CHAPTER 9

Summary, general discussion & future perspectives
SUMMARY

Despite significant advances in the different treatment modalities, the local recurrence rate of laryngeal carcinoma is still 20-40% (1-5). The trend in primary treatment of advanced laryngeal carcinoma (mainly T3) has shifted from laryngectomy towards (chemo)radiation, to preserve function and to reserve surgery for salvage procedures. Mainly due to (chemo)radiation induced changes in normal tissue, detection of recurrent carcinoma can be difficult. As conventional imaging modalities such as CT (computed tomography) and MRI (magnetic resonance imaging) have limited accuracy for the detection of recurrent carcinoma after (chemo)radiotherapy, new diagnostic strategies are evaluated. The current clinical practice consists of direct laryngoscopy with biopsy under general anesthesia, which is invasive, expensive and has a sensitivity of 45% at a first attempt (6). Depending on T-stage, 1.7 to 4.9 direct laryngoscopy procedures per patient are required to detect one recurrence within a time period of 6 months after suspicion was first considered. Previous studies have shown that 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET) seems to have potential in detecting recurrent laryngeal carcinoma after radiotherapy. Because of its high negative predictive value PET might be used to exclude the presence of recurrent laryngeal tumor (7,8).

For patients with proven local tumor after (chemo)radiation, salvage laryngectomy with or without lymph node dissection(s) is the mainstay of treatment. However, it is well recognized that salvage surgery as compared to upfront surgery carries a higher complication risk (fistula 23-34% versus 14%, respectively) with sometimes disappointing cure rates (5-year disease free survival 48-54% versus 61%)(9-15). Surgeons are faced with the challenge to remove sufficient tissue to allow for radical excision of the tumor (as laryngectomy often is the last treatment option with curative intent), while preserving as much normal tissue as possible (as more extensive surgery is associated with a higher risk of complications).

The aim of this thesis was to investigate the role of 18F-FDG-PET in the detection of local recurrent laryngeal carcinoma after (chemo)radiation, and to evaluate the outcome of salvage surgery.

In order to optimize the diagnostic phase in the detection of local recurrence, the clinical value of 18F-FDG-PET for this indication was studied in chapter 2-5. PET assessment is typically by visual interpretation, which is subject to interobserver variation. The extent to which results can be generalized, as an implication for the use of PET in daily clinical practice, depends on the degree of agreement among different observers. In chapter 2 we analyzed the results of 11 nuclear medicine physicians (with head and neck experience) from eight centers accredited by the Dutch Head and Neck Society, who reviewed 30 18F-FDG-PET scans of patients suspected of recurrent laryngeal carcinoma after radiotherapy. Using a 3-category test result scale (positive, equivocal, negative), we found a moderate interobserver agreement (κ = 0.55) in comparison to the reference standard (defined as local recurrence within 6 months after PET). After dichotomization, we calculated test accuracy for a sensitive (equivocal considered positive) and conservative reading strategy (equivocal considered negative). The conservative strategy resulted in a better overall accuracy and interobserver agreement (κ = 0.59 and 0.58) than the sensitive one (κ = 0.43 and 0.51). The mean sensitivity (of observers) ranged from 87% to 97%, and the mean specificity from 81% to
63%. At a prevalence of 23% local recurrences, the negative predictive value of PET was 96% to 99%. 18F-FDG-PET yielded a good negative predictive value for the detection of recurrent laryngeal carcinoma. Based on this pilot study we concluded that the interobserver agreement was acceptable with the sensitive reading strategy. PET seemed therefore useful as a first diagnostic step to select patients for direct laryngoscopy under general anesthesia and may reduce the percentage of futile invasive diagnostics.

