved perfusion by radiotherapeutic effects, whereas in larger hypoxic areas hypoxia will remain as these are too far away from the blood supply [75].

Prognostic effect of clinical parameters

Patients with a positive tumor HPV-status have favorable LRC and OS [88]. This was attributed to the inactivation of the tumor suppressor gene TP53 in HPV-positive tumors, which is reactivated during radiotherapy and results in restoration of normal cell cycle control and

apoptosis. In this study, limited studies reported on differences of tumor stage or HPV-status on functional imaging parameters, but it was suggested that HPV-status contributes to personalized dose de-escalation [10,56]. Large future studies, stratified for these parameters, should evaluate the effect on functional biomarkers.

Optimal imaging timing for LRC and OS prediction

The optimal intratreatment imaging time to identify predictive biomarkers was 2–3 weeks, varying slightly among the biological characteristics. The timeframe of 2–3 weeks intratreatment allows for capturing early perfusion change (after week 2), without the drawback of destroyed tissue diffusion restriction and inflammatory components (after 3 weeks). At 2 or 3 weeks, an ADC_{mean} increase (higher than the optimal cut-off value of 10.8–25%) predicted LRC. At 3 or 4 weeks intratreatment a reduction of absolute SUV_{max} (lower than the optimal cut-off value of 4.25–5.05) as the most powerful predictors for LRC.

The predictive value of early vascular characteristics captured by DCE-MRI was reported minimally. A high blood supply (BF and BV) and low permeability surface at baseline, followed by increasing permeability in the first 1–2 weeks result in better LRC. Limited data suggested that MRI-derived parameters are able to discriminate between LRC and LRF after 2 weeks of treatment and it was suggested that after 3 weeks a reduction of Ktrans or BV under (chemo)radiotherapy was predictive for LRC. This was explained by the damage to the intratumoral microvasculature and cell environment [17,37,38,44,58]. It was shown that radiation-induced inflammation occurs after 3 weeks, which might influence the accurate assessment of predictive ^{18}F-FDG-PET parameters [61].

The most optimal timing for predicting OS was described in three FDG-PET studies and showed that particularly FDG-PET parameters SUV_{max} reduction and TLG were most prognostic at week 3 [69,73,80]. Delta (Δ) absolute values or (percentage) change from baseline to intratreatment values are less effected by confounders of variability of single time imaging [35]. which enables more accurate comparison of patients who underwent imaging with similar acquisition systems for serial scanning, but different from other patients at different scanners and centers.

Applicability to clinical practice

The early identification of response during treatment by functional imaging, could assist patient-tailored treatment adaptation, aiming for similar efficacy, less toxicity and improved quality of life [7]. However, included studies were mainly of hypothesis-generating setup associating functional imaging with tumor characteristics and response, whereas limited recommendations for clinical practice were provided.

Treatment de-escalation was proposed in low-risk patients (e.g. low TNM-stage or HPV-positive [88]) with favorable prognosis is; I) radiation combined with cetuximab instead of cisplatin, II) decreased radiation doses and/or volume, III) radiotherapy instead of chemoradiotherapy [7,10]. Early identification of responders and non-responders was shown to be feasible. Identified low-risk patients may be candidates for treatment de-escalation, this has to be evaluated in future randomized controlled trials including low-risk patients. Based on the included studies, intratreatment DWI could provide a time-efficient and cost-effective early evaluation with low-patient-burden.

Treatment escalation, reported in recent de-escalation studies for patients with unfavorable prognosis based on intratreatment functional imaging would likely benefit from scaling up treatment to normal dose [7]. Included studies recognized predictive imaging parameters, but avoided concrete statements about possible candidates. Changing to surgery or to stop treatment in patients with unfavorable prognosis may result in better quality of life. However, the included hypothesis-generated studies only reported on associations with prognosis. Future studies are necessary to unravel the most accurate functional imaging technique, measuring (percentage) change, without using a data-driven threshold.

Limitations

Even though this review provides an extensive overview of the prognostic value of intratreatment functional imaging, there are some limitations. Firstly, a limited sample size and heterogeneity of studies (i.e. difference in (chemo)radiotherapy dose at time of intratreatment imaging, scanning protocols, acquisition systems and statistical methods) limited the possibility for comparison and the assessment of publication bias [89].

Secondly, included studies dichotomized continuous covariates by selection of a data-driven optimal threshold for categorization of patients. Although selection bias could have occurred, (i.e. type 1 inflation error, overestimating effect measures and difficulty to replicate the optimal threshold), most studies were initial studies to new potentially prognostic imaging techniques, which has to be validated in future studies. Hereby, a limitation of DWI [90] and DCE [91] is that functional imaging values vary, which underlines the importance of reporting internal/external validation in future studies.

Thirdly, the follow-up time was limited (only 6 months) in 15 predictive studies of LRF survival, which can underestimate the incidence of LRF in studies. Furthermore, the differences in biology and clinical behavior between the various cancer sub-sites and clinical behavior among different TNM stages [92] were ignored in most of the included studies. Finally, primary tumors and lymph node metastases were often combined, however in daily practice, both lesion entities are often taken into account. This results in a limited prognostic possibility for differentiating between patients subgroups. Future studies should focus on homogenization of techniques, acquisition methods and reporting of more uniform parameters with differentiation between tumor sites, HPV-status and TNM-stage.

Conclusions

Early tumoral changes from (chemo)radiotherapy can be captured by functional imaging with MRI and ^{18}F-FDG-PET and were predictive of locoregional control and overall survival. A decrease of diffusion restriction (i.e., an increase of ADC_{mean}) and a decrease or persistently low uptake of ^{18}F-FDG (SUV_{max}) in a lesion were most predictive of locoregional control. A persistent high or increased perfusion (blood flow, volume, permeability) on DCE was also predictive for locoregional control. Low intratreatment ^{18}F-FDG uptake (SUV_{max} and TLG) was predictive of overall survival. Optimal timing of functional imaging was between 2 and 3 weeks after start of treatment.

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This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Conflict of interest

None declared

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://

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