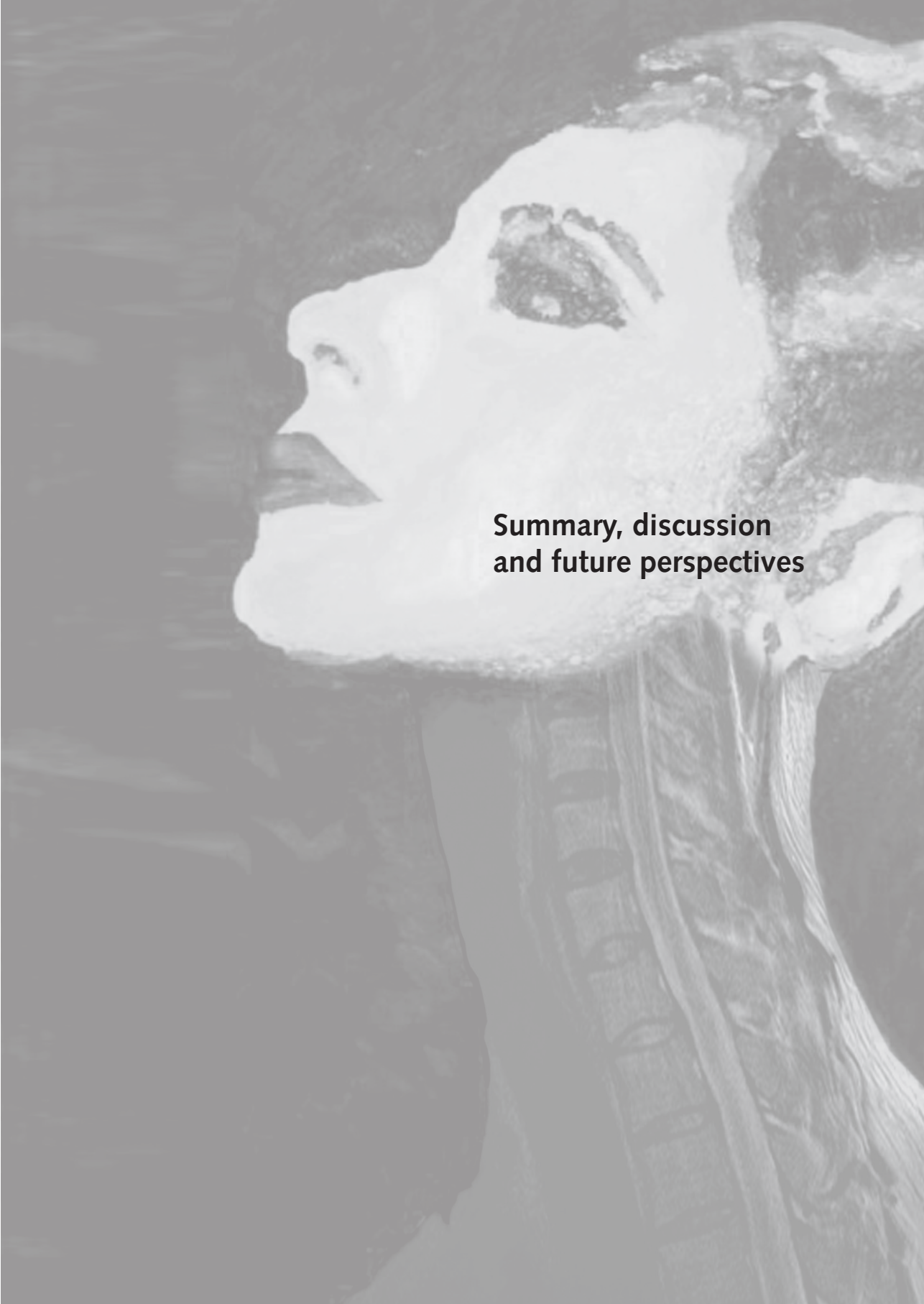

Summary, discussion and future perspectives

SUMMARY AND DISCUSSION

This summary and discussion will first deal with MR imaging parameters of the pretreatment supraglottic and glottic carcinoma, in particular with tumor volume, submucosal tumor tissue extent, and cartilage invasion for prediction of local recurrence after radiation therapy. In addition, the predictive value of MRI lymph nodes parameters in head and neck cancer for prediction of distant metastases is discussed. This is followed by a discussion regarding the predictive value of posttreatment MR imaging parameters for local recurrence after (chemo)radiation therapy.

