Eur Arch Otorhinolaryngol (2009) 266:1441–1448
DOI 10.1007/s00405-008-0878-3

HEAD AND NECK

The cost-effectiveness of ^{18}FDG-PET in selecting patients with suspicion of recurrent laryngeal carcinoma after radiotherapy for direct laryngoscopy

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Received: 26 August 2008 / Accepted: 11 November 2008 / Published online: 29 November 2008

Abstract The aim of this study was to estimate the cost-effectiveness of ^{18}FDG-PET in the selection for direct laryngoscopy in patients with suspicion of recurrent laryngeal carcinoma after radiotherapy. The direct medical costs of 30 patients with suspicion of a recurrence were calculated from the first visit where suspicion was raised until one year after. A conventional strategy, in which all these patients underwent direct laryngoscopy, was compared to an ^{18}FDG-PET strategy in which only patients with a positive or equivocal ^{18}FDG-PET underwent direct laryngoscopy. A sensitivity analysis was performed to examine the influence of the type of camera and 'setting'. The mean costs of an ^{18}FDG-PET strategy were €399 less than a direct laryngoscopy strategy. The type of camera and setting had no influence. In patients with suspicion for recurrent laryngeal carcinoma after radiotherapy, ^{18}FDG-PET seems to be effective and less costly in selecting patients for direct laryngoscopy.

Keywords Cost-effectiveness · Recurrent laryngeal carcinoma · Radiotherapy · ^{18}FDG-PET

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Introduction

Laryngeal cancer is the most common cancer of the head and neck. Each year around 700 new cases of laryngeal carcinoma are diagnosed in The Netherlands [1]. Early laryngeal cancer can usually be managed successfully with either radiotherapy or surgery. Advanced stage disease is often treated with a combination of treatment modalities. Many laryngeal carcinomas are treated with radiotherapy with or without chemotherapy with surgery for salvage in case of recurrence. Depending on tumour stage, the local recurrence rate varies from 10 to 50% [2]. Distinguishing between recurrent carcinoma and radiotherapeutic sequels frequently poses a difficult clinical problem. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used diagnostic methods in primary laryngeal carcinoma. When recurrent laryngeal cancer is suspected they seem to be less effective, unless a base-line posttreatment scan is performed [3–7]. Therefore, patients with clinical suspicion of recurrent laryngeal cancer almost invariably undergo a direct laryngoscopy under general anaesthesia with taking of biopsies. It has been shown that less than 50% of these procedures show recurrence. Therefore, more than 50% of these direct laryngoscopies are futile with unnecessary general anaesthesia and risk of exacerbation of postradiotherapy changes [6]. F18-deoxyglucose (^{18}FDG) Positron Emission Tomography (PET) could be able to distinguish between recurrent tumour and radiation sequelae and the first results of ^{18}FDG-PET in the diagnosis of recurrent laryngeal cancer are promising. In previous studies a specificity of 80–100%, a positive predictive value of 67–89% and negative predictive value of 80–100% has been reported [8–12].

Current health policy makers rightfully dictate the need for economic evaluations of new expensive diagnostic

Table 1 Number of patients in the several tumour and lymph node (N) stages of the primary laryngeal carcinoma

	N0	N1	N2
T1	3	0	0
T2	10	2	1
T3	5	1	0
T4	6	1	1

techniques, such as ^{18}FDG-PET [13]. Next to accuracy data, the cost effectiveness of ^{18}FDG-PET in the diagnosis of recurrent laryngeal cancer thus needs to be investigated. In fact two diagnostic strategies have to be compared: In the conventional strategy all patients undergo direct laryngoscopy under general anaesthesia with taking of biopsies if necessary. In the ^{18}FDG-PET strategy only patients with a positive or equivocal ^{18}FDG-PET undergo direct laryngoscopy. In the latter strategy ^{18}FDG-PET was used as selection method for performing direct laryngoscopy. The aim of the present study was to compare the costs of both strategies.

Patients and methods

Patients and clinical procedures

In this retrospective study, data of 30 patients who were seen between 1998 and 2001 with suspicion of recurrent laryngeal cancer after radiotherapy were analysed. All patients had radiotherapy for a primary laryngeal carcinoma. The distribution of tumour subsites was 63% glottis, 33% supraglottis and 3% subglottis. Ten percent of the patients were staged T1, 43% T2, 20% T3 and 27% T4 (Table 1).

All patients underwent a direct laryngoscopy with biopsies under general anaesthesia as well as a single ^{18}FDG-PET scan. The median interval between the last radiation fraction and the PET scan was 8.7 months (range 2.4–32.1 months). They were all studied after fasting overnight. Preceding the ^{18}FDG-PET studies, the patients' plasma glucose level was measured. Sixty minutes after intravenous administration of 370 MBq, ^{18}FDG imaging of the head and neck region was performed by scanning two bed positions. The ^{18}FDG-PET scans were done by two technologists and a nuclear physician and performed before the laryngoscopy to avoid false-positive ^{18}FDG-PET findings as a result of trauma due to the biopsies taken.