In order to test this hypothesis as described above, a randomized controlled multicenter clinical trial was discussed in chapter 3. The RELAPS study (Recurrent Laryngeal carcinoma PET Study) was designed to evaluate the efficacy of 18F-FDG-PET as first line diagnostic investigation to select patients for direct laryngoscopy with biopsy under general anesthesia, in patients suspected of recurrent laryngeal carcinoma after radiotherapy. Hundred-fifty patients were randomized to direct laryngoscopy under general anesthesia (conventional strategy), or to 18F-FDG-PET, only followed by laryngoscopy under general anesthesia in case of positive or equivocal findings on PET (‘PET-based strategy’). This sensitive reading was used because in clinical practice, missing of a recurrence probably outweighs an unnecessary direct laryngoscopy (no recurrence on direct laryngoscopy nor subsequently within the reference period of 6 months). If laryngoscopy with biopsies did not reveal recurrent tumor, laryngoscopy was repeated within 6 weeks unless clinical signs and symptoms had diminished. In the PET-based strategy patients with a negative PET were not subjected to additional investigations for at least 3 months, unless there was progression of symptoms. The achievable health gain comprises a reduction of the number of avoidable direct laryngoscopies and their consequences.

In chapter 4 we presented the results of the RELAPS study. Forty-five patients (30%) had histopathologically confirmed local disease within 6 months after randomization. The indication for direct laryngoscopy was futile in 53 out of 74 patients (72%) in the conventional strategy, compared to 22 out of 76 (29%) in the PET-based one. This difference can be interpreted as 2.3 patients to be evaluated with PET to avoid at least one unnecessary indication for direct laryngoscopy under general anesthesia. Thirty PET scans were true-negative and 1 was false-negative. Safety of the PET-based strategy was confirmed; we found no adverse effects on the operability of a recurrence or surgical margins of the salvage laryngectomy in the PET-based group. In our subgroup analyses, maybe due to small groups, the number of unnecessary indications for direct laryngoscopies in PET and PET/CT scanned patients was not significantly different. With 12 months as the reference follow-up period, the results were highly similar. This trial showed that in patients suspicious for recurrent laryngeal carcinoma after radiotherapy, PET as the first diagnostic procedure can reduce the need for direct laryngoscopy by more than 50% without jeopardizing quality of treatment.

In a cost analysis, described in chapter 5, we investigated the potential health benefits and cost consequences of introducing 18F-FDG PET in the diagnostic work-up of patients suspected of recurrent laryngeal carcinoma after radiotherapy. The average total costs per patient within 6 and 12 months follow-up were compared between the two diagnostic strategies of the RELAPS study. A micro-costing method was used, based on a detailed inventory and measurement of all resources consumed. Medical incremental costs were calculated. The diagnostic, treatment and follow-up phases were analyzed separately in subgroup analyses. After 6 months of follow-up the mean total
costs per patient in the conventional strategy were 11,784 euro, compared to 11,302 euro in the PET-based strategy, resulting in cost savings of 482 euro per patient with a PET-based strategy. The results of the same analyses for a 12 months follow-up period were comparable, with total costs savings of 1105 euro per patient in favor of the PET-based strategy. Sensitivity analyses confirmed the robustness of the results. Therefore, the introduction of 18F-FDG-PET is the diagnostic work-up is favorable from both clinical and economic perspectives.

The second part of this research is directed towards the treatment of patients with recurrent laryngeal carcinoma after radiotherapy. Patients with proven local tumor after (chemo)radiotherapy will need salvage surgery, often a total laryngectomy with uni- or bilateral lymph node dissection. However, survival rates after salvage surgery can be disappointing, and surgery is extensive with a considerable risk of complications. Clear indications for the selection of patients for salvage surgery are needed to operate only on patients with reasonable survival chances and to exclude patients with irresectable disease. The same holds true for the extent of surgery. No unnecessary extensive surgery should be performed, and survival should not be compromised. Thus far, most series on salvage laryngectomy described relatively inhomogeneous patient populations.

To study the recurrence patterns of laryngeal and hypopharyngeal carcinomas treated by chemoradiation, the follow-up of 136 patients was retrospectively analyzed in chapter 6. Sixty patients had locoregional recurrence, of whom 22 underwent salvage surgery (15 total laryngectomies with uni- or bilateral lymph node dissection and 7 lymph node dissections without laryngectomy). Factors significantly associated with salvage surgery versus no surgery for a recurrence were a) age under 59 years (mean age of whole patient group) and b) laryngeal versus hypopharyngeal carcinoma. After salvage surgery, the postoperative complication rate was 68%, with fistulae in 23% of the patients. More wound healing problems occurred in patients with current alcohol abuse. The five-year disease specific survival rate after salvage surgery was 35%, vs. 70% in patients without treatment failure after chemoradiation.