Pre-treatment laryngeal cancer

Laser therapy, (chemo)radiation therapy (RT) and/or surgery (partial or total laryngectomy) are the modalities of choice for treatment of laryngeal carcinoma. The choice between these modalities is, among others, influenced by site and extent of the lesion. In small tumors, curative RT or endoscopic laser surgery (treatment modality with minimal thermal damage to the surrounding tissue) are the first choices of treatment. In case that tumor control is unlikely to be achieved with (chemo)radiation therapy, primary surgery could be a good alternative. Accurate assessment of the extent of the primary lesion is highly important in relation to the feasibility and application of irradiation treatment.
Radiological techniques, such as CT and MR imaging, may provide additional information about the submucosal extent of the disease. The result of our statistical analyses shows that there are various MR imaging-determined tumor parameters of larynx and subsites of larynx which are significantly associated with local control. Our results show that by classification into low-risk, intermediate-risk and high-risk groups, based on the combination of prognostic MRI-determined parameters, it is possible to identify a subset of patients, who are less likely to be successfully treated with (chemo)radiation therapy and who may better be treated with alternative treatment, e.g. surgery.
In an initial study on predictive value of MR imaging parameters in supraglottic carcinoma treated by radiation therapy (Chapter 1), univariate analysis showed that MR imaging-determined primary tumor volume, involvement of pre-epiglottic space, abnormal signal intensity in thyroid cartilage and extralaryngeal extension beyond thyroid and/or cricoid cartilage were significant predictors of local recurrence rate. Multivariate analysis confirmed that tumor invasion of pre-epiglottic space, abnormal signal intensities in thyroid cartilage adjacent to the anterior commissure and in cricoid cartilage are strong predictors for poor local outcome in supraglottic carcinoma treated with definitive radiation therapy.

In an initial study on the predictive value of MR imaging parameters in glottic carcinoma treated with RT (Chapter 2), univariate analysis showed that MRI-determined parameters (such as primary tumor volume, submucosal tumor extent, abnormal signal intensity in cartilages, and extralaryngeal extension) were all significantly associated with worse local control, while T classification and vocal cord mobility were the only significant clinical parameters associated with local control. Multivariate analysis of clinical and radiologic parameters revealed that hypopharyngeal extension and intermediate T2 signal intensity (SI) in cartilage similar to tumor SI were independent prognostic factors with regard to local control. Intermediate T2 SI in cartilage, which suggests cartilage invasion, and hypopharyngeal extension of the tumor on MR images predict greater likelihood of local failure, whereas high T2 SI, which suggest inflammatory tissue in cartilage, was associated with lower likelihood of local failure.

In a more focused study of laryngeal carcinoma (both supraglottic and glottic) on the predictive value of the degree of contrast enhancement in tumors and its additional value in previously considered MR imaging parameters (Chapter 3), we found that the level of tumoral contrast enhancement was positively related to local control rates. The local failure rate was significantly worse in tumors with a low degree of contrast enhancement than in those with a high degree of enhancement. The biological explanation might be that low contrast enhancement indicates poor vascular supply and subsequent tumor hypoxia, which in turn are associated with therapy resistance, especially in squamous cell head and neck cancer [1-4]. Our results of multivariate analysis confirmed that the degree of contrast enhancement yielded additional prognostic information to anatomic MRI-determined parameters with regard to local control in laryngeal carcinoma.

Tumor volume

We found that MRI-determined tumor volume at presentation was not significantly associated with local control in both supraglottic and glottic tumors after curative RT. Similar results were found by other investigators using CT as imaging modality [5-7]. These authors did not find a significant relationship between CT-determined tumor volume and local control in multivariate analyses [6,7]. In contrast, Gilbert [8], Mancuso [9] and Mendenhall [10] showed that tumor volume as measured on CT images could stratify patients into high-risk and low-risk groups with regard to local control after definitive radiation therapy. Presumably, the findings of these authors do not agree with our results because we have used more sensitive imaging characteristics, such as abnormal signal intensity in cartilage on MR imaging, which has shown to be a predictor of poor local outcome in laryngeal carcinoma [11-13].

