Diagnosis and salvage surgery of recurrent laryngeal carcinoma after radiotherapy

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DIAGNOSIS AND SALVAGE SURGERY OF RECURRENT LARYNGEAL CARCINOMA AFTER RADIOTHERAPY

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CHAPTER 1

General introduction

Head and neck squamous cell carcinoma

Squamous cell carcinoma of the mucosal lining, is the most frequent malignancy of the head and neck region, and accounts for 4% of all malignant tumors worldwide (1). The incidence increases with age, with most patients over the age of 55. More than two thirds of patients with head and neck squamous cell carcinoma (HNSCC) present with advanced stage disease. Laryngeal carcinoma is the most frequent tumor within the head and neck in North-western Europe. In 2012 the annual incidence of laryngeal cancer in the Netherlands was 3.4 per 100,000 individuals (2).

LARYNGEAL CARCINOMA

Anatomy and Physiology

The larynx represents the junction of the upper and lower portions of the airway and essentially serves two functions: protection against aspiration and phonation. The larynx extends from the tip of the epiglottis to the lower edge of the cricoid cartilage and is divided anatomically into three parts: the supraglottis, glottis, and subglottis. The supraglottis extends from the tip of the epiglottis to the level through the paired laryngeal ventricles. Because the supraglottis is derived from the fourth branchial arch, the rich lymphatic drainage runs cranially to the upper deep jugular chains of lymph nodes (level II and III). The glottis is a small area that contains the true vocal cords and extends from the laryngeal ventricles to an imaginary plane approximately 1 cm below the true vocal cords. The subglottis extends from 1 cm below the true vocal cords to the lower edge of the cricoid cartilage. Both the glottis and subglottis have sparse lymphatic drainage, located inferiorly into the lower deep jugular nodes and paratracheal nodes (levels IV and VI). The glottic area mainly serves phonation while the supraglottic area mainly serves protection against aspiration during swallowing (3).

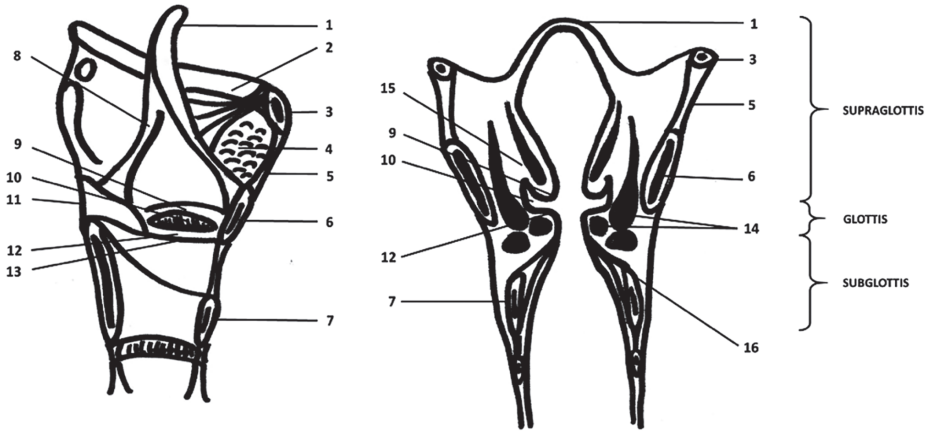

Fig 1. Sagital (left) and coronal (right) view of the larynx. Adapted from reference 3. 1=epiglottis, 2=hyoepiglottic ligament, 3=hyoid bone, 4=preepiglottic fat, 5=thyrohyoid membrane, 6=thyroid cartilage, 7=cricoid cartilage, 8=aryepiglottic fold, 9=false vocal cord, 10=laryngeal ventricle, 11=arytenoid cartilage, 12= true vocal cord, 13= vocal ligament, 14= thyroarytenoid muscles, 15= paraglottic space, 16=conus elasticus.

Epidemiology

There are approximately 700 new patients with laryngeal carcinoma in the Netherlands per year; 200 persons die each year from this disease (4). Laryngeal cancer is more common in males than in females. The worldwide incidence varies per country and age-standardized incidence rates are highest in men in Central and Eastern Europe and Southern Europe and lowest in Eastern Asia, West Africa and Middle Africa (5,6). The variations in incidence rates both between countries and between men and women are likely related to differences in smoking behavior and to a lesser extent to differences in alcohol consumption. The combined effect of these two risk factors is estimated to account for 89% of laryngeal cancer cases (7). Smoking is the largest risk factor for the development of laryngeal cancer, with a synergistic effect of heavy alcohol consumption. Alcohol intake is also a risk factor on its own for supraglottic carcinomas. Patients are typically in their 6th decade of life when laryngeal carcinoma is diagnosed (2,8).

In most of the patients the tumor is localized in the supraglottis (epiglottis, arytenoids, aryepiglottic folds and false vocal cords), or in the glottis (true vocal cords, anterior and posterior commissures), and only 2% in the subglottis. Glottic carcinomas are often diagnosed early (60% stage I) since persistent hoarseness is an early symptom. Supraglottic carcinomas lack specific symptoms (symptoms are: increased mucus production, dysphagia, globus, dry en raw sensitization of the throat) and are therefore diagnosed in a later stage (two-third with stage III or IV) (4).

Staging

The Union of International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) have designated staging by TNM classification to define laryngeal cancer (9,10). The most common localization of distant metastases is in the lung. Further classification into prognostic groups can be made: early stage (stage I-II) and advanced stage (stage III-IV).

Primary treatment

In the treatment of laryngeal cancer preservation of function without compromising chances of cure is challenging. The larynx harbors functions of vocalization, swallowing and respiration. Preservation of an intelligible voice is an important consideration in choosing a treatment modality.

Patients with early-stage disease can very effectively be treated with single-modality larynx-sparing approaches. Small superficial cancers are successfully treated by radiation or surgery alone, including endoscopic laser excision surgery (11-14). Reviews on the outcomes of radiotherapy and laser resections suggest comparable local control and survival with similar low risks of major complications (15,16), although no randomized controlled trial is performed (17). Laser resection is an effective, single use, relatively low-cost treatment which can be repeated (18,19). Lesions that are deeper infiltrating or indistinct from non-tumorous tissue, especially those arising in the context of widespread, abnormal-appearing mucosa, seem to be more suitable for radiation therapy (20-22).

Table 1. TNM classification larynx (7th edition 2009).

Supraglottis	
T1	One subsite with normal mobility
T2	Mucosa of more than one adjacent subsite of supraglottis or glottis or adjacent region outside the supraglottis; without fixation
T3	Cord fixation, or invasion of postcricoid area, pre-epiglottic tissues or paraglottic space, or thyroid cartilage erosion
T4a	Extension through thyroid cartilage; or extension of trachea or soft tissues of neck: deep or extrinsic muscle of tongue, strap muscles, thyroid or oesophagus
T4b	Extension to prevertebral space, mediastinal structures or carotid artery
Glottis	
T1	Limited to vocal cord(s) with normal mobility (a) one cord (b) both cords
T2	Extension to supraglottis or subglottis, or impaired cord mobility
T3	Cord fixation or invasion of paraglottic space or thyroid cartilage erosion
T4a	Extension through thyroid cartilage; or extension to trachea or soft tissues of neck: deep or extrinsic muscle of tongue, strap muscles, thyroid or oesophagus
T4b	Extension to prevertebral space, mediastinal structures or carotid artery
Subglottis	
T1	Limited to subglottis
T2	Extension to vocal cord(s) with normal or impaired mobility
T3	Cord fixation
T4a	Extension through cricoid or thyroid cartilage; extension to trachea, deep or extrinsic muscle of tongue, strap muscles, thyroid or oesophagus
T4b	Extension to prevertebral space, mediastinal structures or carotid artery
All sites	
N1	Ipsilateral single lymph node metastasis ≤3 cm
N2	(a) ipsilateral single lymph node metastasis >3-6 cm (b) ipsilateral multiple lymph node metastases ≤6 cm (c) bilateral, contralateral lymph node metastases ≤6 cm
N3	lymph node metastasis >6 cm
All sites	
M1	Distant metastasis

Table 2. Stage grouping larynx.

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1, T2	N1	M0
	T3	N0, N1	M0
IVA	T4a, T4b	N0, N1	M0
	T1, T2, T3	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

In the last decades the treatment of advanced laryngeal carcinoma has evolved. Advanced laryngeal carcinoma was historically primarily treated by surgery (laryngectomy), but more recently the trend has shifted to (chemo)radiation. Non-surgical treatment is aimed at preservation of voice, normal respiration and swallowing and reserves surgery for salvaging purpose if needed. Two clinical studies had major effects on the management of advanced laryngeal cancer. The first in 1991, found that induction chemotherapy followed by definitive radiotherapy resulted in little difference in survival compared to patients receiving total laryngectomy and postoperative radiotherapy (23). The second, in 2003, reported that concurrent chemotherapy and radiotherapy were superior to sequential chemoradiation or radiotherapy alone for achieving local and regional control when applied to stage III and IV laryngeal cancer with T2, T3, or ´limited´ T4 tumors (24).

Standard fractionation radiotherapy (60-70 Gy at 1.8-2 Gy fraction doses) is the most commonly used modality for early stage cancer (25). Hyperfractionation or accelerated fractionation radiotherapy have shown a higher local control rate with more acute adverse effects, as compared to standard fractionation (26-28). Since a decade intensity-modulated radiation therapy (IMRT) has been incorporated into clinical use, a dynamic radiotherapy technique with the ability to spare vital organs, such as salivary glands, orbital tissue and the central and spinal nervous tissue (29,30).

For advanced laryngeal carcinoma the combination of radiotherapy and chemotherapy is preferred. Concurrent chemoradiotherapy with a platinum-based chemotherapy has become the standard of care (24). The most often used chemoradiation scheme in our center consists of 7 weeks radiotherapy (fraction dose 2 Gy, 5x/week) combined with cisplatin (3 courses of 100 mg/m^2 in week 1, 4 and 7 of radiotherapy).

Although many larynges have been saved by chemoradiation, increasing concern arises about late toxicity and decreased survival (31,32), which might be (partially) attributed to inappropriate patient selection for chemoradiation (33,34). Especially patients with the most advanced stage primary laryngeal carcinoma (stage IV with cartilage invasion or involvement of the soft tissues of the neck) and expected poor tolerance of treatment seem to have better survival chances with primary laryngectomy (34-37).

Local recurrences

A local recurrence is defined according to clinical criteria as the occurrence of carcinoma within three years after and localized less than two cm from the first tumor. Tumors more than two cm away from or after more than three years after the primary tumor are referred to as a second primary tumor (38).

When cancer cells have remained in the patient this can be designated residual disease and outgrowth of these cells is a possible cause of local recurrent cancer. Sometimes these cells can only be detected by sensitive molecular methods and are referred to as 'minimal residual cancer' (39). Also, fields of genetically altered cells surrounding and in the neighborhood of the tumor can be left behind and give rise to a local recurrence, also known as 'second field tumors' (39,40).

The local recurrence rate of laryngeal carcinoma after non-surgical treatment has been reported to be 20-46%, depending on subsite and tumor stage (24,41-44). Surveillance is especially crucial in the first 2-3 years because two-thirds of the local recurrences and persistent or delayed lymph node metastases present in this period (45,46).

Prognosis of patients with a recurrence depends on the time of detection, since late detection is associated with poor survival rates (47-50).

Detection

The detection of recurrent laryngeal carcinoma after (chemo)radiation can be difficult. Symptoms like voice deterioration, pain, dyspnea and dysphagia may be caused by a local recurrence, but can also be the result of post-radiotherapy changes, and are neither very sensitive nor specific (51).

In daily clinical practice standard follow-up consists of physical examination with indirect and fiberoptic laryngoscopy, combined with imaging in selected cases. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound are the anatomic imaging modalities used for detection of recurrent laryngeal carcinoma.

The value of physical examination and anatomic imaging is sometimes limited in the detection of recurrence because of the (chemo)radiation induced changes, such as edema, hyperemia and fibrosis. Conventional imaging depends on soft tissue distortion and contrast enhancement and these are noted in both therapy changes and recurrent tumor. There is growing evidence that these modalities have limitations in their diagnostic accuracy (52-57).

In a survey among head and neck cancer institutions in the Netherlands, 94% of the departments used direct laryngoscopy with biopsies under general anesthesia in case of a suspected recurrence (51). However, in another study we found it often takes several laryngoscopies to detect a recurrence: 31% of the initial laryngoscopies was false-negative (recurrence within 6 months) (51). Furthermore, trauma of multiple biopsies in heavily radiated tissue may initiate superimposed infection, chondritis, failure to heal and further edema (58). On the other hand, some direct laryngoscopies under general anesthesia are performed without showing recurrence and should thus be classified as possibly preventable. In conclusion, there is room for improvement of the diagnostic work-up of these patients.

POSITRON EMISSION TOMOGRAPHY (PET)

General principle

Imaging techniques such as (conventional) MRI, X-ray and CT are primarily used to display anatomy, with changes in size and structure to differentiate between abnormal and normal tissue. PET imaging is a functional modality, providing information of physiological and biochemical activity. Another benefit of PET is that it can image the entire body in a single study, to evaluate the primary tumor, nodal metastases and distant metastases.

PET is based on the administration of a positron emitting pharmaceutical. This type of radio-isotope emits a positron that will travel a distance of a few millimeters. After losing its kinetic energy the positron combines with an electron, converting its mass into energy, and resulting in the formation of two photons or gamma rays with an energy level of 511 keV. This is called annihilation. The photons are simultaneously emitted in opposite directions (under an angle of 180°). A PET camera consists of a ring of detectors placed around the body of the patient. If two photons are detected by detectors on opposite sides within a few nanoseconds, it is assumed that somewhere along the line an event has taken place. This line is referred to as the ´line of response´. By calculation of the crossing of all the lines of response the location of the radiation source can be determined. The current post-image reconstruction resolution of clinical PET systems is 5-7 mm.

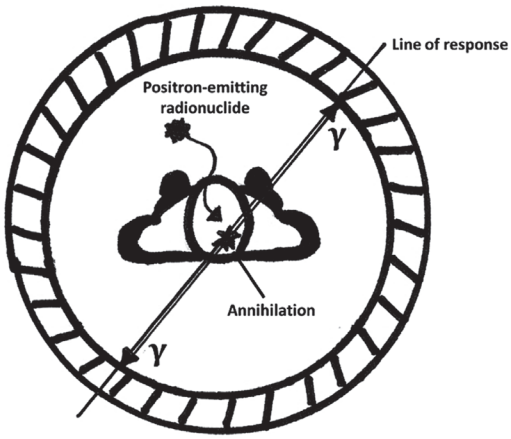

Fig 2. Annihilation, with detection of the two photons (γ radiation) by the PET camera, which surrounds the patient as detector rings.

Tracers

The most frequently used radio-isotope is Fluorine-18 (^{18}F; t½ 110 minutes), but also the shorter-lived Carbon-11 (^{11}C), Nitrogen-13 (^{13}N) and Oxygen-15 (^{15}O) as well as the long-lived Zirconium-89 (^{89}Zr) and Iodine-124 (^{124}I) are used for PET scanning. The radio-isotope is linked to a biomolecule, which leads to a PET tracer. For example, labeling of the glucose analogue deoxyglucose with Fluorine-18 results in 2-[^{18}F]-fluoro-2-deoxy-D-glucose (18F-FDG)(59). In the oncological field

18F-FDG is broadly used as PET tracer, since cancer cells have increased glucose metabolism. Analogous to glucose, 18F-FDG is transported into cells via GLUT-transporters and is converted to 18F-FDG-6 phosphate. However, unlike glucose-6 phosphate, this is not recognized as a substrate for further processing in the glycolytic pathway and thus accumulates within the cells. Hence, 18F-FDG-6 phosphate will preferentially accumulate in those cells with high glucose uptake, such as tumor cells. A whole body PET image represents the biodistribution of the glucose analogue in the body. The main drawback of 18F-FDG as PET tracer for malignancy is the 18F-FDG uptake in noncancerous tissue, with infection and inflammation as the most frequent culprit of misinterpretation.

18F-FDG-PET and laryngeal carcinoma

18F-FDG-PET plays an important growing role in staging, restaging, monitoring treatment and predicting prognosis in patients who have head and neck cancers (60-64). It may be particularly useful to distinguish posttreatment changes from recurrent tumor following radiotherapy (65). For this indication 18F-FDG-PET with or without CT has proven to be more accurate when compared with conventional imaging modalities (56,66). Sensitivity and specificity of 18F-FDG PET for detection of residual or recurrent HNSCC were 92-94% and 82-87%, respectively, in meta-analysis (67,68).

However, infection, inflammation, ulceration and necrosis are known postirradiation sequels associated with increased metabolic activity. As a result, PET scans can be falsely reported as tumor-positive and specificity decreases. To avoid false-positive 18F-FDG accumulation and to enable small residual disease grow to a detectable size, post(chemo)radiation evaluation of the larynx and neck should be done at least 2 months following treatment (62,66,67,69-72). Although specificity after radiotherapy can be disappointing, sensitivity of 18F-FDG-PET is high.

Innovation in PET is focused on improving the poor quality of anatomic localization (using PET/CT and PET/MRI) and limited spatial resolution, and on the development of more specific tracers. When anatomical data is added, it may be less difficult to distinguish between metabolically active benign versus malignant tissue. In general, the combined use of 18F-FDG-PET and contrast-enhanced CT provides similar sensitivity but improved specificity and diagnostic confidence, compared with 18F-FDG-PET alone (73,74). However, a systematic review and meta-analysis did not find a clear benefit of PET/CT over PET alone in head and neck cancer patients following (chemo)radiotherapy or as posttreatment surveillance (67,68,75). Previous PET/CT research has focused on SUV (standardized uptake value) to differentiate between tumor and therapy-induced inflammation. There are no standardized cut-off SUVs to identify residual or recurrent disease in patients with head and neck cancer (76). There are studies indicating that pretreatment 18F-FDG uptake might be inversely related with disease free survival (77).

SALVAGE TREATMENT

Salvage surgery is, if possible, the only therapeutic option with curative intent for residual or locally recurrent carcinoma after (chemo)radiation. For laryngeal carcinoma salvage surgery mostly consists of total (pharyngo-)laryngectomy which can be combined with uni- or bilateral neck dissection. In selected cases postoperative re-irradiation can be regarded. In certain cases, palliative chemotherapy may be the most appropriate therapy, with variable low response rates.

Locoregional control rate after salvage total laryngectomy for recurrent disease is dependent on the T-stage. The locoregional control rate is around 50-80% for T2 (41,78-82), 50% for T3 (78, 83-85), and 20-30% for T4 tumors (78,86). Salvage surgery after chemoradiation is associated with a significantly lower success rate and higher morbidity than upfront surgery (48,87-92).

Laryngectomy as salvage

Total laryngectomy is widely recognized as one of the surgical procedures with the most impact on patients. Surgical resection compromises voice, swallowing, and the airway and may have a negative impact on the patient´s quality of life. Social isolation, job loss, and depression are known sequels. The natural airway is altered by creating a permanent tracheostoma and normal vocal function is eliminated by removing the voice box. Surgical voice restoration using voice prosthesis is the optimal standard for rehabilitation in laryngectomees. The quality of voice is variable (93), but does allow patients to reintegrate into working life.

Various types of open function preservation surgery have been described to avoid total laryngectomy. Partial laryngectomy is mainly performed to allow patients to speak without a stoma, and to minimize the risk of complications. Examples are horizontal and vertical partial laryngectomies or supracricoid laryngectomy (25, 94).

Nevertheless, for most recurrences, partial laryngectomy is no curative option and total laryngectomy will be the only operation of choice. Previous studies showed that depending on the primary tumor site most recurrences are transglottic and largely advanced (rT3-T4) (95). Also, small fields of residual tumor have been found in apparently normal areas of the laryngectomy specimen, indicating the extensiveness of recurrent disease (96,52). Salvage partial laryngectomy seems only suitable in carefully selected patients and indications for this form of surgery vary globally (97).

Salvage laryngectomy is associated with a higher rate of postoperative complications than primary laryngectomy. Problems related to local wound healing, especially the development of pharyngocutaneous fistula, constitute the most common postoperative complication after salvage total laryngectomy (90,98-104).

Neck dissection

The American Academy of Otolaryngology Head and Neck Surgery established a system for classifying cervical lymph nodes into different surgical zones, based on their anatomic locations (105). This system is designed to improve communication regarding the location of abnormal nodes and to ensure reproducible lymph node dissections. Lymph nodes in the neck have been

divided into 6 levels: level I, submandibular triangle; level II, upper jugular; level III, middle jugular; level IV, lower jugular; level V, posterior triangle, and level VI, pre/para- laryngeal and -tracheal lymph nodes.

Pre-operative ultrasound is the most valuable technique to detect and localize lymph node metastases, especially if combined with cytological aspiration (106). However, its value in the clinically negative neck is limited. CT, MR and PET imaging are also used to detect lymph node metastases. In meta-analysis PET has good performance compared to conventional diagnostic tests, but still does not detect disease in half of the patients with metastasis and cN0 (107,108). PET has not shown consistent utility in evaluating small subcentimeter lymph nodes because of its innate limitations in camera resolution, while 40% of metastatic cervical lymph nodes measure less than 7 mm in diameter (109,110).

Unfortunately, posttreatment ultrasound-guided-fine needle aspiration cytology lacked specificity in patients after chemoradiation in a previous study (111). PET/CT is currently advocated as the posttreatment imaging modality of choice, but due to the false-negative rate its use in clinical practice is under debate: some studies find the false-negative rate too high to warrant deferring neck dissection (110,112,113), whereas others find no survival benefit for planned neck dissection as compared to selection for neck dissection by PET/CT (114).

The status of lymph nodes in the neck is a major determinant of the outcome in patients with local recurrence. However, proper management of the neck remains a therapeutic dilemma. There is no consensus over whether or not and how to perform neck treatment in patients with recurrent laryngeal carcinoma.

There is general agreement that patients with less than complete response in the neck after (chemo)radiotherapy should undergo neck dissection to eliminate potential residual viable tumor cells in the nodes (115,116). It has also been accepted that patients with complete response of N1 disease do not require neck dissection (117,118). The controversy is principally centered over whether a clinical complete response predicts eradication of N2-3 disease (113). A review showed that the overall rate of occult lymph node metastases in patients undergoing salvage surgery for recurrent laryngeal carcinoma ranged from 7.5-12% (119).

The type of neck dissection is another area of controversy. There are three main categories of neck dissection (120). Radical neck dissection is the standard basic procedure for cervical lymphadenectomy which includes removal of lymph nodes from levels I to V, with removal of the sternocleidomastoid muscle, the spinal accessory nerve, and the internal jugular vein. Modified radical neck dissection involves removal of lymph nodes from levels I to V (as in radical neck dissection), but with the preservation of at least 1 of the nonlymphatic structures (i.e., sternocleidomastoid muscle, spinal accessory nerve, and/or internal jugular vein). The term selective neck dissection is applied when one or more lymph node level(s) is preserved. There are several types of the selective neck dissection, some of which have traditionally been given specific names (eg, lateral, supraomohyoid, extended supraomohyoid, posterior or central). However, since 2001 it was determined to exclude these ‘named’ selective neck dissections based

on the increased number of variations (121). To facilitate the standardization and referencing of these procedures the levels are described, with the addition of sublevels into the classification (IA: submental nodes, IB: submandibular nodes, IIA and IIB: upper jugular nodes (anterior caudal and posterocranial from spinal accessory nerve), VA: spinal accessory nodes and VB: transverse cervical and supraclavicular nodes). In some selected cases, a superselective or nidusectomy seems feasible (116).

In primary laryngeal carcinoma, most regional lymph node metastases are in the upper and middle jugular chain of nodes (level II and III) (122). It seems therefore, and this was confirmed by previous studies, not necessary to perform a comprehensive neck dissection in patients with limited regional recurrence (111, 116).

In conclusion, since detection of regional recurrence after non-surgical treatment remains difficult, management of the neck constitutes a dilemma in patients with proven local recurrence.

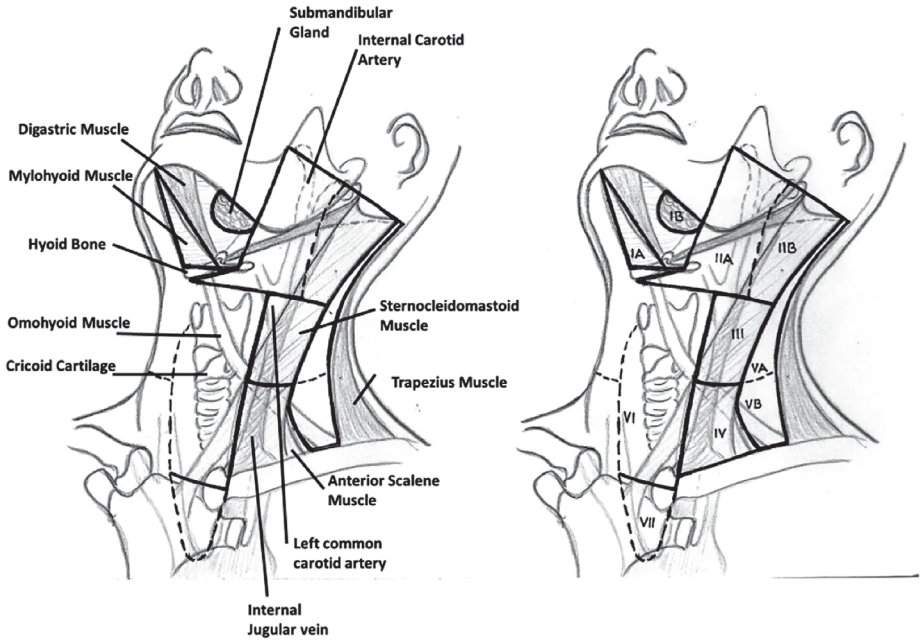

Fig 3. Lymph node levels of the neck in relation to important structures of the neck, used as landmarks for the extension of lymph node dissections. Adapted from reference 123.

COST EFFECTIVENESS

Cost (-effectiveness) analysis (C(E)A) has proven value and is widely used to assist in health care decision making (124). The increasingly competitive medical landscape demands that current and future costs as well as quality of care and patient perspective become central to health care

decision making (125). Anywhere that a determination of the value of a health intervention would be useful is a potential arena for the application of C(E)A.

Cost-effectiveness analysis, compares different costs between treatments in relation to outcomes (effects). Cost-minimization analysis quantifies medical costs without analyzing the effectiveness outcomes, and is used when differences in outcome are not expected.

In the development of new guidelines the government and health insurances promote the importance of cost-effectiveness of expensive medical technologies. A diagnostic imaging technique is considered effective if it provides more accurate data than existing modalities, improves patient management and contributes to better impact on health. Secondarily, there is an increasing aspiration to provide this at reasonable costs. When two diagnostic or treatment strategies are compared, a cost (-effectiveness) analysis can be performed in which the potential health benefits and cost consequences of the new intervention are compared against a reference script (diagnostic or treatment used in best practice). The effect, or primary outcome event, can be diagnosing a patient with a disease, longer survival, or a futile intervention. Costs can be compared between groups. Medical costs concern direct medical costs and direct non-medical costs (for example costs for the patient to travel to the hospital and loss of productivity). Relevant costs here are related to hospitalization, operation and PET scan. By performing sensitivity analysis the impact of the most influential input parameters on the costs and outcomes can be examined.

AIMS AND OUTLINE OF THE THESIS

As (chemo)radiotherapy is currently the most often used treatment for primary laryngeal carcinoma, the role of surgery is evolving from primary surgery towards salvage surgery. Salvage surgery is known to result in a better survival rate when performed timely, but the detection of a local recurrence can be difficult. Therefore, reliable diagnostics to detect the residual or recurrent tumor as early as possible are mandatory. The current standard to detect local recurrence, direct laryngoscopy (with biopsies) under general anesthesia, has several disadvantages. As a result of radiation sequelae, it can be difficult to distinguish scar tissue from tumor, with false-negative biopsies as a consequence. Previous research indicates that 18F-FDG-PET might be reliable enough to exclude the presence of tumor.

When residual or recurrent local tumor is proven, salvage surgery should be considered. Salvage laryngectomy means function loss and postoperative complications and survival is poor. A careful selection should therefore be made, with consideration towards the extent of surgery.

The aims of this thesis was to investigate the role of 18F-FDG-PET in the detection of local recurrent laryngeal carcinoma after (chemo)radiotherapy (**Chapters 2-5**) and to evaluate the outcome of salvage surgery (**Chapters 6-8**).

The role of 18F-FDG-PET in the detection of locally recurrent laryngeal carcinoma

In **Chapter 2** the observer variability in reporting of 18F-FDG-PET to detect recurrent laryngeal cancer, is studied between 11 observers from different centers. Observer variation is the Achilles'

heel of visual imaging interpretation (126). Purpose of this study is to give a nation-wide impression of the accuracy (and its range) of 18F-FDG-PET for this indication in daily clinical practice. At the same time, it was used as a training set for the following RELAPS study.

In **Chapter 3** we describe the design of a randomized controlled multicenter trial (RELAPS: **RE**current **LA**ryngeal carcinoma after radiotherapy, **P**ET **S**tudy). The study is conducted to improve the yield of direct laryngoscopy by setting its indication via PET, randomizing patients either to direct laryngoscopy with biopsies under general anesthesia (conventional strategy) or to 18F-FDG PET only followed by direct laryngoscopy with biopsies under general anesthesia if PET was assessed positive or equivocal for the presence of local disease (PET-based strategy). The assessment and distribution of new technologies is a complex process. There may be either a low level of acceptance of new technologies in the medical community, or, more frequently, overuse. The major benefit of randomization lies in the creation of groups that are similar with respect to all known and unknown prognostic factors allowing an unbiased comparison of different strategies. Another benefit of using a randomized controlled trial is that not only the accuracy of PET is investigated, but an entire strategy. This strategy consists of a diagnostic and treatment combination, allowing to evaluate the total effect on patient outcome.

In **Chapter 4** the results of the RELAPS trial are discussed. The clinical significance of the PET-based diagnostic strategy is evaluated, in relation to the number of futile indications for direct laryngoscopy under general anesthesia. Also, the safety of this strategy and accuracy of PET is studied. Safety is investigated by the percentage of patients with local recurrence undergoing laryngectomy and the percentage of positive margins in each diagnostic strategy arm.

In **Chapter 5** a quantification of medical costs is presented. The mean medical costs of the PET based strategy versus the conventional strategy are studied. Costs are subdivided for diagnostic, treatment and follow-up phase. A sensitivity analysis was performed to examine the impact of different input parameters.

Salvage laryngectomy and neck dissection for recurrent laryngeal carcinoma

In **Chapter 6** the recurrence patterns of hypopharyngeal and laryngeal carcinoma after chemoradiation are investigated. Predictors for salvage laryngectomy and lymph node dissections for locoregional recurrence and outcome are described. In addition, an overview of the outcome in previous studies is presented.

In **Chapter 7** we investigate the functional and oncologic outcome of salvage laryngectomy after previous radiotherapy. Secondary, management of the neck in combination with laryngectomy is discussed and prognosticators are evaluated.

In **Chapter 8** we describe the histopathologic results of paratracheal lymph node dissections that were performed during laryngectomy after previous radiotherapy. Furthermore, the relation between postoperative complications and the extension of the paratracheal dissection is investigated.

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CHAPTER 2

2-Deoxy-2[F-18]FDG-PET for detection of recurrent laryngeal carcinoma after radiotherapy: interobserver variability in reporting

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ABSTRACT

Purpose: To evaluate accuracy and interobserver variability in the assessment of 2-deoxy-2[F-18] fluoro-D-glucose-positron emission tomography (FDG-PET) for detection of recurrent laryngeal carcinoma after radiotherapy.

Procedures: Eleven experienced nuclear physicians from eight centres assessed 30 FDG-PET scans on the appearance of local recurrence (negative/equivocal/positive). Conservative (equivocal analysed as negative) and sensitive (equivocal analysed as positive) assessment strategies were compared to the reference standard (recurrence within 6 months after PET).

Results: Seven patients had proven recurrences. For the conservative and sensitive strategy, the mean sensitivity was 87% and 97%, specificity 81% and 63%, positive predictive values 61% and 46% and negative predictive values 96% and 99%, respectively. Interobserver variability showed a reasonable relation in comparison to the reference standard (kappa = 0.55).

Conclusions: FDG-PET has acceptable interobserver agreement and yields good negative predictive value for detection of recurrent laryngeal carcinoma. It could therefore be used as first diagnostic step and may reduce futile invasive diagnostics.

INTRODUCTION

Laryngeal cancer is the most common primary cancer site of the head and neck, with annually about 700 new cases in The Netherlands (1). Because of the relatively low incidence and the specialised care, the vast majority of laryngeal cancers in The Netherlands are treated in the eight recognised head and neck cancer centres of the Dutch Head and Neck Oncology Cooperative Group.

Parallel to developments elsewhere, non-surgical treatment modalities in our country are more common than in the past due to improved results of altered fractionation schedules in radiation therapy and the addition of chemotherapy to radiation (2–4). The aims of non-surgical treatments are organ preservation and improvement of quality of life (5,6). Especially, in this group of patients, early detection of residual or recurrent tumour is of critical importance because prompt salvage surgery improves control of disease.

The diagnostic accuracy of the currently available diagnostic techniques to diagnose persistent or recurrent disease after (chemo)-radiotherapy is currently limited. Postirradiation inflammation, oedema and necrosis can hamper the detection of residual or recurrent local tumour. CT and MRI rely on structural changes and show a limited accuracy, with reported sensitivities ranging from 50% to 58% and specificities from 33% to 100% for detection of recurrent laryngeal carcinoma (7–14). Direct laryngoscopy under general anaesthesia with biopsies runs the risk of complications (e.g., inducing necrosis, infection and further oedema) when biopsies are taken from irradiated tissue and was false negative in 31% of the initial laryngoscopies in previous research (15).

2-Deoxy-2[F-18]fluoro-D-glucose-positron emission tomography (FDG-PET) is a promising technique for tumour detection after (chemo)radiotherapy. FDG-PET seems more accurate for the detection of recurrent head and neck carcinomas than other diagnostic methods (10,16–22). The reported sensitivity of FDG-PET for the detection of recurrent carcinoma after (chemo)radiotherapy varies between 80% and 100% and the specificity varies between 63% and 93% (12–14,23–28).

Evaluation of PET in these studies is typically by visual interpretation, which is prone to observer variation. To the best of our knowledge, no studies have been conducted to investigate observer variation in a multi-centre setting for this indication.

To evaluate the value of FDG-PET in the detection of recurrent laryngeal carcinoma after radiotherapy, a randomized controlled multi-centre trial was started recently within the framework of the Dutch Head and Neck Oncology Cooperative Group (29). The extent to which the future results can be generalised, and thereby foresee the applicability of PET in daily clinical practice, tends to depend on the degree of agreement among the observers. Therefore, we evaluated the interobserver variability in reporting among 11observers involved in this trial, with a set of FDG-PET scans of patients suspected of having recurrent laryngeal carcinoma after radiotherapy.