In chapter 7 we evaluated the outcome of salvage total laryngectomy in 120 patients with recurrent laryngeal cancer after prior (chemo)radiotherapy. This study showed symptomatic disease in only 66% of the patients, with a median interval of 9 months between treatment and detection of recurrence. Eighty-five percent of tumors were detected at a regular visit. The 5-year disease specific survival was 58%, with positive surgical margins as the only significant predictor for worse survival. The complication rate was 56%. No predictors of complications were identified. A good functional outcome with functional voice prosthesis in 87% and fully oral diet in 84% of the patients was shown. In 31% of the patients lymph node metastases were confirmed, with contralateral metastases in 7% of the initial T1-2N0 tumors. The relatively low rate of symptomatic disease and high rate of tumor-negative lymph node dissections underline that reliable diagnostic techniques are warranted. In this selected group salvage laryngectomy resulted in good oncologic and functional results.
Since the detection of lymph node metastases after radiotherapy remains difficult, the management of the neck in patients with local recurrence constitutes a dilemma, including the extensiveness of the neck dissection. Level VI, the location of the pre/para-laryngeal and –tracheal lymph nodes, was identified by previous studies as a significant prognostic factor for worse survival. However, no clear indications for paratracheal lymph node dissection are defined. In chapter 8, in 191 patients with laryngectomy after (chemo)radiotherapy and bilateral (n=47), unilateral (n=52) or no (n=92) paratracheal lymph node dissection (PTLND), predictors for survival and postoperative complications were evaluated. Out of the four patients with paratracheal metastases, three had glottic carcinoma, all with subglottic extension. This confirms findings of previous studies, that subglottic extension is a risk factor for paratracheal lymph nodes metastases. In 1 patient (2%) it concerned a contralateral metastasis. Bilateral PTLND was associated with significantly more fistulae than unilateral PTLND (40% versus 22%), suggesting a need for better selection for contralateral PTLND. Besides the subglottic extension as a known risk factor for PTLN metastases, no clear arguments for selection are found. The majority of positive paratracheal lymph nodes are <1cm and appear negative on preoperative diagnostic screening.

These studies on salvage surgery subscribe the need for better imaging, mainly to diminish the positive surgical margins, to identify lymph node metastases, and to detect asymptomatic recurrence.
GENERAL DISCUSSION

In this thesis evidence is provided for improvement of the diagnostic path concerning the detection of local recurrent laryngeal carcinoma after previous radiotherapy. 18F-FDG-PET can reliably, safely and cost efficiently be used to select patients suspected of recurrent laryngeal carcinoma for direct laryngoscopy under general anesthesia in daily clinical practice.

PET is less invasive compared to direct laryngoscopy, without general anesthesia and biopsies. It also decreases the use of scarce resources, i.e. admission and operating facilities, and PET offers the ability to scan the entire body for regional and distant metastases.

With the rising medical costs in our current society, more emphasis lies on decreasing costs. Another aspect to be considered is the use of scarce and expensive resources. Resources should be used as efficient as possible.

Studies can give insight in how these resources are used to optimize quality of care. As part of the community-oriented approach in the Netherlands, the Dunning funnel provides four criteria. Care must be necessary, effective, efficient and cannot be left to individual responsibility. All care should be passed through a funnel with four sieves. The first sieve retains care that is unnecessary, based on a community-oriented approach. The second sieve selects on effectiveness, allowing only care confirmed and documented as effective. The third sieve selects on efficiency, which can be measured by using results of cost-effectiveness analyses. The fourth sieve retains care that can be left to individual responsibility. Any care that is retained in one of the four sieves does not seem to be relevant care, in contrast to what flows completely through the funnel and seems to be relevant care and contributes to increase the quality of care. A randomized controlled multicenter trial is the most often used study design, since the effectiveness and efficiency of different strategies can be compared with respect to effects and costs. The power of the study needs to be considered upfront.

The effectiveness of a diagnostic test can be difficult to assess. When an intervention is compared to a reference standard, the intervention can be assessed as cost-effective when the costs are lower. It can also be debated whether a certain percentage of decrease is necessary for a significant effectiveness. Often a randomized controlled trial has a cut-off point for the follow-up. Ideally in a CEA, the effect is also measured with a long-term follow-up being a life time perspective. In general in the CEA modeling techniques will be used in order to extrapolate the effects over a longer period. The outcome measure most often used is the quality adjusted life year (QALY). QALYs offers the possibility to compare the results with other interventions and diseases.