In both (modelled) strategies patients had regular follow-up visits after ^{18}FDG-PET and direct laryngoscopy. Histopathological examination of the biopsy taken or primary tumour status after 12 months of follow-up was used as the reference standard. With the results of both diagnostic tests a decision tree with five paths was constructed (Fig. 1). Salvage laryngectomy was advised in case of recurrence.

Cost effectiveness

The costs of medical consumption in all paths (conventional and ^{18}FDG-PET based) of the decision tree were analysed, as well as the effects.

Costs

The study was performed from an institutional perspective. The follow-up period was 12 months after the outpatient visit, where suspicion of recurrence was raised. This study period was divided in three phases: diagnostic, treatment and follow-up phase. The cost analysis was based on the direct medical costs. Medical tests not related to the laryngeal cancer were not taken into account. The cost categories considered were amongst others, operations, in-hospital days, ^{18}FDG-PET scans, visits, imaging techniques, laboratory examinations, pulmonary function, physical therapy, blood products, speech therapy and pathology. For the most important items in the medical consumption, unit costs by using the microcosting method were calculated. This method is based on an inventory of consumed materials, hospital personal and overhead costs [14, 15]. Unit prices calculated in previous studies and tariffs were used for less expensive tests [16–19]. The mean costs per patient were categorised in operations, in-hospital days, visits and others. The costs were expressed in euros in the year 2003.

Unit cost of ^{18}FDG-PET

The unit cost of the ^{18}FDG-PET scan consisted of costs made for equipment, personal, material and overhead costs.

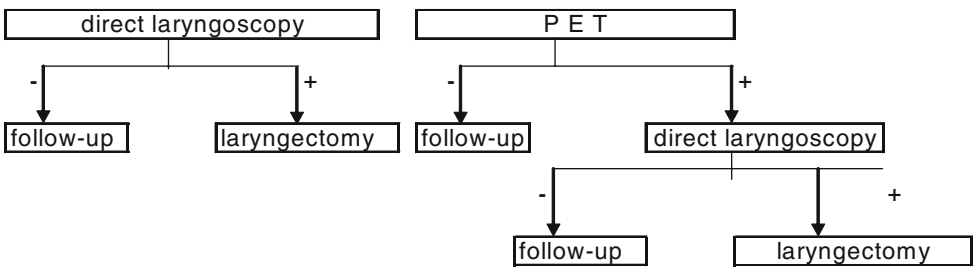

Fig. 1 Study model

Depreciation over 7 years was used to calculate yearly investment costs for the PET scanner. Yearly maintenance costs were 8% of the price paid for the PET scanner and computer equipment. These costs were accounted according to the ^{18}FDG-PET utilisation time for a head and neck ^{18}FDG-PET scan and the time the PET scanner was used per year. The costs of ^{18}FDG were based on the price paid per month for a fixed number of patient injections. The cost of staff was valued by internal unit costs of the hospital accounting system. To account for the overhead costs for infrastructure service, a standard mark up percentage of 35% on all operating costs was used.

For the calculation of a unit cost of ^{18}FDG-PET it is important to distinguish between a covered and a non-covered setting, i.e. in a situation of using ^{18}FDG-PET for research purposes. When not all ^{18}FDG-PET scans are covered, then these scans should be ascribed to the unit costs of the ^{18}FDG-PET scan which are covered. In this study this is called the non-covered academic setting. The unit cost price of the ^{18}FDG-PET and the ^{18}FDG-PET-CT in an academic setting and in a non-covered academic setting were calculated for the standard procedure of 15 min. The cost of the mobile PET scanner was based on the rent paid for the mobile PET scanner and the hospital personal needed. The cost of ^{18}FDG was based on the mean price of 370 MBq charged by Tyco Healthcare (Zaltbommel, The Netherlands). The total costs of both strategies were calculated for the various ^{18}FDG-PET and ^{18}FDG-PET-CT settings.

Effectiveness

The effects were expressed as the number of direct laryngoscopies avoided, mean cost per strategy within 12 months and costs saved per avoided direct laryngoscopy.

Sensitivity analysis

The cost of ^{18}FDG-PET could be influenced by the type of camera (PET, PET-CT, mobile PET) and 'setting' (academic, non-covered academic hospital). Because there were no studies, which compare ^{18}FDG-PET and ^{18}FDG-PET-CT for this specific indication, it is assumed in this analysis that both imaging techniques detect residual laryngeal carcinoma after radiotherapy equally well. The efficiency of ^{18}FDG-PET in the diagnosis of recurrent laryngeal cancer could also depend on the sensitivity and specificity of ^{18}FDG-PET, examination time of ^{18}FDG-PET as well as the prevalence of recurrences in the studied population. The influence of these parameters on the efficiency of ^{18}FDG-PET was therefore analysed in the sensitivity analysis.