MATERIALS AND METHODS

From the VU University Medical Center (VUmc) PET database, we identified 30 FDG-PET scans of consecutive patients with a clinical suspicion of persistent or recurrent laryngeal carcinoma after radiotherapy from the year 1998 to 2000. This suspicion was based on clinical symptoms, office laryngoscopy or diagnostic imaging, other than FDG-PET. Patients' T stages prior to radiotherapy were T1 (n = 4), T2 (n = 16), T3 (n = 5) and T4 (n = 5), N stages were N0 (n = 27) and N1 (n = 3) and none of the patients had distant metastases. The mean age at time of the PET scan was 60.9 ± 11.1 years. The median interval between the last radiation fraction and the PET scan was 8.7 months (range 2.4–32.1 months). As reference standard, we used the results of biopsies and histology or the absence of signs of tumour within 6 months after the PET scan.

PET Imaging

All patients underwent FDG-PET after at least 6-h fasting. Blood glucose levels were measured before scanning. All patients were non-diabetic. The median blood glucose level measured with a glucotouch stick was 5.9 ± 1.6 mmol/l. Sixty minutes after intravenous injection of 370MBq of 18F-FDG, imaging was performed in a full-ring bismuth germanate oxide PET scanner (ECAT EXACT HR+; CRI/Siemens, Erlangen, Germany). Five patients received a dose of 555 MBq because of higher weight. A scanning track from the base of skull to the clavicles was used, i.e. two bed positions per patient, with an acquisition time of 5 min per bed position. PET imaging was done with 2D acquisition using Ordered Subset Expectation Maximization (OSEM 2-16) to reconstruct the images. Attenuation correction was not applied in our clinical practice because of the results of the systemic review by Joshi et al. (30). The acquired images were viewed on a local PC of the participating centre with the PETViewer 2.0.10.570 (Microsoft Windows XP Professional Service Pack 2 (build 2600)).

Data Analysis

The panel of observers consisted of 11 experienced nuclear medicine physicians from the eight Dutch Head and Neck Oncology Cooperative Group medical centres. We recorded the experience of the observers with FDG-PET for this indication in terms of the estimated number of FDG-PET scans for laryngeal cancer they had assessed. Images were reviewed at each site on available PC running under Microsoft Windows (XP/2000). The scans were presented with a PET-viewer that allowed variable gamma and window tuning.

The observers were requested to interpret the PET scans as being indicative for the presence of local residue or recurrence and to classify the result as negative, equivocal or positive. Only increased uptake at the site of the initial primary tumour was used for further analyses. The observers were not provided with specific criteria for determining positivity and negativity. Evaluation was made on an overall basis rather than on a per-lesion basis.

The observers read the scans independently, and clinical information (regarding TNM stage and site of the primary tumour, last radiotherapy fraction, symptoms and the result of other diagnostic tests) was provided to imitate the clinical setting. Correlative anatomic imaging (CT or MRI) was not provided nor were the reports of these scans. There was no time restriction for the

assessment. Observers were blinded for the final clinical classification until they had reported all scans; thereafter, the investigator (LvdP) provided them with these results to improve standardised reading during the following prospective randomized trial. Cases that were scored incorrectly (when compared to the reference) or equivocal by at least nine observers were regarded as difficult cases and are described in the results.

The observers were asked which criteria they used for their interpretation of the FDG-PET scan.

Statistical Analysis

Data were obtained for a sensitive and a conservative PET reading strategy: The PET results were dichotomised by assigning equivocal scores to either the PET-positive or to the PET-negative classifications, respectively. Mean sensitivity, specificity, positive predictive value and negative predictive value were determined for either strategy. A Bayesian plot was used to show the probability of proven tumour within 6months for varying prevalences of tumour. To illustrate the probability of tumour in time after the PET scan for the different strategies and for different observers, a Kaplan Meier analysis was performed. Correlation between experience and diagnostic performance (measured with both conservative and sensitive strategies) and percentage of equivocal scores was evaluated.

To analyse the interobserver variability, we used agreement statistics (κ) with a classification according to Landis et al. (31) (Table 1). Linear-weighted kappa was used to determine interobserver variability of the 11 observers compared to the reference standard and pairwise compared to each other, for both conservative and sensitive strategy.

Table 1. Classification of the interobserver variability with kappa.

Kappa (κ)	Agreement
<0	No agreement other than agreement based on coincidence
0.01–0.19	Slight agreement
0.20–0.39	Fair agreement
0.40–0.59	Moderate agreement
0.60–0.79	Substantial agreement
0.80–0.99	Almost perfect agreement
1	Perfect agreement

RESULTS

Within 6 months after the FDG-PET scan, a local recurrence was histologically proven in seven patients (23%).

For both conservative (equivocal considered negative) and sensitive strategies (equivocal considered positive), the accuracy was determined per observer and depicted in a box plot (Fig. 1). The mean data of the accuracy of the 11 observers are shown in Table 2. For the conservative

reading strategy, mean sensitivity of 87% (range 57–100%), specificity of 81% (range 65–96%), positive predictive value of 61% (range 43–80%) and negative predictive value of 96% (range 88–100%) were found. For the sensitive reading strategy, mean sensitivity of 97% (range 86–100%), specificity of 63% (range 39–87%), positive predictive value of 46% (range 33–70%) and negative predictive value of 99% (range 93–100%) were found.

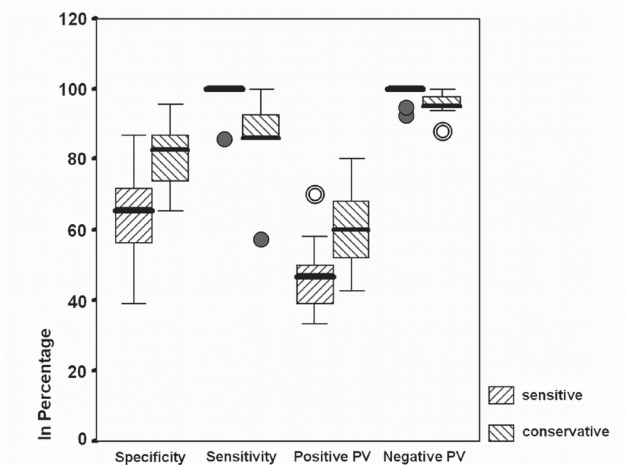

Fig. 1. Accuracy for conservative and sensitive reading strategies depicted in a box-and-whisker plot. The boxes contain the central half of the measurements (heavy line indicating the median). The dots are the values that are extremely far from the central box (outliers).

Table 2. Mean pooled accuracy for conservative (equivocal = negative) and sensitive (equivocal = positive) strategies.

	Conservative strategy (%)	Sensitive strategy (%)
Sensitivity	87	97
Specificity	81	63
Positive predictive value	61	46
Negative predictive value	96	99

In the Bayesian plot (Fig. 2), the two strategies mainly differ in the intermediate ranges of the prior probability of proven recurrence. Also, these differences are larger for the false negatives (lower corner) than for the true (and thus false) positives.

In a Kaplan Meier analysis (Fig. 3), as expected, an observer with a high accuracy (versus the reference) predicted the prognosis for local disease-free control more accurately than an observer with a low accuracy. With the conservative strategy, for both observers, a curve was established with significantly more local recurrences in the PET-positive than in the PET-negative group. Seven recurrences (71%) manifested within 6 months after PET, no recurrences were diagnosed between 6 and 12 months and the remaining two recurrences were seen between 12 and 24 months.

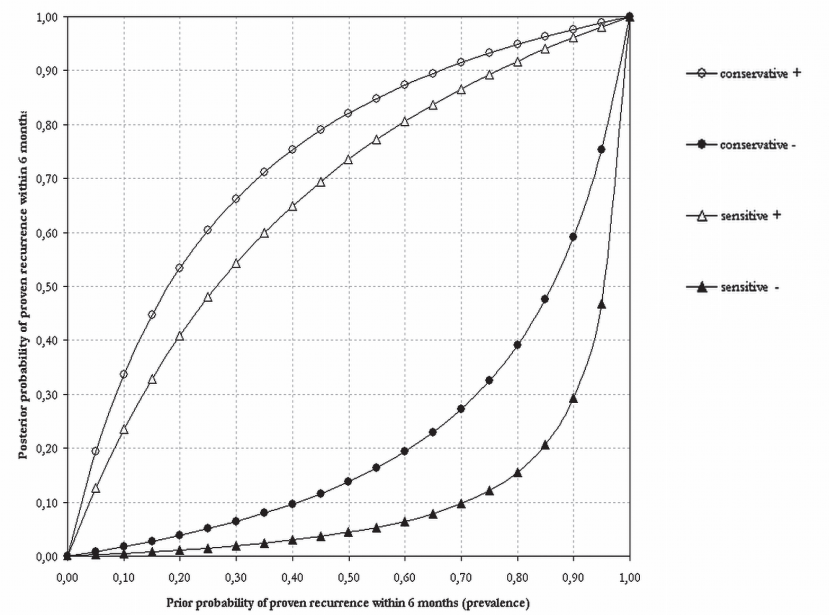

Fig. 2. Bayesian plot with the prior and posterior probability of proven recurrence within 6 months after FDG-PET for the conservative and the sensitive strategies.

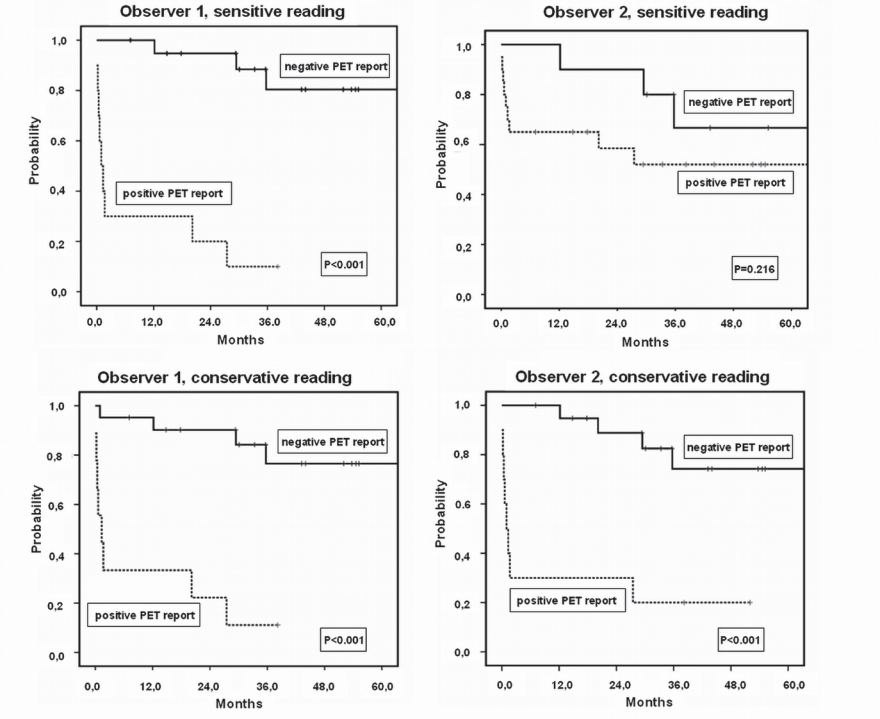

Fig. 3. Kaplan Meier analysis of a proven recurrence after PET, with stratification of the negative and positive assessed patients using the sensitive (a,b) and conservative (c,d) strategies by an observer with high accuracy (observer 1; a,c) and an observer with low accuracy (observer 2; b,d).

The estimated total number of FDG-PET scans for suspected recurrent laryngeal cancer of the observers had assessed previously varied between 0 and 300 (experience with dual head gamma cameras included). There was no statistically significant association between this experience and the number of 'equivocal' scores (p = 0.610, Table 3). The equivocal category was reported at a mean of five (out of 30 cases) per observer (17%, range 1–10). Furthermore, we found no significant correlation between the experience and diagnostic performance (conservative p = 0.360, sensitive p = 0.528, Table 3).

Table 3. Correlations with log-experience between experience of the observers and the number of equivocal score, the accuracy with equivocal as negative (conservative) or positive (sensitive).

	r	p	95% CI of r
Number of equivocals	0.175	0.610	-0.464–0.694
Accuracy (conservative)	0.307	0.360	-0.347–0.760
Accuracy (sensitive)	0.215	0.528	-0.499–0.669

r Correlation coefficient, p significance, 95% CI 95% confidence interval

The interobserver variability in comparison to the reference (local recurrence within 6 months after the PET scan) showed a moderate relation [κ = 0.55; 95% confidence interval (CI): 0.33–0.76]. The interobserver variability as pairwise comparison of the observers, which expresses the consistency between observers, also showed a moderate relation (κ = 0.54; 95% CI: 0.42–0.67).

When reducing the data from a three- to a two-point scale, the conservative strategy proved to result in a better interobserver agreement in comparison to the reference (κ = 0.59; 95% CI: 0.38–0.79) than the sensitive one (κ = 0.43; 95% CI: 0.22–0.63). The same was true for the pairwise comparison of the observers (conservative: κ = 0.58; 95% CI: 0.44–0.71, versus κ = 0.51; 95% CI: 0.37–0.65 for SR).

There were two difficult cases, with much discrepancy between the report of the observers and the reference (Fig. 4; patients #5 and #9). Both cases were negative according to the reference. Patient #5 underwent FDG-PET 5 months after the last radiotherapy fraction for a left-sided T3N1 supraglottic laryngeal carcinoma. Clinical suspicion of recurrence was based on unexplained otalgia. A MRI of the neck showed diffuse paraglottic swelling on both sides (mainly on the right side), which could either be post-irradiation effects or recurrent tumour according to the radiologist (Fig. 5). Five observers scored the PET scan (Fig. 5) as equivocal and six as positive. At direct laryngoscopy, irregular tissue at the left aryepiglottic fold and the epiglottis was seen, but biopsy revealed no malignancy. Three years and 2 months after PET, the patient died with lung metastases, but a local recurrence was never detected.

Patient #9 had a PET scan 2 years after completion of radiotherapy for a left-sided T2N0 glottic carcinoma. The PET scan (Fig. 6) was indicated because the left side of the glottis appeared suspicious at indirect laryngoscopy. CT scan of the neck showed a suspect area just ventral to the lesion described on the PET scan. Seven observers scored the PET scan as positive, three as equivocal and one as negative. Clinical follow-up was uneventful until 2 years, later direct laryngoscopy revealed squamous cell carcinoma at the original tumour site. The laryngectomy specimen contained a squamous cell carcinoma of 1.5 cm in diameter located in the glottis with tumour extension into the thyroid cartilage.

The criteria the observers used for their interpretation were information derived from the PET scan, such as localisation, (a)symmetry and aspect of suspicious areas, diffuse versus focal lesions and the intensity of the suspicious areas compared to the intensity of the background, in combination with the clinical data (localisation of primary tumour, interval between radiation and PET).

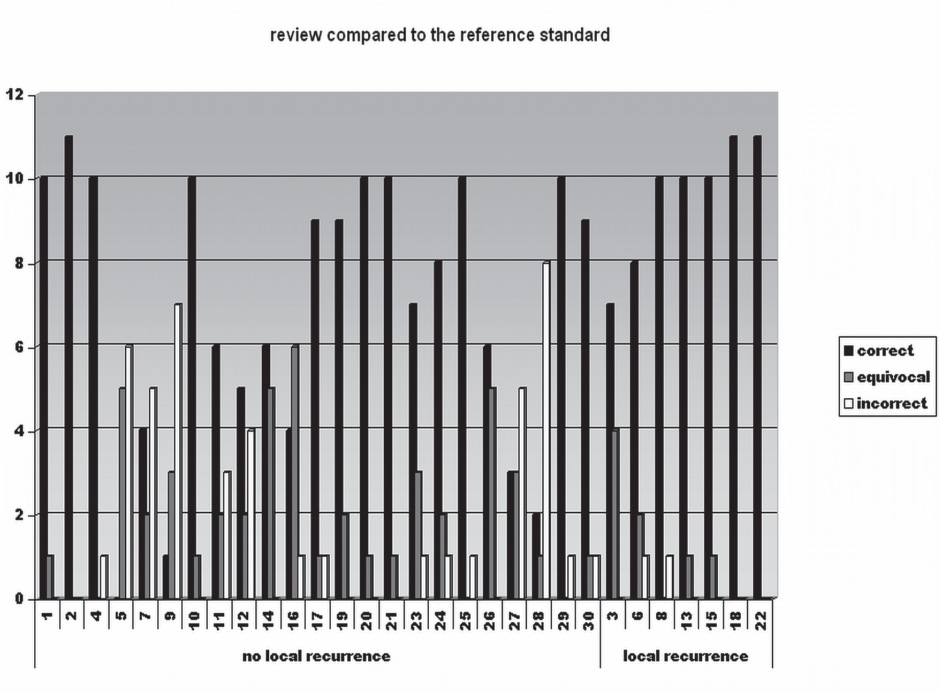

Fig. 4. All 30 cases and the results of the review (correct, equivocal, incorrect) compared to the reference standard (numbers of observers).

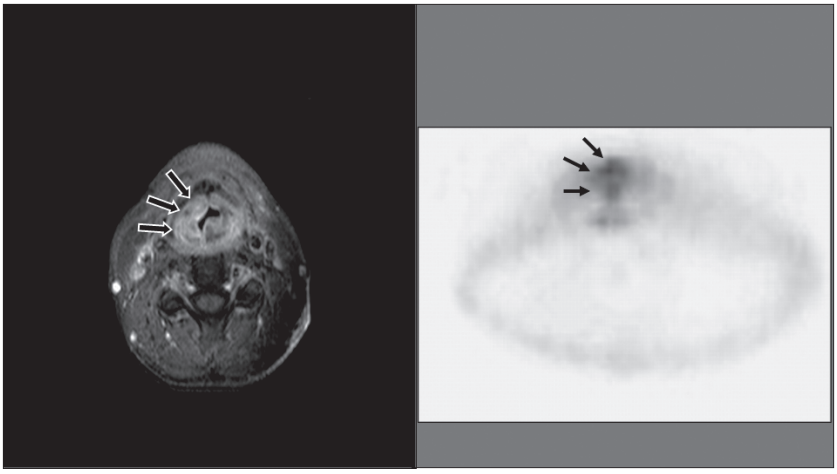

Fig. 5. Patient 5: MRI (STIR, axial) with diffuse paraglottic swelling on both sides, mainly right (arrows). PET (axial) with abnormal supraglottic ventral uptake, on the right side more than on the left side (arrows). Below the arrows is a region with normal uptake, probably caused by uptake in the crico-arythenoid muscle.

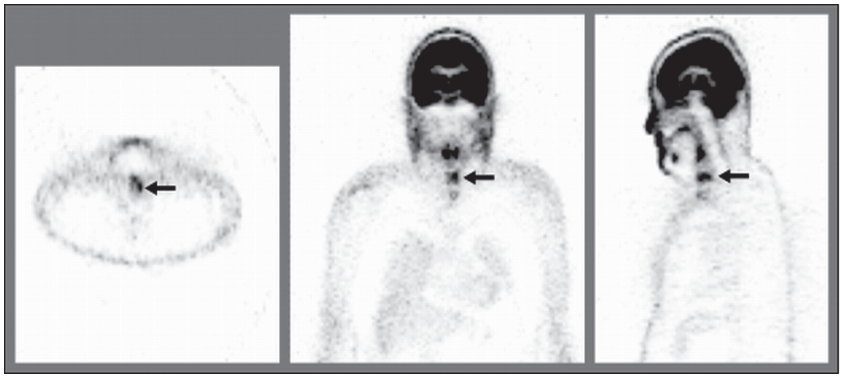

Fig. 6. FDG-PET scan of case 9 (axial, coronal and sagittal images) reviewed as tumour positive by seven observers, equivocal by three observers and negative by one observer (arrows indicate region suspected of tumour).

DISCUSSION

In the present study, we analysed the performance of 11 observers from the eight head and neck cancers centres in The Netherlands for the assessment of FDG-PET scans from patients who were suspected of having a local recurrence of laryngeal carcinoma after primary radiotherapy.

We found a reasonable chance-corrected proportional observer agreement, both in comparison to the reference standard and pairwise. It is difficult to predict how the agreement would change if a larger sample size was studied. To the best of our knowledge, this is the first study that examines the interobserver variability of more than two observers from different institutes in the detection of recurrent laryngeal carcinoma with FDG-PET. Many authors stress the importance of

interobserver agreement (32, 33). Fakhry et al. (34) studied the interobserver variability between two observers of FDG-PET in the detection of recurrent head and neck squamous cell carcinoma and found a good agreement (intraclass correlation coefficient 990). A substantial agreement was also described for metastatic disease. Bohdiewicz et al. (35) found a 90% agreement between two observers who reviewed FDG-PET scans for metastatic disease in the spinal cord, and Lim et al. (36) found a kappa of 0.68 for three observers who reviewed FDG-PET scans for peritoneal metastases. Hashimoto et al. (37) evaluated lung nodules with two observers of FDG-PET and found a kappa of 0.65. In a study performed by Zijlstra et al. (38), 11 observers reviewed FDG-PET scans for suspicion of recurrent lymphoma in 82% to 94% of the tumour-positive patients and 45% of the tumour-negative patients, which were in accordance with the experts.

Because the observer panel in this study consisted of nuclear physicians from all Dutch Head and Neck Cancer Centres, the results give a good impression of the overall diagnostic performance of PET for suspected laryngeal recurrence after radiotherapy in The Netherlands. Especially, since the interobserver agreement was reasonable, an acceptable reproducibility and thereby a general applicability of these results is assumed.

As expected, sensitivity and specificity varied inversely with the threshold of test positivity. Our data (mean sensitivity ranging from 87% to 97%, specificity from 63% to 81%) appear to reflect the distribution of such measures reported in the literature, with sensitivities ranging from 80% to 100% and specificities from 63% to 100% (12,26–28,39,40).

Remarkably, no significant correlation between the accuracy and the experience of the observer was found. Also, no correlation was found between experience of the observers and the number of non-conclusive reports. At first glance, these findings may suggest that no specific experience is needed with FDG-PET for laryngeal carcinoma. Another explanation for this finding could be the lack of clinical feedback during daily practice in which a learning curve cannot be established. Therefore, regular feedback during daily practice seems essential also in situations where proof of presence or absence of disease may be obtained several months after PET. Finally, we recognise that the sample size was relatively small and that some observers reported that they were unfamiliar with interpretation of images without attenuation correction. However, the performance of these observers was not clearly different from the others. Moreover, considering the 95% confidence intervals of the correlation coefficients, it seems unlikely that a larger sample size would change these findings. Unfortunately, it was not possible to compare the correlations between accuracy and the experience of the observer or the number of equivocal scores with previous studies, as previous studies used two or three experienced nuclear physicians without differentiation of the level of experience or the relation with equivocal scores. Zijlstra et al. (38) reported that the experts did not have any equivocal scores, while the less experienced observers did have equivocal scores.

A variable amount of cases were scored equivocal (a median of 17% equivocal reports per observer). Although the number of non-conclusive scores differed greatly per observer (range 0–10), this indicates that in contrast to how data are typically reported, dichotomous results of FDG-PET for recurrent carcinoma may be regarded as an artificial and unwanted simplification. To

explore the effect on diagnostic performance of this phenomenon, we dichotomised the data. The conservative strategy in which the equivocal scores were analysed as negative resulted in a better overall accuracy and a better interobserver agreement (kappa 0.59 and 0.58) than the sensitive strategy (kappa 0.43 and 0.51).

In our population, the prevalence of histologically proven recurrence was 23%. Because the mean reported prevalence is 50% (14,25,27), we compared these prevalences in a Bayesian plot. When the prevalence is 50%, the difference between the two strategies for a negative PET scan, in favour of the sensitive strategy, is larger as compared to the prevalence in the present study.

We assume that in clinical practice, the sensitive reading is used if FDG-PET is used to select patients suspected of recurrent laryngeal carcinoma after radiotherapy for direct laryngoscopy under general anaesthesia. For the physician, the risk of missing a recurrence probably outweighs a futile direct laryngoscopy because early detection of a recurrence can be important for salvage surgery and clinical outcome. An inherent disadvantage of sensitive reading is the higher percentage of false positives and subsequently futile direct laryngoscopies under general anaesthesia and more interobserver variability. It can be expected that the interobserver agreement has improved by the feedback received after the assessment.

We used a disease-free follow-up of 6months as reference standard of patients without recurrence because we assume that local disease manifest itself within this period. Extending this period carries the risk to include recurrent disease that developed after the PET scan. If local recurrences were not detected within the first 6 months, these were diagnosed at least 21 months after the PET scan. It seems highly unlikely that the lead-time of PET would be that long, but we admit that we cannot exclude the possibility of a very slow growing recurrence.

As was shown in the Kaplan Meier analyses (Fig. 3), a negative PET scan was highly predictive for local control, especially in the first 12 months. This suggests that patients with a negative PET scan might be spared a futile laryngoscopy under general anaesthesia and that regular follow-up might be sufficient.

While false-positive reading tends to be a problem, the negative predictive value of FDG-PET is high in both the conservative (96%) and the sensitive strategy (99%). The negative predictive value is, of course, dependent on the prevalence of disease. In the present study, the prevalence was only 23%. In the PET literature, the mean prevalence appears to be about 50% (manuscript in preparation), and high negative predictive values for different prevalence are reported (41). Therefore, it can be anticipated that a negative FDG-PET excludes recurrent disease with a high certainty. With this unique characteristic, FDG-PET may be safely used as the first diagnostic step of triage for invasive procedures in patients suspected of recurrent laryngeal tumour. By filtering the patients with a negative PET scan out of the further diagnostic process, the percentage of futile diagnostic laryngoscopies can probably be diminished.

To further investigate the potential of FDG-PET for this indication, a prospective study with more patients is recommended. In the current study, the images were not attenuation-corrected. In the

future, the fused PET-CT will probably take over the PET alone. Besides the anatomical information of the CT, it also offers the possibility to easily determine the 'standard uptake values' for objective assessment. For the present indication, selection of patients with suspicion of recurrent laryngeal carcinoma after radiotherapy for direct laryngoscopy under general anaesthesia, detailed anatomical information is probably not essential. Uptake in the laryngeal area, which indicates further examination, can be assessed on PET alone. For this indication, no literature is available about the diagnostic value of PET-CT in comparison with PET alone. PET-CT may yield slightly different results, and this will be subject of further study (29). Another relative disadvantage of the present study is the varying interval between the last radiation and the PET scan, with a minimum interval of 2.4 months. McGuirt et al. (41) and Ryan et al. (28) concluded that the accuracy of PET is significantly higher for an interval more than 3 months compared to 1 month.

CONCLUSIONS

While acknowledging that additional confirmation is necessary, we propose in view of the acceptable interobserver agreement that FDG-PET yields good negative predictive value for the detection of recurrent laryngeal carcinoma after radiotherapy. It could therefore be used as a first diagnostic step and may reduce the percentage of futile invasive diagnostics.

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CHAPTER 3

A randomized trial of PET scanning to improve diagnostic yield of direct laryngoscopy in patients with suspicion of recurrent laryngeal carcinoma after radiotherapy

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ABSTRACT

The RELAPS study (REcurrent LAryngeal carcinoma PET Study) was designed to determine whether FDG–PET is of value in the selection of patients for direct laryngoscopy under general anesthesia in patients with suspicion of recurrent laryngeal carcinoma after radiotherapy. In a randomized controlled clinical trial the current diagnostic practice, i.e. all patients undergo direct laryngoscopy, will be compared to a strategy in which FDG–PET selects the patients for laryngoscopy. All eight head and neck cancer centers of the Dutch Head and Neck Oncology Cooperative Group NWHHT will participate in this multicenter trial. The study population consists of patients with clinical suspicion of recurrent T2–T4 laryngeal carcinoma after radiotherapy (without obvious signs of tumor) in whom a direct laryngoscopy under general anesthesia with taking of biopsies is indicated by the local physician. The primary efficacy endpoint is the difference in the number of futile indications for direct laryngoscopy between the conventional diagnostic arm and the FDG–PET based diagnostic arm. An indication for laryngoscopy is classified as futile if this laryngoscopy was negative and no recurrence was diagnosed within 6 months follow-up (gold standard). The FDG–PET based strategy may increase the risk of missing recurrent tumor compared to current practice. Safety endpoints include survival and morbidity due to laryngoscopy with taking of biopsies. Survival rates of both groups will have to be collected outside the time frame of the funded trial. Resectability of recurrent tumor and tumor negative surgical margins after total laryngectomy will be used as proxy endpoints. The trial will also compare quality of life and direct medical costs between both arms.

INTRODUCTION

Laryngeal carcinoma is the most common form of head and neck cancer. When treating patients for laryngeal cancer, the goal is not only to cure but also to preserve function. Early laryngeal cancer can usually be managed successfully with either radiotherapy or surgery. Carefully selected advanced lesions are initially treated by irradiation, with surgery reserved for salvage treatment. With the emphasis on preservation of organ and function, investigational treatment regimes using altered fractionation schedules of radiation and the combination of chemotherapy and radiation have recently emerged. There is a high local control rate of T1 laryngeal cancer treated with radiotherapy. For T2 to T4 laryngeal cancer treated with radiotherapy with curative intent, the rate of recurrence is considerable. In most cases where radical radiotherapy has failed, salvage surgery to treat recurrence remains a successful option.

In patients with symptoms or clinical abnormalities such as severe edema or necrosis, differentiation between recurrent carcinoma and sequelae of radiotherapy can be difficult. The need for biopsy can present a dilemma as the biopsy itself may exacerbate postradiotherapy changes and initiate superimposed infection, (peri)chondritis, failure to heal and further edema (1,2). On the other hand, symptomatic treatment with antibiotics and glucocorticoids will delay adequate treatment of a recurrence. Currently most physicians aggressively pursue potential recurrences, leading to a high rate of futile direct laryngoscopies and a waste of scarce health care resources.

Improvement of this situation requires increasing the *a priori* likelihood of a recurrence before laryngoscopy. In a retrospective cohort study, we defined the diagnostic accuracy and yield of signs and symptoms, the current noninvasive diagnostic techniques and direct laryngoscopy with biopsy in patients with suspicion of recurrent laryngeal carcinoma after radiotherapy. Overall, the current clinical diagnostic strategy led to the detection of a recurrence in only 45% of the direct laryngoscopies. We found that the accuracy of voice complaints, pain, dyspnoea, dysphagia, indirect laryngoscopy, videolaryngostroboscopy and CT or MRI was low (3,4).

The use of positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) seems to be promising. Because FDG–PET relies on the metabolic function of neoplastic cells, it can be an important tool in the detection of small, submucosal recurrences. Furthermore, it has been shown that FDG–PET is able to distinguish tumor recurrence from radiation sequelae in patients treated for laryngeal carcinoma (5).

In The Netherlands almost all laryngeal carcinomas are treated in the eight head and neck cancer centers of the Dutch Head and Neck Oncology Cooperative Group NWHHT. There are no clear guidelines for the diagnostic policy when clinical suspicion of recurrent laryngeal carcinoma after radiotherapy exists. We surveyed the otolaryngologists and radiotherapists in these clinics to review current diagnostic practice. All respondents indicated that they perform direct laryngoscopy under general anesthesia when recurrence is suspected. However, 35% were dissatisfied with the current diagnostic path. Many indicated that they would like to have easier access to a PET-scan facility, since they expected that this technique might improve the diagnostic path.

The assessment and distribution of new technologies is a complex process. There may be either a low level of acceptance of new technologies in the medical community, or, more frequently, overuse. In the setting of recurrent laryngeal carcinoma a trial that randomly allocates patients to either conventional diagnostic work-up or to a work-up based on a new technique may be the best way to determine the value of FDG–PET. The major benefit of randomization lies in the creation of groups that are similar with respect to all known and unknown prognostic factors allowing an unbiased comparison of different strategies.

In our setting the achievable health gain comprises a reduction of the number of futile procedures. The RELAPS study (REcurrent LAryngeal carcinoma PET Study) will compare the current diagnostic practice, i.e. all patients undergo direct laryngoscopy, to a strategy in which FDG–PET selects the patients for laryngoscopy. The trial will also compare quality of life and direct medical costs. Randomization will be stratified by treating institute, T-stage (T2 vs T3–4) and smoking status.

METHODOLOGY

Population

All 8 head and neck cancer centers of the Dutch Head and Neck Oncology Cooperative Group will together recruit 150 patients for this trial. These centers treat more than 90% of all patients with laryngeal carcinoma in the Netherlands. Patients with clinical suspicion of recurrent laryngeal carcinoma after radiotherapy (without obvious signs of recurrent tumor), for whom a direct laryngoscopy under general anesthesia with taking of biopsies is indicated by the local physicians, are invited to participate. Patients have to be older than 18 years of age and give a written informed consent according to the local medical ethical committee regulations. Patients must have received and completed their radiotherapy for a histological proven T2–T4 laryngeal carcinoma for at least 4 months.

Randomization

In a prospective randomized controlled trial, two strategies are compared: 1) conventional strategy: direct laryngoscopy under general anesthesia with taking of biopsies; 2) FDG–PET based strategy: only direct laryngoscopy under general anesthesia with taking of biopsies if FDG–PET is positive or equivocal (Fig. 1). To randomize a patient, the otolaryngologists call the central data center. Eligible patients are randomized by a computer according to the method of minimization. Randomization will be stratified by treating institute, T-stage (T2 vs T3–4) and smoking status.

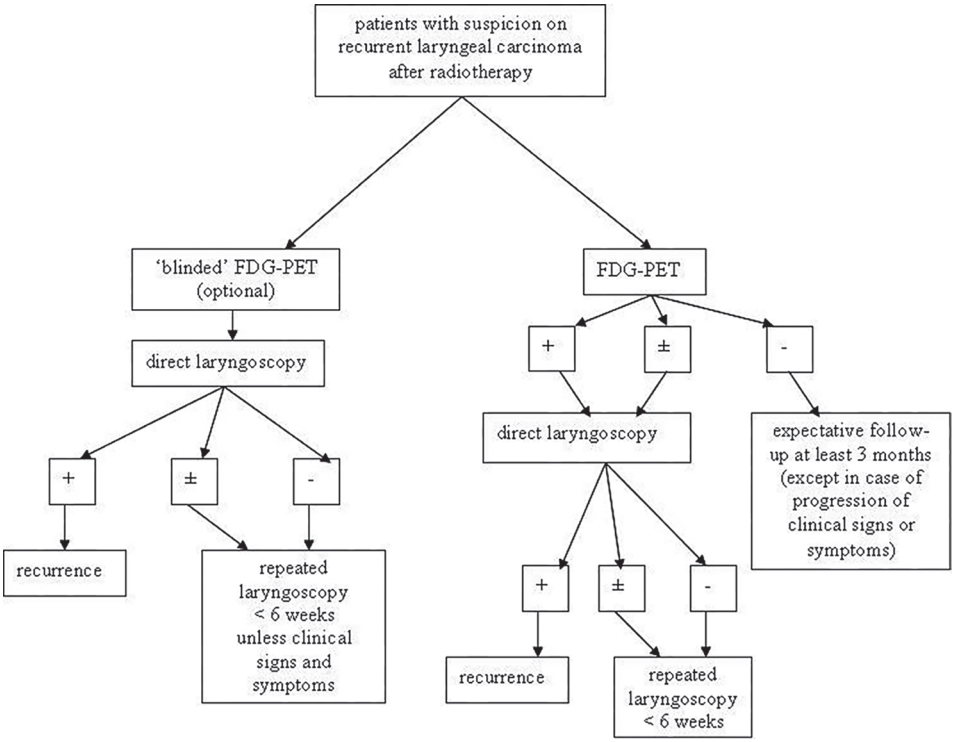

Fig. 1. The design of the RELAPS study.