The main benefit of 18F-FDG-PET is based on its excellent negative predictive value. A prerequisite for a strategy with PET as upfront diagnostic, is a high sensitivity, since recurrent tumor should not be missed. In the RELAPS study with a local recurrence prevalence of 30% a sensitivity of 96% and a negative predictive value of 97% are found. In previous studies a sensitivity of about 90% and negative predictive values of 80-100% have been reported (16-22), with a recurrence prevalence of 25-50% for T2-T4 laryngeal cancer after radiotherapy (7,23-26). Since the prevalence of local
recurrence in the RELAPS study is within this reported range, the patient group included in the RELAPS study is representative for the daily clinical practice.

A limitation of the RELAPS study is the long period between initiation and completion of the study. Technological innovation has continued. The predicted residual inefficiency after implementation of 18F-FDG-PET relates to its lack of specificity, that inefficiency was 29 % in the RELAPS study. Coregistered images allow a direct correlation between FDG uptake and anatomic structures, thus potentially reducing false-positive results and increasing specificity. Unfortunately, meta-regression analysis showed no significant difference in posttreatment accuracy between standalone PET and integrated PET/CT (27).

Early detection is essential, since delayed diagnosis of recurrent disease results in a higher chance of distant metastases. In one-third of the patients local recurrence is asymptomatic, warranting regular visits especially in the first year. The median interval between radiotherapy and detection of recurrent laryngeal carcinoma was 9 months in our studies, which is comparable with the interval reported by others (28). Intensifying the follow-up schedule with shorter intervals should be considered, although an excessively high number of routine visits would have to be performed to increase the detection rate for asymptomatic recurrences. PET/CT might stratify patients for follow-up intensity, with a reduction of the follow-up frequency of patients with complete (metabolic) response on posttreatment PET/CT (29,30). The European Laryngological Society (ELS) recommends a follow-up between 4 and 8 weeks in the first 2 years, and from 3 to 6 months thereafter (31).

A better insight in tumor recurrence patterns and individual risk estimation might also improve the early detection and therefore early salvage surgery of recurrences. Tumor recurrence patterns may offer a guide during outpatient clinic visits concerning lead time of recurrence, presentation of signs and symptoms, physical examination and imaging. Risk estimation concerns personalized management based on the characteristics of an individual tumor and the patient. This offers the ability to predict more specifically than based on the TNM-stage and localization of a tumor alone, what the individual chances are for treatment response, recurrence and survival.

Narrow-band imaging (NBI) is another technique which seems to be of value for early detection of local disease after (chemo)radiotherapy (32-36). This technique is based on light with filtered wavelengths of 415 (blue light) and 540 nm (green light), corresponding to the peaks of hemoglobin, thus highlighting the capillary network, and deeper levels, enhancing the submucosal vessels. Due to their neo-angiogenic pattern, superficial carcinomas and their extensions are better identified.

Just as the identification of suspect lesions can be obscured by the effects of (chemo)radiotherapy, so is the determination of the extension of a recurrence during salvage surgery to achieve a macroscopic clearance. New intraoperative visualization techniques using near-infrared (NIR) fluorescence optical imaging are being developed to improve discrimination between healthy and cancer tissue (36-38). NBI has been successfully used intraoperatively for better tumor delineation of superficial resection margins during transoral laser resection of early glottis cancer (39).
In case of proven locoregional recurrence, salvage surgery is an option for a selected group of patients. Younger patients with laryngeal instead of hypopharyngeal recurrence are more often candidates for salvage surgery, probably because they have less comorbidity and are able to undergo surgery. Salvage laryngectomy with lymph node dissection offers good oncologic and functional outcome in a selected group of patients: after radiotherapy and chemoradiotherapy 5-year local control rates of 70% and 58%, and 5-year overall survival rates of 50% and 27% were found, respectively. This is in line with 5-year locoregional control rates of 70% and 5-year overall survival of 31-57% reported by other studies (13,40,41). Although results are difficult to compare with a lack of homogeneity in these studies (local versus locoregional recurrence, differences in primary and salvage treatment). Besides surgical margins, no independent predictor for survival was found. Although patients were meticulously selected for salvage total laryngectomy, the incidence of positive surgical margins was still 10%, also in line with previous studies (40,42-45).