Statistical analysis

In this study the mean costs per patient per cost category are reported. The 95% variance was calculated for each category in each phase. Statistical significance between the various strategies was not calculated due to the small number of patients.

Results

Clinical results

The direct costs of 30 patients, 22 men and 8 women (mean age 64.0; range 52–82) were examined. The prevalence of recurrent laryngeal cancer in this study was 0.233.

For direct laryngoscopy the sensitivity, specificity, positive as well as the negative predictive value in this study were 1.0 since no additional recurrences were detected during 12 months of follow-up. The positive test probability was 0.233. The negative test probability was 0.767. For ^{18}FDG-PET the sensitivity was 1.0, the specificity was 0.86. The positive and negative predictive values were, respectively, 0.64 and 1.0. The positive test probability was 0.367. The sensitivity of 1.0 in this study implied that no patient was denied a direct laryngoscopy if selection was based on ^{18}FDG-PET. In total 19 direct laryngoscopies would have been avoided if ^{18}FDG-PET was used for selection.

There were four false-positive ^{18}FDG-PET scans in the ^{18}FDG-PET strategy for which no obvious explanation other than post-radiotherapy inflammatory changes was found. Four patients with recurrent laryngeal cancer had a total laryngectomy. None of these patients with recurrent tumour were suitable for partial laryngectomy. One patient refused, another patient died within 1 month and in one patient the tumour was inoperable. Two patients underwent microlaryngoscopy and CO_2-laser treatment of oedema because of dyspnoea complaints. The costs of these operations were also taken into account.

Cost analysis

The unit cost price of ^{18}FDG-PET amounted to € 521 (Personal (P) €29; Material (M) €356; Overhead (O) €135). The cost price of ^{18}FDG-PET in a non-covered academic setting, amounted to € 1156 (P €333; M € 523; O €300). The cost price of a mobile ^{18}FDG-PET was € 611 (P € 29; M € 423; O € 158).

The mean costs were assigned to four categories; operations, in-hospital days, visits and others (Table 2). The mean costs per patient for the conventional strategy were, respectively, €2.205, €1.480 and €9.545 for the diagnostic,

Table 2 Mean costs (95% CI) in euros per patient per strategy per phase per cost category

Path	Phase	Operations		In hospital days		Visits		Other		Mean costs	Mean costs
		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Phase	Per path
SCOPIE TN	Diagnosic	429.96	298.26–561.28	1,096.35	981.00–1,211.70	89.15	88.68–89.61	438.35	437.80–438.89	2,053.80	
	Treatment	317.13	38.10–596.16	34.26	−1.75–70.27	6.72	6.72–6.72	45.38	44.84–45,93	403.50	
	Follow-up	1,062.74	233.01–1,892.47	5,826.00	−834.92–12,486.92	644.27	641.88–646.66	1,721.37	1,718.44–1,724.29	9,254.37	€11.712
SCOPIE TP	Diagnosic	412.00	289.32–534.59	1,350.86	1,066.01–1,635.70	158.66	152.61–164.71	779.29	774.70–783.88	2,700.81	
	Treatment	3,537.97	1,457.38–5,618.56	337.71	136.30–539.13	7.36	7.36–7.36	1,133.32	1,104.24–1,167.85	5,016.36	
	Follow-up	290.79	−92.95–674.37	7,547.71	2,650.28–12,445.15	439.33	419.15–459.52	2,221.88	2,208.53–2,235.22	10,499.71	€18.217
PET TN	Diagnosic	0.00		124.42	−8.45–257.29	94.89	94.66–95.92	827.06	2.16–316.63	1,046.37	
	Treatment	383.89	40.66–727.13	41.47	−2.82–85,76	8.14	8.14–8.14	54.94	54.21–55.66	488.44	
	Follow-up	1,043.63	31.49–20,558.81	5,827.05	−2,348.64–14,002.74	644.99	642.39–648.27	1,730.90	1,726.53–1,735.27	9,246.57	€10.781
PET FP	Diagnosic	593.50	148.48–1,038.52	1,280.50	1,087.44–1,473.56	61.88	56.41–67.35	1,001.37	470.71–489.94	2,937.25	
	Treatment	0.00		0.00		0.00		0.00		0.00	
	Follow-up	1,154.00	297.68–2,009.32	5,821.00	582.10–11,059.90	640.84	602.51–679.18	1,676.08	1,656.81–1,695.35	9,291.93	€12.229
PET TP	Diagnosic	412.00	289.32–532.59	1,350.86	1,066.01–1,635.70	158.66	152.61–164.71	1,300.29	774.70–783.88	3,221.81	
	Treatment	3,537.97	1,457.38–5.618,56	337,71	136.30–539.13	7.36	7.36–7.36	1,133.32	1,104.24–1,167.85	5,016.36	
	Follow-up	290.79	−92.85–674.35	7,547.71	2,650.28–12,445.15	439.33	419.15–549.52	2,221.88	2,208.53–2,235.22	10,499.71	€18.738

