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Summary and future prospects

Summary

When treating patients with laryngeal carcinoma, preservation of the functions of the larynx, phonation, breathing and swallowing, is a vital goal. Therefore, non-surgical treatment options have gained popularity. Surgical salvage is kept in reserve for recurrence. In a previously radiated larynx, however, recurrent carcinoma is not easily distinguished from radiotherapeutic sequels. Since early detection is essential for successful salvage surgery, this creates a clinical problem. Chapters 2-5 of this thesis address this problem.

When distant metastases are detected in head and neck squamous cell carcinoma (HNSCC) patients with primary disease, treatment is altered and prognosis is unfavourable. These patients are usually not considered curable and will receive palliative treatment. Screening for distant metastases is performed to spare these patients from undergoing futile extensive treatment. The optimal screening method for these patients is still debated. Chapters 6-8 of this thesis address this clinical problem.

The aims of this thesis were the evaluation of the daily clinical practice and the possibilities of imaging techniques in order to detect recurrent laryngeal carcinoma after prior radiotherapy (**Chapters 2-5**) and distant metastases in patients with extensive primary head and neck carcinomas (**Chapters 6-8**).

In **Chapter 2** the current daily practice is described through a questionnaire among clinicians and retrospective analysis of a cohort of patients clinically suspected of a recurrent laryngeal carcinoma after radiotherapy. The questionnaire showed that 94% of the physicians in departments in the major institutions treating head and neck cancer in The Netherlands used direct laryngoscopy as a diagnostic technique. Imaging (MRI, CT, ^{18}FDG-PET) did not play an important role.

All 131 patients in the cohort suspected of recurrence had undergone 207 direct laryngoscopies under general anaesthesia with biopsies. In 70 (53%) patients the first laryngoscopy was negative. Twenty-two (31%) of them turned out to be false negative within 6 months. Sixty-five (31%) futile laryngoscopies were performed in 37 patients that remained disease free.

A systematic review is described in **Chapter 3.** This was performed to summarise the available evidence in patients with suspicion of recurrent laryngeal carcinoma after radiotherapy. An attempt was made to determine the diagnostic accuracy of CT and MRI scans, ^{201}Tl scintigraphy and ^{18}FDG-PET in these patients.

Surprisingly, no articles on CT, MRI or ^{201}Tl scintigraphy were found which met the inclusion criteria. Eight articles on ^{18}FDG-PET were available. In 3 articles ^{18}FDG-PET was compared to CT or MRI.

The internal and external validity of the articles was described to compare their quality. Because of the small number of studies, it was not possible to create subgroups. A quantitative analysis using a random effects model was performed. The pooled estimates (95% confidence interval) for sensitivity and specificity of ^{18}FDG-PET were 89% (80%-94%) and 74% (64%-83%).

Chapter 4 is a pilot study on ^{18}FDG-PET in detecting recurrent laryngeal carcinoma after radiotherapy, in which interobserver variation was measured to determine its usefulness in routine clinical practice.

Thirty consecutive patients underwent ^{18}FDG-PET and direct laryngoscopy under general anaesthesia with taking of biopsies. The reference was the absence or appearance of a local recurrence within the 12 months following ^{18}FDG-PET. Eight patients had biopsy proven recurrent laryngeal carcinoma. First the scans were evaluated by 2 observers. This showed a sensitivity of 88% and a specificity of 82%

Then the scans were reviewed by 9 observers to determine interobserver variability. The observers had a moderate to reasonable agreement with a weighted kappa of 0.45 vs. the clinical gold standard. The weighted kappa for interobserver variability was 0.54.

An estimation of the cost-effectiveness of ^{18}FDG-PET in the selection for direct laryngoscopy in patients with suspicion of recurrent laryngeal carcinoma after radiotherapy is performed in **Chapter 5**. The direct medical costs of 30 patients were calculated from the first visit where suspicion was raised till 12 months later. A strategy in which all patients undergo direct laryngoscopy was compared to an ^{18}FDG-PET strategy in which only patients with a positive or equivocal ^{18}FDG-PET undergo direct laryngoscopy.