Salvage surgery after radiotherapy is known to result in higher complication rates than primary surgery, with total complication rates up to 77% (12,14,15,46-48). The addition of chemotherapy increases the complication risk even further (15). We found a total complication rate of 56% after radiotherapy and 73% after chemoradiotherapy, with fistula in 30% and 23% of the patients, respectively. Other risk factors associated with fistula are: tumor subsite, T-stage, postoperative hemoglobin <12.5 g/L and positive surgical margins (49). The use of a pectoralis major flap as a protective layer between mucosa and skin reduces the risk of fistula formation (15,50). In our results this was not confirmed, maybe because we used the flap besides for mucosal reconstruction already mainly in patients with an expected high risk of fistula formation. Besides the use of pectoralis major flaps, other factors may affect the risk of fistula formation; e.g. the closure technique of the surgical defect, the start of oral intake, the use of a salivary stent and the use of antibiotics (15,51). A salivary bypass tube is used by some clinics for circumferential fasciocutaneous reconstructions to reduce late stricture formation and may also reduce the frequency of fistula (52). There are no uniform guidelines regarding these factors. Research focusing on the optimal peri-operative protocol, specific for salvage laryngectomy, is warranted.

Besides local recurrence, (recurrent) lymph node metastases can also be difficult to detect. Because some lymph node metastases are left undetected, a policy is to treat the neck even when the neck has been classified clinically as node-negative. This strategy prevents disease in the neck becoming more advanced once previously occult metastases become clinically apparent or are detected late during follow-up. Thus, some patients receive unnecessary treatment, which in the case of neck dissection encompasses a surgical procedure potentially causing disfigurement and associated morbidity. The alternative approach of watchful waiting entails careful monitoring of the neck with the risk of delayed treatment in some patients.

The decision to perform a neck dissection following (chemo)radiation is clear when patients have proven residual neck disease. However, distinguishing between residual metastasis and chemoradiation sequelae is difficult in most cases with a residual neck mass, since post-treatment induration and fibrosis obscure accurate clinical assessment. The difficulty in evaluating for recurrence has made salvage neck surgery less effective and late recurrences in the neck rarely surgically salvageable (53). Therefore, planned neck dissections after curative (chemo)radiation
were performed, as a reliable assessment of the pathological status after chemoradiation remained often difficult (54,55).

While previous research suggests that lymph node dissection can be withheld in a subset of patients based on prediction of recurrence patterns (56), we found metastases in both ipsi- and contralateral necks even in patients with small tumors, in line with the findings of Farrag et al (55). This warrants reliable diagnostic techniques or reliable prediction models to exclude regional disease in order to refrain: a) unnecessary contralateral lymph node dissections and b) unnecessary extensive lymph node dissections. This may lead to more selective lymph node dissections in order to reduce the complication rates and to preserve a lymphatic barrier for recurrent and second primary tumors. In our retrospective studies not all patients underwent the same extent of neck dissection. It was therefore not possible to develop an algorithm which patient should receive a selective neck dissection.

PET might give guidance in the decision to perform lymph node dissections or not. For the pretreatment detection of occult cervical lymph node metastases in the clinical N0 neck, 18F-FDG PET is still not sufficiently reliable to avoid elective treatment of the neck (57,58). This can be theoretically expected because of the limited resolution of the current PET scanners. Nevertheless, 18F-FDG-PET may provide important information about involvement of lymph nodes. According to meta-analyses on the diagnostic performance of posttreatment 18-F FDG PET in head and neck cancer, PET has a high negative predictive value (94%) for lymph node metastases (21,22,27).

A recent randomized controlled trial assessed the noninferiority of PET-CT-guided surveillance (performed 12 weeks after the end of chemoradiotherapy, with neck dissection performed only if PET-CT showed an incomplete or equivocal response) to planned neck dissection in patients with stage N2 or N3 disease. Survival was similar among patients both arms, but surveillance resulted in considerably fewer operations and it was more cost-effective (59).

