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Phase III randomised trial

Effectiveness of an ^{18}F-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 ^{18}F-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 ^{18}F-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.

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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 ^{18}F-fluorodeoxyglucose positron-emission tomography (^{18}F-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 ^{18}F-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 ^{18}F-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, CT-chest, 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 ^{18}F-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 ($n = 76$).

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

Table 1
Baseline characteristics of the patients.

Variable	Conventional strategy CWU ($N = 74$)	^{18}F-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%)	(5%)

PET/CT. Median delay between injection of ^{18}F-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).

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)

Table 2
Follow-up of the patients.

Variable	Conventional strategy CWU (N = 74)	^{18}F-FDG-PET based strategy PWU (N = 76)	p-Value
Direct laryngoscopies per patient – No. 6 months			p = 0.027 (Cochran–Armitage trend test)
0 laryngoscopies	2	20	
1 laryngoscopies	53	39	
2 laryngoscopies	19	14	
3 laryngoscopies	–	1	
4 laryngoscopies	–	1	
5 laryngoscopies	–	–	
Direct laryngoscopies per patient – No. 12 months			p = 0.028 (Cochran–Armitage trend test)
0 laryngoscopies	2	17	
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.

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).

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.

Discussion

This trial demonstrates that a diagnostic strategy including ^{18}F-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
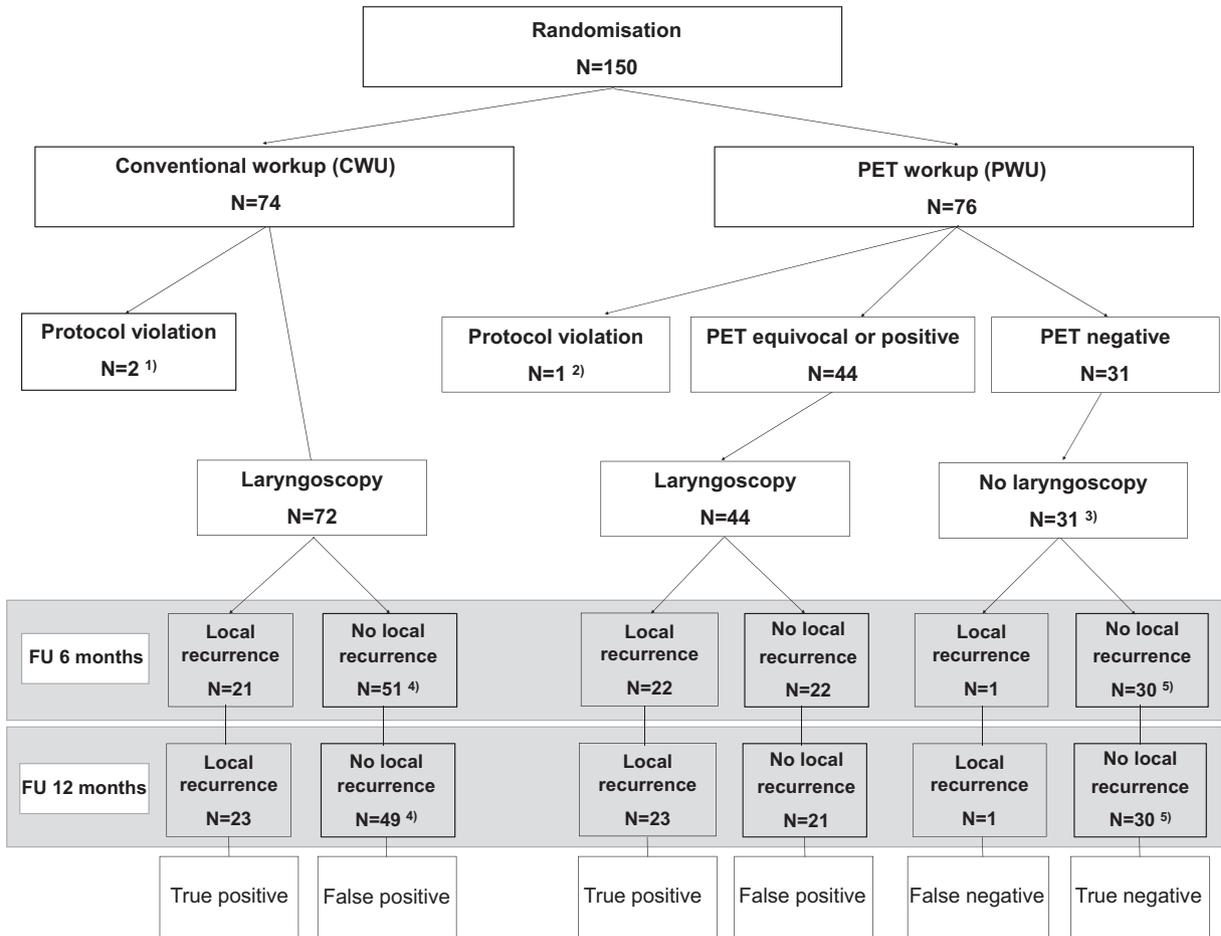
Fig. 1. Flow chart of included patients, based on six month follow-up. (1) two patients: no laryngoscopy, (2) one patient: no PET, local tumor, (3) one patient: although PET was negative, laryngoscopy was performed, (4) two patients: follow-up <6 months, (5) three patients: follow-up <6 months.
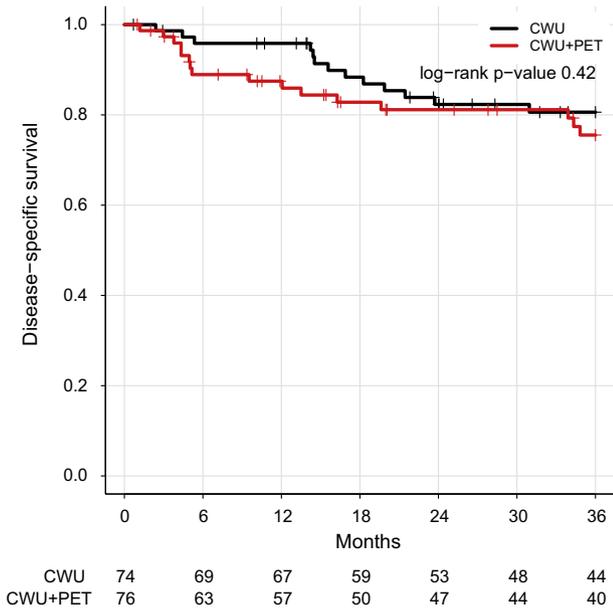