PET procedures

PET scans are performed in the local head and neck centers. For the purpose of this study, PET centers have to guarantee to perform the scan within 2 weeks. Prior to scanning, the patients need to fast for 6 h. The 20 min head and neck acquisition starts about 1 h after injection of 370 MBq FDG, with a scanned trajectory from skull base to clavicle. PET images are made with "state of the art techniques" according to local protocols. The data supplied by the physician contains only the stage, (sub)site and side of the laryngeal carcinoma of initial presentation. The scoring of laryngeal lesions is visually related to the neck background activity, using a three-point scale: negative (no abnormal activity more than background), equivocal and positive (enhanced tracer uptake in the larynx not compatible with physiological uptake). This interpretation is communicated to the referring physician by telephone and confirmed in writing.

Conventional strategy arm: all patients will undergo direct laryngoscopy. Per center it is optional to make a 'blinded' FDG–PET of each patient. Before the start of the study, each center has to decide to perform a FDG–PET in each patient or not. This FDG–PET will not be examined until the end of the study. If a biopsy shows recurrent tumor the patients will be scheduled for a total (or partial) laryngectomy. If the direct laryngoscopy is negative or equivocal a direct laryngoscopy will be repeated unless clinical symptoms or signs diminish over time. The reason for abandoning the second direct laryngoscopy has to be specified in the case report form.

FDG–PET based strategy arm: all patients undergo FDG–PET. When the result is positive or equivocal, a direct laryngoscopy under general anesthesia will be performed. If the biopsy shows recurrent tumor, the patient will be scheduled for a total (or partial) laryngectomy. In case of a negative or equivocal direct laryngoscopy, the direct laryngoscopy will be repeated without exception. If the FDG–PET is negative, expectative follow-up (no additional investigations) has to be maintained for at least 3 months. In case of a progression of clinical symptoms or signs within the first 3 months, a direct laryngoscopy is indicated.

Follow-up

Patients will visit the outpatient clinic on a regular basis (4–8 weeks). Follow-up of at least 6 months after inclusion is mandatory. Because repeated negative biopsies do not exclude the presence of a recurrent tumor, a combination of pathological examination and 6 months follow-up will be used as 'gold standard'.

Outcome parameters

The primary efficacy endpoint is the difference in the number of futile *indications* for direct laryngoscopy under general anesthesia between the conventional diagnostic arm and the FDG–PET based diagnostic arm. An indication for laryngoscopy is classified as futile if this laryngoscopy was negative and no recurrence was diagnosed within 6 months follow-up. An indication is considered justified if a recurrence is diagnosed at laryngoscopy (procedure result true positive) but also if the recurrence is diagnosed within 6 months after a negative procedure (laryngoscopy result false negative).

To answer the question whether a FDG–PET based strategy can be more cost-effective and safe, secondary endpoints include costs, operability of a recurrence, surgical margins of the salvage laryngectomy and quality of life.

Safety

The FDG–PET-based strategy may increase the risk of missing recurrent tumor compared to current practice. The protocol calls for early referral for direct laryngoscopy in case of progression of clinical symptoms, which will minimize the delay of a diagnosis.

Safety endpoints include survival and morbidity due to laryngoscopy with taking of biopsies. Two, three and fiveyear survival rates of both groups will have to be collected outside the time frame of the trial. Resectability of recurrent tumor and tumor negative surgical margins after total laryngectomy will be used as proxy endpoints. We will consider the FDG–PET based strategy to be equivalent in safety when the outcome of these parameters are better, equal, or no more than 5% worse, compared to the conventional strategy.

Quality of life

Quality of life will be measured by questionnaires (EORTC QLQ-C30, QLQ-H&N35 and EQL-5D). The timing is: 1) before the direct laryngoscopy, 2) at the first visit in the outpatient clinic after direct laryngoscopy or FDG-PET, and 3) 6 months after randomization. The results will be compared between both arms (6–8).

Sample size calculation

Before the trial was designed, a pilot FDG–PET study was performed in which a percentage of futile indications for direct laryngoscopy of 38% was found [4, manuscript in preparation]. In the largest prospective accuracy study FDG–PET would have reduced the number of futile indications by two-third (66%). With this reduction (from 38% to 13%) as our aim, sample size calculation on Fisher's Exact test with a two-sided significance level of 0.05 and a power of 85%, reveals a requirement of 59 patients per group. However, considering the nature of the experimental technique in terms of burden to patients or physicians a larger number of patients has to be accrued in the trial. Moreover, the data used for above mentioned power analysis are based on a limited number of reported patients. The trial is therefore open for an accrual period of 28 months, with a minimum of 150 patients.

Data-analysis

The number of futile indications for surgical procedures in both groups,will be simply expressed as a binomial value and can be tested using a Chi-square test (or non-parametric alternative). In secondary analyses, logistic regression will allow the inclusion of certain potentially confounding variables into the analyses, such as age of the patient, clinical stage at initial presentation, but also number of recurrent tumors and the percentage recurrences suitable for 'salvage' total laryngectomy at the end of the study. Test characteristics (sensitivity, specificity, positive and negative predictive values) of the two selection strategies will be compared. As laryngoscopy itself is not a perfect test, the presence or absence of recurrent disease will be determined in the whole of the 6-month follow-up. Thus, as indicated previously the selection strategy for laryngoscopy is considered true positive if a direct laryngoscopy is indicated and a recurrence is diagnosed within 6 months, even if the initial direct laryngoscopy was negative. In this case the indication was justified. The selection strategy is considered to be false positive if a direct laryngoscopy is indicated and no recurrence is diagnosed within 6 months. In this case the indication was futile. The selection strategy is considered to be true negative when a laryngoscopy is not indicated, not performed and no recurrence is diagnosed within 6 months. In this case the lack of indication is justified. Finally, the selection strategy is considered to be false negative when a laryngoscopy is not indicated (and not performed) but a recurrence is diagnosed within 6 months. In this case, the lack of indication is false (Table 1). Because of the expected low risk of PET imaging and the relative short accrual time, no interim statistical analysis is planned.

Table 1. Comparison of strategy outcome with gold standard.

		Recurrence within 6 months	
		Yes	No
Strategy: indication for laryngoscopy	Yes	True positive: laryngoscopy justified	False positive: laryngoscopy futile
	No	False negative: lack of indication false	True negative: lack of indication justified

Economic evaluation

The average total costs per patient will be determined for a period of 6 months or until local recurrence is diagnosed; from the moment of suspicion of recurrent laryngeal carcinoma after radiotherapy until the 6 months follow-up, local recurrence or death, whichever occurs first. Since salvage treatment is far more costly than the diagnostic procedures, the period after diagnosis of recurrence will not be included in this analysis. The study will focus on direct medical costs and record the following cost types: hospital days, daycare treatments, outpatient visits, medical procedures, diagnostic tests (including FDG–PET), surgical interventions (including laryngoscopy), radiotherapy, blood products and medications. The volumes of the mentioned cost items will be extracted from hospital databases and patient files. For the most relevant cost items new unit costs will be determined, reflecting real resource use, including a raise for overhead costs [9]. To determine these unit costs, the micro-costing method will be used. This method is based on a detailed inventory and measurement of all resources consumed (10). For items with low costs or a negligible influence (due to low average numbers), Dutch tariffs will be used. Costs of medication will be based on a Dutch pharmacotherapeutic reference (11). If the follow up period is less than 6 months, no discounting will be applied. Total costs, based on resource use multiplied by unit prices, will subsequently be calculated and compared for the diagnostic strategies. If FDG–PET proves to be clinically effective, sensitivity analysis based on accuracy measures provided by this study, together with information from the literature, will be performed.

Logistics

Prior to the study, a test-set of 30 FDG–PET scans will be sent to the participating nuclear medicine physicians in each center. In this way the inter-observer variation can be examined and if necessary the interpretation can be standardized. The presence of recurrent tumor will be scored (scale: negative, equivocal, positive). Medical-Ethics approval will be requested for each center. Before starting the trial a plenary meeting will be organized. During the trial a newsletter with accrual data will be sent every 3 months.

DISCUSSION

The introduction of new health technology requires justification of cost-effectiveness for specific clinical indications. A diagnostic imaging technique is considered ‘effective’ if it not only provides more accurate data than existing modalities, but also improves patient management, and ultimately it should contribute to have a favorable impact on health status at reasonable costs. Randomized clinical trials are extremely rare in the evolution of diagnostic tests. Acceptance of new diagnostic tests seems to be based on published accuracy studies for a certain indication. As a consequence, new and expensive but not optimally effective techniques often diffuse into clinical practice, potentially slowing down innovations in other areas (12). Accuracy studies provide information which is indicative but may be of little relevance to the actual effectiveness of a test (13).

We have documented an unsatisfactory diagnostic process in the follow-up after treatment of laryngeal carcinoma, and propose a trial that examines the potential for FDG–PET in this setting. In a pilot study we showed that PET might substantially reduce the number of futile indications for laryngoscopies. We felt a randomized trial was the only way to overcome the problem of variable and uncontrollable factors in the regular clinical diagnostic workup. In a randomized trial the experimental strategy is used in real clinical practice instead of a model, in which the application and decision making of an experimental strategy may be different.

In the proposed randomized trial eligibility criteria for patients have been kept to a minimum to guarantee fast accrual and generalizability. Patients without diagnostic dilemma are excluded: e.g. patients with clinically evident recurrent disease and patients with T1 tumors. In the latter, recurrence is highly unlikely due to effective radiotherapy. Immediately after radiotherapy FDG–PET may show increased uptake in the irradiated area so that it is less reliable at that stage. It has been shown that from 4 months after radiotherapy FDG–PET was a better predictor for the presence or absence of residual or recurrent carcinoma (14). Since relatively few patients (14–20% (3,5)) present with suspected recurrence within 4 months after completed radiotherapy, we decided to include only patients presenting with suspected recurrence beyond this time interval.

Patients are stratified for center, T-stage (T2 versus T3/4) and smoking, as these factors are likely to affect the rate of laryngoscopies (3).

PET scans are examined by the local specialists to improve applicability of the trial results. To examine the interobserver variation and standardize interpretation a test-set of 30 FDG–PET scans will be sent to the participating nuclear medicine physicians in all centers before the start of the study. A 'blinded' FDG–PET is optional in the conventional arm. These images will not be examined until the end of the study so that its result does not affect decision making in the control arm. At the same time, these data are suited to improve the estimation of test accuracy measures. Centers with ethical concerns in this respect will not use the option of the blinded PET scan in the control arm.

The follow-up period in this study is at least 6 months after FDG–PET; it is expected that recurrent tumor will become manifest in this period (3).

In the proposed study the results of the current 'state of art' techniques are analyzed. Therefore, participating centers are asked to scan with the best PET techniques available. Since in this trial a substantial number of patients will undergo PET/CT, the opportunity will be taken to compare PET alone, CT alone and integrated PET/CT in a homogeneous group of patients. Until now, there is only one report on PET/CT in a very heterogeneous group of patients with laryngeal cancer: different treatment modalities (radiotherapy with or without chemotherapy and surgery with or without radiotherapy) and different indications (locoregional recurrence, distant metastases, staging and response to treatment).

In the study design we expect that the delay due to a false negative FDG–PET result is minimal, because direct laryngoscopy is permitted if signs and symptoms progress. Therefore, we expect that this potential delay does not affect curability and prognosis. However, this has to be

evaluated. Endpoints to determine the safety of the FDG–PET based strategy, as compared to the conventional strategy, include morbidity due to laryngoscopy with taking of biopsies and survival. Compared to the conventional arm, the FDG–PET based selection strategy is considered to be safe when the overall survival of the FDG–PET arm is less than 5% lower than the conventional strategy. Since this follow-up period is too long to fit in the granted study time schedule, we will compare the 2, 3 and 5 year survival rates of both groups beyond the final report of the study.

Because of the limited follow-up time within the grant proxy prognostic indicators, e.g. operability of recurrent tumor and tumor negative surgical margins after total laryngectomy have to be used. It is debatable between which limits the alternative prognostic factors should be considered similar. In a retrospective study of direct laryngoscopies under general anesthesia for suspicion of recurrent laryngeal carcinoma after radiotherapy, 91% of the recurrences were eligible for salvage surgery (3). In the literature this figure ranges from 87–95% (15–18). In a retrospective analysis in our institute the results of 61 salvage total laryngectomies were analyzed. In 5% of the total laryngectomies, at least one of the surgical margins was positive (or close). If only T2–T4 recurrent laryngeal carcinomas were taken into account this figure was 6%. In the literature the incidence of positive margins in a salvage laryngectomy depends on the T stage, ranging from 4% to 20% (15–19). Because of the increasing application of larynx preservation treatments, nowadays more advanced tumor stages are treated with radiotherapy (with or without chemotherapy). In previous studies probably a relatively lower number of advanced stages have been included compared to what will happen in the present protocol. Therefore, the aforementioned figures may be higher in the present protocol. We will determine these endpoints (e.g. operability and surgical margins) as an alternative safety analysis at the end of the proposed study, to check if there is a clinically substantial difference. To make definitive conclusions on safety of the FDG–PET based strategy, we will await the long-term follow-up.

The decrease of quality of life and utility induced by the laryngoscopies and their associated morbidity will be assessed by the EORTC QLQ-C30, the QLQ-H&N35 and the EQL-5D questionnaires (6–8).

In accordance with the study assumption that diagnostic strategies should be equivalent, a cost minimization analysis will be performed to compare the FDG–PET based strategy to the conventional strategy. Savings are expected to come from requiring less laryngoscopies. If the clinical study does show a clinical difference between the strategies, this can be altered in a cost-effectiveness analysis. This will not influence the approach and the data collection of the cost analysis. The clinical study is aimed at investigating the impact of a diagnostic strategy within the hospital. Therefore, analysis will be focused on the hospital's perspective, including only direct medical costs in the hospital.

The Dutch Head and Neck Oncology Cooperative Group has developed guidelines for laryngeal carcinoma in 1999 (20). Currently, there are no guidelines for the use of PET in head and neck cancer. Hopefully, this trial will be helpful in defining cost-effective use and the optimal application of this technique, when the guidelines for laryngeal carcinoma are updated by the Dutch Head and Neck Oncology Cooperative Group.

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CHAPTER 4

Effectiveness of an 18F-FDG-PET based strategy to optimize the diagnostic trajectory of suspected recurrent laryngeal carcinoma after radiotherapy: The RELAPS multicenter randomized trial

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ABSTRACT

Purpose: The purpose of this study is to evaluate the efficacy of 18F-FDG-PET as first-line diagnostic investigation, prior to performing a direct laryngoscopy with biopsy under general anesthesia, in patients suspected of recurrent laryngeal carcinoma after radiotherapy.

Patients and methods: 150 patients suspected of recurrent T2–4 laryngeal carcinoma at least two months after prior (chemo)radiotherapy with curative intent for resectable disease were randomized to direct laryngoscopy (CWU: conventional workup strategy) or to 18F-FDG-PET only followed by direct laryngoscopy if PET was assessed 'positive' or 'equivocal' (PWU: PET based workup strategy), to compare the effectiveness of these strategies. Primary endpoint was the number of indications for direct laryngoscopies classified as unnecessary based on absence of recurrence, both on direct laryngoscopy and on six month follow up. Safety endpoints comprised resectability of recurrent lesions and completeness of surgical margins following salvage laryngectomy.

Results: Intention-to-treat analyses were performed on all randomized patients (CWU: n = 74, PWU: n = 76). Tumor recurrence was similar in both groups: 45 patients (30%; 21 CWU, 24 PWU) within six months. In 53 patients in the CWU arm (72%, 95% CI: 60–81) unnecessary direct laryngoscopies were performed compared to 22 in the PWU arm (29%, 95% CI: 19–40) ($p < 0.0001$). The percentage of salvage laryngectomies (resectability) and positive surgical margins were similar between CWU and PWU (81%, 63% respectively, $p = 0.17$, and 29%, 7%, respectively, $p = 0.20$). The prevalence of the combination of local unresectability and positive margins is in the CWU group 24% and in the PWU group 8%. No difference ($p = 0.32$) in disease specific survival between both groups was found.

Conclusion: In patients with suspected 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.

INTRODUCTION

For most patients with residual or recurrent laryngeal carcinoma who have been treated by chemo) radiation for initially resectable disease, timely detection increases the likelihood of successful surgical salvage. Dysphonia, dyspnoea, or local primary site pain, especially if progressive, can be a sign of recurrent laryngeal carcinoma. However, differentiating tumor and sequelae of radiotherapy is often difficult: in one study only 50% of all patients with severe edema or necrosis had residual or recurrent cancer (1). Current clinical practice mandates direct laryngoscopy with biopsy under general anesthesia – an invasive, expensive procedure with a low yield of recurrence of 53% at a first attempt (2). Depending on T-stage, between two and five direct laryngoscopy procedures are usually required to detect one recurrence within a time period of six months after suspicion was first considered (2). After a first negative direct laryngoscopy, 31% of patients will manifest a proven recurrence within the subsequent six months of observation (2). In addition, biopsy itself exacerbates post-radiotherapy changes, which further reduces the sensitivity of subsequent procedures. Current imaging techniques offer no help: neither CT nor MRI can reliably differentiate cancer from post-irradiation changes in laryngeal carcinoma (3). However, positron emission tomography shows potential to improve the yield and allow for better tissue targeting of direct laryngoscopy and biopsy. In a systematic review, the pooled sensitivity and specificity of 18F-fluorodeoxyglucose positron-emission tomography (18F-FDG-PET) for the detection of recurrent laryngeal carcinoma after radiotherapy were reported as 89% and 74%, respectively, with a mean prevalence rate of recurrence of 50% (3). Experience from the centers of the Dutch Head and Neck Society (NWHHT) reported that the interobserver variability in scoring PET scans from a pilot study was reasonable ($\kappa = 0.55$) (4). A randomized controlled trial was required to determine the utility of 18F-FDG-PET in distinguishing post-treatment changes from cancer and thus decrease unnecessary direct laryngoscopies.

The goal of RELAPS (REcurrent LAryngeal carcinoma after radiotherapy PET Study) was to compare the current conventional (traditional) workup comprising direct laryngoscopy and biopsy to a strategy with PET as a first diagnostic test to select patients for such a workup. The primary outcome measure was the number of 'unnecessary' indications for direct laryngoscopies under general anesthesia, defined as the number of patients with procedures where no local recurrence could be detected by biopsy or during follow-up.

METHODS

Patients

Eligible patients were clinically suspected (at indirect or flexible laryngoscopy or because of patient's complaints) of local residual or recurrent disease at least two months after completed (chemo)radiotherapy with curative intent for a resectable T2–4 laryngeal carcinoma, with a clinical indication for direct laryngoscopy and biopsy under general anesthesia (abbreviated as 'direct laryngoscopy'). Exclusion criteria were age below 18 years, clinically evident recurrence (in which case direct laryngoscopy would only be indicated to confirm recurrence histopathologically and assess its extent; such procedure would be performed regardless of imaging results), and pregnancy. The eligibility criterion of the minimal interval between radiotherapy and randomization was changed after trial commencement from four to two months to investigate the target group in daily clinical practice, because high negative predictive values of PET after eight weeks were reported (5).

The protocol was published (6) and approved by ethics committees as required in The Netherlands and Belgium. All patients provided written informed consent. Seven University and two Community Hospitals recruited patients for the study that was designed in collaboration with the Dutch Head and Neck Society (NWHHT).

Randomization and masking

Patients were enrolled by the treating physician, registered at the Comprehensive Cancer Centre Amsterdam by telephone and then centrally randomized to either the conventional workup comprising direct laryngoscopy and biopsy under general anesthesia (CWU), or to 18F-FDG-PET, with direct laryngoscopy under general anesthesia only in cases with positive or equivocal PET findings (PWU). Allocation was performed by a central office on-site computer combined with allocations kept in a locked, unreadable computer file that investigators can access only after the characteristics of an enrolled participant are entered. A stratified permuted-block procedure randomized patients to the groups on a 1:1 ratio. Strata comprised current smoking (yes/ no), institute of treating physician, and T-stage (T2/T3–4). Neither patients, investigators nor central office personnel were masked to the diagnostic group chosen by the allocation procedure.

Procedures

Patients in the CWU group underwent direct laryngoscopy under general anesthesia, combined with biopsies when indicated during direct laryngoscopy at the discretion of the attending head and neck surgeon. If direct laryngoscopy (with biopsies) was negative or equivocal, this procedure was repeated within six weeks, unless clinical signs and symptoms had decreased or resolved. In the PWU group, patients with a negative PET scan received no further investigations (imaging or direct laryngoscopy) for at least another three months, except in case of progression of clinical signs or symptoms. In both study groups, patients with histopathologically proven recurrence were considered for total (or partial) laryngectomy based on an assessment of resectability. This assessment included MRI or CT of head and neck and chest X-ray, CTchest, ultrasound guided fine-needle aspiration cytology and/or PET(-CT) where indicated.

After an initial negative PET or negative direct laryngoscopy, the head and neck surgeon evaluated the patient every four to eight weeks, for at least a period of 12 months. Outpatient clinic visits, hospital admission, operative procedures, additional imaging and histological recurrence of tumor, the results of any surgical procedure, and death were documented during the follow-up period.

Data were collected by the assistant investigator (LvdP). The principal (RdB) and assistant investigator had access to all data and vouch for the completeness and accuracy of the reported data and analyses. Statistical analyses were performed by a clinical statistician (HvT).

PET(-CT) scans were performed in the local head and neck center, per protocol within two weeks after inclusion of each patient. Patients fasted for 6 h before the scan. A 20 min head and neck acquisition of images was started 1 h after injection of 100–587 MBq 18F-FDG (dose dependent on body weight and scanner) and the scanned trajectory included skull base to clavicle. The data supplied by the physician contained the pre-treatment stage, site and side location of the laryngeal carcinoma, and the date of the cessation of the last dose of radiation treatment. Results were communicated to the referring clinician by phone and confirmed in a written report. Assessment of the PET images was performed visually by the local nuclear medicine physician. The larynx was assessed by degree of abnormal uptake, anatomical confidence and side, and summarized in a three-point scale: negative, equivocal, or positive regarding local tumor status. The PET report also included information on lymph node involvement and distant metastases in the field of view (extending beyond head and neck area according to local preference).

The primary efficacy parameter was the difference in the number of unnecessary indications for direct laryngoscopies between the CWU and PWU arms after 6 and 12 months of date of clinical suspicion for recurrent cancer (i.e. from randomization). An indication for direct laryngoscopy was classified as unnecessary if no recurrence was diagnosed on direct laryngoscopy nor subsequently within the reference follow-up period of 6 months (primary period) or 12 months (secondary period) from date of clinical suspicion of cancer. Importantly, in the CWU group an indication for direct laryngoscopy was considered justified (necessary) in all cases where recurrence was diagnosed within the reference follow-up period (tumor positive pathology), even if the original direct laryngoscopy found no recurrence (false negative result). To guard against possible adverse effects of PET delaying detection of potentially resectable recurrences safety end points comprised resectability of recurrent lesions (percentage of laryngectomies performed in case of recurrence) and surgical margins of a salvage laryngectomy (percentage of positive margins of laryngectomy specimen).

Statistical analysis

With a reduction (from 38% to 13%) as our aim, a sample size calculation on Fisher's Exact test with a two-sided significance level of 0.05 and a power of 85%, revealed a requirement of 59 evaluable patients per group (6). In the anticipation that 20% of patients would not be evaluable a total of 150 patients were randomized equally to the two study arms. Because of the expected low risk of PET imaging and the relatively short accrual time, no interim statistical analysis was planned. Efficacy analyses were performed according to the intention-to-treat principle, followed by per-protocol-analyses. Logistic regression was performed to account for potentially confounding variables (age,

smoking and clinical stage at presentation before radiotherapy). Proportions were tested using the Chi-square statistic or Fisher's Exact test if considered more appropriate. Continuous variable was compared using *t*-tests or Wilcoxon two-sample rank test in case of non-normal distribution. Time-to-event analysis was performed using the method of Kaplan–Meier. Disease-specific survival was defined as time from randomization to death due to disease (laryngeal cancer) and overall survival included all deaths irrespective of the cause of death. For overall survival the log-rank and cox-proportional hazard analysis were used to compare groups and to calculate hazard ratios and 95% confidence intervals. Disease-specific survival between the groups (at 12 months) was compared in the context of competing risks using Gray's method (7).

RESULTS

Patients

Between February 2005 and February 2009, 150 patients attending eight collaborating centers, members of the Dutch Head and Neck Society, and one Belgian center (seven university and two community/categorical hospitals) were randomly assigned to the CWU (n = 74) or the PWU strategy (n = 76).

Table 1. Baseline characteristics of the patients.

Variable	Conventional strategy CWU (N = 74)	18F-FDG-PET based strategy PWU (N = 76)
Gender – No. (%)		
Male	58 (78%)	60 (79%)
Female	16 (22%)	16 (21%)
Age		
Mean (SD) – year	60 (9)	64 (11)
<65 year – No. (%)	52 (70%)	38 (50%)
≥65 year – No. (%)	22 (30%)	38 (50%)
Primary tumor site – %		
Supraglottic	39 (53%)	43 (57%)
Glottic	34 (46%)	33 (43%)
Subglottic	1 (1%)	
Primary tumor stage – %		
T2	43 (58%)	44 (58%)
T3	27 (37%)	25 (33%)
T4	4 (5%)	7 (9%)
Primary node stage – %		
N0	60 (81%)	61 (80%)
N1	6 (8%)	6 (8%)
N2a		
N2b	2 (3%)	3 (4%)
N2c	6 (8%)	6 (8%)
N3		
Previous treatment – %		
Radiotherapy	70 (95%)	72 (95%)
Chemoradiotherapy	4 (5%)	4 (5%)

The groups were balanced with respect to the baseline characteristics of the patients, except for age (Table 1). Randomization resulted in an equal distribution of symptoms and findings after diagnostic flexible endoscopic laryngoscopy (see Appendix). The median time from completion of radiotherapy to entry into the study was 10 and 7 months for CWU and PWU, respectively. In the PWU group 54 patients underwent PET only and 21 patients PET/CT. Median delay between injection of 18F-FDG and scan was 60 min (range 42–99). All patients were normoglycemic at PET (mean serum glucose: CWU 5.6, PWU 5.8). The median (IQR) time interval between randomization and the first direct laryngoscopy was 18 days (12–24) in CWU patients, vs. 27 days (17–40) in patients with positive or equivocal PET in the PWU group (p = 0.0002), and 84 days (57–134) for PWU patients with progression of clinical signs and symptoms who underwent direct laryngoscopy despite a negative PET (Wilcoxon two-sample test).

Table 2. Follow-up of the patients.

Variable	Conventional strategy CWU (N = 74)	18F-FDG-PET based strategy PWU (N = 76)	p-Value
Direct laryngoscopies per patient – No. 6 months			
0 laryngoscopies	2	20	p = 0.027 (Cochran-Armitage trend test)
1 laryngoscopies	53	39	
2 laryngoscopies	19	14	
3 laryngoscopies	-	1	
4 laryngoscopies	-	1	
5 laryngoscopies	-	-	
Direct laryngoscopies per patient – No. 12 months			
0 laryngoscopies	2	17	p = 0.028 (Cochran-Armitage trend test)
1 laryngoscopies	49	41	
2 laryngoscopies	20	16	
3 laryngoscopies	2	1	
4 laryngoscopies	1	-	
5 laryngoscopies	-	1	
Local disease within 6 months – No. (%)	21 (28)	24 (32)	
Local disease within 12 months – No. (%)	23 (31)	25 (33)	0.95
Total deaths – No. (%)			
Cumulative at 6 months	5 (7)	13 (17)	
Cumulative at 12 months	5 (7)	19 (25)	0.003[a]
Disease specific deaths – No. (%)			
Cumulative at 6 months	3 (4)	8 (11)	
Cumulative at 12 months	3 (4)	9 (12)	0.08[b]
Salvage surgery – No. (%)			
Local disease with salvage within 6 months	17 (81)	15 (63)	
Local disease with salvage within 12 months	18 (78)	16 (64)	0.44

[a] Logrank p-value at 12 months.
[b] Gray's test at 12 months.

The number of tumor recurrences was similar in both groups: 45 patients (30%; 21 CWU, 24 PWU) within six months and 48 (32%; 23 CWU, 25 PWU) within 12 months. Likewise, time from randomization to recurrence was similar (HR = 0.93, p = 0.81). Laryngectomy was performed in 81% (95% CI 57–94) of CWU vs. 63% (95% CI 41–80) of PWU patients with a recurrence (p = 0.17, Table 2). Median time from randomization to laryngectomy with positive resection margins was six (n = 5; range 1–33) and one (n = 1) months for CWU and PWU, respectively. In the CWU group, four patients had no salvage laryngectomy because of: metastases (n = 2) and non-tumor related factors (n = 2). In the PWU group, nine biopsy positive patients did not proceed to laryngectomy because of: unresectable primary tumor (n = 1), metastases (n = 2), non-tumor related factors (n = 6). The prevalence of positive resection margins was not significantly different between the groups (CWU 29% (95% CI 10–56), PWU 7% (95% CI 2–32); p = 0.2). The prevalence of the combination of local unresectability and positive margins is in the CWU group 24% (5 positive margins/ 21 recurrences) and in the PWU group 8% (1 local unresectable + 1 positive margins/24 recurrences).

Primary outcome

Indication for direct laryngoscopy was classified as unnecessary in 53 (72%) CWU compared to 22 (29%) PWU patients (difference 43%, 95% CI: 27–58; p < 0.0001). This absolute difference in unnecessary indications for direct laryngoscopies of 43% can be interpreted as 2.3 patients to be evaluated with PET (95% CI: 1.7–3.7) to avoid at least one unnecessary indication for direct laryngoscopy. Direct laryngoscopies were unnecessary after PET in 19/54 (35%, 95% CI: 23–49) and after PET/CT in 3/21 (14%, 95% CI: 3–36, p = 0.13) PWU patients.

Adjustment for potential confounders (stratification factors and age) did not essentially change this difference. Current smoking was associated with an increased probability for an unnecessary direct laryngoscopy (p = 0.02, Logistic regression). Seven patients died within six month follow-up without overt recurrence. In all per-protocol analyses (excluding three patients) the difference in unnecessary direct laryngoscopies between CWU and PWU remained significant. In none of the prespecified subgroup analysis a difference in number of unnecessary indications for direct laryngoscopies was found between PET and PET/CT.

Thirty PET findings were true negative and one was false negative. The latter concerned a PET/CT with negative PET but positive (diagnostic) CT, followed by a direct laryngoscopy within one month; however, the patient refused total laryngectomy. In the PWU arm, in 22/44 patients (50%; 95% CI: 36–64) direct laryngoscopies did not yield a tumor-positive biopsy (difference with CWU 21%; 95% CI: 1–41; p = 0.03), this group comprised 12 positive and 10 equivocal PET scans.

Between 6 month and 12 month follow-up, three local recurrences were identified (two CWU, one PWU). In all three patients the (first) direct laryngoscopy after randomization had shown no evidence of recurrent disease.

The flow chart of the included patients is presented in Fig. 1.

With 12 months as the reference follow-up period, indication for direct laryngoscopy was classified as unnecessary in 69% (95% CI 57–79) of CWU, compared to 28% (18–39) of PWU patients (p <

0.0001). Stratified analyses and per protocol analyses were highly similar to the six-month results. At 12 months after randomization, the total number of tumor-negative biopsies taken during direct laryngoscopy was 81 in the CWU arm vs. 58 in the PWU arm (p = 0.04).

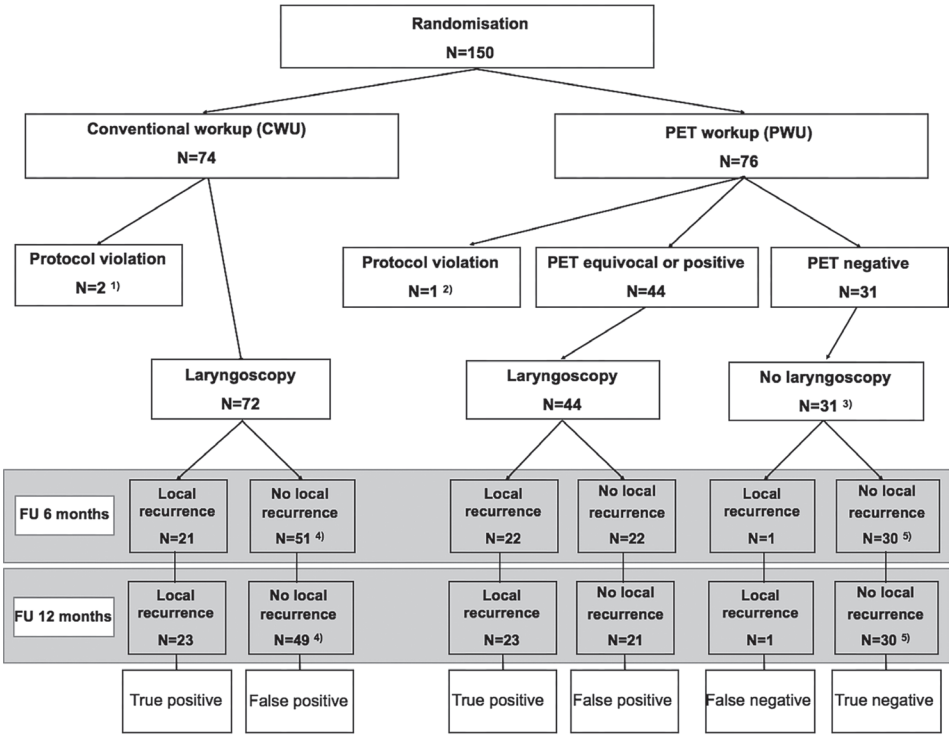

Fig. 1. Flow chart of included patients, based on six-month follow-up. (1) two patients: no laryngoscopy, (2) one patient: no PET, local tumor, (3) one patient: although PET was negative, laryngoscopy was performed, (4) two patients: follow-up <6 months, (5) three patients: follow-up <6 months.

Follow-up

The mean number of outpatient clinic visits in the first year was similar: 6 CWU vs. 5 PWU independent of the PET results in the latter arm. In the first six months of follow-up five CWU patients died: due to progressive disease (n = 3: 2 local and 1 locoregional disease); cardiovascular disease (n = 1); and chest dyspnea without evidence of recurrence (n = 1). In the same period 13 PWU patients died; due to progressive disease (n = 8: 3 local, 1 regional disease and 4 distant metastases), cardiovascular disease (n = 3), infection (n = 1), and primary lung cancer (n = 1). In three of four patients with distant metastases these had already been identified by PET. In the next six months another six patients died, all in the PWU group, due to progressive disease (n = 1: distant metastases after laryngectomy), cardiovascular disease (n = 1), primary pulmonary carcinoma (n = 2), car accident (n = 1), and pulmonary edema without evidence of cancer (n = 1). No difference (p = 0.32) in disease specific survival between both groups was found. Disease specific and overall survival Kaplan–Meier curves for the first 36 months are shown in Figs. 2 and 3.