Especially bilateral paratracheal lymph node dissections are associated with an increased risk of fistulae. The relatively rare paratracheal lymph node metastases are mainly found in patients with primary glottic carcinoma with subglottic extension. Subglottic extension was also identified as a risk factor for paratracheal lymph node metastases in other studies, as was maximal axial diameter of ≥5 mm of paratracheal lymph nodes on CT or MRI and clinical positive cervical status (60). When at least one of these risk factors was present, a high sensitivity (90% for CT and 100% for MRI) and low specificity (19% for CT and 32% for MRI) was found. The reported incidence in literature of paratracheal lymph node metastases in patients who undergo laryngectomy is higher (9-20%), but was investigated in mainly untreated patients, contrary to patients with recurrence after radiotherapy (61-65). In previously untreated patients with laryngeal carcinoma with subglottic extension, the reported rate of paratracheal lymph node metastases was 27% (66). A drawback of this study is its retrospective character. It concerned a variety of surgeons with potential differences in surgical techniques and extent of paratracheal dissections. Also, a limited number of paratracheal lymph node metastases was found.
FUTURE PERSPECTIVES

The solid evidence of the value of 18F-FDG-PET as first diagnostic for the detection of laryngeal carcinoma in patients suspected of local recurrence, stresses the need to adjust the clinical protocols. 18F-FDG-PET should be implemented in the national guideline for the selection of patients for a direct laryngoscopy with biopsy in case of suspicion on recurrent laryngeal carcinoma after radiotherapy (67).

In the presented research mainly PET, and sometimes PET/CT was used. RELAPS showed no significant difference in accuracy between PET and PET/CT, indicating that PET only data are representative for the currently used PET/CT. In the future, image fusion of PET combined with MR imaging might result in further improvement of the diagnostic accuracy. The combination of PET/MR will hopefully decrease the number of false-positive PET scans early after radiotherapy as a result of nonspecific tracer uptake caused by inflammation (68,69). Another advantage of MRI is that it is thought to provide an edge over CT in some specific situations, including perineural spread of tumors and the infiltration of important anatomical landmarks, such as the prevertebral fascia and great vessel walls (70). Moreover, 18F-FDG uptake can be correlated with the functional information obtained by new MRI techniques (69).

18F-FDG is a glucose analogue-based tracer, known to be sensitive for both tumor and inflammation. Other tracers, more specific for tumor, might increase the accuracy of PET as well. 18F-labelled fluoro-3-deoxy-3-L-fluorothymidine (18F-FLT) reflects cellular proliferation. Compared to 18F-FDG, the uptake of 18F-FLT decreases earlier after initiation of therapy (71). Increased amino acid metabolism is another well-known characteristic of a tumor. Compared to the glucose derivate 18F-FDG, the uptake of amino acids in macrophages and other inflammatory cells is lower, which should theoretically result in a higher specificity (71).

Not only the indications, but also the techniques of MR imaging are evolving, with diffusion-weighted MR imaging (DW-MRI) as a promising technique for early and late follow-up after (chemo)radiotherapy and for the detection of recurrent carcinoma (69,72-74). After (chemo) radiotherapy, residual changes or even masses may be observed, and conventional morphologic MR imaging currently encounters difficulty in helping distinguish between benign posttreatment alterations and residual cancer. Qualitative DW-MRI analysis after treatment is performed by means of visual assessment of signal intensity on DW images. Because tumor regions are solid and have increased cellular density, there is a reduction in diffusion of water molecules in these regions, resulting in low ADC (apparent diffusion coefficient) values on DW-MRI. On the contrary, inflammation results in an increase of diffusion of water molecules, with a high ADC. Both visual assessment and quantitative analysis in which the ADC of a mass is used may help distinguish between residual cancer and benign posttreatment changes (74,75). DW-MRI proved to be more specific than MRI without diffusion in the anatomic distorted tissue after radiotherapy (75-78). These results also seem to be already applicable early after the start of (chemo)radiotherapy (77,79). Although the use of DW-MRI as part of PET/MRI may not provide additional information and thus might be dispensable in the presence of PET (80). However, for response evaluation after
chemoradiotherapy for advanced nodal disease in head and neck cancer DW-MRI seems to add to the accuracy of 18F-FDG-PET-CT (81). More research is needed to determine the added value of DW-MRI to 18FDG-PET.