	0	6	12	18	24	30	36
CWU	74	69	67	59	53	48	44
CWU+PET	76	63	57	50	47	44	40

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

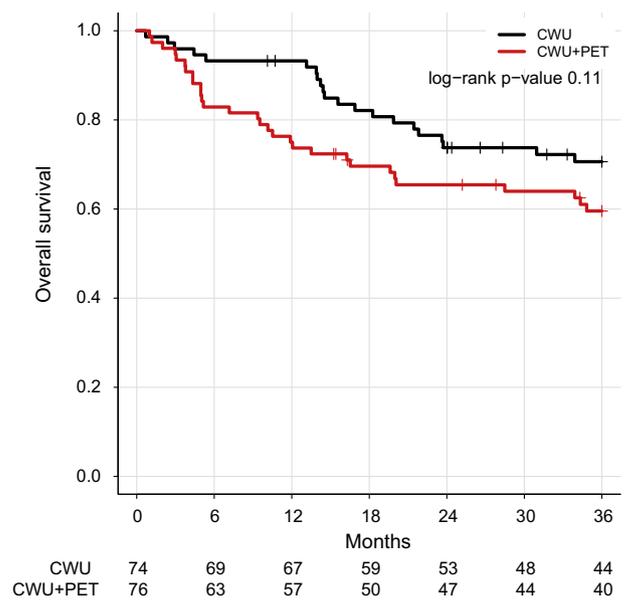|	0	6	12	18	24	30	36
CWU	74	69	67	59	53	48	44
CWU+PET	76	63	57	50	47	44	40

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

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 ^{18}F-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 ^{18}F-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%.

Conflicts of interest

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.10.010.

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