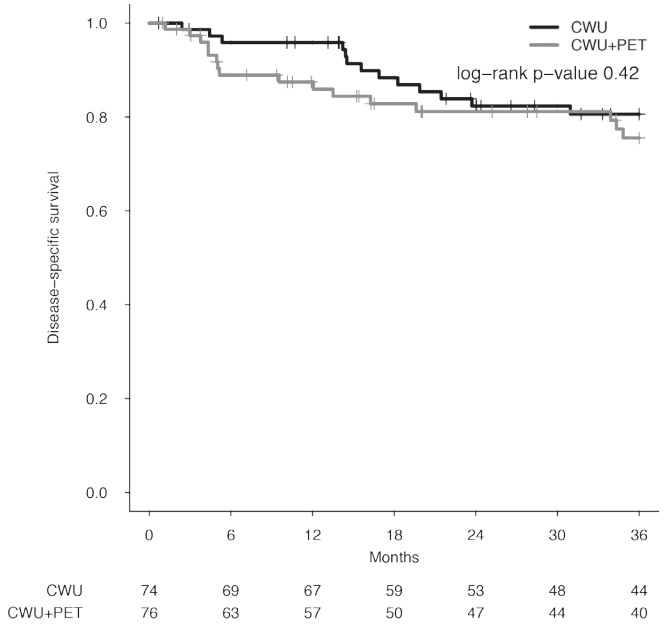

Fig. 2. Disease specific survival for CWU and PWU arms.

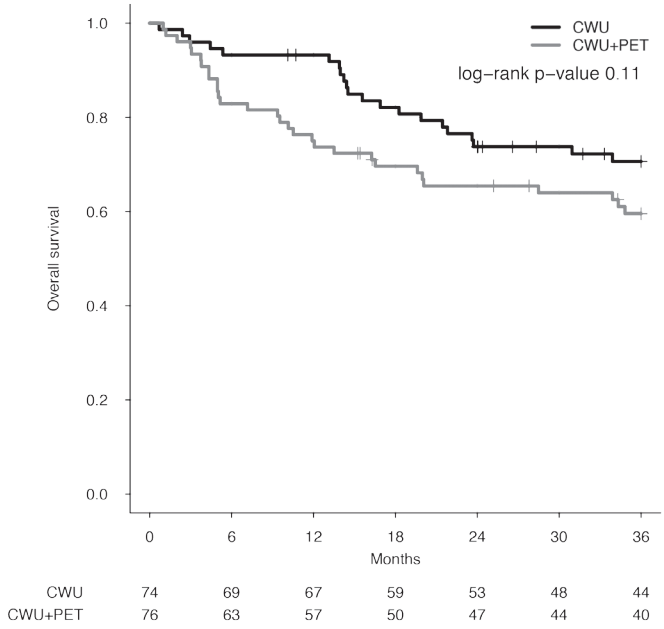

Fig. 3. Overall survival for CWU and PWU arms.

DISCUSSION

This trial demonstrates that a diagnostic strategy including 18F-FDG PET can effectively exclude disease recurrence in patients treated for laryngeal carcinoma, strongly and safely reducing the need for invasive procedures such as direct laryngoscopy.

Without the need for hospitalization and anesthesia, and lacking bothersome side effects, PET is clearly a more acceptable procedure for these patients than direct laryngoscopy. A reduction in unnecessary procedures also increases efficiency of expert personnel and saves resources. PET also allows entire body scanning in the same setting, enabling the detection of regional and distant metastases (8–10).

A prerequisite to forego a diagnostic technique (in this case direct laryngoscopy) is diagnostic safety. Preferably detection of recurrent disease should not be delayed, and any delay should not worsen prognosis. This trial documented such safety of the 18F-FDG-PET based strategy: results of the operability of a recurrence and surgical margins of the salvage laryngectomy in the PWU group were comparable with the CWU group. The decision to perform a salvage laryngectomy depends on several factors: unresectability but also comorbidity, patient's wish (refusal) and metastases. The main reason to consider a local recurrent laryngeal cancer unresectable is that positive margins are expected. Since adjuvant options after previous radiotherapy are very limited, patients with such a recurrence will not undergo salvage laryngectomy. Therefore, it is better (with more power) to combine patients with local unresectable recurrence and positive margins and compare this number in both groups as a proxy for safety. The PWU group did not worse than the CWU group. Also, time to laryngectomy with positive resection margins was not increased in the PWU group as compared to the CWU group. The disparity in number of deaths within 12 months seems to be coincidental and not due to undetected disease. This is confirmed by the similar disease specific survival between both groups after follow-up of 36 months.

Only one 18F-FDG-PET scan was false negative. False negative results are most frequently ascribed to size (<10 mm) (11). In this specific case it concerned a PET/CT scan, and because the CT scan was positive the negative PET was inconsequential: a direct laryngoscopy was performed without delay. In our proposed PET based strategy (without CT), this recurrence would have been missed and a laryngectomy would have been postponed unnecessarily. This case is remarkable because combination of PET and CT in an integrated PET/CT scanner in some series particularly reduces the false-positive rather than the false-negative observations, thereby improving specificity (8,12,13). 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. Gupta et al. found in a meta-regression analysis no significant difference between post-treatment stand-alone PET and integrated PET/CT (14).

Strengths of this study include the randomized design and the follow up. Also, the study was embedded in the routine clinical practice in a wide range of participating hospitals, including both university and community settings, which increases its generalizability. A diagnostic imaging technique is considered 'effective' if it not only provides more accurate data than existing

modalities, but also improves patient management, and ultimately it should contribute to have a favorable impact on health status at reasonable costs. In this study we provide not only indicative data as in an accuracy study but also information on the actual effectiveness of PET.

Although PET is able to decrease the number of direct laryngoscopies substantially, still 50% of patients selected for direct laryngoscopy underwent this procedure unnecessarily, leaving room for further improvement.

In conclusion: This trial shows that in patients suspected of recurrent or persistent laryngeal cancer only those with positive or equivocal PET findings should undergo a confirmatory direct laryngoscopy. This strategy seems to be safe and will reduce the number of unnecessary invasive procedures by more than 50%.

Appendix. Table Symptoms & Flexible endoscopie & Normoglycemia for CWU and PWU arms.

Randomized pts (ITD)		**CWU N= 74**	**CWU+PET N= 76**	**Total N= 150**	**P-value**
Pain	Total	42 (56.8%)	42 (55.3%)	84 (56.0%)	
Referred otalgia	Total	26 (35.1%)	35 (46.1%)	61 (40.7%)	Chi P= 0.1735
Stridor	Total	18 (24.3%)	19 (25.0%)	37 (24.7%)	
Voice detoriation	Total	52 (70.3%)	54 (71.1%)	106 (70.7%)	
Swallowing complaints	Total	31 (41.9%)	40 (52.6%)	71 (47.3%)	Chi P= 0.1878
Weight loss	Total	21 (28.4%)	23 (30.3%)	44 (29.3%)	
Other	Total	11 (14.9%)	19 (25.0%)	30 (20.0%)	Chi P= 0.1208
Flexible endoscopie	probably benign	10 (14%)	5 (7%)	15 (10%)	
	equivocal	40 (54%)	45 (59%)	85 (57%)	
	probably malign	16 (22%)	18 (24%)	34 (23%)	
	invalid	6 (8%)	7 (9%)	13 (9%)	
	missing	2 (3%)	1 (1%)	3 (2%)	
Serum glucose glucotouch	Mean (range)	5.6 (4.7-8.1)	5.8 (3.6-9.9)	5.8 (3.6-9.9)	Krusk. P=0.81974
	N	16	53	69	
Serum Glucose lab	Mean (range)	5.7 (4.5-9.9)	5.9 (3.5-9.6)	5.8 (3.5-9.9)	Krusk. P=0.20702
	N	17	33	50	

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CHAPTER 5

Assessment of an (18)F-FDG-PET based diagnostic strategy to quantify medical costs of suspected recurrent laryngeal cancer after radiotherapy: The RELAPS multicenter randomized trial

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ABSTRACT

Purpose: To quantify medical costs of an ^{18}F-Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG PET) based diagnostic strategy in patients with suspected recurrent laryngeal cancer with prior definitive (chemo-)radiotherapy.

Methods: REcurrent LAryngeal carcinoma PET Study (RELAPS), a prospective multicenter randomized controlled trial, recruited 150 patients from eight collaborating centers, members of the Dutch Head and Neck Society, and one Belgian center. Diagnostic algorithms comprised conventional work-up (CWU), direct laryngoscopy with biopsy under general anesthesia, and ^{18}F-FDG PET followed by laryngoscopy, only for positive or equivocal findings. Standard reference comprised histopathology and clinical follow-up at 6- and 12-months, respectively. Health outcomes were diagnostic performance and percentage of unnecessary procedures. Dutch healthcare perspective was used to obtain input parameters from hospital databases, patient records, literature and publicly available sources.

Results: Indication for direct laryngoscopy was classified unnecessary in 49 CWU patients [68%, 95%CI: 56-79] compared to 21 PWU patients [28%, 95%CI: 18-40, p<0.0001]. The absolute difference was 40%. PWU had a sensitivity of 96% [95%CI, 78-100], specificity of 59% [95%CI, 44-72], a PPV of 52% [95%CI, 37-68] and a NPV of 97% [95%CI, 83-100]. At 12-months, total mean medical costs per patient for PWU and CWU were €12,670 and €13,776, respectively. An incremental cost advantage of €1,105 was achieved in favor of PWU (at 6-months; €482). Sensitivity analysis showed that the most influential parameters were hospitalization, operations and the cost of PET.

Conclusions: The PWU-based diagnostic work-up is favorable from clinical and economic perspectives in patients with suspected recurrent laryngeal cancer after radiotherapy.

INTRODUCTION

Laryngeal cancer is the most frequently diagnosed squamous cell carcinoma of the head and neck. Early stage laryngeal carcinomas are often treated with radiotherapy. In the past three decades, treatment paradigm for patients with advanced stage laryngeal carcinoma has shifted from surgery to radiotherapy with or without chemotherapy, and salvage in reserve for eventual residual or recurrent disease (1,2). Clinically, differentiation between recurrent disease and effects after radiation is often difficult. Conventionally, direct laryngoscopy with biopsy under general anesthesia has been the preferred method for detecting recurrent disease. However, biopsy may exacerbate post-radiation changes (such as edema, radionecrosis and fibrosis) and initiate infection (2-4). Approximately, 50% of patients with severe edema or necrosis after radiotherapy are shown to have recurrence (4). Precise selection based on noninvasive techniques is essential to reduce the number of unnecessary direct laryngoscopy practices. Imaging modalities that rely solely on morphologic criteria, such as computed tomography (CT) or (conventional) magnetic resonance imaging (MRI), have limited accuracy. Whilst, ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography (PET) with or without CT has shown to have a promising role in the diagnosis of recurrent laryngeal cancer (5-8).

REcurrent LAryngeal carcinoma PET Study (RELAPS), a prospective multicenter randomized controlled trial, was conducted from 2005 until 2009 to assess the implementation of ^{18}F-FDG PET in the diagnostic work-up of patients suspected of recurrent laryngeal carcinoma treated with radiotherapy (3,9). The RELAPS trial, designed in collaboration with the Dutch Head and Neck Society, compared conventional work-up (CWU), direct laryngoscopy with biopsy under general anesthesia, with the ^{18}F-FDG PET work-up (PWU), direct laryngoscopy only for positive or equivocal PET findings.

The assessment of expensive medical technologies is increasingly important to inform stakeholder and future investment decisions. The aim of our study was to quantify the potential health benefits and cost consequences of introducing ^{18}F-FDG PET as a non-invasive selection tool (for direct laryngoscopy) in the diagnostic work-up of patients with suspected recurrent laryngeal cancer after radiotherapy.

MATERIALS AND METHODS

Patients

Eligible to participate were patients of ≥18 years, with suspected residual or recurrent local disease after (chemo-) radiotherapy with curative intent, for stage T2-T4 laryngeal cancer. 150 patients were randomly assigned from eight collaborating centers of the Dutch Head and Neck Society, and one Belgian hospital (seven university and two community/categorical hospitals). Stratification of patients was performed based on the treating institute, tumor stage and smoking status. Table I depicts baseline characteristics of the patients included in the study. Exclusion criteria were <2 months interval between radiotherapy and suspicion of recurrence, pregnancy, lactation and clinically evident recurrence. The independent ethics committees, in the Netherlands and Belgium, approved the study protocol. All patients provided written informed consent. Further details of the clinical study are presented elsewhere (9).

Diagnostic Algorithms

In the PET work-up (PWU), patients underwent ^{18}F-FDG PET scans within two weeks following inclusion. Patients fasted six hours before each scan. Head and neck acquisition started one hour after injection of 370MBq ^{18}F-FDG. Focally enhanced PET uptake other than physiological uptake was interpreted as recurrent laryngeal cancer. The larynx was assessed for degree of abnormal uptake, anatomical confidence, site and side, which resulted in a three-point scale: negative (no recurrence), equivocal or positive (local recurrence) (9). In the event of a positive or equivocal finding, direct laryngoscopy under general anesthesia with or without biopsy was performed. If the biopsy indicated recurrent disease, the patient was scheduled for laryngectomy. A negative ^{18}F-FDG PET scan was followed by a minimum period of three months without additional investigation, unless clinical signs and symptoms progressed. Results were compared with the true lesion status obtained by histopathology or at 6- and 12-months clinical follow-up, respectively. As in all clinical studies concerned with diagnostic techniques: true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) outcomes were assessed. In the conventional work-up (CWU), if the biopsy showed recurrent disease, the patient was scheduled for laryngectomy. If there was no recurrent disease (negative biopsy), the patient was evaluated every 4-8 weeks (depending on the local preference) for the duration of clinical follow-up.

Outpatient clinic visits, hospital admissions, operative procedures, additional imaging, histological recurrence of tumor, the results of any surgical procedure and death were documented during the follow-up period. The primary endpoint was the number of unnecessary direct laryngoscopy with or without biopsy, which was defined as tumor-negative laryngoscopy, as well as 6- and 12-months absence of local recurrence (9). Sensitivity, specificity, positive and negative predictive values were reported.

Table 1. Patient and disease characteristics of the RELAPS randomized trial (Intention-To-Treat).

Patient and Disease Characteristics		
Parameter	**CWU (n=74)**	**^{18}F-FDG PET (n=76)**
Age (%)		
Median (range)	60 (40-81)	64 (39-90)
<65yr	52 (70%)	38 (50%)
≥65yr	22 (30%)	38 (50%)
Sex (%)		
Female	16 (22%)	16 (21%)
Male	58 (78%)	60 (79%)
Primary Tumor Site (%)		
Supraglottic	39 (53%)	43 (57%)
Glottic	34 (46%)	33 (43%)
Subglottic	1 (1%)	-
Primary Tumor Stage (%)		
T2	43 (58%)	44 (58%)
T3	27 (37%)	25 (33%)
T4	4 (5%)	7 (9%)
Primary Node Stage (%)		
N0	60 (81%)	61(80%)
N1	6 (8%)	6 (8%)
N2a	-	-
N2b	2 (3%)	3 (4%)
N2c	6 (8%)	6 (8%)
N3	-	-
Prior Treatment (%)		
Radiotherapy	70 (95%)	72 (95%)
Chemo-radiotherapy	4 (5%)	4 (5%)

Abbreviations: CWU: conventional strategy; PWU: ^{18}F-FDG PET-based strategy

Cost analysis

The RELAPS trial database was reviewed by two investigators (RZ, SG) to collect detailed information for the cost analysis. The reported period of 6- and 12-months after randomization were analyzed. The components of care were quantified by three distinct categories: initial diagnosis, subsequent assessment-treatment and follow-up. Total medical costs attributable to each cost component were calculated. Costs of hospitalization (inpatient care episode) were calculated as the per diem prices multiplied by the length of stay (10). Outpatient costs were assigned based on visits to hospital. A list of major unit prices and their sources is presented in supplementary table 1. All medical costs, hospital days, daycare treatment, outpatient visits, medical procedures, diagnostic

tests, surgical interventions and (re-) irradiation were expressed in 2014 Euros. Where necessary, costs were adjusted to 2014 values using consumer price index (11). Costs were presented with mean, median, standard deviation, standard error and 95% confidence intervals. The analysis was conducted from the Dutch healthcare perspective (12).

Sensitivity Analysis

The impact of various input parameters was examined by one-way sensitivity analysis. The ranges for sensitivity, specificity and recurrence were based on 95% confidence intervals (CI). All cost items, including the input value of PET were varied ±50%.

Statistical Analysis

Mean medical costs per patient were calculated. Standard error and 95%CI of the mean were calculated by non-parametric bootstrap analysis based on 1000 samples. For continuous variables, comparisons between groups were performed using the Mann-Whitney U test. A p-value <0.05 was considered statistically significant. (SPSS Statistics Version 22.0. Armonk, New York: IBM Corp., USA).

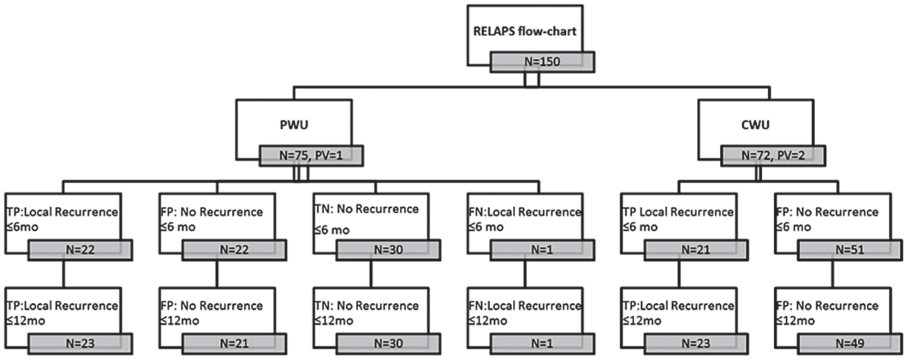

Fig. 1. Schematic representation of patient randomization (per protocol).
Abbreviations: PWU: Positron Emission Tomography Work-Up; PV: Protocol Violation; N: Number of Patients; CWU: Conventional Work-Up; TP: True Positive; FP: False Positive, TN: True Negative; FN: False Negative

Supplementary Table 1. Unit Costs (2014 Euros).

Unit Costs (2014 Euros)		
	Value	**Source**
Diagnostics		
PET[1] scan whole-body	€ 1,163	Dutch Healthcare Authority
PET scan partial	€ 856	Dutch Healthcare Authority
Laryngoscopy with biopsy	€ 531	VU University Medical Center
Operations/Treatment		
Laryngectomy/Pharyngectomy	€ 4,361	VU University Medical Center
Hemithyroidectomy	€ 1,676	VU University Medical Center
Total Strumectomy	€ 3,846	VU University Medical Center
Neck Dissection (MR) [2]	€ 5,134	VU University Medical Center
Neck Dissection (S)[3]	€ 1,998	VU University Medical Center
Reconstruction (FRFF)[4]	€ 2,313	VU University Medical Center
Reconstruction (PMMF)[5]	€ 6,230	VU University Medical Center
Reirradiation	€ 3,794	VU University Medical Center
Hospital-related/Other		
Inpatient Day	€ 632	Dutch Healthcare Institute
Intensive Care Day	€ 2,400	Dutch Healthcare Institute
Outpatient Visit	€ 142	Dutch Healthcare Institute
Daycare Treatment	€ 276	Dutch Healthcare Institute
Consultation by telephone	€ 15	Dutch Healthcare Institute
Other Imaging		
X-Thorax	€ 56	Dutch Healthcare Authority
CT[6]	€ 217	Dutch Healthcare Authority
MRI[7]	€ 278	Dutch Healthcare Authority
US[8]	€ 86	Dutch Healthcare Authority

All values are reported in 2014 Euros. Decimal digits were rounded to the nearest whole number.

[1]Positron Emission Tomography

[2]Modified Radial

[3]Selective

[4]Free Radial Forearm Flap

[5]Pectoralis Major Myocutaneous Flap

[6]Computed Tomography

[7]Magnetic Resonance Imaging

[8] Ultrasound

Supplementary Table 2. ^{18}F-FDG PET diagnostic performance results (12 months & 6 months).

^{18}F-FDG PET 12 months	Value	95% CI
Sensitivity	95.83%	78.88% to 99.89%
Specificity	58.82%	44.17% to 72.42%
Positive Likelihood Ratio	2.33	1.66 to 3.26
Negative Likelihood Ratio	0.07	0.01 to 0.49
Disease Prevalence	32.00%	21.69% to 43.78%
Positive Predictive Value	52.27%	36.69% to 67.54%
Negative Predictive Value	96.77%	83.30% to 99.92%
^{18}F-FDG PET 6 months	**Value**	**95% CI**
Sensitivity	95.65%	78.05% to 99.89%
Specificity	57.69%	43.20% to 71.27%
Positive Likelihood Ratio	2.26	1.63 to 3.14
Negative Likelihood Ratio	0.08	0.01 to 0.52
Disease Prevalence	30.67%	20.53% to 42.38%
Positive Predictive Value	50.00%	34.56% to 65.44%
Negative Predictive Value	96.77%	83.30% to 99.92%

RESULTS

Clinical outcomes

Based on the RELAPS trial protocol (CWU N=72, PWU N=75), at 6 months follow-up, indication for direct laryngoscopy was classified unnecessary in 51 CWU patients [71%, 95%CI: 59-81] compared to 22 PWU patients [29%, 95%CI: 19-41, p<0.0001]. The absolute difference between two groups was 42%. PWU group had a sensitivity of 96% [95%CI, 78-100], specificity of 58% [95%CI, 43-71], a positive predictive value (PPV) of 50% [95%CI, 35-65] and a negative predictive value (NPV) of 97% [95%CI, 83-100]. At 12 months follow-up, indication for direct laryngoscopy was classified unnecessary in 49 CWU patients [68%, 95%CI: 56-79] compared to 21 PWU patients [28%, 95%CI: 18-40, p<0.0001]. The absolute difference between two groups at 12 months was 40%. PWU group had a sensitivity of 96% [95%CI, 78-100], specificity of 59% [95%CI, 44-72], a PPV of 52% [95%CI, 37-68] and a NPV of 97% [95%CI, 83-100]. Supplementary table II depicts diagnostic performance results of the ^{18}F-FDG PET in the study. Overall, one patient had a negative ^{18}F-FDG PET scan but proven recurrence (FN). TN findings (n=30) changed the patient management profoundly by reducing the number of unnecessary operations and procedures. The number of tumor recurrences was similar in both groups: 45 patients [30%; 21 CWU, 24 PWU] at 6 months and 48 patients [32%; 23 CWU, 25 PWU] at 12 months.

However, when equivocal results were considered negative (no recurrent disease), the sensitivity, specificity, PPV and NPV (at 12 months) were 92%, 78%, 67% and 95%, respectively.

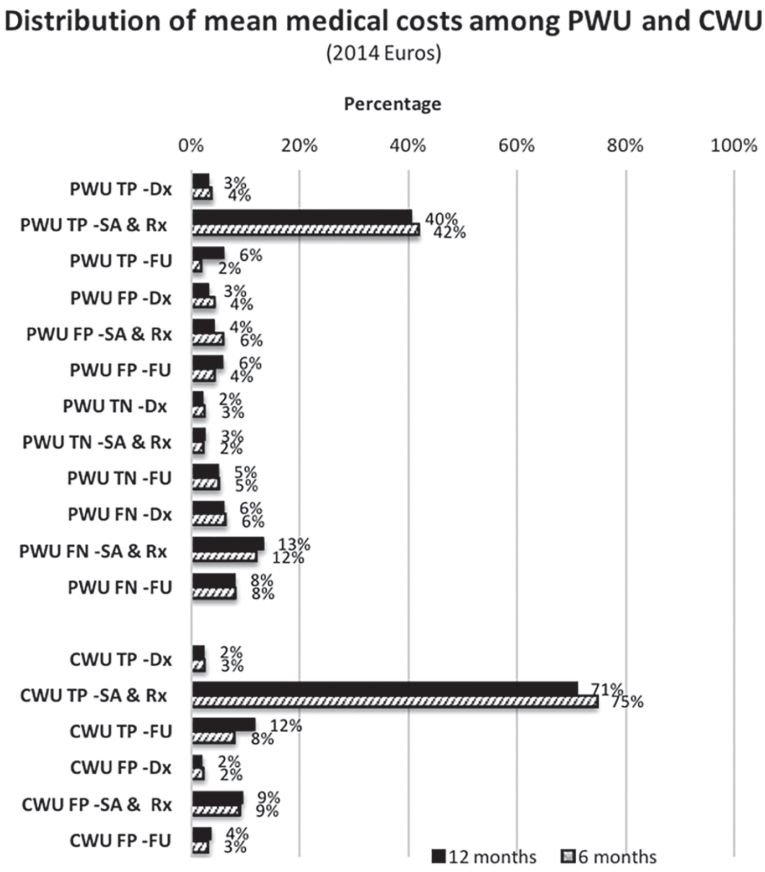

Fig. 2. Distribution of total (mean) medical costs among PWU and CWU patients.
Abbreviations: PWU: Positron Emission Tomography Work-Up; CWU: Conventional Work-Up; TP: True Positive; FP: False Positive, TN: True Negative; FN: False Negative; Dx: Initial Diagnosis; SA & Rx: Subsequent Assessment & Treatment; FU: Follow-up

Health economic outcomes

Total mean medical costs per patient at 6 months follow-up were €11,302 and €11,784 for PWU and CWU, respectively. At 12 months follow-up, total mean medical costs per patient for PWU and CWU amounted to €12,670 and €13,776, respectively. Table II depicts mean medical costs at 12-month follow-up with standard error and 95%CI based on 1000 bootstrap samples. Supplementary table III depicts mean medical costs at 6-month clinical follow-up. The incremental cost difference resulted in an overall cost advantage of (in favor of PWU) €482 and €1,105, for 6- and 12-months follow-up, respectively. The most influential parameters were hospitalization, operations and the cost of PET. In order to fully assess the value of a medical technology and provide recommendations for stakeholders, the effectiveness measure of two interventions would ideally include patient reported preferences; namely quality-of-life (QoL). In our study, the primary health outcome measure was the number of unnecessary indications for direct laryngoscopy in the

PWU compared to the CWU. Although QoL scores were collected at three time points during the trial (randomization, three-weeks and six-months), no significant differences were observed within and between groups. Hence, QoL as a health measure may not be sensitive (enough) to capture differences per groups (and subgroups) of laryngeal cancer patients in this setting (unpublished data). However, the mean QoL score at baseline (at randomization), for laryngeal cancer patients with clinical suspicion of recurrence after radiotherapy was 0.696 (unpublished data). This baseline QoL score may serve as a reference for future evaluations of cost-utility analysis in this context.

Sensitivity analyses

The following parameters were varied in one-way sensitivity analyses: 95% CI for sensitivity, specificity, recurrence and ±50% for cost parameters (operations, hospitalization, PET imaging). The results of the sensitivity analyses are presented in table III. In the RELAPS randomized trial, recurrence was 32% [95%CI, 22-44]. The probability of recurrence analyzed in our study was plausible, when previous studies were considered (13). The results of the sensitivity analysis suggest that the higher the probability of clinically evident recurrence, the lower the (cost-effective) value of introducing ^{18}F-FDG PET in this setting. In our study, the weighted average value of PET was € 954. This weighted average was calculated by multiplying the proportion of whole-body PET scans (32%) and partial PET scans (68%) with their corresponding cost proxies obtained from the Dutch Healthcare Authority (14).

Moreover, we assessed equivocal findings of the RELAPS trial based on three scenarios (at 12-months). In the first scenario, all ^{18}F-FDG PET equivocal findings were considered negative (no recurrent disease). In this case, the absolute difference of unnecessary operations and procedures avoided between PWU and CWU increased to 52%. In the second scenario, PET equivocal findings were considered positive (local recurrence) and all deceased patients at the end of the follow-up period were assumed to have had recurrent disease. In this second case, the absolute difference of unnecessary operations and procedures avoided between PWU and CWU was 40%. Lastly, in the third scenario, ^{18}F-FDG PET equivocal findings were considered positive (local recurrence) but all deceased patients at the end of the follow-up period were assumed to have died from other causes. In this scenario, the absolute difference of unnecessary procedures avoided between PWU and CWU decreased to 23%. In all of the examined scenarios, PWU was the favorable strategy compared to CWU.

Table 2 (a). ^{18}F-FDG PET work-up Mean Medical Costs (2014 Euros, 12 months).

Mean Medical Costs (12 months) 2014 Euros					
^{18}F-FDG PET work-up					
PET True Positive (12 months) N=23		Mean Medical Costs	Bootstrap SE	95% Confidence Interval Lower	Upper
Initial Diagnosis	Mean	€ 1,711.30	€ 93.11	€ 1,555.92	€ 1,928.67
	SD	€ 449.44	€ 164.49	€ 190.90	€ 709.63
Subsequent Assessment & Treatment	Mean	€ 22,041.09	€ 3,865.69	€ 14,622.50	€ 30,044.80
	SD	€ 18,530.13	€ 3,423.46	€ 11,300.97	€ 24,318.27
Follow-up	Mean	€ 3,276.96	€ 978.68	€ 1,498.95	€ 5,257.41
	SD	€ 4,902.59	€ 1,305.46	€ 1,832.12	€ 6,925.50
Total Costs	Mean	**€ 27,029.43**	**€ 4,091.72**	**€ 19,266.10**	**€ 35,356.45**
	SD	**€ 19,881.10**	**€ 3,393.67**	**€ 12,709.08**	**€ 25,893.29**
PET False Positive (12 months) N=21		Mean Medical Costs	Bootstrap SE	95% Confidence Interval Lower	Upper
Initial Diagnosis	Mean	€ 1,731.52	€ 66.48	€ 1,594.43	€ 1,855.16
	SD	€ 310.39	€ 46.14	€ 213.52	€ 387.12
Subsequent Assessment & Treatment	Mean	€ 2,319.00	€ 399.59	€ 1,534.05	€ 3,102.76
	SD	€ 1,867.17	€ 304.51	€ 1,144.98	€ 2,352.13
Follow-up	Mean	€ 3,218.19	€ 1,352.58	€ 1,045.68	€ 6,174.94
	SD	€ 6,468.59	€ 2,334.57	€ 1,265.21	€ 9,662.01
Total Costs	Mean	**€ 7,268.90**	**€ 1,415.96**	**€ 4,960.70**	**€ 10,473.43**
	SD	**€ 6,730.13**	**€ 2,296.26**	**€ 2,192.88**	**€ 10,065.57**
PET True Negative (12 months) N=30		Medical Costs	Bootstrap SE	95% Confidence Interval Lower	Upper
Initial Diagnosis	Mean	€ 1,221.07	€ 65.14	€ 1,097.24	€ 1,347.73
	SD	€ 357.15	€ 48.09	€ 257.33	€ 439.34
Subsequent Assessment & Treatment	Mean	€ 1,413.77	€ 453.12	€ 596.48	€ 2,387.59
	SD	€ 2,571.11	€ 686.89	€ 1,174.76	€ 3,667.81
Follow-up	Mean	€ 2,731.80	€ 1,440.77	€ 617.29	€ 5,902.26
	SD	€ 7,989.27	€ 3,316.13	€ 352.43	€ 12,705.30
Total Costs	Mean	**€ 5,366.73**	**€ 1,827.82**	**€ 2,489.07**	**€ 9,320.27**
	SD	**€ 10,184.09**	**€ 3,970.61**	**€ 1,389.02**	**€ 16,214.43**
PET False Negative (6mo) N=1		Medical Costs			
Initial Diagnosis		€ 3,287.10			
Subsequent Assessment & Treatment		€ 7,237.56			
Follow-up		€ 4,421.91			
Total Costs		**€ 14,946.57**			

Table 2 (b). Conventional work-up Mean Medical Costs (2014 Euros, 12 months).

Mean Medical Costs (12 months) 2014 Euros Conventional work-up					
CWU True Positive (12 months) N=23		Mean Medical Costs	Bootstrap SE	95% Confidence Interval	
				Lower	Upper
Initial Diagnosis	Mean	€ 877.30	€ 84.14	€ 715.70	€ 1,038.91
	SD	€ 411.58	€ 45.93	€ 304.14	€ 479.15
Subsequent Assessment & Treatment	Mean	€ 26,144.83	€ 3,080.67	€ 20,602.63	€ 32,319.14
	SD	€ 14,891.37	€ 1,877.74	€ 10,606.57	€ 18,147.91
Follow-up	Mean	€ 4,319.17	€ 1,127.28	€ 2,373.43	€ 6,929.31
	SD	€ 5,609.83	€ 1,451.97	€ 2,510.00	€ 7,876.47
Total Costs	Mean	**€ 31,341.30**	**€ 3,554.53**	**€ 25,091.42**	**€ 38,719.69**
	SD	**€ 17,227.77**	**€ 2,472.18**	**€ 11,866.26**	**€ 21,258.29**
CWU False Positive (12 months) N=49		Mean Medical Costs	Bootstrap SE	95% Confidence Interval	
				Lower	Upper
Initial Diagnosis	Mean	€ 747.73	€ 49.26	€ 650.48	€ 845.27
	SD	€ 358.15	€ 57.29	€ 251.59	€ 473.73
Subsequent Assessment & Treatment	Mean	€ 3,464.98	€ 802.46	€ 2,139.36	€ 5,258.74
	SD	€ 5,754.57	€ 1,842.63	€ 1,523.49	€ 8,649.28
Follow-up	Mean	€ 1,317.57	€ 294.05	€ 824.69	€ 1,973.85
	SD	€ 2,074.57	€ 629.90	€ 865.45	€ 3,166.97
Total Costs	Mean	**€ 5,530.35**	**€ 1,074.13**	**€ 3,724.95**	**€ 7,929.64**
	SD	**€ 7,631.92**	**€ 2,329.62**	**€ 2,410.84**	**€ 11,407.36**

Table 3 (a). One-way sensitivity analysis (per protocol, PWU N=75, CWU N=72) (12 months).

SENSITIVITY	Total PWU/patient	Total CWU/patient	Δ (PWU-CWU)
(95% CI) 78%	€ 12,026	€ 13,775	-€ 1,749
96%	**€ 12,670**	**€ 13,775**	**-€ 1,105**
(95% CI) 100%	€ 12,831	€ 13,775	-€ 944

SPECIFICITY	Total PWU/patient	Total CWU/patient	Δ (PWU-CWU)
(95% CI) 44%	€ 12,873	€ 13,775	-€ 902
59%	**€ 12,670**	**€ 13,775**	**-€ 1,105**
(95%CI) 72%	€ 12,442	€ 13,775	-€ 1,333

RECURRENCE	Total PWU/patient	Total CWU/patient	Δ (PWU-CWU)
(95%CI) 22%	€ 10,725	€ 13,775	-€ 3,051
32%	**€ 12,670**	**€ 13,775**	**-€ 1,105**
(95%CI) 44%	€ 15,168	€ 13,775	€ 1,393

Table 3 (b). One-way sensitivity analysis: Influential Cost Drivers (per protocol) (12 months).