A second promising MR technique in head and neck cancer is dynamic contrast-enhanced MR imaging (DCE-MRI, MRI perfusion) (82). Tumor blood flow can be imaged and quantified with this dynamic MRI. Low perfusion (and hypoxia) is a marker for poor response to radiotherapy and poor prognosis (82-84). Although DCE-MRI is mainly investigated as a prognostic tool to predict response to radiotherapy, preliminary results suggest that it can also be used to monitor treatment response (85-87). PET/contrast-enhanced MRI might be superior compared to contrast-enhanced PET/CT to specify unclear 18F-FDG uptake related to possible tumor recurrence (88). In the future, amide proton transfer-weighted T3 imaging (APTwMRI) and proton MRI spectroscopy might also play a role (69,89).

In the time-course of treatment, the characteristics of hypoxic subvolumes change. It has been demonstrated that the rapid onset or reversal of tumor vascular normalization during anti-angiogenic therapy can be detected by MR perfusion techniques (90,91). In this way patients at risk for residual disease can be identified and with strict follow-up an early evaluation for salvage surgery seems possible. These hypoxic imaging techniques could therefore contribute to the establishment of the optimally individualized treatment.

PET is also capable of imaging the degree of hypoxia within the tumor. For future hypoxia research with PET/MRI, especially the combination of MRI perfusion with 18F-FAZA PET seems promising (92). Another interesting tracer is (62)Cu-ATSM ((62)-Cu-diacyethyl-bis (N4)-methylsemithiocarbazone) (93,94). MRI and PET may be used in conjunction either to monitor the same physiological parameter for cross-validation or to monitor different stages of metabolic activity.

In the RELAPS study a minimum time interval between radiotherapy and PET was 2 months. Radiation induced inflammation can lead to false-positive findings at 18F-FDG PET in the early post radiation period, but previous studies showed no benefit in delaying imaging beyond 8 weeks (95). With the current quality of PET, especially combined with CT or MRI, accuracy at an interval shorter than 2 months might be suitable as well (96). New studies need to be conducted to investigate the accuracy of PET as function of time after radiotherapy. The sooner a recurrence is detected, the better the survival chances are.

The treatment of advanced laryngeal cancer is now at a point where the current standard of care, concurrent chemotherapy and radiotherapy (in case of recurrence followed by salvage surgery), needs to be reexamined. The survival of patients with laryngeal cancer is decreasing the past two decades, instead of improving (97,98). During this same period, there has been an increase in the nonsurgical treatment of laryngeal cancer (99). Initial treatment of T3N0M0 laryngeal cancer (all sites) resulted in poor 5-year relative survival for those receiving either chemoradiation or irradiation alone when compared with that of patients after surgery with irradiation and surgery alone. In contrast, identical survival rates were observed for the subset of T3N0M0 glottic cancers initially treated with either chemoradiation or surgery with irradiation (98,100). The
management of T4 laryngeal cancer remains controversial. There are studies suggesting worse survival with organ preservation therapy compared with laryngectomy (101-103), while others suggest comparable survival (100). The decreased survival may be related to changes in patterns of management, the most dramatic being the increase in chemoradiation, and decrease in surgery as initial cancer management. It can also reflect an inappropriate shift away from ‘the standard of care’ (101). With the latest data there seems to be enough evidence to say that treatment of T4 advanced larynx cancer should consider total laryngectomy since survival outcomes appear better than with chemoradiotherapy in most reports (104). Patients should probably be more carefully selected for the best treatment modality. An individualized approach is also warranted when the primary treatment is decided. Not only the tumor extent and pretreatment laryngeal function is critical for the treatment selection, but the expected tolerance of the treatment on the basis of performance status and comorbidities, particularly cardiopulmonary chronic disease (101). When factors influencing patients’ decisions in advanced laryngeal cancer were assessed, the quality of the treatment outcome had a greater effect than treatment modality (105). Another factor to consider in the selection of treatment, is the hospital and medical resources for a chemoradiation treatment (104). All resources for the administration of treatment, follow-up and surgical salvage should be available with a high level of skills and cooperation among various disciplines.