Intralaryngeal compartments

The critical submucosal spaces inside the larynx are the pre-epiglottic and paraglottic spaces [14]. Tumors in pre-epiglottic and paraglottic space enhance differently on T1-weighted MR images after the contrast administration: tumor tissue within pre-epiglottic space enhances at a low degree, whereas tumor tissue involving the paraglottic space enhances strongly. The results in our patient population with supraglottic carcinoma revealed a strong relationship between tumor involvement of the pre-epiglottic space and local tumor control probability (Chapter 1). The pre-epiglottic space is composed predominantly of fat, which has low attenuation on CT images and high signal intensity on MR images. According Giron et al. [15], both techniques have similar performance in the evaluation of the pre-epiglottic space. Fletcher and Hamberger [16] reported on the results of a study in 173 patients treated with primary radiation therapy for supraglottic carcinoma and concluded that the pre-epiglottic space is poorly vascularized. Based on their results, they suggested that the anoxic compartment of tumors penetrating this space must be substantial. This might explain the relatively higher resistance to radiation therapy (and higher cure rates with surgery) in such tumors [17]. In our study (Chapter 1), invasion of the pre-epiglottic space was the strongest independent predictor of local control of supraglottic carcinoma. The poor blood supply of the pre-epiglottic space may cause hypoxia in tumor tissue. Low degree of contrast enhancement on MR imaging may therefore be expected in patients with tumor involvement to pre-epiglottic space (Chapter 3) and may correlate with a poor prognosis.

Hamilton et al. [18] reported that the hypopharyngeal involvement of a tumor would be useful as potential indicator of local control in laryngeal cancer treated with RT. Moreover, they also showed a significant relationship between CT-determined tumor volume of T2- and T3-stage laryngeal glottic carcinoma and local control [18]. In our study on patients with laryngeal glottic cancer (Chapter 2), the second most important prognostic factor was extension into the hypopharynx as assessed on MR images, which might be explained by a combination of large tumor volume and deep tissue extension. Both intermediate T2 SI in cartilage and hypopharyngeal tumor extension were potential confounders for the association between tumor volume and local control.

Cartilage involvement

MR imaging has been reported to be highly sensitive in depicting cartilage invasion and to be more accurate than CT [19,20]. In a preliminary study, tumor invasion of the cartilages, as shown by CT, was not found to be significant predictor of local recurrence [5]. CT may enable detection of cartilage invasion, but it may fail to enable detection of early cartilage invasion because of the

large variability of ossification patterns in the laryngeal cartilages. As reviewed by Castelijns et al. [21], abnormal MR signal intensity patterns in cartilage combined with large tumor volume were associated with worse prognosis. In our study, dealing with patients with supraglottic carcinoma (Chapter 1), a significant relationship was found between abnormal MR imaging signal intensity patterns in cartilages (thyroid, cricoarytenoid and thyroid at anterior commissure) and local outcome.

In initial reports by Becker et al. [22,23] and Zbaren et al. [24], it was thought that apparent inability to differentiate between non-tumorous inflammatory changes and tumor by using MR imaging may lead to overestimation of neoplastic invasion in laryngeal carcinoma. According to our study, abnormal MR imaging signal patterns in cartilage of laryngeal supraglottic carcinoma (thyroid, cricoarytenoid, and thyroid at anterior commissure) without distinguishing different signal intensities as seen on T2 images, were correlated with the risk for tumor recurrence. However, in glottic carcinoma, these MRI-determined abnormal signal patterns in cartilage did not reach significance when compared with more specific T2-weighted MR SI. Becker et al. [25] recently showed that signal intensities may enable differentiation between neoplastic and inflammatory tissue in cartilage as found on T2-weighted spin-echo MR images. They considered T2 signal higher than that of the adjacent tumor to indicate inflammation, and T2 signal similar to that of the adjacent tumor (with intermediate SI) as neoplastic invasion, which was compared with the histological reference standard. The proposed MR imaging criteria appear to enable improved differentiation of neoplastic cartilage invasion from peritumoral inflammation [25]. According to our results, the most important independent prognostic factor on glottic carcinoma turned out to be intermediate T2-signal in cartilage as assessed on MR images, which was significantly associated with worse local control (Chapter 2). Curtin described that this, more intermediate T2-signal, advanced into the typical pattern thought to indicate tumor, called "evil gray" and has a definite importance in the larynx but may apply to other areas as well; separating true tumor from a marginal inflammatory response when applied to the mandible or even skull base [26]. Comparing histological findings with preoperative imaging signal intensity patterns would be very difficult in many of these areas, but one can certainly compare the response to various therapies with the signal intensity patterns. The implications in potential surgical resections are obvious. However, a more precise demarcation of the gross tumor volume may allow a more confined and precise irradiation, in particular of the boost volume.