PET	Costs PWU (per patient)	Costs CWU (per patient)	Δ (PWU-CWU)
(+)50%	€ 13,147	€ 13,775	-€ 628
(-)50%	€ 12,193	€ 13,775	-€ 1.582
Operations	**Costs PWU (per patient)**	**Costs CWU (per patient)**	**Δ (PWU-CWU)**
(+)50%	€ 13,261	€ 14,628	-€ 1,367
(-)50%	€ 12,080	€ 12,923	-€ 843
Hospitalization	**Costs PWU (per patient)**	**Costs CWU (per patient)**	**Δ (PWU-CWU)**
(+)50%	€ 17,118	€ 18,741	-€ 1,623
(-)50%	€ 8,223	€ 8,810	-€ 587

DISCUSSION

In the treatment paradigm of laryngeal cancer, randomized control trials that investigate the potential clinical and economic benefits of expensive diagnostic technologies are scarce. REcurrent LAryngeal carcinoma PET Study (RELAPS), was conducted to assess the application of ^{18}F-FDG PET in the diagnostic work-up of patients suspected of recurrent laryngeal carcinoma previously treated with radiotherapy. A diagnostic imaging technique is considered effective; if it provides more accurate data than existing modalities, improves patient management and contributes to better impact on health at a reasonable cost. Our study shows that ^{18}F-FDG PET diagnostic work-up can successfully tailor laryngeal cancer patients with suspected recurrence to necessary procedures. Our results also show that total mean medical costs were lower in the PWU compared to CWU due to an overall reduction of unnecessary procedures, mainly hospitalization. The robustness of our results were confirmed by sensitivity analyses.

Previous studies have reported the health economic impact of introducing ^{18}F-FDG PET in laryngeal cancer patients suspected of recurrence (15,16). These studies indicated that ^{18}F-FDG PET was a cost-effective tool in selecting patients for direct laryngoscopy with biopsy under general anesthesia. However, these studies were limited in scope due to limited sample size and retrospective design. By means of a larger sample size and a prospective study design, the RELAPS randomized trial corroborates the existing evidence that ^{18}F-FDG-PET is potentially cost-effective in detecting recurrent laryngeal carcinoma after radiotherapy.

In our study, the diagnostic performance of ^{18}F-FDG-PET was in accordance with published literature in this context (5,6,17). In the RELAPS randomized trial only one patient was identified as false negative (FN) at the end of the follow-up period. FN finding was defined as an incorrectly categorized patient with no local recurrence, while recurrent disease was present. This patient had a negative PET scan and a positive CT scan and underwent direct laryngoscopy with biopsy within the first month of evaluation.

Supplementary Table 3 (a). ^{18}F-FDG PET work-up Mean Medical Costs (2014 Euros, 6 months).

Mean Medical Costs (6 months) 2014 Euros					
^{18}F-FDG PET work-up					
PET True Positive (6months) N=22		Mean Medical Costs	Bootstrap SE	95% Confidence Interval	
				Lower	Upper
Initial Diagnosis	Mean	€ 1,828.23	€ 67.94	€ 1,694.87	€ 1,961.04
	SD	€ 323.01	€ 37.78	€ 238.51	€ 379.66
Subsequent Assessment & Treatment	Mean	€ 19,638.32	€ 3,192.37	€ 13,783.04	€ 26,248.40
	SD	€ 15,555.65	€ 2,533.40	€ 10,736.51	€ 20,259.20
Follow-up	Mean	€ 2,920.91	€ 986.19	€ 1,238.90	€ 5,031.01
	SD	€ 4,683.89	€ 1,202.08	€ 1,885.28	€ 6,410.26
Total Costs	Mean	**€ 24,387.41**	**€ 3,375.51**	**€ 18,094.44**	**€ 31,310.14**
	SD	**€ 16,560.86**	**€ 2,223.57**	**€ 11,915.64**	**€ 20,560.29**
PET False Positive (6months) N=22		Mean Medical Costs	Bootstrap SE	95% Confidence Interval	
				Lower	Upper
Initial Diagnosis	Mean	€ 2,048.09	€ 112.84	€ 1,829.44	€ 2,289.86
	SD	€ 552.82	€ 100.38	€ 328.98	€ 712.94
Subsequent Assessment & Treatment	Mean	€ 2,865.32	€ 920.26	€ 1,453.53	€ 5,011.61
	SD	€ 4,500.28	€ 1,893.84	€ 1,107.41	€ 7,126.69
Follow-up	Mean	€ 2,038.14	€ 766.71	€ 673.46	€ 3,639.37
	SD	€ 3,667.45	€ 1,098.44	€ 1,222.28	€ 5,240.82
Total Costs	Mean	**€ 6,951.50**	**€ 1,313.13**	**€ 4,684.15**	**€ 9,758.03**
	SD	**€ 6,271.25**	**€ 1,912.85**	**€ 2,254.70**	**€ 9,167.57**
PET True Negative (6months) N=30		Mean Medical Costs	Bootstrap SE	95% Confidence Interval	
				Lower	Upper
Initial Diagnosis	Mean	€ 1,252.60	€ 91.83	€ 1,067.01	€ 1,435.88
	SD	€ 515.93	€ 62.79	€ 366.63	€ 614.97
Subsequent Assessment & Treatment	Mean	€ 1,139.57	€ 437.92	€ 420.49	€ 2,130.30
	SD	€ 2,475.27	€ 733.70	€ 995.87	€ 3,616.65
Follow-up	Mean	€ 2,463.23	€ 1,400.75	€ 364.98	€ 5,654.77
	SD	€ 7,970.51	€ 3,270.43	€ 208.34	€ 12,399.48
Total Costs	Mean	**€ 4,855.30**	**€ 1,794.71**	**€ 2,141.53**	**€ 8,912.11**
	SD	**€ 10,221.51**	**€ 3,939.07**	**€ 1,487.48**	**€ 15,957.07**
PET False Negative (6months) N=1		Medical Costs			
Initial Diagnosis		€ 3,039.73			
Subsequent Assessment & Treatment		€ 5,689.56			
Follow-up		€ 3,854.61			
Total Costs		**€ 12,583.89**			

Supplementary Table 3 (b). Conventional work-up Mean Medical Costs (2014 Euros, 6 months).

Mean Medical Costs (6 months) 2014 Euros **Conventional work-up**					
CWU True Positive (6mo) N=21		Mean Medical Costs	Bootstrap SE	95% Confidence Interval	
				Lower	Upper
Initial Diagnosis	Mean	€ 874.67	€ 117.00	€ 672.72	€ 1,115.38
	SD	€ 554.81	€ 137.55	€ 285.78	€ 771.62
Subsequent Assessment & Treatment	Mean	€ 24,936.43	€ 3,307.16	€ 18,526.47	€ 31,757.26
	SD	€ 15,178.59	€ 2,037.49	€ 10,561.64	€ 18,308.74
Follow-up	Mean	€ 2,714.95	€ 854.35	€ 1,162.88	€ 4,546.71
	SD	€ 4,020.92	€ 897.35	€ 1,547.32	€ 5,191.68
Total Costs	Mean	**€ 28,526.05**	**€ 3,451.19**	**€ 22,162.41**	**€ 35,597.83**
	SD	**€ 15,690.98z**	**€ 1,878.44**	**€ 11,428.46**	**€ 18,664.85**
CWU False Positive (6mo) N=51		Mean Medical Costs	Bootstrap SE	95% Confidence Interval	
				Lower	Upper
Initial Diagnosis	Mean	€ 822.18	€ 64.08	€ 698.33	€ 954.35
	SD	€ 456.97	€ 39.12	€ 365.59	€ 524.34
Subsequent Assessment & Treatment	Mean	€ 3,014.35	€ 722.80	€ 1,833.48	€ 4,643.61
	SD	€ 5,370.57	€ 1,742.96	€ 1,358.94	€ 8,093.71
Follow-up	Mean	€ 1,055.02	€ 284.09	€ 584.39	€ 1,702.17
	SD	€ 2,064.91	€ 596.94	€ 886.22	€ 3,070.20
Total Costs	Mean	**€ 4,891.57**	**€ 957.98**	**€ 3,329.90**	**€ 6,981.82**
	SD	**€ 7,081.50**	**€ 2,116.19**	**€ 2,107.98**	**€ 10,500.23**

There are a few aspects of our study that deserve attention. The results of the RELAPS trial indicate that ^{18}F-FDG PET can reliably rule out recurrence in patients with a low pre-test probability of the disease. Overall, this observation may suggest that the higher the probability of recurrence, the lower the value of introducing PET in this setting. Hence, when recurrent tumor is clinically evident, selection for direct laryngoscopy by PET is not recommended.

Acquisition costs and daily use of PET scans are important determinants of unit cost calculations (18). In our analysis, although the input value of PET was obtained as a proxy, it was varied in sensitivity analysis. The results of the sensitivity analysis showed that the conclusions of this study were robust. Furthermore, a recent study in the Netherlands reported that the unit cost of ^{18}F-FDG PET for head and neck cancer patients was € 1,172 per scan. This reported unit price falls within the range of our cost calculations (19).

Pharmacoeconomic guidelines recommend using a time horizon that allows inclusion of all relevant costs and effects (20). Although the longest duration of follow-up was 12-months in our study, consideration of a longer time horizon would not alter the conclusions. A longer time horizon carries the risk of diagnosing second primary tumors (9,21,22). Hence, local recurrence based differences in costs and effects based on correct diagnosis of the primary tumor were the main objectives of our analyses.

Hustinx et al. have shown that post-radiotherapy ^{18}F-FDG PET findings have high negative predictive value (NPV) and are significant prognostic factors that can help in guiding the management of head and neck patients after definitive treatment (23). Although PET imaging may have a role in prognosis, our study did not consider the potential health impact and cost-consequences of improved patient selection on survival.

Finally, one could argue that the diagnostic performance results of ^{18}F-FDG PET versus ^{18}F-FDG PET/CT scans may differ. It has been documented that PET/CT provides better localization of increased tracer uptake and reduces the number of equivocal PET findings in various settings (7,8,24,25). However, a meta-analysis showed that there was no significant difference between diagnostic accuracy of PET versus PET/CT in post-treatment response assessment and surveillance imaging of head and neck cancer patients (17). Similarly, in the subgroup analysis of the RELAPS trial, ^{18}F-FDG PET (35%, 95%CI: 23-49) and ^{18}F-FDG PET/CT (14%, 95%CI: 3-36) results were not significantly different (p=0.13). Although this subgroup was small, our findings were based on the overall diagnostic performance results reported in the clinical trial (9).

CONCLUSION

The ^{18}F-FDG PET based diagnostic work-up is favorable from both clinical and economic perspectives in laryngeal cancer patients with suspected recurrence after radiotherapy.

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CHAPTER 6

Salvage surgery in post-chemoradiation laryngeal and hypopharyngeal carcinoma: outcome and review

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ABSTRACT

Our objective was to evaluate recurrence patterns of hypopharyngeal and laryngeal carcinoma after chemoradiation and options for salvage surgery, with special emphasis on elderly patients. In a retrospective study all patients who underwent chemoradiation for hypopharyngeal and laryngeal carcinoma in a tertiary care academic center from 1990 through 2010 were evaluated. Primary outcome measures were the survival and complication rates of patients undergoing salvage surgery, especially in elderly patients. Secondary outcome measures were the predictors for salvage surgery for patients with locoregional recurrence after failed chemoradiotherapy. A review of the literature was performed. Of the 136 included patients, 60 patients had recurrent locoregional disease, of whom 22 underwent salvage surgery. Fifteen patients underwent a total laryngectomy with neck dissection(s) and 7 neck dissection without primary tumour surgery. Independent predictors for salvage surgery within the group of 60 patients with recurrent disease, were age under the median of 59 years ($p = 0.036$) and larynx *vs.* hypopharynx ($p = 0.002$) in multivariate analyses. The complication rate was 68% (14% major and 54% minor), with fistulas in 23% of the patients. Significantly more wound related complications occurred in patients with current excessive alcohol use ($p = 0.04$). Five-year disease free control rate of 35%, overall survival rate of 27% and disease specific survival rate of 35% were found. For the 38 patients who were not suitable for salvage surgery, median survival was 12 months. Patients in whom the tumour was controlled had a 5-year overall survival of 70%. In patients selected for salvage surgery age was not predictive for complications and survival. In conclusion, at two years follow-up after chemoradiation 40% of the patients were diagnosed with recurrent locoregional disease. One third underwent salvage surgery with 35% 5-year disease specific survival and 14% major complications. Older patients selected for salvage surgery had a similar complication rate and survival as younger patients.

INTRODUCTION

Treatment of advanced stage squamous cell carcinoma of larynx and hypopharynx constitutes a challenging situation. Cisplatin-based chemoradiation is an established treatment for selected moderately advanced laryngeal and hypopharyngeal carcinoma, as it may be organ and function sparing (1-4).

For recurrent disease, salvage laryngectomy or neck dissection may be available as a curative option for selected patients. However, the complication rate of salvage surgery after chemoradiation is relatively high. Wound healing problems are a well-known consequence of surgery in irradiated patients. Fistula rates of 11-58% after salvage laryngectomy are reported (5-11). Due to further locoregional recurrence after salvage laryngectomy, distant metastases, second primaries and other causes, the 5-year overall survival is in the range of 31-57% (12-15). The literature suffers from heterogeneity as to tumour site, previous therapy and salvage therapy.

Herein, we aim to provide insight into the recurrence pattern after chemoradiation for laryngeal and hypopharyngeal carcinoma and the options for salvage surgery. We were specifically interested in the complications after salvage surgery, with focus on age. Moreover, the outcome of patients after salvage surgery is evaluated.

MATERIALS AND METHODS

Patients

Sixty patients with locoregional disease after chemoradiation were identified from a database of 136 patients with laryngeal or hypopharyngeal squamous cell carcinoma treated by chemoradiation with curative intent between January 1990-April 2010. The hospital charts of these patients were retrospectively reviewed. In all patients response to chemoradiation was evaluated within or at 3 months after treatment, unless patients had died during or shortly after the chemoradiation. Resectability prior to treatment was determined by physical examination, imaging and endoscopy. Approval of the Medical Ethics Committee of the VU University Medical Center in Amsterdam was obtained. Patient and treatment characteristics are shown in Table I.

We defined chemoradiation as the combined use of cisplatin based chemotherapy and/or targeted therapy and radiotherapy for the primary treatment. Different schemes are used. Fourteen patients were treated according to an alternating scheme (cisplatin 20 mg/kg and 5-FU 200 mg/kg (i.v.) in week 1, 4, 7 and 10; radiotherapy in week 2, 3, 5, 6, 8 and 9, total dose 60 Gy) and 13 according to a sequential scheme (cisplatin 100 mg/kg and 5-FU 1000 mg/kg i.v., 4 courses; followed by 7 weeks radiotherapy, total dose 70 Gy). Twenty-four patients were treated with concomitant intravenous administration of 3 × 100 mg/m2 cisplatin on day 1, 22 and 43 with simultaneous radiotherapy. Two patients were treated according to the intra-arterial chemoradiation schedule consisting of four consecutive weekly selective intra-arterial infusions of cisplatin (150 mg/m2) followed by intravenous sodium thiosulphate rescue combined with simultaneous radiotherapy. All patients were irradiated daily for 6-7 weeks to a total dose of 70 Gy (2 Gy per fraction, 5-6/week). Two patients were treated according to the concomitant intravenous cisplatin protocol, in combination with cetuximab. Five patients received weekly cetuximab (loading dose 400 mg/m2, followed by weekly 250 mg/m2) with daily radiotherapy for 7 weeks to a total dose of 70 Gy. Both sides of the neck were radiated in all patients, regardless of the lymph node status.

Definitions

Postoperative complications were categorised into surgical complications (fistula, infection, necrosis, haemorrhage and chyle leakage), pneumonia and other complications (e.g. spondylodiscitis). Complications were classified as major if they required re-operation.

Statistics

Statistical analysis was performed with SPSS 15.0. Survival rates were calculated with the Kaplan-Meier method, with follow-up intervals calculated from the date of salvage surgery. Univariate analysis of survival parameters was done using the log-rank test. Univariate analyses of complication patterns were assessed by utilizing the $\chi 2$-test or the independent-samples T-test whenever applicable. Multivariate analysis of survival was performed with Cox regression. A model developed by Tan et al. (16) with stratification factors for survival, was applied to our population.

Table 1. Patient characteristics of 60 patients with locoregional disease after chemoradiation.

Variables	N	Percentage (%)
Gender		
Male	51	85
Female	9	15
T-stage (prior to chemoradiation)		
T2	3	5
T3	30	50
T4	27	45
N-stage (prior to chemoradiation)		
N0	15	25
N1	7	12
N2a	3	5
N2b	13	22
N2c	17	28
N3	5	8
Primary site		
Hypopharynx	35	58
Larynx	25	42
Operability		
Unresectable	4	7
Organ preservation approach	56	93
Chemoradiation schedule		
Cisplatin IA*	2	3
Cisplatin IV*	24	40
Cisplatin/5-FU alternating**	14	24
Cisplatin/5-FU sequential***	13	22
Cetuximab****	5	8
Cetuximab/TPF/Cisplatin or Carboplatin****	2	3

*concurrent four intra-arterial cisplatin (150 mg/m^2) infusions or three intravenous cisplatin (100 mg/m^2) infusions . In both schemes patients were radiatedwith 70 Gy irradiation (6-7 weeks); **cisplatin 20 mg/kg and 5-FU 200mg/kg intravenously in week 1, 4, 7, 10; radiotherapy in week 2, 3, 5, 6, 8, 9, total dose 60 Gy; ***cisplatin 100 mg/kg and 5-FU 1000 mg/kg intravenously, 4 courses; followed by 7 weeks radiotherapy, total dose 70 Gy; **** weekly cetuximab in combination with 7 weeks radiotherapy, total dose 70 Gy; *****2-4 courses of TPF (Docetaxel, Platinum, Fluorouracil), followed by cisplatin or carboplatin with concurrent 70 Gy radiotherapy (7 weeks), in some patients cetuximab was given during this treatment.

RESULTS

After a median follow-up of 25 months (range 0-130 months), 60 patients (44%) had presented with recurrent disease. One-third of the patients with recurrent disease (n = 22) underwent salvage surgery for local, regional or locoregional disease. This is 16% of the total group of patients initially treated by chemoradiation. Twenty-four percent of patients with laryngeal carcinoma *vs.* 10% of patients with hypopharyngeal carcinoma underwent salvage surgery. Two-thirds of patients (n = 38) were not suitable for salvage surgery because of distant metastases (n = 30), poor general condition of the patient (n = 3), refusal of surgery by the patient (n = 1) or unresectability of the tumour (n = 4).

Of the 6 patients with an initial unresectable tumour, 4 patients developed recurrent disease, which was not statistically different from the organ preservation (initial resectable) group. Two patients developed distant metastases and 2 patients were diagnosed with persistent unresectable local disease. Independent predictors for salvage surgery within the group of 60 patients with recurrent disease, were age younger than 59 years (p = 0.036) and larynx *vs.* hypopharynx (p = 0.002) in multivariate analyses. Gender, T and N-stage were not associated with surgery for salvage. The median interval between radiotherapy and recurrence for the 22 patients was 4 months.

The study population consisted of 19 males and 3 females with a median age of 59 years (range: 40-69 years), with primary tumours in larynx (n = 15) and hypopharynx (n = 7) (Table II).

Neck dissection was performed in all patients. In 15 patients the salvage operation consisted of a total laryngectomy with unilateral (n = 2) or bilateral (n = 13) neck dissection. In 7 patients the surgery was limited to a neck dissection because the primary was controlled.

Histopathological examination of total laryngectomy with neck dissection showed negative resection margins in 11 patients (74%), close margins in 2 patients (13%) and microscopic positive margins in 2 patients (13%). Of the patients with neck dissection without laryngectomy 6 had negative resection margins (86%) and 1 microscopic positive margins (14%). No difference in histopathological results between the larynx and hypopharynx was found. Of the two patients with positive margins one was treated with postoperative radiotherapy, but he developed a local recurrence for which he received palliative chemotherapy. One of the patients with close margins developed a recurrence at the stoma and oesophagus, and underwent palliative radiotherapy and chemotherapy.

Reconstruction

The pectoralis major myocutaneous or myofascial pectoralis major (PM) flap was the most often used flap after total laryngectomy with or without pharyngectomy. Primary closure was only possible with smaller defects. With larger defects, when between one-third and three-quarters of the pharyngeal circumference has been resected, reconstruction was performed by utilising a pectoralis major myocutaneous PM flap. A circumferential pharyngeal defect not extending into the chest was free radial forearm flap (FRFF). A myofascial PM flap was also used to reinforce pharyngeal defects (17). The mucosal defect was closed primarily in 9 of the 15 patients (60%),

Table 2. Patient and salve surgery characteristics.

Patient	Gender	Age	T	N	Site	Recurrence	Larynx	ND	Reconstruction	Subsequent reconstruction
1	F	52	4	1	Hypopharynx	Local	Laryngectomy	Bilateral	FRFF+PM	PM
2	M	57	3	2b	Larynx	Regional	-	Unilateral	PC	
3	M	64	4	0	Larynx	Local	Laryngectomy	Unilateral	PM	
4	M	63	4	0	Larynx	Local	Laryngectomy	Bilateral	PM	PM
5	M	62	4	0	Larynx	Local	Laryngectomy	Unilateral	PM	
6	M	59	3	2c	Hypopharynx	Regional	-	Bilateral	PM	
7	M	41	3	0	Hypopharynx	Local	Laryngectomy	Unilateral	PM	
8	M	55	4	2c	Larynx	Local	Laryngectomy	Bilateral	PM	
9	M	67	4	0	Larynx	Local	Laryngectomy	Bilateral	PM	
10	M	57	3	2b	Larynx	Local	Laryngectomy	Bilateral	PM	
11	M	52	4	3	Hypopharynx	Regional	-	Unilateral	PM	
12	M	49	3	2a	Larynx	Regional	-	Unilateral	PC	$
13	M	54	4	2c	Larynx	Locoregional	Laryngectomy	Bilateral	PC	
14	M	58	2	2b	Hypopharynx	Regional	-	Unilateral	PC	
15	M	53	3	2c	Larynx	Local	Laryngectomy	Bilateral	PM	
16	M	55	3	0	Larynx	Local	Laryngectomy	Bilateral	PM	
17	M	61	3	2c	Hypopharynx	Regional	-	Unilateral	PM	
18	F	59	3	0	Larynx	Local	Laryngectomy	Bilateral	PM	
19	M	69	4	0	Larynx	Local	Laryngectomy	Bilateral	PM	
20	F	67	3	1	Larynx	Local	Laryngectomy	Bilateral	PM	
21	M	58	4	3	Hypopharynx	Local	Laryngectomy	Bilateral	PM	
22	M	64	3	2c	Larynx	Regional	-	Unilateral	PM	

$ 1 year after ND : total salvage laryngectomy with FRFF and PM, followed by a second PM for complications.

ND= neck dissection, PC= primary closed, PM= pectoralis major flap, FRFF= free radial forearm flap

reconstructed with a PM flap in 5 patients, and reconstructed with a free radial forearm flap (FRFF) in 1 patient. A PM flap to prevent wound healing problems was used in 9 of the 15 patients with a total laryngectomy and in 4 of the 7 patients with a neck dissection without laryngectomy.

Postoperative complications

No perioperative death occurred. Postoperative complications were observed in 15 (68%) of the 22 patients (Table III). Three patients experienced major complications that required re-operation. This concerned fistula in two patients and a bleeding in one patient that were closed with a (second) PM flap during re-operation. Most of the complications concerned wound healing problems (n = 13; 59%), as fistula (n = 5), wound dehiscence or wound infection (n = 7) or haemorrhage (n = 1). Other complications were pneumonia and spondylodiscitis in 2 patients.

Univariate analysis showed significantly more wound healing problems in patients with excessive alcohol intake (8 of 16 patients (50%) *vs.* none of 5 patients, p = 0.04). Furthermore, none of the following parameters were predictive for the development of postoperative complications: tobacco use or excessive alcohol intake at the time of presentation for the primary tumour, T- or N-stage, site of the primary tumour and age under the median of 59 years. No significant reduction in overall complications, wound related complications or fistula was found in our group of patients with a PM flap after neck dissection compared to patients with a primarily closed neck dissection.

Table 3. Postoperative complications for the total salvage surgery group, the group with an opened pharynx vs. the group with a closed pharynx.

Complications	Total		Pharynx open		Pharynx closed	
	N	%	N	%	N	%
None	7	31%	4	27%	3	43%
Wound healing	13	59%	9	59%	4	57%
- Infection or dehiscence	7	31%	5	32%	2	29%
- Haemorrhage	1	5%	0	0%	1	14%
- Fistula	5	23%	4	27%	1	14%
Pneumonia	1	5%	1	7%	0	0%
Other	1	5%	1	7%	0	0%
Total	22	100%	15	100%	7	100%

Survival

Overall, 5-year disease free control rate was 35%, with 5-year locoregional and distant metastases control rates of 54% and 77%, respectively. Five-year overall survival was 27% (median 30 months) (Fig. 1), and disease specific survival was 35% after salvage surgery. For the 38 patients with residual or recurrent disease after chemoradiation who were not suitable for salvage surgery median survival was 12 months. Patients with tumour control (n = 76) had a 5-year survival of 70% (median 96 months) (Fig. 1). In uni- and multivariate analyses no significant predictors for overall survival after salvage surgery were found. Thus, age under or above the median 60 years was not

a predictor factor for survival. The model of Tan et al. (16) stratified patients with none, one or two of the following

predictors for post salvage overall survival: stage IV (*vs.* other stages) and simultaneous (*vs.* local or regional) failure. When this model was applied to our population, no significant differences between the groups could be found (Fig. 2), although the group with stage IV disease showed a worse overall survival compared to patients with stage II or III disease (Fig. 3).

With a median length of follow-up after salvage surgery of 26 months (range 6-127 months), recurrent disease was found in 12 of the 22 patients (64%). These recurrences included local and/or regional recurrences in 8 patients and distant metastases in 4 patients. Local recurrences, regional recurrences and distant metastasis developed after a median interval of 6.5 months (range 2.5-14.3), 7.5 months (range 4.4-14,3) and 3.7 months (range 0-28.2) after salvage surgery, respectively.

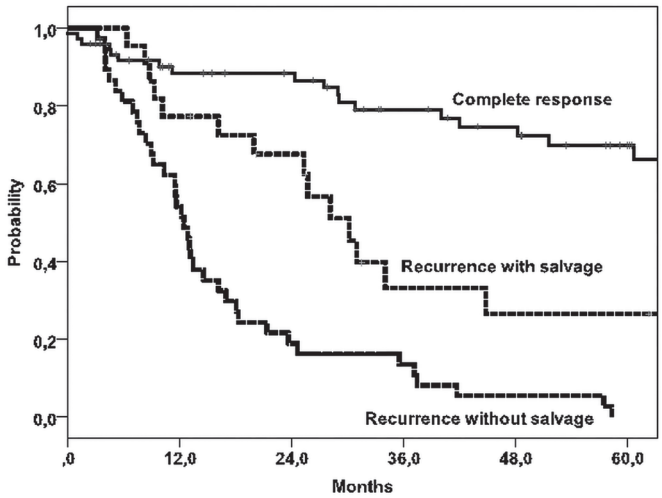

Fig. 1. Five-year survival after the last treatment (chemoradiation or salvage surgery).

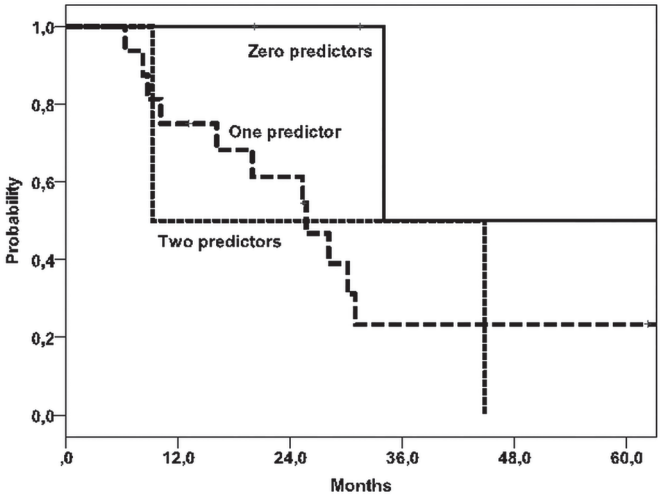

Fig. 2. Survival after salvage surgery with model according to Tan et al. (16). Comparison between patients with zero, one or two of the following presalvage predictors: stage IV versus other stages and simultaneous locoregional versus local or regional failure. No significant difference between the three groups was found.

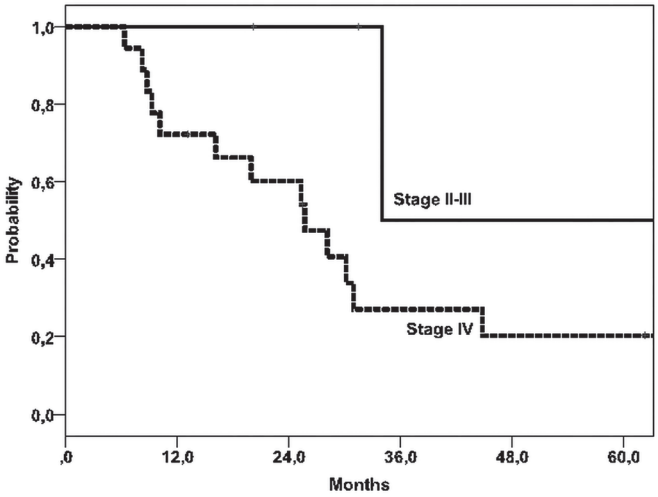

Fig. 3. Survival after salvage surgery with model according to Tan et al. (16). Comparison between patients initial stage IV versus initial non-stage IV disease. A trend (p=0.05) towards a worse survival for patients with initial stage IV disease was found.

DISCUSSION

In this study, 37% of the patients with local and/or regional recurrences after chemoradiation for a laryngeal or hypopharyngeal tumour underwent salvage surgery, which is similar to rates reported by other authors, 33-66% (7,14,16,18). A larger proportion of patients with recurrent laryngeal than hypopharyngeal tumours underwent salvage surgery. This is in accordance with the report by Esteller et al. (18) Independent predictors for salvage surgery within in the group of patients with locoregional failure, were age less than 59 year and larynx primary (*vs.* hypopharynx). Fifteen patients underwent laryngectomy with neck dissection and 7 patients neck dissection only.

The rates of complications after salvage surgery are known to be high, with wound related complications and especially pharyngocutaneous fistula as a major problem. In this study 23% of patients developed a fistula. Review of the literature shows complication rates of 5-78%, with fistula in 4-73% of the patients (Table IV). Studies are difficult to compare, because of lack of homogeneity in patients (tumour site, stage) and in primary treatment (radiotherapy, chemoradiation).

If wound healing problems are likely, pedicled PM flaps are very useful to cover important structures in the neck with well vascularised, non-irradiated tissue. In the present study, in 59% of the patients a PM flap was used for prevention of wound related complications. Unfortunately, no significant reduction in overall complications, wound related complications or fistula was found in our group of patients with a PM flap after neck dissection compared to patients with a primarily closed neck dissection. In our population only patients with considerable postradiation effects who were considered to be prone to wound healing problems underwent reconstruction with PM flap in the neck. Most studies evaluating reconstructive methods are conducted in patients undergoing salvage laryngectomy (Table V). Similar to our results, no difference in the incidence of local wound complications or fistula between the groups with and without PM flap was found by Gil et al. (5) and Righini et al. (19). Although it was an effective technique to prevent major complications, free vascularised tissue reinforcement did not alter the overall fistula rate as compared to when no flap was used, as reported by Fung et al. (20) Smith et al. (21) reported a significant reduction in fistula formation in patients with as compared to patients without PM flap reconstruction, but the percentage of patients with initial chemoradiation *vs.* primary surgery was not described. Sayles et al. (10) performed a review and meta-analysis of 33 studies, and found only 10% fistula for salvage laryngectomy with onlay flap-reinforced closure compared to 28% fistula for salvage laryngectomy when no flap was used. Recently Paleri et al. (22) described in a systematic review of nearly 600 patients a reduced risk of fistula by one-third in patients who have flap reconstruction/reinforcement. Reconstruction of the mucosal defect using a PM flap may be associated with a higher rate of fistulae as compared to primary closure whereas a PM flap used as layer between mucosa and skin may reduce the risk of fistula formation. According to Righini et al. (19), fistula formation in postradiotherapy salvage surgery was reduced from 73% to 13% when a flap was used in the subgroup of patients with diabetes mellitus, a history of vascular disease or a poor nutritional status. Tsoe et al. (8) and Withrow et al. (23) suggest to reconstruct laryngectomy defects with an ALT (anterolateral thigh) or FRFF flap, as the incidence of fistula was low in their study.

Besides hypoalbuminaemia, neck dissection, comorbidities with diabetes mellitus or ischaemic heart disease, Tsoe et al. (8) found that reconstruction of the pharynx with primary closure had a statistically significant increased rate of fistula formation. On the contrary, Shemen et al. (24) and Herranz et al. (25) found an increase in complication rate when flap reconstruction was required. These patients had no history of radiation, and probably had a greater defect when a flap was required. Ganly et al. (26) found no association between wound complications and flap reconstruction or neck dissection. The only significant independent predictor found was chemoradiation. Other suggested potential predictors for increased wound complications and fistula are: postoperative haemoglobin level lower than 12.5 g/dl, albumin level less than 40 g/l, prior tracheotomy, preoperative radio- an/or chemotherapy, concurrent neck dissection, radical neck dissection, poor nutritional status, tobacco and excessive alcohol use, poor renal and hepatic function, radiotherapy doses in excess of 70 Gy, early removal of drains (within 3 days of operation), vacuum drain duration and surgery extended to the pharynx or hypopharynx cancer (11,27-31). We found more wound related complications in patients with current excessive alcohol use. This might be caused by immunosuppression due to ethanol, or alcohol-related lifestyle factors such as certain dietary deficiencies owing to unevenly composed diets (32).

Whether the interval between chemoradiotherapy and salvage surgery influences the risk of fistula formation remains uncertain. Increased incidence of wound complications was reported when the interval was shorter (23,25,33). However, Lavertu et al. (34) and Weber et al. (35) found no significant difference between groups with short and longer interval between chemoradiation and salvage surgery. Inohara et al. (36) found no difference in complication incidence between salvage surgery for persistent or recurrent disease. We also did not find an association between interval and complication rate.

Comparing our results in patients with salvage laryngectomy: a) after previous radiotherapy in a previous study (15); to b) after previous chemoradiotherapy in the present study, shows a worse 5-year prognosis for local disease control (58% *vs.* 70%) and overall survival (27% *vs.* 50%) in the chemoradiotherapy group. The total complication rate is 73% after chemoradiotherapy *vs.* 56% after radiotherapy. The 5-year overall survival of 27% is comparable to other series, with a relatively better survival for patients with recurrent laryngeal carcinoma (compared to hypopharyngeal) or patients with a regional recurrence (Table IV). Even after adjusting for covariates, Goodwin (37) found that a history of chemotherapy was associated with poorer survival after salvage surgery, suggesting a more aggressive tumour biology (38). Because of the low survival and high complication rates, the profit of salvage surgery is sometimes questioned. Salvage surgery is definitely worthwhile

in a subset of patients. Reliable predictors for survival after salvage surgery are needed. Tan et al. (16) suggested a model with stage IV tumours and concurrent local and regional failures as independent negative predictors. Esteller et al. (18) found no significant differences in survival when analysed according to the classification of Tan. We found a worse survival for stage IV initial tumours. Other suggested potential predictors for a worse survival are: residual disease, older age, N3, positive resection margins and neck nodes with extranodal spread (18,38,39).