The mean costs for the detection of recurrent laryngeal cancer with direct laryngoscopy in the conventional strategy were € 13.230. The mean costs of an ^{18}FDG-PET strategy were € 12.831. Therefore an ^{18}FDG-PET strategy is not more costly than the conventional strategy.

To evaluate the daily practice concerning screening for distant metastases preoperatively, a questionnaire was performed among investigators in the 12 departments treating head and neck cancer in The Netherlands in **Chapter 6**.

All investigators returned the questionnaire. There was no uniformity and indeed a substantial variation in the indications for screening and methods of screening. There is a need for clear guidelines for screening for distant metastases in patients with head and neck cancer.

Chapter 7 describes the evaluation of a diagnostic strategy. In a previous study, risk factors for developing distant metastases in patients with head and neck cancer were established. Chest CT scan turned out to the best diagnostic tool for pretreatment screening

in these patients. In this study 109 consecutive patients with HNSCC scheduled for extensive treatment and at least one risk factor underwent chest CT.

A total of 20 lung metastases and 1 liver metastasis were found. The chest CT had a sensitivity of 73% and a specificity of 80%. To better detect distant metastases before treatment and thus to avoid futile extensive treatment, a more sensitive, preferably whole-body, technique is desirable.

In order to improve the sensitivity of screening described in Chapter 6, **Chapter 8** prospectively compared the yield of whole-body ^{18}FDG-PET and chest CT to detect distant metastases and synchronous primary tumours in a pilot study. Thirty-four consecutive patients, with extended HNSCC, underwent both techniques. Both chest CT and ^{18}FDG-PET detected 2 lung lesions, but ^{18}FDG-PET detected 2 additional second primary tumours in the abdomen. There was an added value in 6% of the patients of whole-body ^{18}FDG-PET versus chest CT.

Future prospects

The results described in this thesis warrant further investigation of the possibilities of ^{18}FDG-PET. In the population of patients who are suspected of a recurrent laryngeal carcinoma after radiotherapy for a T2-T4 tumour, a prospective randomised clinical trial, the RELAPS study, is currently performed within the Dutch Head and Neck Cooperative Group [1]. To avoid futile direct laryngoscopies under general anaesthesia, selection based on ^{18}FDG-PET is investigated. A conventional strategy is compared to a strategy based on ^{18}FDG-PET. In the conventional arm, patients undergo direct laryngoscopy with biopsies. When recurrence is found, treatment obviously follows. When histopathology is equivocal or negative, direct laryngoscopy is performed again after 6 weeks, unless the symptoms subside. In the ^{18}FDG-PET arm, patients first undergo ^{18}FDG-PET. When the result is positive or equivocal, direct laryngoscopy is performed. When negative, a follow-up period of 3 months is started, unless symptoms progress. Reference standard is a follow-up of 6 months and results of direct laryngoscopy with biopsies.

To further investigate the value of whole-body ^{18}FDG-PET in detecting distant metastases and synchronous primary tumours in patients with extensive primary HNSCC, a prospective observational study was started, the SCHOOL study, in 3 Head and Neck Centres in The Netherlands. In this study patients underwent both ^{18}FDG-PET and conventional chest CT. The yield of the 2 techniques separately and in combination was determined as well as interobserver agreement of CT and ^{18}FDG-PET, the costs of

diagnostic work-up and extensive treatment for advanced HNSCC with palliative or curative intent, and the cost-effectiveness of screening based on conventional diagnostic work-up and ^{18}FDG-PET [2]. In addition, a validation of the reviewing criteria found in the SCHOOL study will be performed as well as a study to determine the value (accuracy, reduction of futile extensive treatments and associated costs) of integrated PET-CT in screening for distant metastases and second primary tumours in head and neck cancer patients, as compared to CT, PET and visual correlation of PET and CT.