MR sequences using fat saturation were not included in the MR imaging protocols of our retrospective studies. It is possible that the addition of such sequences might further enhance the signal intensity difference between inflammatory

and neoplastic cartilage changes. Application of strong weighted T2-weighted MR images enable better differentiation of neoplastic cartilage invasion from peritumoral inflammation. However, we did not evaluate this additional T2-weighted information regarding differentiation between tumor tissue and peritumoral infiltration in cartilage among patients with supraglottic carcinoma. Until recently, the presence of clear cartilage invasion on CT or MR imaging was a relatively hard indication for total laryngectomy. It is incorrect to postulate that radiation therapy cannot cure a substantial number of lesions in which cartilage is involved; minimal cartilage involvement in patients with low-staged tumors does not imply a bad prognosis [11,12]. Subgroups of patients may have a higher risk of local failure than others. Imaging gives the opportunity to detect more limited degrees of cartilage involvement, and to evaluate the impact of this more limited involvement on treatment outcome. In Chapter 2 we showed that glottic tumors with intermediate signal intensity in cartilages on T2-weighted MR images (suggestive for cartilage invasion) have a rather poor outcome. The local control rate in these cases was only 27% after 2 years in comparison with 84% and 87% in cases of tumor with nonossified cartilage or not suspected cartilage invasion. These results may have impact on T staging, because neoplastic cartilage invasion changes the T stage. TNM staging system is, among others, developed for prognostic purposes. Regarding tumor extension in cartilages, the most recent revision in TNM classification guidelines [27,28] states that tumors with "thyroid cartilage erosion" and "through cartilage" would mean T3 and T4, respectively. We believe that MR imaging findings are therefore essential in the work-up for T staging of laryngeal carcinoma.

No conclusions can be drawn concerning extralaryngeal extension of the tumor beyond these cartilages, because of the limited number of patients with extralaryngeal abnormalities. The prognosis for patients with extralaryngeal extension at diagnostic imaging may be expected to be worse. Fiorella et al. [29] reported a high incidence of relapse of the tumor in the cases with extralaryngeal extension of T3 glottic carcinoma treated surgically. There was a significant correlation between decrease in survival rates and contemporaneous increase in peri-laryngeal extension of the tumor, even if microscopic [29]. Nevertheless, this characteristic did not adversely affect the likelihood of local control in our patients, probably because such abnormalities are treated primarily with laryngectomy at our institution.

Pre-treatment neck and distant metastases

Lymphatic metastasis is the most important mechanism in the spread of most head and neck squamous cell carcinomas (HNSCC). The presence of lymph node metastases determines to a great extent the chances of locoregional cure or

the development of distant metastases. In case of patient with already present distant metastases, there is generally no possibility of cure. Early detection may be of use in order to prevent local-regional treatment with considerable acute and late morbidity, such as concomitant chemoradiation and or extensive surgery with postoperative radiotherapy, particularly in case of extensive metastatic disease. In some cases, e.g. when only a solitary metastatic deposit is present, aggressive treatment of locoregional and metastatic disease may be an option and in some cases even curative [30]. Also in these circumstances, early detection may be beneficial.