In this series age was an independent predictor for salvage surgery. Older patients were less frequently candidate for salvage surgery if recurrent tumour was diagnosed. Elderly patients with head and neck cancer generally have multiple and more severe comorbidity (40). Comorbidity is associated with a higher complication rate and poorer survival after major surgery (41-43). Selection of elderly patients based on comorbidity seems to be the explanation for the similar complication rate and survival after salvage surgery. Moreover, patients with severe comorbidity would not have been treated with chemoradiation in the first place and therefore not included in this study.

In conclusion, one third of the patients with local and/or regional disease after chemoradiation underwent salvage surgery. Most of the patients not suitable for salvage surgery had distant metastases. Forty percent of the laryngectomies needed a flap reconstruction to cover mucosal defects. Patients who were at forehand more prone to wound healing failures underwent reconstruction with a PM flap in the neck to prevent wound related complications. One in four patients developed a pharyngocutaneous fistula. Only current excessive alcohol use was associated with complications. No significant independent predictors of survival were identified. The 5-year overall survival rate was 27% after salvage surgery. Older patients with recurrent laryngeal or hypopharyngeal carcinoma after chemoradiation selected for salvage surgery have a similar complication and survival rate compared to younger patients.

Table 4. Previous studies on complications and survival outcome in patients with salvage surgery after chemoradiotherapy for squamous cell carcinoma of the hypopharynx and larynx.

Authors	Year	N	Site	Comp	Fistula	LR y=year	OS y=year	DSS y=year	Remarks
Stoeckli (7)	2000	36	L	28%	14%			63% (5y)	RT and CRT
Stoeckli (7)	2000	9	H	40%	11%			20% (5y)	RT and CRT
Leon (14)	2001	28	L	21%	17%		57% (5y)		Endoresection
Weber (35)	2003	75	L	~59%	~30%	74% (2y)	69-71% (2y)		
Ganly (26)	2005	38	L	53%	32%				
Clark (13)	2006	138	L/H	70% (salvage)	31%		31% (5y) (salvage)		PT: none, RT, CRT
Fung (20)	2007	14	L		29%				Interposition graft. pharyngectomy defects
Furuta (44)	2008	34	L	47% wound	24%				
Gil (5)	2009	18	L		39%				PL/TL, RT and CRT
Patel (6)	2009	17	L		24%				CRT or RT?
Relic (45)	2009	16	L/H		73%		38% (3y)		1 PL
Tsou (8)	2010	48	H		58%				
Paleri *(46)	2011	>350	L			87% (2y)	83% (3y)	91% (2y)	RT and CRT, PL
vd Putten (15)	2011	120	L			70% (5y) 79% (5y) regional	50% (5y)	58% (5y)	RT and CRT, TL
Klozar (47)	2012	208	L/H		34%				RT and CRT
Sewnaik (48)	2012	24	L/H	92%					
Patel (9)	2013	359	L/H		27%				RT and CRT, primLE
Li (12)	2013	100	L			70%(5y)		55-70%(5y)	RT and CRT, survival
Basheeth (49)	2013	45	L/H	44%					Major complications, N0
Suzuki (50)	2013	24	H	33%			50%(2y)		

Sayles *(10)	2014	33 st	L/H		34%				
Timmermans (31)	2014	98	L/H		26%				RT and CRT, primLE
Omura (51)	2014	42	H					40%(3y)	RT and CRT, ICT
Powell (52)	2014	45	L/H		22%				
Suslu (11)	2015	151	L/H		13%				RT and CRT, ICT
Sassler (30)	1995	18	HN	61% major	50%				Sequential CRT
Newman (53)	1997	17	HN	35%	20%				
Lavertu (34)	1998	26	HN	46%	4%				
Goodwin (37)	2000	109	HN	20%	6%			Med 21.5 months	PT: surgery, RT, CRT (17%)
Goodwin * (37)	2000	1633	HN	39%			39% (5y)		PT: surgery, RT, CRT
Agra (54)	2003	124	HN	78% (CRT)					PT: surgery, RT, CRT
Gleich (55)	2004	48	HN			20%(5y)		15% (5y)	Local recurrence
Taussky (56)	2005	17	HN N	76%	24%		46% (3y) 13% (5y)		RT and CRT
Morgan (57)	2007	38	HN	11%	5%				Local compl 23%
Encinas (58)	2007	26	HN	31%					Article not available
Richey (39)	2007	38	HN	24%		42% (2y)	27-60% (1,2y)		
Tan (16)	2010	38	HN	63%			43% (2y) 37% (5y)		
Inohara (36)	2010	30	HN	30%	7%		74-87% (3y)		
Esteller (18)	2011	32	HN	28%	19%		34% (5y)		
Simon (59)	2011	21	HN	33%	10%				
Leon (60)	2015	24	HN	63%			26%(5y)		CRT
				13%			70%(5y)		Bioradiotherapy
Present study		22	HN	73%	23%	58% (5y)	27% (5 y)	36% (5y)	

Authors	Year	N	Site	Comp	Fistula	LR y=year	OS y=year	DSS y=year	Remarks
Davidson (27)	1999	34	N	38%	12%				37% CRT
Stenson (61)	2000	69	N	25%	10%				
Newkirk (62)	2001	33	N						13 CRT,20 RT
Grabenbauer (63)	2003	56	N	25%	4%		44%(5y)	55%	Planned ND
Kutler (64)	2004		N	~30%					Only abstract
Brizel (65)	2004	52	N	8% major		75% (4y)	77%(4y)		Planned ND in N2-3. survival cCR
Frank (66)	2005	39	N	5% surgical					
vd Putten (67)	2007	61	N			79% (5y)	36% (5y)		
Nouraei (68)	2008	41	N			95%(5y)		64%(5y)	Survival hemineck
Vedrine (69)	2008	28	N	14% severe					
Christopoulos (70)	2008	32	N	13%					
Lango (71)	2009	65	N	18%	5%				55%CRT
Relic (45)	2009	12	N	8%					
Hillel (72)	2009	41	N	17%					
Bremke (73)	2009	25	N	24%					
Goguen (28)	2010	105	N	37%					
Robbins (74)	2012	30	N					60%(5y)	SSND, CRT
Yirbesoglu (75)	2013	44	N			71-73% (3y)	55-64% (3y)		

*=systematic review: Comp=complications, LR=locoregional control rate, OS=overall survival, DSS=disease specific survival, L=larynx, H=hypopharynx, HN=head and neck, N=neck, y=year, DFS=disease free survival, CRT=chemoradiotherapy, RT=radiotherapy, CT=chemotherapy, ND=neck dissection, PT=previous treatment, PL=partial laryngectomy, TL=total laryngectomy, primLE= primary laryngectomy, SSND=super selective neck dissection, st=studies, ICT=induction chemotherapy

Table 5. Comparison of pharyngocutaneous fistula in patients with salvage laryngectomy with and without flap reinforcement. In two studies the flap was besides for reinforcement, also used to reconstruct pharyngeal defects (21,23).

Authors	Year	N	Site	Flap	Fistula	WC	Fistula No flap	WC No flap	P	Remarks
Righini (19)	2005	60	larynx	PMMF	23%		50%		0.06	Radiotherapy
			larynx	PMMF	13%		73%		0.018	Subgroup: diabetes mellitus, vascular history, poor nutritional status
Fung (20)	2007	41	larynx	FVT	29%	0%	30%	15%	n.s.	
Patel (6)	2009	17	larynx	PMF	0%		57%		0.02	(Chemo)radiotherapy
Gil (5)	2009	80	larynx	PMMF	27%		24%		n.s.	PMMF 64% CRT, nonPMMF 25% CRT
Smith (21)	2003	223	larynx	PMF	<1%		23%			
Withrow (23)	2007	37	larynx	FRFF	18%		50%			FRFF 41%CRT, nonFRFF 35%CRT
Patel (9)	2013	359	larynx	PMF FVT	15% 25%		34%		0.02 0.07	(Chemo)radiotherapy
Powell (52)	2014	45	larynx	FVT/PMF	0%		26%			
Sayles *(10)	2014	33 studies	larynx	Onlay flap	10%		28%		0.001	(Chemo)radiotherapy
Paleri *(22)	2014	591	larynx							Pooled relative risk 0.63 (reduction one third compared to no flap)

*=systematic review , WC = wound complications, P = p-value, PMMF = pectoralis major myofascial flap, FVT = free vascularized tissue, PMF = pectoralis major flap, FRFF = free radial forearm flap, CRT = chemoradiotherapy

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CHAPTER 7

Salvage laryngectomy: Oncological and functional outcome

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ABSTRACT

The purpose of the research was to evaluate postoperative complications, functional outcome and survival after salvage laryngectomy. Second, to evaluate the management of the neck in combination with a laryngectomy in this group of patients. A retrospective analysis of all patients who underwent total laryngectomy for residual or recurrent squamous cell laryngeal carcinoma after (chemo)radiotherapy between November 1990 and June 2007 was performed. Of the 120 patients that were included, the complication rate was 56% (33% major and 23% minor). In univariate analyses, T-stage ($p = 0.05$), bilateral neck dissection ($p = 0.09$) and ASA score ($p = 0.08$) showed a trend for postoperative major complications. Lymph node metastases were found in 26% of the neck dissection specimens, with a trend towards more regional disease at higher initial N-stage ($p = 0.06$) and T-stage ($p = 0.08$). Five-year disease specific survival was 58%. In univariate analyses pre-operative chemoradiation (vs. radiation) ($p = 0.0001$), N3 neck ($p = 0.001$) and positive surgical margins ($p = 0.02$) were significant predictors for a worse disease specific survival, but only positive surgical margins ($p < 0.001$) maintained significance in multivariate analysis. Eighty-seven percent of the patients were able to produce speech using a voice prosthesis, and 84% of the patients were able to have a 'normal' or 'soft' diet. There was an almost significant increase in mean body mass index (BMI) 6–12 months postoperative ($p = 0.057$). Laryngectomy after radiotherapy offers good survival, with a substantial risk of complications and good functional outcome.

INTRODUCTION

Radiotherapy is the mainstay of treatment for most laryngeal carcinomas except the very early and late stages (1). However, a substantial number of patients will need salvage surgery for residual or recurrent disease after (chemo)radiotherapy (2-9). It is well recognized that surgery after (chemo) radiotherapy carries the risk of complications with sometimes disappointing salvage rates (6,9-20). Total laryngectomy or laryngopharyngectomy remains the standard treatment for salvage after radiotherapy, while partial laryngectomy is reserved for very few selected cases.

Management of the clinically negative neck in this setting remains subject of debate. The rate of occult metastasis at salvage laryngectomy for patients with a clinically negative neck is reported to be 10–14% for glottic and 20–28% for supraglottic tumors (21-23).

The present study aims to review the results in patients who underwent salvage total laryngectomy for residual or recurrent disease after prior (chemo)radiotherapy in a large tertiary referral centre. We evaluated postoperative complications, neck management, survival and functional outcome.

PATIENTS AND METHODS

In 120 patients who were diagnosed with residual or recurrent laryngeal cancer after prior (chemo) radiotherapy, laryngectomy was performed in the period 1990–2007. Patient, tumor and treatment characteristics were recorded for these patients. The median interval between radiotherapy and detection of residual or recurrent tumor was 8.7 months (range 1.7–34 months). Patients with indications other than recurrent or persistent cancer were excluded. Details of the primary tumor were shown in Table 1. The median age at the time of the start of (chemo)radiotherapy was 62 years (range 40–87 years). Most patients (n = 114; 95%) had received radiotherapy as a single treatment modality, whereas 6 patients had received combined chemotherapy and radiotherapy. Radiotherapy was given in a schedule of daily 2 Gy with a total dose of 70 Gy (range 58–74 Gy). Chemotherapy consisted of cisplatin (100 mg/m2), with or without 5-FU (1000 mg/m2). Information about the presentation of the residual or recurrent disease was retrospectively recorded from the patients charts: symptomatic or asymptomatic disease and detection during outpatient consultations.

The ASA (American Society of Anesthesiologists) score was used as parameter of comorbidity (24). Postoperative complications were classified as (a) none, (b) minor, and (c) major. Minor complications were those that needed no or minor interventions. Major complications were those that needed surgery or admission on the intensive care unit or those that led to death. Complications were designated as perioperative if they occurred within the first 30 days postoperative and as late term if they were diagnosed more than 30 days after laryngectomy. Functional outcome included nutritional intake (normal, soft, liquid, oral nutritional supplements and nasogastric tube or gastrostomy), postoperative (change in) BMI and speech. Information was based on information from the clinical notes at the interval 6–12 months postoperatively.

Statistical difference between two independent groups was calculated by the Chi-square test. The Trend test was used where appropriate. Statistical difference between two paired samples was tested with the paired T-test. Survival analyses were performed with the Kaplan–Meier method (log-rank test). Multivariate analysis of survival was performed with Cox regression, multivariate analysis of complications with logistic regression. Statistical analyses were carried out using SPSS 15.0 (SPSS, Chicago, USA).

Table 1. Patient, previous tumor and treatment, and salvage laryngectomy details.

	N	%
N	120	
Sex		
Male	105	88
Female	15	12
Primary site (before radiotherapy)		
Supraglottic	40	33
Glottic	79	66
Subglottic	1	1
T-stage (before radiotherapy)		
T1	24	20
T2	58	48
T3	23	19
T4	15	13
N-stage (before radiotherapy)		
N0	104	87
N1	10	8
N2a	0	0
N2b	3	3
N2c	3	3
N3	0	0
(Chemo)radiotherapy		
Radiotherapy	114	95
Chemoradiotherapy	6	5
Pharyngectomy		
No	0	0
Partial	115	96
Total	5	4
Thyroidectomy		
No	6	5
Hemi	104	87
Total	10	8
Neck dissection		
No	15	12
Unilateral	57	48
Bilateral	48	40
Paratracheal lymph node dissection		
No	44	37
Unilateral	42	35
Bilateral	34	28
Flap reconstruction		
No	101	84
Yes	19	16
Voice prosthesis		
No	13	11
Yes, primary	103	86
Yes, secondary	4	3
Histopathology		
Negative margins	108	90
Positive margins	12	10

RESULTS

In 66% of the patients recurrent disease was symptomatic. Eighty-five percent of tumors were detected at a regular visit. At the time of laryngectomy, 34% of the patients smoked and 28% used more than moderate amount of alcohol (on average > 2 units/day). The median age at laryngectomy was 63 years (range 42–88 years). Patients were classified as ASA II (67%) and ASA III (33%).

Table 1 represents the details of surgery. A voice prosthesis was inserted during laryngectomy in 103 patients (86%), and secondary in another 4 patients (3%) with a median interval of 7.9 months (range 2.3–14.3 months) after laryngectomy. Flaps used during total laryngectomy were pectoralis major (n = 19) and free radial forearm (n = 1). Thirteen patients (11%) received post-operative re-irradiation with a median dose of 60 Gy (range 50–70 Gy).

Of the 67 patients (56%) with post-operative complications, 40 (33%) had major complications. Mortality related to postoperative complications was 3% (3 patients, 1.4–6.5 months after laryngectomy). Most surgical interventions were (secondary) flap reconstructions for wound healing problems and neopharyngeal dilatations. In Table 2 and Fig. 1 the type of complications and the interval after laryngectomy at which they occurred are shown. Fistulas were the most frequently seen complication (n = 36; 30%), appearing mainly within the first 2 weeks after surgery. Airway problems (pneumonia, tracheitis) were seen throughout the follow-up period, whereas swallowing problems were mainly late complications (requiring dilatation). The following other complications occurred: cardiovascular, abdominal (gastric bleeding, ileus), and systemic complications, and femur fracture caused by a fall. Univariate analysis demonstrated that the variables advanced Tstage (p = 0.053), ASA score (p = 0.084) and neck dissection (p = 0.089) showed a trend towards the development of major complications (Table 3). In a multivariate logistic regression model no significant independent predictors of major complications were identified. Complications, major complications or fistulas were not increased after re-irradiation. Moreover, most complications developed before radiotherapy was started.

Table 2. Post-operative complications (more than one complication per patient possible).

Complications	Total-number (N)	Percentage (%)	Early (N)	Late (N)
Pharyngocutaneous fistula	36	30	28	8
Wound dehiscence	8	7	7	1
Wound infect	1	1	1	0
TE-fistula re-operation	6	5	0	6
Haemorrhage	8	7	4	4
Swallowing problems	9	8	0	9
Airway problems	10	8	4	6
Other complications	11	9	5	6
Total	89			

TE-fistula=trachea-esophageal fistula

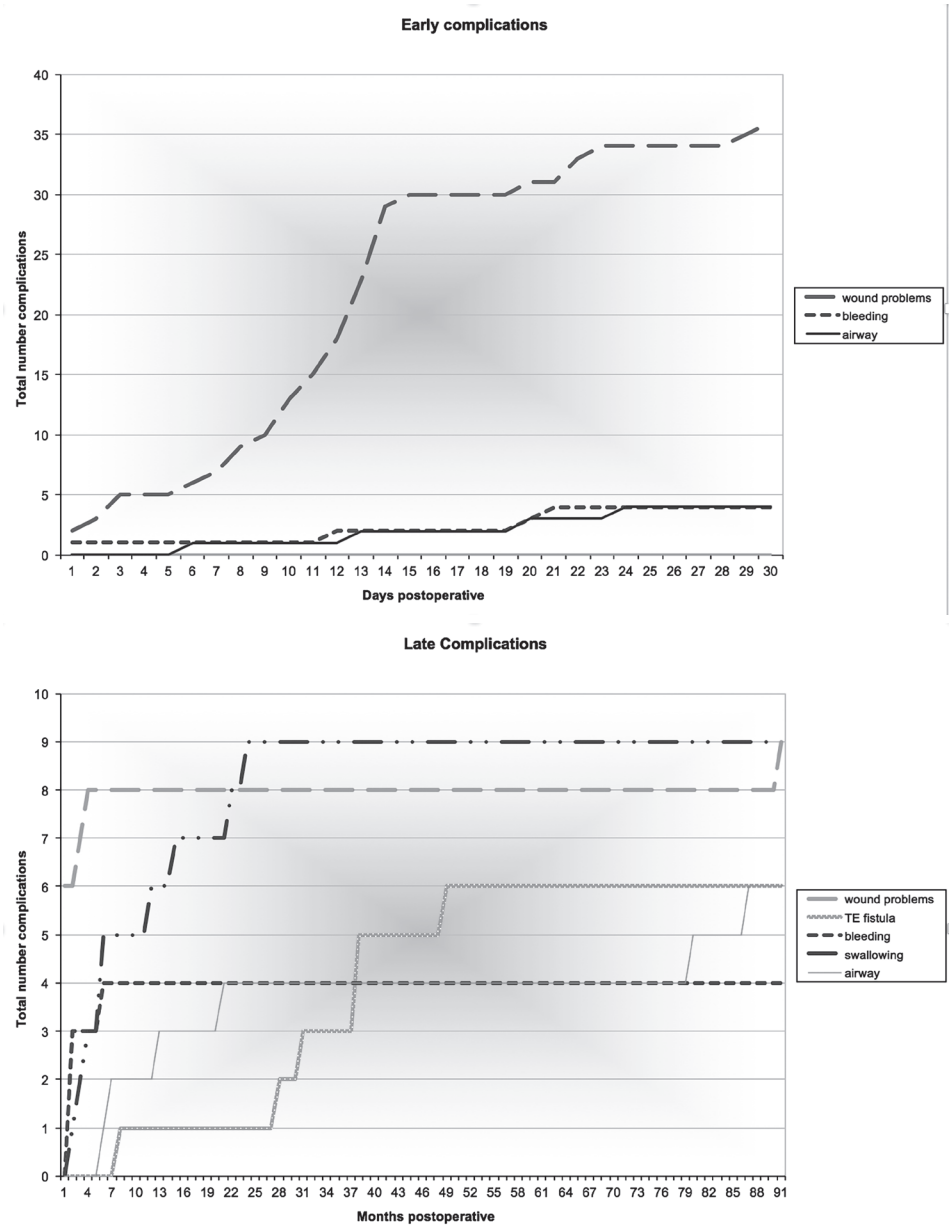

Fig. 1. Cumulative number of complications within the first 30 days after laryngectomy in days (a), and after 30 days post-laryngectomy in months (b). The category 'wound problems' is comprised of 'fistula', 'wound dehiscence' and 'wound infection'. TE fistula: problems with tracheo-esophageal fistula.

Of the 120 patients, 40 (33%) underwent unilateral and 31 (26%) bilateral neck dissections: 34 (modified) radical neck dissections and 68 selective neck dissections (level II–IV). Seventy-six patients underwent unilateral (n = 42) or bilateral (n = 34) paratracheal lymph node dissection.

High N-stage (p = 0.06) and T-stage (p = 0.08) of the initial tumor and tumor site did not significantly predict involvement of the neck. Of the patients with initially staged T1-2N0 carcinoma, 15% had ipsilateral and 7% contralateral metastases detected in the neck dissection specimens or during follow-up while their primary site was controlled. For patients with T2N+ or T3-4 staged carcinoma these figures were 27% and 16%, respectively. Of the 27 tumor positive neck dissections (19 ipsi- and 8 contralateral), 5 were selective neck dissections, all with negative margins. Of the 22 tumor positive (modified) radical neck dissections, 1 ipsilateral and 1 contralateral neck dissection had positive margins, and 16 specimens had metastases limited to levels II–IV.

Twenty-eight neck levels contained tumor in the ipsilateral and 12 levels in the contralateral lymph node specimens, predominantly located in levels II, III and IV (Fig. 2). In three patients metastases were found in the paratracheal lymph nodes; in two patients as a single localization, in one patient combined with metastases in levels II and III.

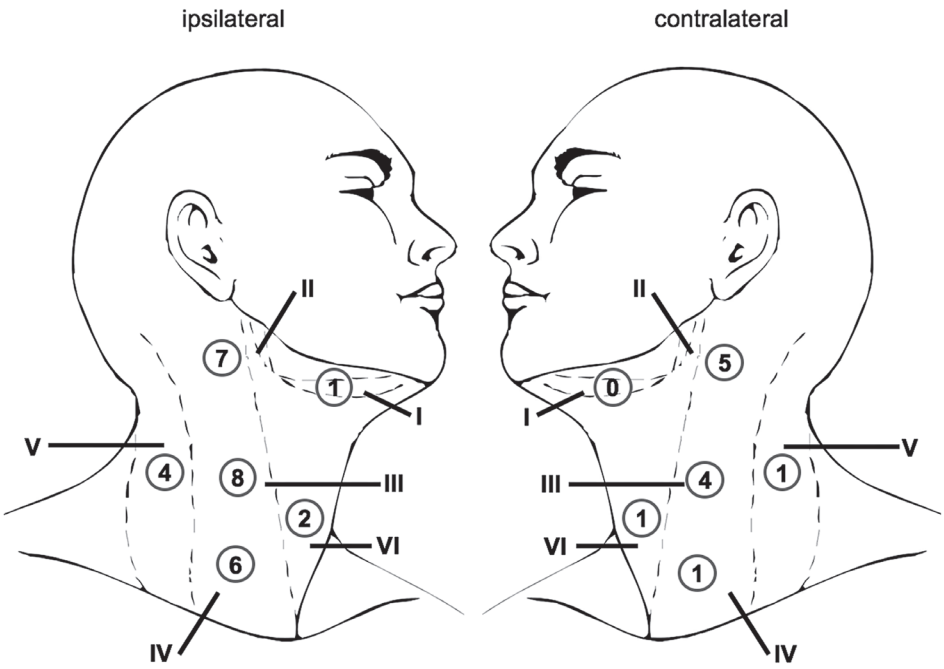

Fig. 2. Anatomic localization of the 6 different lymph node levels of the neck. The numbers in the circles refer to the number of patients with lymph node metastases in this level of the specimen.

Within 1 year after total laryngectomy 87% of the patients were able to produce speech by means of a voice prosthesis, 9% used esophageal speech, 1% an electrolarynx and 3% used writing and sign language to communicate. In the patient records of 94 patients (84%) the nutritional intake after laryngectomy was described as 'normal' or 'soft' (68% and 16%, respectively). Eighteen patients (16%) experienced serious intake problems: 4% used only liquids, 3% was dependent on

oral nutritional supplements and 9% on a nasogastric tube or gastrostomy. No significant median gain or loss in weight or change in body mass index (BMI) was found 6–12 months after the operation (p = 0.057, mean BMI + 1.5 after 6–12 months).

Five year disease free control was 57% (local, regional and distant free of disease: 70%, 79% and 86%, respectively). Thirty-five patients (29%) had local recurrent disease after the salvage total laryngectomy, in 12 patients combined with regional recurrence. Eight patients underwent a second salvage operation: 6 a neopharyngectomy, and 2 a composite resection. Twenty patients (17%) had regional recurrent disease after the salvage laryngectomy. One patient had residual disease after an incomplete resection. No isolated regional recurrences were observed after selective neck dissection (8/68 patients with selective neck dissection had received postoperative radiotherapy). Five patients whose primary was controlled developed the recurrence in their nonoperated neck (1 ipsilateral, 2 bilateral and 2 contralateral). Salvage neck dissection was performed in five patients (25%), in 1 patient followed by radiotherapy. Five-year overall survival was 50% and disease specific survival was 58%. Prior treatment with chemotherapy (p = 0.0001), higher N-stage (p = 0.001) and positive surgical margins (p = 0.018) were significant predictive variables for worse disease specific survival in univariate analysis (Table 3). In multivariate analysis positive surgical margins (p < 0.0001) was a statistically significant (Cox regression, forward stepwise) predictor for worse disease specific survival. Patients with re-irradiation for a locoregional recurrent disease after salvage laryngectomy had an estimated 5-year disease free survival of 42% and overall survival of 37%.

Table 3. Uni- and multivariate analyses for major postoperative complications and disease free survival (p-value).

Variables	Major complications (p-value)		Disease free survival (p-value)	
	Univariate	Multivariate	Univariate	Multivariate
Gender	0.328	0.261	0.513	0.372
Primary tumor site	0.169	0.564	0.207	0.728
T stage	**0.053**	0.193	**0.085**	0.726
N stage	0.950	0.328	**0.001**	0.358
Chemotherapy	0.552	0.570	**0.0001**	0.109
Smoking	0.268	0.302	0.661	–
Alcohol	0.551	0.649	**0.090**	–
ASA score	**0.084**	**0.085**	0.704	0.272
Interval RT-laryngectomy	0.732	0.447	0.636	0.455
Neck dissection (no/uni/bi*)	**0.089**	**0.089**	–	–
Flap reconstruction	0.738	0.772	–	–
Surgical margins	–	–	**0.018**	**<0.0001**
Symptomatic disease	–	–	0.473	0.600

* No neck dissection vs unilateral neck dissection vs. bilateral neck dissection.

DISCUSSION

The disease specific 5-year survival of 58% after salvage laryngectomy for residual or recurrent carcinoma after previous radiotherapy found in the present study is in line with other studies, reporting 29% to 66% (6,9,14,17). Although patients were meticulously selected for salvage laryngectomy, local residual or recurrent disease developed in 29% of the patients. This reflects the aggressive behavior of these recurrent tumors after (chemo)radiation and the diagnostic limitations in selecting patients for salvage treatment. Since salvage treatment is the only option for cure, physicians and patients will be tempted to perform salvage laryngectomy even if there is uncertainty about the surgical margins which will be achieved.

Negative surgical margins were a significant independent predictor for better disease specific survival. The incidence of positive surgical margins in the present study was 10%, which is within the range of figures found in other studies (4–20%) (6,17,25-27). Although a relatively high incidence of treatment related complications is reported, re-irradiation should be considered for patients with high risk of locoregional failure, as it seems to improve locoregional control rates (28). Chondroradionecrosis is probably the most important complication hampering the use of re-irradiation. Therefore, re-irradiation can probably be used with less risk of severe complications after laryngectomy compared to re-irradiation when the laryngeal skeleton is still present. In this study 11% of the patients underwent postoperative re-irradiation. There was no significant difference in complication rate and extent between patients with and without re-irradiation. Studies to evaluate the feasibility of the addition of chemotherapy to re-irradiation are ongoing.

The median interval between radiotherapy and detection of recurrent laryngeal carcinoma was 8.7 months, which is comparable with the 10.7 months as reported by others (29). This underlines the importance of regular visits at the outpatient clinic during follow-up. Especially since residual or recurrent disease was in most cases detected during regular visits. The low number of asymptomatically detected recurrences might be increased by a follow-up schedule with shorter intervals, but according to Ritoe et al. (30) this would require an excessive number of prescheduled visits, due to a short lead time.

The management of cervical lymph nodes in patients undergoing laryngeal surgery for residual or recurrent cancer after prior radiotherapy is still controversial. As some investigators suggest that neck dissection can be withheld in a subset of patients (31), others recommend bilateral neck dissection for all patients with recurrent T3-4 tumors or supraglottic cancers (23). When ipsi- and contralateral neck dissections were analyzed together, a trend towards more positive neck dissection specimens in patients with higher N-stage ($p = 0.06$) and T-stage of the primary tumor ($p = 0.08$) was found. Nevertheless, 16% ipsilateral and 5% contralateral tumor-positive necks were found in patients with T1-2 laryngeal carcinoma. Farrag et al. (32) reported tumor-negative necks in 88% of the patients undergoing salvage laryngeal surgery for residual or recurrent laryngeal carcinoma after primary radiotherapy, compared to 69% in this study.

To avoid over- and undertreatment at the neck diagnostic techniques which reliably detect recurrent lymph node metastasis are warranted. A negative predictive value of CT for neck metastasis of 94–97% is reported, with good sensitivity (75–97%) but with specificity ranging from 24% to 93% (32-34). FDG-PET seems to have better specificity. Yao et al. (31) reported that sensitivity, specificity and negative predictive value was 100%, 94% and 100% for FDG-PET in patients 12 weeks after (chemo)radiotherapy for stage N2a or higher, and concluded that neck dissection can safely be withheld in PET-negative patients. A high negative predictive value of FDGPET was also described by Brkovich et al. (35) and Porceddu et al. (36), (sensitivity 75–83% and specificity 65–94%). Recent studies suggest that sentinel node biopsy is promising, with a sensitivity of 89% (37,38).

Most of the regional metastases were found in levels II, III and IV, all selective neck dissections had negative margins and no isolated regional recurrence occurred. This suggests that a selective neck dissection might be an option to consider, especially for the contralateral neck. In this series, in only 2.7% of paratracheal lymph node dissections vital tumor was found. Other authors reported higher incidences of 9–26% of paratracheal lymph node metastases (39-42), although most of these studies did not include patients with recurrent disease.

Salvage surgery after radiotherapy is known to result in higher complication rates than primary surgery (11,15,19,43), with complication rates up to 77% for salvage laryngectomy (9,11,13,14,16,18,19,25,43–49) and pharyngocutaneous fistula in up to 50% of the patients (9,11,13,14,18,43–46,48,49). The addition of chemotherapy to prior radiotherapy increases the complication risk of a laryngectomy: whereas overall complication rates of 28–34% and fistula rates of 12–16% are reported for laryngectomy after prior radiotherapy (9,11,13), these figures are 35–61% and 25–50% after chemoradiotherapy, respectively (11,18,49). In the present study no significant increased risk for complications or fistulas was found, but only 6 of the 120 patients had received chemoradiotherapy. A higher complication rate is reported for patients with neck dissections and flap reconstructions of mucosal defects (50,51). In our study more complications were found after bilateral neck dissection.

Ninety-six percent was able to produce speech by means of a prosthetic valve or esophageal speech. Tracheoesophageal speech with a prosthetic shunt is known to have high success rates after laryngectomy in general (95%) (52) and after salvage laryngectomy (80–100%) (53,54). Still, patients with an intact larynx after chemoradiation demonstrated significantly higher scores on voice related quality of life measurements than did laryngectomy patients (55). Salvage laryngectomy seems to be followed by more voice prosthesis related complications than primary laryngectomy (53,56). Starmer et al. (53) found a higher frequency of leakage around the prosthesis, frequency of prosthesis dislodgement and number of size changes in the first 6 months after laryngectomy. Patient education regarding monitoring for early signs of complications and ways to address these complications may show promise for improving patient outcomes (53). In general, a satisfactory swallowing function was obtained, as 84% of the patients was able to consume an orally 'normal' or 'soft' diet. Fung et al. (55) reported that nutritional mode consisting of oral intake alone without nutritional supplements was achieved in 64% of the patients with a salvage laryngectomy, while in another study a complete oral intake of 93% was described (54). In a study comparing patients after chemoradiation with patients after salvage laryngectomy, no

difference in overall swallowing was found (55). In this retrospective study, functional outcome was measured without quality of life questionnaires. The post-operative maintenance of weight is in line with the good results of nutritional intake.

The present study shows that salvage total laryngectomy results in good oncologic and functional outcome. However, it should be realized that in this study the results of this salvage treatment are analyzed in a selected group of patients who were considered to be suitable for salvage laryngectomy.

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CHAPTER 8

Paratracheal lymph node dissection during laryngectomy after previous (chemo)radiotherapy: a retrospective analysis of complications and histopathological results

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ABSTRACT

Objectives: To evaluate complications and histopathological results of paratracheal lymph node dissection (PTLND) at laryngectomy after (chemo)radiotherapy.

Design, setting and participants: In a retrospective analysis, complications and histopathological results of paratracheal lymph node dissections were analysed in 191 patients with a recurrent or second primary laryngeal or hypopharyngeal carcinoma following radiotherapy with or without chemotherapy.

Main outcome measures: The percentage of complications in patients with bilateral, unilateral or without PTLND.

Results: Forty-seven patients underwent laryngectomy with bilateral paratracheal lymph node dissection, 52 with unilateral and 92 without paratracheal lymph node dissection. Although the difference in total complications was not significant, significantly more fistulae developed in patients with bilateral paratracheal lymph node dissection (40% versus 22%; P = 0.016). In multivariate analysis, this difference maintained significant (P = 0.038). Pathological examination of the lymph node dissection specimen showed tumour in 3 of the 96 ipsilateral dissections (3%) and in 1 of the 50 contralateral dissections (2%). This suggests that if unilateral instead of a bilateral paratracheal lymph node dissection had been performed, 17% less fistulae would have occurred in this group of patients, while paratracheal lymph node (PTLN) metastases would have been missed in one patient. Three of four patients with paratracheal lymph nodeparatracheal lymph node metastases had glottic carcinoma, all with subglottic extension.

Conclusion: Because of the low incidence of lymph node metastases and the increased risk of fistulae, there is a need for a strict selection of patients who need a bilateral paratracheal lymph node dissection at laryngectomy after previous (chemo)radiotherapy.