So far, ^{18}FDG is the most commonly used tracer in PET imaging in head and neck. Ongoing studies are examining the possibilities of new tracers. As described in chapter 3, Cobben et al. [3] compared fluorine-18 labelled thymidine with ^{18}FDG in laryngeal cancer. Carbon-11 labelled methionine showed promising results in differentiating between inflammation and malignant tumour in rats in a study by Zhao et al. [4]. Pre-treatment C11 labelled tyrosine PET was compared to post-treatment tyrosine PET for therapy evaluation in laryngeal cancer patients by De Boer et al. [5]. Both sensitivity and specificity were 100%. Börjesson et al. [6] combined PET and the monoclonal antibody U36 (immuno-PET) labelled with Zirconium-89 to detect HNSCC lymph node metastases. However, till now none of these tracers has found its way into daily practice.

To improve imaging in HNSCC, cross-sectional imaging techniques (CT and MRI) are combined with functional imaging (PET). The disease can then be characterised both anatomically and functionally. The fusion of PET and CT has already proven to be more accurate for the detection of malignancy in the head and neck region than either modality alone. Agarwal et al. [7] describe in a recent review the surplus value of PET/CT in staging advanced HNSCC, finding unknown primary tumours, radiation treatment planning, monitoring treatment response, restaging and identifying recurrent HNSCC.

PET/MRI is a new and promising multi-modality imaging device successfully studied in a preclinical setting [8]. Advantages of MRI over CT: MRI uses no ionising radiation and produces high soft-tissue contrast and provides spectroscopic information and functional MRI. Furthermore PET/MRI allows for simultaneous data acquisition. Pichler et al. [9] describe an overview of current working prototypes.

Both CT and MRI by themselves, not just in fusion techniques, show new possibilities in oncology. Recent technical developments may improve the results of CT and MRI found in this thesis. At present, a chest CT is performed using a multidetector CT scanner during breath-holding. The slices currently used are much thinner than before and this is likely to improve the sensitivity. MRI has improved both due to the introduction of faster MR imaging techniques (whole-body MR imaging) and newer pulse sequences (short term inversion recovery (STIR) and diffusion MRI). Due to the introduction of multi-receiver channel MR, whole-body MRI has become clinically feasible, with substantially reduced examination

times [10]. Whole-body MRI shows potential in detecting metastasis of primary head and neck tumours [11]. STIR imaging uses an alternative MR imaging sequence that provides suppression of signal from fat and additive effects of T1 and T2 mechanisms on tissue brightening. Because most tumour-related abnormalities have both long T1 and long T2 relaxation times, such an additive effect on tissue brightening may improve lesion conspicuity and sensitivity of lesion detection [12]. Whole-body STIR can be used for the primary tumour, but showed especially good results in metastastic spread to bone, liver and central nervous system and bone marrow disease [10,13,14].

Diffusion weighted MRI attempts to assess the diffusion capacity of tissue. Due to tumour proliferation, the tumour regions have increased cellular density and this results in a reduction of diffusion of water molecules through these regions. It provides information on extracellular space tortuosity, tissue cellularity and the integrity of cellular membranes [15-18]. This technique has a very short scanning time and adds no extra cost to patients who are already undergoing MRI. The molecular motion can be determined by calculating the apparent diffusion coefficient (ADC) with diffusion-weighted MRI. Hypercellular tissue, such as in malignant tumours will show low ADC values. Diffusion weighted whole-body MR imaging may be used for characterisation of neck lymph nodes, to diferentiate between persistent or recurrent cancer and treatment-induced tissue changes and to confirm or exclude metastatic disease or a second primary tumour [19-21]. Both techniques can be used in whole-body MRI scanning. However, the role of these new (whole-body) MR techniques in clinical management is yet to be established by additional studies.

In the next few years, it might be expected that the indications for ^{18}FDG-PET will become clearer and promising new tracers and scanners will find their way into the daily clinical setting, after first establishing their applicability.

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