In our retrospective study with 311 patients with HNSCC (Chapter 4), we investigated the prognostic significance of pretreatment MR imaging of cervical lymph nodes for development of distant metastases. This may be readily accepted by clinicians and be easily used for distant staging guidelines. We found that presence of lymphatic metastasis with extranodal spread (ENS) was the only independent prognostic factor. We were able to identify 3 distinct prognostic groups (i.e., patients without enlarged nodes, patients with enlarged nodes without ENS and patients with enlarged nodes with ENS on MR imaging); if confirmed prospectively this classification would enable the identification of a subset of patients at high risk for the development of distant metastases after initial treatment. Especially, our patients with enlarged lymph nodes at lowjugular/posterior triangle (oropharyngeal cancer) or at paratracheal level (laryngeal cancer), or with contralateral enlarged nodes (laryngeal and oral cavity cancer), and extranodal spread are at high risk for developing distant metastases and this subset of patients might benefit from supplementary imaging screening (CT-chest, PET-CT) [31]. The final results showed that extranodal spread of lymph node metastases as assessed on MR imaging was the most important prognostic factor for the development of distant metastases, both in the entire study population as well as in specific groups according to different tumor sites. These findings suggest that the presence of ENS is more important than other lymph node parameters, macroscopic ENS is more important than microscopic ENS [32]. Although it was previously thought that ENS occurred only in large nodes, it is reported that ENS can also occur in approximately 23% of non-enlarged nodes [33]. The presence of extranodal spread in metastatic nodes significantly affects treatment planning and prognosis of the patient with head and neck cancer. Recently, Kimura et al. [34] attempted to evaluate the predictive capability of MR imaging for the extranodal spread in the neck of 109 patients. He found that nodal size (=short-axis diameter), shaggy margin (=irregular nodal margin on gadolinium-enhanced T1-weighted images), and flare sign criteria (=the presence of high SI in the interstitial tissues around and extending from a metastatic node on fat-suppressed T2-weighted images) were independent and significant MR imaging findings suggestive of extranodal

spread in the metastatic nodes. These authors obtained 77% sensitivity and 93% specificity with the flare sign, 65% sensitivity and 99% specificity with the shaggy margin, and 80% sensitivity and 85% specificity with the size criterion (cut-off point=16 mm) [34]. Future studies should show and if the prognostic value of ENS, as defined with these more specified MRI criteria, will also be an important prognostic factor for the development of distant metastases. Intra- and interobserver variation in detecting of ENS should be investigated.

The detection of retropharyngeal lymph node metastases may have serious implications for choice of treatment. These lymph nodes are generally beyond the limits of neck dissection and suggest a very poor prognosis [35]. However, in our study, no significant association was found with distant metastases, which may be due to limited number of patients with retropharyngeal nodes (5%).

It has also been reported that paratracheal lymph node metastases carry a high risk of metastases to the mediastinum and distant sites [36]. The numbers of these lymph nodes in the entire study population was relatively low and not of statistical significance (Chapter 4). In the subset of patients with laryngeal carcinoma the presence of paratracheal lymph node metastases was significantly associated with the development of distant metastases.

The metastatic work-up in patients with HNSCC by using the proposed MR imaging criterion for lymph node development may be useful for the development of a treatment plan. Patients with low-risk disease have a DMFSR (distant-metastasis free survival rate) of 94% at 2 years (Chapter 4), and screening for distant metastases is unlikely to be cost-effective and may therefore not be performed. In the high-risk group as defined with the proposed MR nodal criteria (risk to develop distant metastases within 2 years of 41%), patients should be screened routinely and comprehensively for the detection of distant metastases. Radiation therapy was reported to improve survival of the patients with lymphatic metastasis with ENS compared with the ENS-positive patients who did not receive RT [37]. In addition, selective neck dissection instead of radical neck dissection could be a choice for patients with ENS-negative metastatic nodes [38].

Post-treatment laryngeal cancer

Monitoring response during non-surgical treatment is one of the challenges in head and neck cancer today. Accurate evaluation of the response to (chemo) radiation by clinical examination may be hampered by posttreatment fibrosis, edema, inflammation, or scarring. According to our study, combined MR imaging before and after primary treatment may be helpful in evaluating response in laryngeal carcinoma treated by radiotherapy. In the retrospective evaluation of 80 patients with laryngeal carcinoma on post-RT MRI examinations in Chapter

5, symmetric post-RT changes without detectable mass (score 1) are strongly indicative for ultimate control at the primary site. When post-RT MRI shows discrete mass or asymmetric post-RT changes at the primary site, the pre-RT MRI high-risk profile and hyperintense mass on T2-weighted images are strong indicators for local failure after curative RT that requires further evaluation to exclude local recurrence. Especially the identification of patients who are at high-risk (post-RT MRI score 3=focal mass with a maximal diameter of more than 1cm, or less than 50% estimated tumor volume reduction) of local failure in our study was highly significant with regard to local control. Only 1 out of 26 patients in the posttreatment score 3 group remained free of disease at the primary site and proved to have osteoradionecrosis mimicking tumor recurrence. Our results are consistent with CT studies that report 10% local control rate at 2 years for patients in the score 3 group [39], and a high significance of predicting the likelihood of local control in laryngeal carcinoma [39,40]. Application of the post-RT MRI scoring system within the two pretreatment risk groups resulted in an additional stratification in either group into three subgroups at different risks of local recurrence. The post-RT scoring system was demonstrated to be a better prognosticator than the pretreatment MRI risk profile.