INTRODUCTION

The reported incidence of paratracheal lymph node (PTLN) metastases in (mainly previously untreated) patients with total laryngectomy ranges from 9% to 20% (1-5). The indications for and extent of paratracheal lymph node dissections (PTLND) are not well defined and mainly depend on the surgeon's preference. Previous studies identified the presence of PTLN metastases as a significant prognostic factor for worse survival (1,6,7). Plaat et al. (2) found that PTLN metastases with extranodal spread was associated with poorer overall survival. Paratracheal lymph node dissection was shown to significantly adversely affect disease-free survival as an independent factor (8). Also, metastatic disease involving the PTLN has been seen in recurrent disease, particularly peristomal recurrence (9,10), suggesting the likely prognostic significance of positive paratracheal metastatic spread (5). Because the role of PTLND is not clear, the risks associated with this procedure should also be considered. To our knowledge, the relation between laryngectomy with PTLND and complications has not been evaluated before. It is known that salvage laryngectomy, compared to laryngectomy in previously untreated patients, carries a high risk of postoperative (local) complications (11,12).

The goal of this study was to retrospectively evaluate the incidence of complications in a group of patients with laryngectomy after previous (chemo)radiotherapy with no, unilateral or bilateral PTLND.

PATIENTS AND METHODS

From November 1990 to June 2007, 191 patients underwent laryngectomy after previous (chemo) radiotherapy for a laryngeal or hypopharyngeal carcinoma at the VU University Medical Center in Amsterdam. Forty-seven patients underwent laryngectomy with bilateral PTLND, 52 patients with unilateral PTLND and 92 patients without PTLND (Fig. 1).

Laryngectomy was performed for residual disease (≤3 months after radiotherapy) in 15 patients, recurrent disease (>3 months after radiotherapy) in 143 patients and primary tumour in 33 patients. The median detection time from the last radiation was 9.6 months (range 1.1–347.9 months). Patients were followed for recurrent disease after laryngectomy for a median of 29 months (range 0.5–177.7 months).

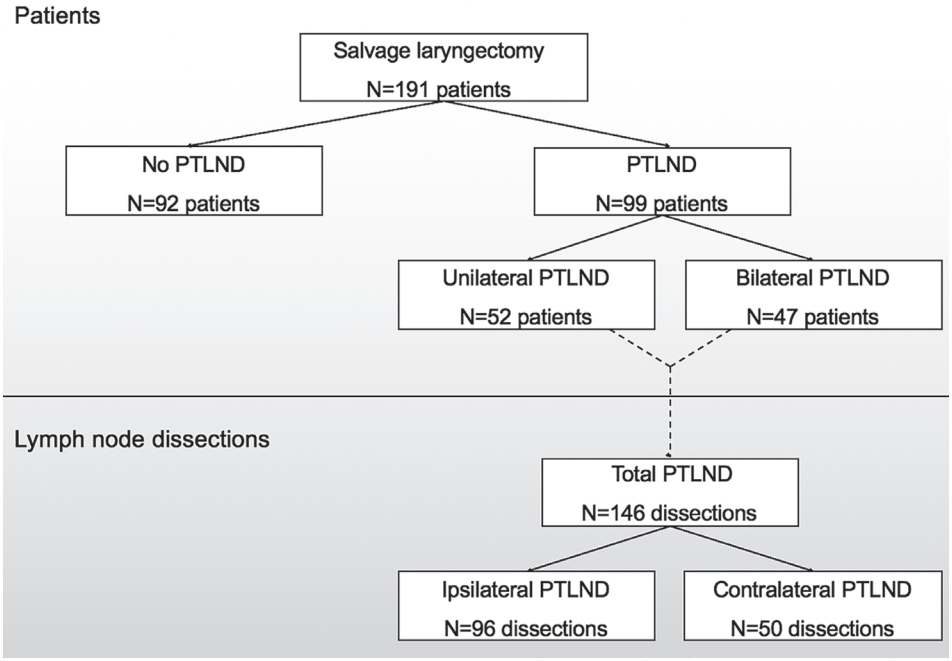

Fig. 1. Flow diagram of patients and paratracheal lymph node dissections (PTLND).

Table 1 gives the details of patient, tumour and previous treatment characteristics. Serious medical comorbidity (ASA > 2) was present in 37% of the patients. The majority reported use of alcohol and tobacco at the time of laryngectomy. For staging the pre-treatment, TNM classification was used. Overall, 74% of patients were irradiated for T1 or T2 tumours; 14% of patients had a clinically positive neck (cN+). While the vast majority of patients with laryngeal carcinoma had early-stage disease, patients with hypopharyngeal cancer were staged T3–T4 in 54% and N+ in 46%.

Twenty-one patients underwent accelerated radiotherapy, and one underwent hyperfractionated radiotherapy. The median dose of definitive radiotherapy was 68 Gy, ranging from 51 to 74.4 Gy. Most patients were irradiated with a daily fraction dose of 2 Gy (range 1.8–4 Gy). Table 2 gives details of the surgery performed during salvage laryngectomy. Most patients underwent total laryngectomy (82%) with partial pharyngectomy (93%) and hemithyroidectomy (67%), in 18% of the patients combined with flap reconstruction.

If a PTLND was performed, this involved dissection of the lymph nodes between the trachea and the carotid artery from the cricoid to thoracic inlet. Landmarks of the distal margins along the paratracheal gutter were the superior mediastinum as far inferiorly as possible, through the cervical approach. The surgical rationale for performing this procedure was based on the personal preference and judgement of the head and neck surgeon, because guidelines for PTLND were not available during the study period.

Complications were retrospectively assessed and categorised. All complications in the operation area were defined as local complications: with and without re-intervention. Local complications were subdivided into pharyngocutaneous fistulae, haemorrhage, wound dehiscence (without infection or fistula) and wound infection (without fistula).

Statistics

Statistical difference between two independent groups was calculated by the chi-square test. The trend test was used where appropriate. Variables put in univariate analyses are listed in Table 3. Variables excluded from multivariate analyses were not significant in univariate analyses. To investigate confounding, multivariate analyses were conducted. For this, logistic regression was used in two steps: in the first step, only the variable of interest was entered in the model. In a second step, a potentially confounding variable was added to the model. Subsequently, the relative change in the coefficient of the variable of interest was assessed. An increase or decrease of 10% was used to determine confounding. Variables put in multivariate analyses are listed in Table 5. Statistical analyses were carried out using spss 15.0 (Statistical Package for the Social Sciences; IBM, Somers, NY, USA).

Table 1. Patient, tumour and previous tumour stage and treatment characteristics

Characteristics	All patients (n = 191) (%)	No PTLND (n = 92) (%)	Unilateral PTLND (n = 52) (%)	Bilateral PTLND (n = 47) (%)
Sex				
Male	167 (87)	84 (91)	43 (83)	40 (85)
Female	24 (13)	8 (9)	9 (17)	7 (15)
Smoking (at the time of laryngectomy)				
No	125 (65)	60 (65)	35 (67)	30 (64)
Yes	66 (35)	32 (35)	17 (33)	17 (36)
Alcohol (at the time of laryngectomy)				
No	61 (32)	25 (27)	22 (42)	14 (32)
Yes	130 (68)	67 (73)	30 (58)	33 (68)
ASA				
1–2	121 (63)	58 (63)	34 (65)	29 (62)
>2	70 (37)	34 (37)	18 (35)	18 (38)
Location				
Hypopharynx	13 (7)	3 (3)	5 (10)	5 (11)
Supraglottic	51 (26)	25 (27)	16 (31)	10 (21)
Glottic	126 (66)	64 (70)	31 (59)	31 (66)
Subglottic	1 (1)	0 (0)	0 (0)	1 (2)
Initial T-stage (at the time of radiotherapy)				
T1	62 (33)	40 (43)	13 (25)	9 (19)
T2	78 (41)	34 (37)	23 (44)	21 (45)
T3	31 (16)	12 (13)	12 (23)	7 (15)
T4	20 (11)	6 (7)	4 (8)	10 (21)
Initial N-stage (at the time of radiotherapy)				
N0	165 (86)	81 (88)	48 (92)	36 (77)
N1	17 (9)	5 (6)	3 (6)	9 (19)
N2a	0 (0)	0 (0)	0 (0)	0 (0)
N2b	3 (2)	2 (2)	0 (0)	1 (2)
N2c	5 (3)	4 (4)	0 (0)	1 (2)
N3	1 (1)	0 (0)	1 (2)	0 (0)
Prior treatment				
Radiotherapy	182 (95)	88 (96)	52 (100)	42 (89)
Chemoradiotherapy	9 (5)	4 (4)	0 (0)	5 (11)

Table 2. Details of surgical procedure during salvage laryngectomy

Feature	All patients (n = 191) (%)
Laryngectomy	
Partial laryngectomy	35 (18)
Total laryngectomy	156 (82)
Pharyngectomy	
Partial pharyngectomy	177 (93)
Total pharyngectomy	14 (7)
Thyroidectomy	
No thyroidectomy	46 (24)
Partial thyroidectomy	127 (67)
Total thyroidectomy	18 (9)
Neck dissection	
No neck dissection	92 (48)
Unilateral neck dissection	53 (28)
Bilateral neck dissection	46 (24)
Flap reconstruction	
No	156 (82)
Yes	35 (18)

RESULTS

One hundred and eleven patients (58%) developed 137 complications after laryngectomy. Local complications were pharyngocutaneous fistulae (n = 51; 27%), haemorrhage (n = 11; 6%), wound dehiscence (n = 9; 5%) and wound infection (n = 5; 3%).

Univariate analyses (Table 3) showed significantly more local complications in case of women, smoking, no alcohol, primary tumour on other location than glottis, advanced T-stage, N+ neck, high radiotherapy total and fraction dose, total laryngectomy and pharyngectomy and bilateral lymph node dissection. More pharyngocutaneous fistulas were seen in case of smoking, primary tumour on other location than glottis, N+ neck, high radiotherapy total and fraction dose, and bilateral lymph node dissection. There were more wound infections in patients with the age below the median 63 years. Univariate analyses showed more haemorrhage in women, advanced T-stage, chemoradiotherapy and bilateral lymph node dissection. Univariate analyses showed no significant difference in complications between patients with radiotherapy and patients with chemoradiotherapy.

The occurrence of overall complications was not significantly different in the groups of patients with unilateral or bilateral PTLND and the group of patients without PTLND (Table 4). A significant difference in local complications was found between the three subgroups (P = 0.05), mainly caused

Table 3. Univariate analyses of complications after laryngectomy. Variables in the box with significant P-values are the factors with more complications

Variable	Local complications (P-value)	Pharyngocutaneous fistulae (P-value)	Wound dehiscence (P-value)	Wound infection (P-value)	Haemorrhage (P-value)
Sex	**0.02 (female)**	0.20	0.89	0.61	**0.01 (female)**
Smoking	**0.02 (smoking)**	**0.01 (smoking)**	0.94	0.23	0.43
Alcohol	**0.04 (no alcohol)**	0.10	0.41	0.56	0.31
Glottic	**0.03 (other location)**	**0.01 (other location)**	0.44	0.50	0.87
T-stage	**0.03 (advanced)**	0.19	0.88	0.56	**0.02 (advanced)**
N-stage	**0.02 (N+)**	**0.04 (N+)**	0.22	0.37	0.65
RT total dose	**0.01 (high)**	**0.003 (high)**	0.62	0.79	0.36
RT fraction dose	**0.02 (high)**	**0.01 (high)**	0.39	0.92	0.10
Chemotherapy	0.64	0.28	0.49	0.61	**0.03 (chemotherapy)**
ASA	0.36	0.92	0.23	0.43	0.20
Laryngectomy	**0.01 (total)**	0.70	0.53	0.96	0.44
Pharyngectomy	**0.002 (total)**	0.31	0.34	0.82	0.13
Flap reconstruction	0.12	0.89	0.76	0.20	0.43
Age	0.17	0.70	0.67	**0.03 (age < 63 yr)**	0.31
PTLND	**0.05 (bilateral)**	**0.03 (bilateral)**	0.82	0.81	**0.05 (bilateral)**

PTLND, paratracheal lymph node dissection; Glottic, initial tumour glottic versus other locations; N-stage, N+ versus N0, RT, radiotherapy; ASA, ASA > 2 versus ASA 1–2; PTLND, No or unilateral versus bilateral PTLND. Bold values are considered statistically significant (P < 0.05).

by high percentage of complications in the group with bilateral dissection. The same increase was found in univariate analyses of the relation between the three subgroups and haemorrhage (P = 0.05) and fistulae (P = 0.03).

As in all previous analyses, post hoc significance was only found between the group with bilateral PTLND and the other two groups (no and unilateral PTLND), the last two groups were combined in one group to evaluate the specific effect of a bilateral PTLND (Table 4).

For local complications the T-status, N-status, total and fraction dose of radiotherapy were identified as confounding factors in multivariate analysis. The relation between bilateral PTLND and local complications lost its significance after correction for these confounders (Table 4).

Table 4. Univariate and multivariate analyses of complications after laryngectomy (overall, local and specific) in patients with no, unilateral and bilateral paratracheal lymph node dissection (PTLND)

	No. of patients					
Type of complication	**All patients (%)**	**No PTLND (%)**	**Unilateral PTLND (%)**	**Bilateral PTLND (%)**	**Univariate analysis (P-value)**	**Multivariate analysis (P-value)**
Overall complications						
No	80 (42)	43 (47)	20 (38)	17 (36)	0.20	
Yes	111 (58)	49 (53)	32 (62)	30 (64)		
Local complications						
No	120 (63)	62 (67)	35 (67)	23 (49)	**0.05**	0.74
Yes	71 (37)	30 (33)	17 (33)	24 (51)		
Pharyngocutaneous fistulae						
No	140 (73)	72 (78)	40 (77)	28 (60)	**0.03**	**0.04**
Yes	51 (27)	20 (22)	12 (23)	19 (40)		
Wound dehiscence						
No	182 (95)	88 (96)	50 (96)	44 (94)	0.64	
Yes	9 (5)	4 (4)	2 (4)	3 (6)		
Wound infection						
No	186 (97)	90 (98)	50 (96)	46 (98)	0.92	
Yes	5 (3)	2 (2)	2 (2)	1 (2)		
Haemorrhage						
No	180 (94)	88 (96)	51 (98)	41 (88)	**0.05**	0.19
Yes	11 (6)	4 (4)	1 (2)	6 (13)		

Bold values are considered statistically significant (P < 0.05).

Pharyngocutaneous fistulae, which was the most frequent complication, occurred significantly more frequently in patients with a bilateral PTLND (40%), compared to patients with no or unilateral PTLND (22%) (P = 0.016). In multivariate analysis, N-status before previous (chemo)radiotherapy

(N0 versus N+) and total and fraction dose of radiotherapy appeared to be confounding factors (Table 5). Although confounding was present, the difference between bilateral and no or unilateral PTLND maintained its significance (P = 0.038, Table 3). For haemorrhage, where T-status and radiotherapy fraction dose were identified as confounding factors, correction for confounding factors resulted in a loss of significance of the relation between bilateral PTLND and postoperative haemorrhage (Table 4).

Table 5. Confounding analyses for the relation between fistulae and bilateral paratracheal lymph node dissection (PTLND). N-status (N0 versus N+ before radiotherapy), radiotherapy total dose and radiotherapy daily fraction dose were identified as confounding factors.

Fistulae in the groups of no / unilateral and bilateral PTLND						
Confounder	**(P)**	**B-solo**	**B-conf**	**RelDiff**	**P-s**	**P-c**
Smoking	+	0.865	0.879		+	+
Alcohol		0.865	0.898		+	+
ASA		0.865	0.865		+	+
Glottic	+	0.865	0.902		+	+
T		0.865	0.803		+	+
N	+	0.865	0.761	+	+	+
RT total dose	+	0.915	0.771	+	+	+
RT fraction dose	+	0.956	0.817	+	*	+

ASA, ASA > 2 versus ASA1–2; Glottic, initial tumour glottic versus other locations; N-stage, N+ versus N0, RT, radiotherapy.
(P), significance of relation between the potential confounder and the outcome; B-solo, coefficient of variable of interest without the confounder in the model; B-conf, coefficient of variable of interest with the confounder in the model; RelDiff, magnitude of relative change of B-raw into B-confounded as indication for confounding; P-s, significance of B-raw; P-c, significance of B-confounded.
P: +<0.05, *<0.01.
RelDiff: +>10%, *>50%.

The locations of the 51 pharyngocutaneous fistulae were retrospectively determined. Fistulae mainly developed above the stoma (55%); 37% were located in the margins of the stoma and 8% under the stoma. No statistical correlation was found between the location of the fistulae and the type of PTLND (no, uni- or bilateral).

Paratracheal lymph node metastases were found in 4 of the 146 PTLND specimens. Three patients had ipsilateral metastases, while 93 other ipsilateral paratracheal dissections were free of tumour. Of the 50 contralateral paratracheal dissections, one patient had a contralateral metastasis. In two patients, the PTLN metastasis was the only regional localisation of tumour. The primary tumours of the patients with PTLN metastases were located in the glottic area in three patients, all with subglottic extension, and hypopharynx in one patient. The initial T- and N-stage of these tumours were T1 (n = 1), T2 (n = 1) and T3 (n = 1) with N0 (n = 2) and N1 (n = 1) for the ipsilateral positive patients, and T1N0 for the contralateral positive patient.

Retrospectively, performing a unilateral instead of a bilateral PTLND would seem to increase the risk of missing contralateral paratracheal metastases with 4% (95% confidence interval: 1–15%).

DISCUSSION

Laryngectomy is often combined with neck dissection (especially in advanced stage disease), but the paratracheal nodal group is not routinely included in the dissection. The rate and extensiveness of PTLND mostly depend on the personal preference of the surgeon (13). If high-risk factors are present, the surgeon will probably be more reluctant to perform PTLND. In patients with subglottic extension, the risk of PTLN metastases is 27% (13). For laryngeal tumours, the 'at-risk' nodal groups include the paratracheal area (4,14), and the presence of PTLN metastases, especially with extra nodal spread (2), is associated with stoma recurrence (4,6,9,10,15–17) and poor survival (5,7,8).

Synopsis of new findings

While the above-mentioned arguments plead for a routine PTLND, we found significantly more postoperative fistulae after laryngectomy with bilateral PTLND. Forty percent of the patients with bilateral PTLND developed a fistulae, compared to 22% with no or unilateral PTLND. Despite confounding factors, bilateral PTLND appeared to be an independent risk factor for the development of fistulae in multivariate analyses. Local complications and postoperative haemorrhage lost significance in multivariate analyses but might be associated with bilateral PTLND when evaluated in a larger patient group. All patients with proven PTLN metastases and glottic carcinoma had subglottic extension.

Comparisons with other studies

To our knowledge, the present study is the first to analyse the relationship between PTLND and postoperative complications in patients who underwent laryngectomy after previous (chemo)radiotherapy. Biermann et al. (18) described the complications of thyroidectomy with PTLND. All reported complications, e.g. permanent pareses of the recurrent nerve, permanent hypocalcaemias and short-term tracheotomy, seemed to be related to the thyroidectomy and not specifically to the PTLND.

Based on our findings of a markedly increased rate of fistulae in patients with bilateral PTLND, we would not recommend performing contralateral PTLND. In our study, only 1 of the 50 contralateral PTLND contained metastases. However, Plaat et al. (2) found contralateral PTLN metastases in 21% of the PTLND. It is difficult to weight reduction in the risk of fistulae with increase in the risk of peristomal recurrence when PTLN metastases are not surgically removed after failed radiotherapy.

An argument in favour of routinely performing contralateral PTLND is the limited accuracy of preoperative diagnostics to identify PTLN metastases. Timon et al. (4) found positive paratracheal nodes with diameters varying from 0.3 to 3 cm, the majority measuring <1 cm and appearing negative preoperatively. Other authors also reported the difficult and limited estimation of PTLN status with preoperative palpation, ultrasonography, CT and MRI (19), owing to the limitations in the assessment of small lymph nodes (16). Okada et al. (20) compared PET/CT with contrast-enhanced CT for lymph node metastases (including PTLNs) in patients with oesophageal cancer. Sensitivity and specificity were 60% and 100% for PET/CT and 56% and 97% for contrast enhanced CT. The smallest lymph node metastasis detectable by PET/CT was 6 mm. In previously irradiated patients, it might be even more difficult to assess the lymph node status preoperatively.

The presence of PTLN metastases does not seem to be related to the presence of cervical lymph nodes in other levels. Our study had a relatively low rate of PTLN metastases (4/146), but despite this, in two patients this was the only localisation of lymph node metastases. This was supported by previous studies, in which 16% to 38% of the patients with PTLN metastases had no other lymph node metastases (2,4).

We included only patients with laryngectomy after previous (chemo)radiotherapy. Most studies reported on PTLND in patients without previous therapy, or in a combined patients group with and without previous therapy. Salvage laryngectomy is accompanied by an increased rate of complications, compared to laryngectomy in untreated patients (11). The increased rate of fistulae after bilateral PTLND in our study might not be present in previously untreated patients with laryngectomy. Also, the rate of PTLN metastases was less than that described in other studies, which might be related to a different lymph node drainage structure in previously irradiated patients (21). Also, lymph node metastases might have been eradicated as a result of previous (chemo) radiotherapy, while there was residual tumour on the primary site. Radiotherapy combined with chemotherapy might result in an additional risk of complications. However, the present study did not support this hypothesis. It must be borne in mind, however, that the small number of chemotherapy patients (n = 9) might have biased these data. Another difference compared to the previously untreated patients is the increased risk of complications after radiotherapy in a previously irradiated area. To prevent stoma recurrence in case of PTLN metastases, postoperative radiotherapy is suggested (4,5,9,15,16). However, re-irradiation is known to result in increased rate of complications (22).

Drawbacks of the study

The main drawback of this study is the retrospective analyses. The present study is the first to explore the relationship between PTLND after (chemo)radiotherapy and complications, but further research is necessary to draw further conclusions. Also, to be able to evaluate a large group of patients, a wide time window was used in which a variety of surgeons have been performing the operations with small modifications of techniques over the years. Moreover, because the borders of level VI are not clearly defined, the extent of a PTLND may vary somewhat (23). A more homogeneous group would have been preferable. In this study, all patients with salvage laryngectomy were included. Inclusion of patients with hypopharyngeal carcinoma as primary tumour site might be argued because these tumours have a different lymphatic drainage and because this concerned a small number of patients (7%) with potential bias. However, in univariate analyses, no significant difference was found for different primary tumour sites. And also in multivariate analyses, no significant difference was found between glottic tumour and other sites showed no significance. The results should also be interpreted with caution for hypopharyngeal carcinoma because this study included largely early-stage disease (T1–2: 74%, N0: 86%), while the included hypopharyngeal carcinomas concerned more advanced-stage tumours (T1–2: 46%, N0: 54%). In general, it should be kept in mind that this study concerned mainly early-stage initial disease.

Clinical applicability of the study

The results of this study emphasise the need to make a well-considered decision to perform PTLND. Survival rates are important for patients undergoing extensive surgery as (salvage) laryngectomy, but complication rates should also be kept in mind.

CONCLUSIONS

Bilateral PTLND in patients undergoing laryngectomy after previous (chemo)radiotherapy is shown to significantly adversely affect the risk of postoperative pharyngocutaneous fistulae. As the incidence of contralateral PTLN metastases was low, a strict selection of patients undergoing contralateral PTLND is warranted. If subglottic extension is diagnosed, patients should certainly undergo PTLND, because all patients with glottic carcinoma and PTLN metastases had subglottic extension.

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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-[^{18}F]-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 ($\kappa = 0.55$) 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 ($\kappa = 0.59$ and 0.58) than the sensitive one ($\kappa = 0.43$ 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 stand-alone 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-diacetyl-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.

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CHAPTER 10

Samenvatting, discussie en toekomstperspectieven

SAMENVATTING

Van de patiënten met larynxcarcinoom ontwikkelt 20-40% een lokaal recidief, ondanks sterke vooruitgang in behandelingsmodaliteiten (1-5). Voor de primaire behandeling van vergevorderde larynxcarcinomen (voornamelijk T3) was de voorkeursbehandeling een laryngectomie. Inmiddels is de voorkeursbehandeling (chemo)radiatie, met als doel het preserveren van functie en het reserveren van chirurgie voor 'salvage' procedures. Met name door (chemo)radiatie geïnduceerde veranderingen in normaal weefsel kan de detectie van een recidief carcinoom moeilijk zijn. Omdat conventionele beeldvormingsmodaliteiten zoals CT ('computed tomography') en MRI ('magnetic resonance imaging') een beperkte accuratesse hebben voor de detectie van een recidief carcinoom na (chemo)radiotherapie, worden nieuwe diagnostische strategieën onderzocht. De huidige klinische praktijk bestaat uit een directe laryngoscopie met biopten onder algehele anesthesie, die invasief en duur is, en dat een sensitiviteit van slechts 45% bij een eerste scopie heeft (6). Afhankelijk van het T-stadium zijn er gemiddeld 1,7 tot 4,9 directe laryngoscopieën onder narcose per patiënt nodig om een recidief te detecteren in een periode van 6 maanden na de eerste verdenking hierop. Eerdere studies lieten zien dat 18F-FDG-PET potentieel een grote rol kan spelen bij detectie van een recidief larynxcarcinoom na radiotherapie. Door de hoge negatief voorspellende waarde kan PET gebruikt worden om een recidief larynxcarcinoom uit te sluiten (7,8).

Voor patiënten met een bewezen lokaal recidief na (chemo)radiatie is een salvage laryngectomie met of zonder lymfklierdissectie de aangewezen behandeling, dit alhoewel het bekend is dat salvage chirurgie een hoog complicatierisico kent met soms teleurstellende ziektevrije overlevingspercentages ten opzichte van primaire chirurgie (respectievelijk: fistels 23-34% versus 14%, en 5-jaars ziektevrije overleving 48-54% versus 61%)(9-15). Chirurgen worden geconfronteerd met de uitdaging om genoeg weefsel te verwijderen zodat de tumor radicaal verwijderd is (aangezien laryngectomie vaak de laatste optie met curatieve mogelijkheden is), en tegelijkertijd om zoveel mogelijk weefsel te sparen (aangezien uitgebreidere chirurgie geassocieerd is met een hoger complicatierisico).

Doel van het beschreven onderzoek in dit proefschrift was om de waarde van 18F-FDG-PET bij de detectie van een recidief larynxcarcinoom na (chemo)radiotherapie te onderzoeken en de uitkomsten van salvage chirurgie voor recidief tumor vast te stellen.

Om de diagnostische fase van detectie van een lokaal recidief te optimaliseren, werd de rol van 18F-FDG-PET bij deze indicatie bestudeerd in **Hoofdstukken 2-5**.

Beoordeling van PET-resultaten wordt gekenmerkt door visuele interpretatie, dat onderhevig is aan interobservervariatie. Een sterkere overeenstemming tussen de verschillende beoordelaars geeft een meer betrouwbare generaliseerbaarheid van de resultaten en zegt daarmee iets over de toepasbaarheid van PET in de dagelijkse praktijk. In **Hoofdstuk 2** analyseerden we de resultaten van 11 nucleair geneeskundigen (met ervaring in het beoordelen van PET-scans van het hoofd-halsgebied) werkzaam bij één van de 8 centra van de NWHHT (Nederlandse Werkgroep Hoofd Hals Tumoren). Zij beoordeelden 30 18F-FDG-PET scans van patiënten verdacht van een recidief

larynxcarcinoom na radiotherapie. Bij een beoordeling met een driepuntsschaal (positief, dubieus en negatief) was de interobservervariatie in vergelijking tot de referentie (lokaal recidief binnen 6 maanden na PET) redelijk (κ = 0,55). De gegevens werden gereduceerd van een driepunts- naar een tweepuntsschaal, en de test-accuratesse werd bepaald voor een sensitieve (d.w.z. 'dubieus' beschouwd als positief) en conservatieve ('dubieus' beschouwd als negatief) strategie. De conservatieve strategie resulteerde in een betere accuratesse en interobserver-overeenkomst (κ = 0,59 en 0,58) dan de sensitieve strategie (κ = 0,43 en 0,51). Omdat het missen van een recidief zwaarder weegt dan het onnodig verrichten van een scopie onder narcose zal in de klinische praktijk de sensitieve manier van beoordelen gebruikt worden. De gemiddelde sensitiviteit (van observers) varieerde van 87% tot 97%, en de gemiddelde specificiteit van 81% tot 63%. Met een prevalentie van 23% lokale recidieven was de negatief voorspellende waarde van PET 96% tot 99%. Op basis van deze pilot studie concludeerden we dat 18F-FDG-PET een goede negatief voorspellende waarde voor de detectie van een lokaal recidief larynxcarcinoom had en dat de interobserver-overeenkomst bij de sensitieve strategie acceptabel was. PET leek dan ook goed bruikbaar als eerste diagnostische stap, en zou het percentage onnodige invasieve diagnostische onderzoeken kunnen reduceren.

Om deze hypothese te testen, werd een gerandomiseerde multicenter studie opgezet en bediscussieerd in **Hoofdstuk 3**. De RELAPS studie (REcidief LArynx carcinoom PET Studie) werd ontwikkeld om te bepalen of 18F-FDG-PET van waarde is bij de selectie van patiënten voor een directe laryngoscopie onder narcose wanneer er verdenking is op een recidief larynxcarcinoom. Honderdvijftig patiënten werden gerandomiseerd voor een directe laryngoscopie onder narcose (conventionele strategie), of voor 18F-FDG-PET, alleen gevolgd door een directe laryngoscopie onder narcose bij positieve of twijfelachtige bevindingen op PET (op PET-gebaseerde strategie). Deze sensitieve beoordeling werd gebruikt omdat het missen van een recidief in de klinische praktijk waarschijnlijk zwaarder weegt dan een onnodige directe laryngoscopie (geen recidief bij directe laryngoscopie onder narcose of in de daarop volgende follow-up periode tot 6 maanden na inclusie). Indien bij de laryngoscopie geen tumor werd gevonden, werd de laryngoscopie binnen 6 weken herhaald, tenzij de klachten of symptomen waren afgenomen. In de op PET-gebaseerde strategie kregen patiënten met een negatieve PET geen aanvullende onderzoeken in de eerste 3 maanden, tenzij er progressie van symptomen was. De beoogde gezondheidswinst bestaat uit een afname van het aantal te vermijden (onnodige) directe laryngoscopieën onder narcose en de consequenties hiervan.

In **Hoofdstuk 4** werden de resultaten van de RELAPS studie gepresenteerd. Vijfenveertig patiënten (30%) hadden histopathologisch bewezen lokale ziekte binnen 6 maanden follow-up. De indicatie voor een directe laryngoscopie was onnodig in 53 van de 74 patiënten (72%) in de conventionele strategie, vergeleken met 22 van de 76 patiënten (29%) in de op PET-gebaseerde strategie. Dit verschil kan worden geïnterpreteerd als 2,3 patiënten die met PET onderzocht moeten worden om 1 onnodige indicatie voor directe laryngoscopie onder narcose te vermijden. Dertig PET scans waren juist-negatief en 1 was fout-negatief. De veiligheid van de op PET-gebaseerde strategie werd bevestigd; we vonden geen nadelige effecten op de operabiliteit van het recidief of op de chirurgische marges van de salvage laryngectomie in de op PET-gebaseerde groep. In subgroepanalyses waren

de aantallen onnodige indicaties voor een directe laryngoscopie niet significant verschillend voor de patiënten gescand met PET versus PET/CT; dit zou een gevolg kunnen zijn van de kleine omvang van de groepen. Bij een referentieperiode van 12 maanden follow-up in plaats van 6 maanden zijn de resultaten sterk vergelijkbaar. Deze studie laat zien dat het bij patiënten met een mogelijk recidief larynxcarcinoom na radiotherapie veilig is om alleen een directe laryngoscopie onder narcose te verrichten bij patiënten met positieve PET bevindingen, waarmee het aantal onnodige procedures kan worden verminderd met meer dan 50%.

In een kosteneffectiviteitstudie, beschreven in **Hoofdstuk 5**, werden de potentiële gezondheidsvoordelen en consequenties qua kosten onderzocht van het introduceren van 18F-FDG PET bij de diagnostische work-up van patiënten verdacht van recidief larynxcarcinoom na radiotherapie. De gemiddelde totale kosten per patiënt bij een follow-up periode van 6 en 12 maanden werden vergeleken tussen de twee diagnostische strategieën van de RELAPS studie. Een microkosten methode werd gebruikt, gebaseerd op een gedetailleerde inventarisatie en meting van alle gebruikte middelen. Incremental cost-effectiveness ratios (ICER's) werden berekend. De diagnostische, behandeling en follow-up fases werden apart geanalyseerd in subgroep analyses. Na 6 maanden follow-up waren de gemiddelde kosten per patiënt in de conventionele strategie 11.784 euro, vergeleken met 11.302 euro in de op PET-gebaseerde strategie, resulterend in een kostenbesparing van 482 euro per patiënt in de op PET-gebaseerde groep. De resultaten van dezelfde analyses bij een 12 maanden follow-up periode waren vergelijkbaar, met een totale kostenbesparing van 1105 euro per patiënt in de op PET-gebaseerde groep. ICERs waren dominant ten gunste van de PET arm, en de sensitiviteitsanalyse bevestigde de robuustheid van de resultaten. Concluderend is de introductie van 18F-FDG-PET in de diagnostische work-up bij verdenking op een recidief larynxcarcinoom na radiotherapie veelbelovend vanuit zowel klinisch als economisch perspectief.

Het tweede deel van dit onderzoek richt zich op de behandeling van patiënten met recidief larynx carcinoom na eerdere radiotherapie. Patiënten met bewezen lokaal tumorrecidief na (chemo)radiotherapie komen zoveel mogelijk in aanmerking voor zogenaamde 'salvage' chirurgie, meestal betreft dit een totale laryngectomie met uni- of bilaterale lymfklierdissectie. De overlevingspercentages na salvage chirurgie kunnen echter teleurstellend zijn, en de operaties zijn uitgebreid met een aanzienlijk risico op complicaties. Duidelijke indicaties voor de selectie van patiënten voor salvage chirurgie zijn nodig om alleen patiënten met redelijke overlevingskansen te opereren en om patiënten met irresectabele ziekte te excluderen. Hetzelfde geldt voor de uitgebreidheid van de operatie. Er dient geen onnodig uitgebreide operatie te worden uitgevoerd, en de overlevingskans moet niet in gevaar gebracht worden. Tot nu toe betreft beschreven onderzoek naar salvage laryngectomie veelal relatief inhomogene patiëntpopulaties.

Om de recidiefpatronen van met chemoradiotherapie behandelde larynx- en hypofarynxcarcinomen te bestuderen, werd de follow-up van 136 patiënten retrospectief geanalyseerd in **Hoofdstuk 6**. Zestig patiënten hadden locoregionaal recidief, waarvan 22 salvage chirurgie ondergingen (15 totale laryngectomieën met uni- of bilaterale lymfklierdissectie en 7 lymfklierdissecties zonder laryngectomie). Factoren die significant geassocieerd waren met het in aanmerking komen voor salvage chirurgie versus geen chirurgie voor recidief waren a) leeftijd onder 59 jaar (gemiddelde

leeftijd van totale patiënten groep) en b) larynx- versus hypofarynxcarcinoom. Het postoperatieve complicatiepercentage na salvage chirurgie was 68%, met fistels in 23% van de patiënten. Meer wondgenezingsproblemen traden op bij patiënten met excessief alcohol gebruik. De vijf-jaars ziekte specifieke overleving was 35%. De vijf-jaars overleving van patiënten zonder recidief tumor was 70%.