There is a need to better identify which patients will not respond to therapy. For PET there is an increasing interest in volumetric parameters of metabolism such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) as prognostic predictors of outcome, although no cut-off value has been established yet (106,107).

With both PET and (DW- or DCE-) MRI it seems possible to predict in the early stage of non-surgical treatment which patients are at risk to be a non-responder (77,79,87,108-115). Functional imaging modalities are potentially complementary and should be considered in combination to guide potential treatment adaptation strategies (116). Identification of non-responders after two of the planned six to seven weeks (chemo)radiotherapy offers the ability to further intensify treatment, or to cancel futile further (chemo)radiotherapy and change to surgical treatment. An early switch to laryngectomy with postoperative radiotherapy in reserve will theoretically increase survival rates for this group. A recent meta-analysis showed a 3.55-fold increased risk of death and a 4.73-fold increased risk of progression or recurrence of head and neck cancer for patients with positive findings on 18F-FDG PET or PET/CT during and after treatment (117). Although there is predictive value for response, during and early after treatment 18F-FDG PET studies were not so highly predictive for outcome as those obtained late after the completion of therapy (117-120).

18F-FDG-PET scans can also be used for radiotherapy planning, since 18F-FDG-avid head and neck tumors are likely to require 10-30% more dose than 18F-FDG-non-avid tumors (121).

Besides response prediction of treatment response based on imaging techniques, personalized care based on other tumor characteristics like biomarkers are being developed (122-127). Biomarker research is focused on characteristics of the primary tumor and serum-markers, for example. Further differentiation of the tumor using biomarkers should provide a way to precise prediction of response of this particular tumor to (chemo)radiotherapy.
Combining current clinical assessment with gene expression profiling of the primary tumor to predict nodal disease seems promising for the future to develop new clinical decision models. A gene expression signature for distinguishing metastasizing from N0 was developed and re-evaluated first for oral and oropharyngeal cancer (127,128). For laryngeal cancer another gene expression profile was found to be associated with lymph node metastases (129) and unfavorable disease-free survival (130).

Another possible opportunity to improve decision-support in treatment according to tumor characteristics is by using radiomics (131). Radiomic analysis quantifies tumor image intensity, shape and texture. Data on radiomics of head and neck cancer patients identified a general prognostic phenotype, which is associated with underlying gene-expression patterns. The technique seems promising but needs extensive validation. With the low prevalence a large amount of patients are needed to perform individual patient data meta-analyses, with standardized imaging.

Preliminary results suggest that assessment of circulating tumor cells should prove useful for identification of patients who benefit from treatment intensification, since the detection of circulating tumor cells after surgery was related to poor survival in patients with head and neck cancer (132). Serial monitoring of circulating tumor DNA for the detection of occult metastatic disease in breast cancer patients proved highly accurate in preliminary research (133). This method can be studied in head and neck cancer to evaluate circulating tumor DNA as a monitoring tool for early metastasis detection, therapy modification, and to aid in avoidance of overtreatment.

In case of a proven recurrence, salvage surgery will be discussed. Selection criteria for salvage surgery and its extent need to be further specified and individualized. Algorithms for salvage surgery will primarily focus on optimizing of the survival rates, and secondarily on preventing of complications. Early and reliable detection of recurrence may increase survival chances. Wound healing related problems are the main complications after salvage surgery. Tissue engineering with growth factors might contribute to better wound healing in heavily radiated tissue (134-136). In the era of personalized medicine, future research needs to be focused on the refinement of the treatment strategy and the posttreatment diagnostic strategy for detection of recurrence, with more individualized selection criteria. Numerous patient, tumor and treatment factors need to be considered. Personalized medicine will be the future of laryngeal cancer diagnosis and treatment.

The results and approach of this RELAPS study, will hopefully lead to more multicenter controlled trials, including cost-effectiveness analysis, in a broader context. The application of PET, or PET in combination with other imaging techniques in the future, might be used to prevent unnecessary treatments for other indications, such as lymph node dissections after (chemo)radiotherapy. PET is also used in other indications, like treatment monitoring and response assessment of (chemo) radiotherapy. When combining randomized controlled trials with piggyback cost-effectiveness analysis, including quality of life measurement, the use of PET in clinical practice can be further optimized.
REFERENCES