The potential role of MR imaging in distinguishing tumor recurrence from radiation fibrosis on the basis of signal intensity on long repetition time (TR) /echo time (TE) (T2-weighted) pulse sequences for several head and neck carcinomas treated with radiotherapy has been described [41-43]. In these studies tumors that appeared hyperintense on T2-weighted MR images after radiation therapy, were significantly correlated with pathologic findings [42,43]. Tomura et al. [43] showed that pretreatment T2-weighted imaging is feasible for differentiating viable from nonviable tumor tissue in irradiated carcinoma of the tongue. Changes in tumors induced by irradiation are caused by the direct effect of irradiation on the tumor cells, impairment of the blood supply, and fibrosis and hyalinization of the stroma. Radiation changes were histologically graded into four groups (I, minimal cellular changes; II, presence of cellular changes and partial destruction of the tumor; III, only nonviable tumor cells; IV, no tumor cells), and were compared with SI and the degree of contrast enhancement of the tumor on MR images [42]. However, the prolonged T2-value is not specific for tumor and may be seen in radiation edema or infection. Three patients with a hyperintense mass in our study (Chapter 5), proved to be false positive. Ebner et al. [44] found that MR imaging was useful in distinguishing recurrent tumors in the female pelvis from posttreatment fibrosis in six patients. They emphasized that signal intensities from radiation changes vary over time; fatty replacement changes are seen and abnormal soft tissue with decreased T2-weighted signal intensity is suggestive of posttreatment scarring rather than recurrent tumor [44-46]. The hyperintensity on T2-weighted MR

imaging in recurrent tumors may be caused by an increased intracellular water content of tumor cells and tumoral edema.

CT findings of the laryngeal carcinoma within 3 to 6 months post-RT are reported to be often nonspecific [47,48]. MRI examination less than 4 months after the end of RT may be very helpful as a baseline to distinguish mass and complete remission. The results of our study (Chapter 5) showed that recurrence followed later than 5 months (median value) after completing (chemo)radiation was detectable more easily on MR imaging than tumor recurrence earlier than 4 months after treatment. Lell et al. [45] reported that in the first 3-4 months, edema, tumor necrosis, and acute or chronic inflammation may lead to signal changes equivalent to tumor, but that with long intervals, these changes minimized and distinguishing between tumor and post-RT changes became more effective. Progression of abnormal MRI findings is strongly predictive for recurrence, such that an early MR imaging might lead to earlier detection of recurrence than those of clinical examination (26% of local failure in this study). Patients with "suspicious" post-RT MR study should be followed by imaging at regular intervals, and any urge to biopsy prematurely could be avoided. The trauma caused by biopsies in irradiated tissue may initiate infection, further edema and failure to heal. Brouwer et al. [49] reported that 53% of the first direct laryngoscopes performed because of suspicion of recurrent laryngeal carcinoma after RT were negative. Baseline and follow-up post-treatment CT or MR imaging may improve detection of recurrent laryngeal carcinoma after (chemo)radiation. Hermans et al. [40] showed that follow-up CT, after an initial post-treatment CT, detected about 40% of local failures prior to clinical examination. Imaging should be sensitive enough to detect recurrence in a stage at which surgical salvage (total laryngectomy, in some circumstances partial laryngectomy) remains possible. Comoretto et al. [50] reported a higher accuracy of MR imaging with 92% than PET-CT with 86% in depicting residual and/or recurrent nasopharyngeal carcinoma. There were 5 patients with false-negative tumor lesion on PET-CT of 63 patients compared to one patient with recurrent tumor lesion on MR imaging. These results are due to various factors such as use of dynamic contrast-enhanced MR study for detecting the fibrotic changes, less structural distortion due to new techniques of radiation therapy with relative sparing of surrounding areas, and additional MR information in assessing skull base involvement and intracranial infiltration [50]. The use of MR imaging for assessment of tumor recurrence during and after the end of (chemo)radiation therapy may be indicated.