In **Hoofdstuk 7** evalueerden wij de uitkomsten van salvage totale laryngectomie bij 120 patiënten met recidief larynxcarcinoom na eerdere (chemo)radiotherapie. Deze studie toonde symptomatische ziekte in slechts 66% van de patiënten, met een mediaan detectie-interval van 9 maanden tussen behandeling en detectie van recidief tumor. Vijfentachtig procent van de tumoren werd gevonden bij een reguliere controle-afspraak. De 5-jaars ziekte specifieke overleving was 58%, met positieve snijranden als enige significante voorspeller voor een slechtere overleving. Het complicatie percentage was 56%. Er werden geen significante voorspellers van complicaties gevonden. Goede functionele uitkomsten met een functionele stemprothese in 87% en volledig oraal dieet in 84% van de patiënten werden geconstateerd. Lymfkliermetastasen werden in 31% van de patiënten aangetroffen, met contralaterale metastasen in 7% van de initiële T1-2N0 tumoren. Het lage percentage symptomatische ziekte en het hoge percentage tumor-negatieve lymfklierdissecties onderschrijven dat betrouwbare diagnostische technieken nodig zijn. In deze geselecteerde groep resulteerde salvage laryngectomie in goede oncologische en functionele resultaten.

Omdat het detecteren van lymfkliermetastasen in de hals na eerdere radiotherapie moeilijk blijft, vormt daarmee ook de behandeling van de hals bij patiënten met een lokaal recidief een dilemma, net als de uitgebreidheid van de eventuele halsklierdissectie. Alhoewel eerdere studies de aanwezigheid van paratracheale lymfkliermetastasen (level VI) hebben geïdentificeerd als een significante prognostische factor voor een slechtere overleving, zijn geen duidelijke indicaties voor het verrichten van een paratracheale lymfklierdissectie gedefinieerd. In **Hoofdstuk 8** werden 191 patiënten met een laryngectomie na (chemo)radiotherapie en bilaterale (n=47), unilaterale (n=52) of geen (n=92) paratracheale lymfklierdissectie (PTLKD) geëvalueerd. Drie van de vier patiënten met paratracheale metastasen had een glottisch larynxcarcinoom, allen met subglottische uitbreiding. Dit bevestigt de bevinding van eerdere studies dat subglottische uitbreiding een risico factor voor de aanwezigheid van paratracheale lymfkliermetastasen is. In 1 patiënt (2%) betrof het een contralaterale metastase. Bilaterale PTLKD was geassocieerd met significant meer fistels dan unilaterale PTLKD (40% versus 22%), indicerend dat een strenge selectie voor het verrichten van een contralaterale PTLKD noodzakelijk is. Behoudens subglottische extensie als reeds bekende risicofactor werden geen andere selecterende factoren gevonden. De meerderheid van de positieve paratracheale lymfklieren zijn kleiner dan 1 cm en lijken negatief bij preoperatieve diagnostische screening.

Deze studies naar salvage chirurgie onderschrijven de behoefte aan beter beeldvormend onderzoek, met name om het aantal positieve chirurgische snijvlakken te verminderen, lymfkliermetastasen te identificeren en om asymptomische recidieven te detecteren.

DISCUSSIE

In dit proefschrift is bewijs aangeleverd voor verbetering van het diagnostische pad bij de detectie van een lokaal recidief larynxcarcinoom na eerdere radiotherapie. 18F-FDG-PET kan in de dagelijkse praktijk betrouwbaar, veilig en kosteneffectief worden gebruikt om patiënten verdacht van recidief larynxcarcinoom te selecteren voor directe laryngoscopie onder narcose.

Het belangrijkste voordeel van deze strategie is dat PET minder invasief is, zonder narcose en biopsie. Het vermindert tevens het gebruik van schaarse middelen, zoals opname- en operatiefaciliteiten, en PET biedt de mogelijkheid om tegelijkertijd het gehele lichaam te scannen op regionale en afstandsmetastasen.

Door de stijgende medische kosten in onze huidige maatschappij ligt er meer nadruk op verlaging van de kosten. Een ander aspect is het gebruik van schaarse middelen en dure faciliteiten. Faciliteiten moeten zo efficiënt mogelijk worden gebruikt.

Onderzoek kan inzicht geven in hoe deze faciliteiten het best ingezet kunnen worden om de kwaliteit van zorg te optimaliseren. Als onderdeel van de maatschappij georiënteerde benadering in Nederland, gaat de tunnel van Dunning uit van 4 criteria. Zorg moet noodzakelijk zijn, effectief, efficiënt, en kan niet aan de individuele verantwoordelijkheid worden overgelaten. Alle zorg moet door een tunnel met vier zeven. In de eerste zeef blijft onnodige zorg achter, vanuit een maatschappij georiënteerde benadering gezien. De tweede zeef selecteert op effectiviteit, en laat alleen zorg door die bewezen en gedocumenteerd effectief is. De derde zeef selecteert op efficiëntie, wat gemeten kan worden door de resultaten van kosten-effectiviteitsanalyses te gebruiken. De vierde zeef houdt zorg achter die overgelaten kan worden aan de individuele verantwoordelijkheid. Alle zorg die achterblijft in een van de vier zeven wordt gezien als niet-relevante zorg, in tegenstelling tot de zorg die door de tunnel vloeit en daarmee wordt gezien als relevante zorg en bijdraagt aan een verbetering van de kwaliteit van zorg.

Een gerandomiseerde multicenter trial is het meest gebruikte studie design, want hierin kunnen zowel de effectiviteit als de efficiëntie van verschillende strategieën worden vergeleken in het kader van effecten en kosten. De power van de studie moet vooraf bepaald worden.

De effectiviteit van een diagnostische test kan lastig te bepalen zijn. Bij het vergelijken van een interventie ten opzichte van de referentie, wordt de interventie als kosteneffectief gezien wanneer de kosten hiervan lager zijn. Er kan ook beargumenteerd worden dat er een bepaald percentage van kostenvermindering voorwaarde is voor een significante effectiviteit.

Een gerandomiseerde trial heeft meestal een afkappunt voor de follow-up. Idealiter zou in een kosteneffectiviteitsanalyse het effect ook gemeten worden met een lange termijn follow-up vanuit een levenslang perspectief. In kosteneffectiviteitsanalyses worden modeling technieken gebruikt om de effecten te extrapoleren naar een langere periode. De meest gebruikte uitkomstmaat is de quality adjusted life year (QALY). QALY's bieden de mogelijkheid om resultaten te vergelijken met andere interventies en ziektes.

De toegevoegde waarde van 18F-FDG PET is gebaseerd op de zeer goede negatief voorspellende waarde. Een voorwaarde voor een strategie met PET als eerste diagnostische middel is een hoge sensitiviteit, aangezien recidief tumor niet gemist mag worden. In de RELAPS studie werd een negatief voorspellende waarde van 97%, een sensitiviteit van 96% en een prevalentie van lokaal recidief van 30% gevonden. In eerdere studies werd een sensitiviteit van ongeveer 90% gerapporteerd en een negatief voorspellende waarde van 80-100% (16-22), en een recidief prevalentie van 25-50% beschreven voor T2-T4 larynxcarcinoom na radiotherapie (7,23-26). De prevalentie van lokaal recidief in onze studie (30%) is dus vergelijkbaar met de literatuur. Dit suggereert dat de resultaten van de RELAPS studie representatief zijn voor gebruik in de klinische praktijk.

Een beperking van de RELAPS studie is de lange periode tussen aanvang en einde van de studie. De technologische innovatie is voortgeschreden. De voorspelde residuele inefficiëntie na implementatie van 18F-FDG PET is gerelateerd aan het gebrek aan specificiteit van 18F-FDG PET. Deze inefficiëntie was 29% in de RELAPS studie. Synchroon verkregen beelden bieden de mogelijkheid tot een directe correlatie tussen FDG opname en anatomische structuren, waarmee de fout-positieve resultaten gereduceerd en de specificiteit verbeterd zouden kunnen worden. Helaas liet een meta-regressie analyse in een grote meta-analyse geen significant verschil in accuratesse zien tussen PET en geïntegreerde PET/CT bij de detectie van recidief hoofd-halskanker na radiotherapie (27). Ook in onze studie werd geen significant verschil gevonden.

Vroege detectie is essentieel, aangezien recidief ziekte vaak samen gaat met afstandsmetastasen. In een derde van de patiënten is het lokale recidief asymptomatisch, wat pleit voor reguliere controles met name in het eerste jaar. Het mediane interval tussen radiotherapie en detectie van recidief larynxcarcinoom was 9 maanden in onze studies, wat vergelijkbaar is met het interval gerapporteerd door anderen (28). Een follow-up schema met korte intervallen tussen de controles zou overwogen kunnen worden, hoewel een excessief hoog aantal routine controle bezoeken zou moeten plaatsvinden om het detectie percentage van asymptomatische recidieven te verbeteren. PET/CT zou patiënten kunnen stratificeren voor de intensiteit van de follow-up, met een afname van de follow-up frequentie voor patiënten met complete (metabolische) respons op PET/CT na behandeling (29,30). De Europese laryngologische vereniging ELS (European Laryngological Society) adviseert een follow-up periode tussen 4 en 8 weken in de eerste 2 jaar, en van 3 tot 6 maanden daarna (31).

Een beter inzicht in recidief patronen en een betere inschatting van het individuele risico zou mogelijk ook de vroege detectie kunnen verbeteren, waarmee salvage chirurgie vroeger kan plaats vinden. Recidiefpatronen kunnen een leidraad vormen tijdens poliklinische controle ten aanzien van het interval waarin het recidief zich manifesteert, presentatie van symptomen, lichamelijk onderzoek en imaging. Risico-inschatting behelst een gepersonaliseerd beleid wat gebaseerd is op de karakteristieken van een individuele tumor en de patiënt. Dit biedt de mogelijkheid om specifieker dan alleen gebaseerd op het TNM-stadium en lokalisatie van de tumor, te voorspellen wat de individuele kansen zijn voor respons op behandeling, recidief en overleving.

'Narrow-band imaging' (NBI) is een andere techniek die van waarde lijkt bij de vroege detectie van lokale ziekte na (chemo)radiotherapie (32-35). Deze techniek is gebaseerd op licht met gefilterde golflengtes van 415 (blauw licht) en 540 nm (groen licht), corresponderend met de pieken van hemoglobine, waarmee het capillaire netwerk wordt uitgelicht, en diepere lagen, waarmee submucosale vaten worden uitgelicht. Door het patroon van nieuwvorming van vaten worden oppervlakkige carcinomen beter geïdentificeerd.

Niet alleen de aanwezigheid van recidief tumor is lastig te diagnosticeren in bestraald weefsel, ook het bepalen van de uitbreiding van tumor, waarmee tijdens salvage chirurgie macroscopisch complete verwijdering bereikt kan worden, is moeilijk. Nieuwe intra-operatieve visualisatie technieken die gebruik maken van 'near-infrared' (NIR) fluorescentie optische beeldvorming worden ontwikkeld om beter onderscheid tussen gezond en kanker weefsel te kunnen maken (36-338). NBI is succesvol gebruikt om tijdens een transorale laser resectie van kleine larynxtumoren een betere afgrenzing van het oppervlakkige deel van de tumor te visualiseren (39).

In het geval van een bewezen locoregionaal recidief, is salvage chirurgie een optie voor een geselecteerde groep patiënten. Jongere patiënten met larynx- in plaats van hypofarynxcarcinoom zijn vaker kandidaat voor salvage chirurgie, waarschijnlijk omdat zij minder comorbiditeit hebben en daardoor beter in staat zijn om chirurgie te ondergaan. Salvage laryngectomie met halsklierdissectie biedt goede oncologische en functionele uitkomsten in een geselecteerde groep patiënten. Na radiotherapie en chemoradiotherapie waren de 5-jaars lokale controle percentages respectievelijk 70% en 58%, en de 5-jaars overlevingspercentages respectievelijk 50% en 27%. Dit is in lijn met de 5-jaars locoregionale controle van 70% en 5-jaars overleving van 31-57% zoals gerapporteerd in andere studies (13,40,41). Deze resultaten zijn echter matig vergelijkbaar door een gebrek aan homogeniteit (lokaal versus locoregionaal recidief, verschillen in primaire en salvage behandeling). Naast de status van de chirurgische marges van de resectieranden werd geen onafhankelijke voorspeller van overleving gevonden. Ondanks de zorgvuldige selectie van patiënten voor salvage laryngectomie was de incidentie van positieve chirurgische snijvlakken nog 10%, wat ook in lijn is met eerdere studies (40,42-45).

Van salvage chirurgie na radiotherapie is bekend dat het resulteert in een hoger complicatie-percentage dan primaire chirurgie, met complicatie-percentages tot 77% (12,14,15,46-48). De combinatie met chemotherapie verhoogt het complicatierisico verder (15). Wij vonden een complicatie-percentage van 56% na radiotherapie en van 73% na chemoradiotherapie, met fistels in respectievelijk 30% en 23% van de patiënten. Andere risicofactoren die geassocieerd zijn met het ontstaan van fistels zijn: tumor sublokalisatie, T-stadium, postoperatief hemoglobine gehalte <12,5 g/L en positieve chirurgische snijvlakken (49). Het gebruik van een pectoralis major lap als beschermende laag tussen mucosa en huid zou het risico op fistels kunnen reduceren (15,50). In ons onderzoek bij een sterk geselecteerde groep patiënten met een verhoogd risico op fistels kon dit niet bevestigd worden. Naast het gebruik van de pectoralis major lap, zijn er andere factoren die het risico op fistels zouden kunnen beïnvloeden, zoals de sluitingstechniek van de chirurgische wond, de start van orale voeding, het gebruik van een speekselstent en het gebruik van antibiotica (15,51). Een speekselstent wordt gebruikt in sommige klinieken voor circumferentiële fasciocutane reconstructies om het ontstaan van late stricturen te verminderen

en het percentage fistels te reduceren (52). Er zijn geen nationale of internationale richtlijnen met betrekking tot deze factoren. Onderzoek naar het optimale peri-operatieve protocol, specifiek voor salvage laryngectomie, is nodig.

Niet alleen een lokaal recidief maar ook (recidief) lymfkliermetastasen kunnen moeilijk te detecteren zijn. Omdat sommige lymfkliermetastasen niet gedetecteerd worden is het behandelen van de hals, zelfs als de hals klinisch gestadiëerd is als tumor-negatief, een veelgebruikte strategie. Deze strategie voorkomt dat ziekte in de hals vergevorderd is op het moment dat occulte (verborgen) metastasen klinisch zichtbaar worden of laat in de follow-up gedetecteerd worden. Hierdoor ondergaan sommige patiënten achteraf een onnodige behandeling. In het geval van een halsklierdissectie behelst dit een chirurgische procedure de gepaard kan gaan met morbiditeit, waaronder schouderfunctieklachten en cosmetische bezwaren. De alternatieve benadering van ´watchful waiting´ behelst het nauwkeurig controleren van de hals, met het risico op een verlate behandeling in sommige patiënten.

Als patiënten bewezen residuele ziekte in de hals hebben na (chemo)radiatie is het duidelijk dat er een halsklierdissectie moet worden verricht. Alhoewel bij een persisterende zwelling in de hals het onderscheid tussen residuele lymfkliermetastasen en weefselveranderingen als gevolg van de chemoradiatie lastig te maken is in veel gevallen, omdat induratie en fibrose na de behandeling een accurate beoordeling bemoeilijken. Deze problemen bij de evaluatie van de hals na chemoradiatie resulteren in minder effectieve salvage halsklierdissecties, en late recidieven in de hals zijn zelden chirurgisch curatief te behandelen (53). Omdat een betrouwbare beoordeling van de pathologische status na chemoradiatie moeilijk bleek, werden geplande lymfklierdissecties verricht na in opzet curatieve (chemo)radiatie (54,55).

Terwijl eerder onderzoek suggereert dat geen halsklierdissectie behoeft te worden verricht bij een subgroep van patiënten gebaseerd op de voorspelling van recidief patronen (56), vonden wij zelfs bij patiënten met kleine tumoren zowel ipsi- als contralaterale metastasen in de hals, wat in lijn is met de bevindingen van Farrag et al (55). Betrouwbare diagnostische technieken om regionale ziekte uit te sluiten zijn nodig om onnodige (contralaterale) halsklierdissecties en onnodig uitgebreide halsklierdissecties te voorkomen. Dit zou kunnen leiden tot meer selectieve halsklierdissecties om het complicatierisico te verminderen en om de lymfatische barrière in geval van recidief of tweede primaire tumor te behouden. In onze retrospectieve studies ondergingen niet alle patiënten een even uitgebreide halsklierdissectie. Daarom was het niet mogelijk om een algoritme te ontwikkelen om te bepalen welke patiënt een selectieve halsklierdissectie zou moeten ondergaan.

PET zou ook kunnen helpen bij de beslissing om wel of geen halsklierdissectie te verrichten. 18F-FDG PET is bij de detectie van occulte cervicale lymfkliermetastasen in de klinische N0 hals niet betrouwbaar genoeg om een electieve halsklierdissectie te vermijden (57,58). Dit kan theoretisch verwacht worden gezien de beperkte resolutie van de huidige PET scanners. Desondanks kan 18F-FDG PET belangrijke informatie verschaffen over de betrokkenheid van lymfklieren. Volgens een meta-analyse naar de diagnostische waarde van 18-F FDG PET na behandeling van hoofdhals-kanker heeft PET ook een hoge negatief voorspellende waarde (94%) bij detectie van

lymfkliermetastasen (21,22,27).Een recente gerandomiseerde studie onderzocht het verschil tussen PET-CT geleide follow-up (verricht 12 weken na chemoradiotherapie, met halsklierdissectie bij patiënten met incomplete of onduidelijke respons op PET-CT) en geplande halsklierdissectie bij patiënten met N2 of N3 gestadiëerde ziekte. De overleving was gelijk in beide studie-armen, maar de PET-CT geleide follow-up resulteerde in minder operaties en was meer kosten-effectief (59).

Bilaterale paratracheale lymfeklierdissecties zijn in het bijzonder geassocieerd met een verhoogd risico op fistels. De relatief zeldzame paratracheale lymfkliermetastasen worden met name gevonden bij patiënten met een primair glottisch larynxcarcinoom met subglottische uitbreiding. Subglottische uitbreiding was in andere studies ook geïdentificeerd als risicofactor voor paratracheale lymfekliermetastasen, evenals een maximale axiale diameter van ≥5 mm van de paratracheale klieren op CT of MRI, en een klinisch positieve status van de lymfeklieren in de rest van de hals (60). Indien minstens één van deze risicofactoren aanwezig was, werd een hoge sensitiviteit (90% voor CT en 100% voor MRI) en een lage specificiteit (19% voor CT en 32% voor MRI) gevonden. De in de literatuur gerapporteerde incidentie van paratracheale lymfkliermetastasen in patiënten die een laryngectomie ondergaan is hoger (9-20%) dan in onze studie, maar dit was met name onderzocht in onbehandelde patiënten in tegenstelling tot onze patiënten met recidief na eerdere radiotherapie (61-65). In 27% van de onbehandelde patiënten met larynxcarcinoom met subglottische uitbreiding werden paratracheale lymfkliermetastasen gevonden (66). Een nadeel van onze studie is het retrospectieve karakter waardoor verschillende chirurgen met verschillende chirurgische technieken verschillend kunnen zijn geweest in de uitgebreidheid van de paratracheale lymfeklierdissectie. Een andere beperking is het kleine aantal paratracheale lymfkliermetastasen.

TOEKOMSTPERSPECTIEVEN

Nu de waarde van 18F-FDG-PET als eerste aanvullend diagnostisch onderzoek bij verdenking op een lokaal recidief larynxcarcinoom na radiotherapie is aangetoond, dienen richtlijnen en protocollen te worden aangepast (67).

In het gepresenteerde onderzoek werd met name PET, en soms PET/CT, gebruikt. RELAPS toonde geen significant verschil in accuratesse aan tussen PET en PET/CT, wat suggereert dat data van PET zonder CT representatief zijn voor het huidige PET/CT tijdperk. In de toekomst zal beeldfusie van PET in combinatie met MRI mogelijk resulteren in een verdere verbetering van de diagnostische accuratesse. De combinatie van PET/MRI zal hopelijk het aantal fout-positieve PET scans vroeg na radiotherapie als gevolg van non-specifieke tracer opname door inflammatie doen verminderen (68,69). Een ander voordeel van MRI is de verwachte toegevoegde waarde ten opzichte van CT in bepaalde specifieke situaties, waaronder perineurale groei van tumoren en infiltratie in belangrijke anatomische structuren, zoals de prevertebrale fascie en grote bloedvaten (70). Daarnaast kan 18F-FDG opname worden gecorreleerd aan functionele informatie, verkregen met nieuwe MRI technieken (69).

18F-FDG is een op glucose gebaseerde tracer, bekend om zijn sensitiviteit voor zowel tumor als inflammatie. Andere tracers, meer specifiek voor tumor, kunnen de accuratesse van PET mogelijk ook verbeteren. 18F-gelabelde fluoro-3-deoxy-3-L-fluorothymidine (18F-FLT) is gerelateerd aan cellulaire proliferatie. De opname van 18F-FLT neemt sneller af na start van therapie, vergeleken met 18F-FDG (71). Verhoogd aminozuur-metabolisme is een andere bekende eigenschap van tumoren. Vergeleken met het glucosederivaat 18F-FDG is de opname van aminozuren lager in macrofagen en andere inflammatoire cellen, wat theoretisch zou moeten resulteren in een hogere specificiteit (71).

Niet alleen de indicaties, maar ook de techniek van MRI is geëvolueerd. Diffusie-gewogen MRI (DW-MRI) is een veelbelovende techniek voor vroege en late follow-up na (chemo)radiotherapie en voor de detectie van een recidief carcinoom (69,72-74). Na (chemo)radiotherapie kunnen restafwijkingen en afwijkingen als gevolg van de behandeling worden gevonden. Met de huidige conventionele morfologische MRI technieken worden problemen ervaren in het onderscheiden van benigne veranderingen na behandeling en kanker-residu. Kwalitatieve DW-MRI analyse na behandeling wordt uitgevoerd door visuele beoordeling van de signaal intensiteit op de diffusie gewogen beelden.

De verhoogde cellulaire densiteit in tumorweefsel resulteert in een reductie van diffusie van watermoleculen waardoor de ADC (‘apparent diffusion coefficient’) laag is op plaatsen waar tumorweefsel aanwezig is. Tegengesteld resulteert inflammatie in een verhoogde diffusie van watermoleculen, met een hoge ADC-waarde. Zowel kwalitatieve (visuele) als kwantitatieve analyses kunnen helpen bij het onderscheiden van kanker-residu en benigne veranderingen na behandeling (74,75). DW-MRI heeft bewezen specifieker te zijn dan MRI zonder diffusie bij na radiotherapie morfologisch verstoorde weefsels (75-78). DW-MRI lijkt ook al vroeg na de start van radiotherapie bruikbaar te zijn (77,79). Het is nog onduidelijk of DW-MRI als onderdeel van

PET/MRI een toegevoegde waarde heeft (80). Bij respons evaluatie na chemoradiotherapie voor vergevorderde lymfekliermetastasering van hoofdhals-kanker lijkt DW-MRI de accuratesse van 18F-FDG-PET-CT te verbeteren (81).

Een tweede veelbelovende MRI techniek bij hoofdhals-kanker is de dynamische MRI met contrast (DCE-MRI, MRI perfusie) (82). De bloeddoorstroming door de tumor kan in beeld gebracht worden en kwantitatief uitgedrukt worden met dynamische MRI. Weinig perfusie (en hypoxie) in de tumor lijkt een marker voor een slechte respons op therapie en een slechte prognose (82-84). Hoewel DCE-MRI met name wordt onderzocht als prognostisch middel om respons na radiotherapie te voorspellen, zou het ook gebruikt kunnen worden om respons tijdens behandeling te kunnen monitoren (85-87). PET/MRI met contrast zou superieur kunnen zijn aan PET/CT met contrast om onduidelijke 18F-FDG opname, mogelijk gerelateerd aan tumorrecidief, te specificeren (88). In de toekomst kunnen amide proton transfer gewogen T3 imaging (APTwMRI) en proton MRI spectroscopie mogelijk een rol spelen (69,89).

Gedurende de behandeling veranderen de karakteristieken van de hypoxische subvolumes. Het is aangetoond dat met MRI perfusie technieken de verandering van tumor vascularisatie tijdens anti-angiogenetische therapie kan worden aangetoond (90,91). Op deze manier kunnen patiënten met een hoog risico op residuele ziekte geïdentificeerd worden en kunnen voor een strikte follow-up en een vroege evaluatie afgesproken worden. Dit draagt bij aan de totstandkoming van de optimale individuele therapie.

Met diverse PET-tracers, waaronder 18-FAZA, kan hypoxie in de tumor in beeld gebracht worden. Voor onderzoek naar hypoxie met PET/MRI lijkt de combinatie van MRI perfusie met 18F-FAZA PET veelbelovend (92). Een andere interessante tracer is (62)Cu-ATSM ((62)-Cu-diacetyl-bis (N4)-methylsemithiocarbazone) (93,94). MRI en PET kunnen gebruikt worden om dezelfde fysiologische parameter te monitoren voor cross-validatie of om verschillende stadia van metabolische activiteit te monitoren.

In de RELAPS studie was het minimum interval tussen radiotherapie en PET 2 maanden. Radiatie geïnduceerde inflammatie kan leiden tot fout-positieve bevindingen met 18F-FDG PET in de vroege follow-up periode na radiotherapie, maar eerdere studies lieten geen voordeel zien in het wachten met PET tot een periode langer dan 8 weken (9). Met de huidige kwaliteit van PET, met name gecombineerd met CT of MRI, is de accuratesse bij een interval korter dan 2 maanden mogelijk ook voldoende (96). Nieuwe studies zullen opgezet moeten worden om de accuratesse van PET als functie van de tijd na radiotherapie te onderzoeken. Des te eerder een recidief is ontdekt, des te beter de overlevingskansen zijn.

De behandeling van gevorderd larynxkanker is nu op een punt dat de huidige standaard behandeling, gecombineerde chemotherapie en radiotherapie met bij recidief tumor salvage chirurgie achter de hand herbeoordeeld dient te worden. De overlevingspercentages van patiënten met larynxkanker nemen af de laatste twee decennia, in plaats van toe (97,98). Gedurende dezelfde periode is een toename van de niet-chirurgische behandeling bij larynx kanker gesignaleerd (99). Primaire behandeling van T3N0M0 larynxkanker (alle sublokalisaties)

met chemoradiotherapie of radiotherapie alleen resulteerde in een slechtere 5-jaars overleving vergeleken met een operatie met of zonder radiotherapie. Daarentegen werden vergelijkbare overlevingspercentages gevonden voor patiënten met T3N0M0 glottisch larynx carcinoom die primair werden behandeld met chemoradiotherapie versus operatie met radiotherapie (98,100). De optimale behandeling van patiënten met T4 larynx kanker blijft controversieel. Sommige studies tonen een verminderde overleving voor patiënten die primair behandeld zijn met (chemo)radiatie vergeleken met laryngectomie (101-103), terwijl anderen een vergelijkbare overleving beschrijven (100). De afgenomen overlevingspercentages kunnen gerelateerd zijn aan veranderingen in managementpatronen, waarvan de meest ingrijpende de toename van chemoradiotherapie en de afname van chirurgische behandeling als primaire behandeling is. Het kan ook een onterechte afdwaling van ´de standaard behandeling´ weergeven (101). Gebaseerd op de laatste data lijkt er genoeg bewijs te zijn om voor T4 vergevorderd larynx kanker een totale laryngectomie te overwegen, aangezien in de meeste studies de overlevingskansen beter lijken dan met chemoradiotherapie (104). Patiënten moeten waarschijnlijk beter geselecteerd worden voor de beste behandelingsmodaliteit. Een geïndividualiseerde benadering is voor de primaire behandeling belangrijk. Niet alleen de uitbreiding van de tumor en de functionaliteit van de larynx voorafgaand aan behandeling zijn belangrijke criteria voor therapie keuze, maar ook de verwachte draagbaarheid van de behandeling op basis van de ´performance status´ en comorbiditeit, met name cardiopulmonaire chronische ziekte (101). Bij inventarisatie van factoren die de beslissingen van patiënten rondom (een gevorderde vorm van) larynx kanker beïnvloeden, bleek de kwaliteit van na de behandeling belangrijker dan de behandelingsmodaliteit zelf (105). Een andere factor om te betrekken bij de selectie van de behandeling is de ziekenhuisstructuur en medische voorzieningen voor een chemoradiatie behandeling (104). Alle voorzieningen noodzakelijk voor het uitvoeren van de behandeling, de follow-up en salvage chirurgie moeten beschikbaar zijn met een hoog kwaliteitsniveau en optimale samenwerking van de verschillende disciplines.

Er is behoefte aan een betere identificatie van patiënten die niet zullen reageren op therapie. Bij PET is er toenemend interesse voor volumetrische parameters van metabolisme zoals Metabolisch Tumor Volume (MTV) en Totale Laesie Glycolyse (TLG) als prognostische predictoren voor uitkomst, alhoewel er nog geen afkapwaarde is vastgesteld (106,107).

Met zowel PET als (DW- of DCE-)MRI lijkt het mogelijk om in de vroege fase van niet-chirurgische behandeling te voorspellen welke patiënten niet zullen reageren op therapie (77,79,87,108-115). Functionele beeldvormende modaliteiten zijn potentieel complementair en moeten daarom als combinatie worden onderzocht bij het ondersteunen van strategieën om behandelingen tussentijds aan te passen (116). Identificatie van non-responders na twee van de geplande zeven weken (chemo)radiotherapie biedt de mogelijkheid om behandeling verder te intensiveren, of om eventueel zinloze verdere (chemo)radiotherapie te staken en over te gaan op een chirurgische behandeling. Een vroege verandering van primaire (chemo)radiatie naar een laryngectomie met postoperatieve radiotherapie als reserve zal theoretisch de overlevingspercentages kunnen verhogen in deze groep. Een recente meta-analyse liet een 3,55 keer verhoogd risico op overlijden en een 4,73 keer verhoogd risico op progressie of recidief van hoofd-halskanker zien bij patiënten met suspecte bevindingen op 18F-FDG PET of PET/CT gedurende en na behandeling (117). Er is dus een voorspellende waarde voor respons op therapie, maar de 18F-FDG PET studies tijdens en

vroeg na therapie waren niet zo sterk voorspellend voor uitkomst als de scans verkregen lang na het beëindigen van therapie (117-120).

18F-FDG PET scans kunnen ook gebruikt worden voor radiotherapie-planning, aangezien 18F-FDG-avide hoofd-halstumoren een 10-30% hogere dosis nodig lijken te hebben dan niet-18F-FDG PET-avide tumoren (121).

Naast predictie van respons op basis van beeldvormende technieken, wordt getracht de zorg te personaliseren op basis van andere tumorkarakteristieken zoals biomarkers (122-127). Biomarker-onderzoek focust bijvoorbeeld op karakteristieken van de primaire tumor en serum-markers. Verdere differentiatie met biomarkers zou een betere voorspelling van respons op (chemo) radiotherapie moeten kunnen opleveren.

Het combineren van de huidige klinische onderzoeken met genexpressie profilering van de primaire tumor om lymfkliermetastasen te voorspellen, lijkt veelbelovend voor de toekomst om nieuwe klinische beslissingsmodellen te ontwikkelen. Een genexpressie profiel om metastasering van N0 mondholte- en orofarynxkanker te identificeren is reeds ontwikkeld en geherevalueerd (127,128). Voor larynxkanker is een ander genexpressie profiel gevonden, geassocieerd met lymfkliermetastasen (129) en slechte ziektevrije overleving (130).

Een mogelijkheid met potentie om beslissingen in de behandelstrategie te verbeteren vanuit tumor karakteristieken is het gebruik van radiomics (131). Een analyse gebaseerd op radiomics kwantificeert de intensiteit, vorm en textuur van de tumor. Met de data van radiomics van hoofd-halskankerpatiënten werd een algemeen prognostisch fenotype geïdentificeerd, geassocieerd met onderliggende genexpressie-patronen. Deze techniek lijkt veelbelovend maar behoeft uitgebreide validatie. Met de lage prevalentie van recidief tumor is een grote hoeveelheid patiënten vereist om meta-analyses van individuele patiënten data te kunnen verrichten, en is gestandaardiseerde beeldvorming een voorwaarde.

Vroege onderzoeksresultaten suggereren dat circulerende tumorcellen gebruikt kunnen worden voor de identificatie van patiënten die baat hebben bij het intensiveren van de behandeling (132). De detectie van circulerende tumorcellen na chirurgie bleek namelijk gerelateerd aan een slechte overleving bij patiënten met hoofd-halskanker. Seriële bepalingen van circulerend tumor DNA voor de detectie van occulte metastasen van borstkanker bleek zeer accuraat in voorbereidend onderzoek (133). Deze methode zou bij hoofd-halskanker bestudeerd kunnen worden om te evalueren of circulerend tumor DNA gebruikt kan worden voor vroege detectie van afstandsmetastasen, om te trachten onnodige uitgebreide locoregionale behandeling te voorkomen.

Bij een bewezen recidief tumor zal salvage chirurgie aan de orde komen. Selectiecriteria voor salvage chirurgie en de uitgebreidheid daarvan moeten worden gespecificeerd en geïndividualiseerd. Algoritmes voor salvage chirurgie zullen er primair op gericht zijn om de overlevingskansen te verbeteren, en secundair om complicaties te voorkomen. Vroege en betrouwbare detectie van recidief kan de overlevingskansen verbeteren. Wondgenezingsproblemen zijn de belangrijkste complicaties na salvage chirurgie. Weefseltechnologie met groeifactoren kunnen mogelijk

bijdragen aan een betere wondgenezing in sterk bestraald weefsel (134-136). In het tijdperk van gepersonaliseerde zorg, zal toekomstig onderzoek zich moeten focussen op verfijning van de behandelstrategie en diagnostische strategie na behandeling, gericht op detectie van recidieven, met meer gepersonaliseerde selectiecriteria. Vele patiënt-, tumor- en arts-gerelateerde factoren moeten overwogen worden. Gepersonaliseerde zorg zal de toekomst zijn van de diagnostiek en behandeling van kanker.

De resultaten en opzet van de RELAPS studie zullen hopelijk in een bredere context leiden tot meer gerandomiseerde multicenter trials met kosteneffectiviteits analyes. De toepassing van PET, of PET in combinatie met andere beeldvormende technieken, kan mogelijk ook gebruikt worden om andere onnodige behandelingen te voorkomen, zoals bijvoorbeeld lymfklierdissectie na (chemo)radiotherapie. PET wordt ook gebruikt voor andere indicaties zoals predictie van respons op (chemo)radiotherapie. Met de combinatie van gerandomiseerde trials en kosteneffectiviteits analyses, inclusief kwaliteit van leven metingen, kan het gebruik van PET in de klinische praktijk verder worden geoptimaliseerd.

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