FUTURE PERSPECTIVES

The largest area of potential improvement in head and neck imaging will likely come from other MRI-modalities, such as diffusion-weighted MRI (DW-MRI) and to a lesser extent from perfusion MRI, especially in the differentiation between tumor versus inflammation tissue, and between recurrent tumors versus posttreatment changes. DW-MRI is a non-invasive technique, which is able to evaluate the microenvironment of tissue by measuring water movement. Due to tumor proliferation, tumor regions have increased cellular density resulting in a reduction of diffusion of water through these regions.

The potential use of DW-MRI for *in vivo* characterization of tissue in head and neck lesions was reported by Wang et al. [51] where was showed restricted water movement for malignant lesions, than for benign lesions in the head and neck. The heterogeneity of the head and neck region with numerous air-soft tissue interfaces is anatomically highly demanding region and makes DW-MRI in this region prone to non-interpretable imaging. Including echo planar (EPI)-based parallel imaging to DW-MRI, blurring and chemical shift artifacts, and image distortion are reduced [51,52]. Potentially, DW-MRI may be useful for characterization of cervical lymph node metastases, to differentiate between persistent or recurrent tumor and treatment-induced tissue changes [53-55]. Vandecaveye et al. [56] evaluated DW-MRI as compared with turbo-spin-echo (TSE) MR imaging of 33 patients scheduled for surgical treatment of biopsy-proved head and neck squamous cell carcinoma for the detection of nodal metastases. Their findings suggests that DW-MRI can be complementary to conventional MR imaging; quantification of diffusion weighted imaging enables the detection of subcentimeter nodal metastases, providing information that is additional to that generated with anatomic imaging; it cannot yet depict micrometastases smaller than 4 mm. This may lead to closer conformity between the radiation target volume and the regional tumor extent and thus potentially decrease treatment-induced side effects. DW-MRI may also be helpful for differentiation between neoplastic tissue and post-RT inflammatory or necrotic tissue as the differences in tissue microstructure, which are expected to create differences in proton mobility. Vandecaveye et al. [57] described the appearance of recurrent tumoral tissue on DW-MRI in patients presented for possible tumor recurrence in the larynx after radiation therapy for squamous cell carcinoma (SCC). They demonstrated that diffuse hyperintensity on the apparent diffusion coefficient (ADC) maps in the normal soft tissues of the larynx correlated with expected post-therapeutic alterations, such as inflammation and interstitial edema, promoting free movement of protons. Contrary, detected hypointense lesions on the ADC map, contrasting with the surrounding tissue, were histologically proven recurrent SCC. Further

studies are needed to validate the reproducibility and diagnostic accuracy of the technique and the image interpretation are required before DW-MRI of head and neck SCC can be used as routine in the clinic.

Another promising modality for differentiation between tumoral and non-tumoral disease after completing (chemo)radiation treatment of head and neck cancer may be perfusion MRI. To our knowledge, reports on this topic are scarce. The usefulness of dynamic maneuvers has increased with the improvement in temporal and spatial resolution that allow good delineation of small moving structures like laryngeal structures; this could provide important information about the local extent of tumor [58]. The measurements of tumor perfusion assessed with dynamic CT have been shown to be helpful in predicting response to radiation therapy as well as induction chemotherapy in head and neck cancer [59-61]. CT perfusion (CTP) provides the unique ability to non-invasively quantify the microvascular blood flow of tissue. The results of these studies confirm the hypothesis that less-perfused tumors respond poorly to radiotherapy and/or chemotherapy. More recent developments have resulted in more biologically targeted therapy, with newer chemotherapy agents targeted to specific proteins overexpressed by certain tumors. These advances announce the age of "individualized therapy" with specific treatment regimes 'designed' to treat each individual tumor's unique biological characteristics. The next, and some would argue the most important step, is to attempt to determine a tumor's response during treatment. Biological imaging information, such as that obtained with CT/MRI perfusion or MRI diffusion techniques, can predict if a tumor is less likely to respond to certain non-surgical organ preservation therapy and has the potential for increasing local control and overall survival with less complications.

The fusion of PET and CT has already proven to be more accurate for the detection of malignancy in the head and neck. PET-MRI is a new promising multi-modality imaging device successfully studied by Judenhofer et al. [62] as a new approach for functional and morphological imaging.

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