TN true negative, *TP* true positive, *FP* false positive, *CI* confidence interval

Table 3 Mean and median costs in euros per phase per path

Path	Description	Diagnostic phase		Treatment phase		Follow-up phase		Total	
		Mean	Median	Mean	Median	Mean	Median	Mean	Median
1	Laryngoscopy + follow-up	€2.054	€1.918	€403	€0	€9.254	€1.729	€11.712	€3.595
2	Laryngoscopy + laryngectomy	€2.701	€2.303	€5.016	€4.548	€10.500	€8.822	€18.217	€16.246
	Mean costs laryngoscopy per patient	€2.205		€1.480		€9.545		€13.230	
3	PET + follow-up	€1.046	€935	€488	€0	€9.247	€1.639	€10.781	€2.418
4	PET + laryngoscopy + follow-up	€2.937	€2.603	€0	€0	€9.292	€7.764	€12.229	€10.367
5	PET + laryngoscopy + laryngectomy	€3.222	€2.928	€5.016	€4.603	€10.500	€9.517	€18.738	€18.554
	Mean cost PET per patient	€1.806		€1.480		€9.545		€12.831	

treatment and follow-up phase, resulting in overall mean costs of €13.230. For the ^{18}FDG-PET-based strategy the mean costs per patient for the different phases were, respectively, €1.806, € 1.480 and €9.545. The overall mean costs per patients for the ^{18}FDG-PET-based strategy were €12.832 (Table 3). Therefore, a diagnostic strategy in which ^{18}FDG-PET would have been used to select patients for direct laryngoscopy costs €399 less per patient than the conventional strategy in which all patients with suspicion of recurrent laryngeal carcinoma after radiotherapy had a direct laryngoscopy. Because in the ^{18}FDG-PET-based strategy 19 of the 30 patients would not undergo a direct laryngoscopy, ^{18}FDG-PET saves €630 per avoided laryngoscopy. The costs of the follow-up phase consisted mainly of costs of surgical treatment in case of recurrence.

Sensitivity analysis

In an academic setting the strategy based on FDG-PET, ^{18}FDG-PET-CT and mobile ^{18}FDG-PET cost between €309 and €399 less per patient compared to the conventional strategy (Table 4). In a non-covered academic setting the strategy based on ^{18}FDG-PET and ^{18}FDG-PET-CT cost, respectively, €236 and €344 more than the conventional strategy. An increase of the prevalence and a decrease of the specificity resulted in an increase of the mean cost of the ^{18}FDG-PET scenario. Specificity above 0.5 and prevalence less than 0.5 resulted in lower mean costs per patient for the ^{18}FDG-PET scenario (Table 5).

Discussion

In this retrospective study the cost-effectiveness of an ^{18}FDG-PET-based strategy in comparison with a conventional strategy in patients with suspicion of recurrent laryngeal carcinoma after radiotherapy was determined. ^{18}FDG-PET had a sensitivity and specificity of 1.0 and 0.86, respectively. The costs of the ^{18}FDG-PET-strategy were €399 lower per patient than the conventional method using a direct laryngoscopy for all patients. Therefore, it can be concluded that ^{18}FDG-PET is effective and not costlier in selecting patients with suspicion of recurrent laryngeal carcinoma after radiotherapy for direct laryngoscopy under general anaesthesia. This was the case for all settings of ^{18}FDG-PET and ^{18}FDG-PET-CT, except from cases when the costs of research are not fully covered.

The need for economic evaluations of new technologies like PET has been recognised. Nevertheless, economic evaluations have remained under-utilised in nuclear medicine. Furthermore economic evaluation studies in nuclear medicine differed widely in terms of form of evaluation, outcome measures and costing [20]. Only one study calculated the costs of ^{18}FDG-PET in the diagnosis of recurrent laryngeal cancer. In a limited cost-effectiveness study, Bongers et al. [21] found that implementation of ^{18}FDG-PET using a dual-head camera in the detection of recurrent laryngeal cancer has additional costs of 64 Euro per patient. In the present study a more extensive cost-analysis is performed using a dedicated full-ring PET-scanner. The

Table 4 Mean costs per patient per setting (costs in euros)

	PET (CT)	Direct laryngoscopy	PET(CT) vs. laryngoscopy
PET academic setting	€12.831	€13.230	−€399
PET non-covered academic setting	€13.466	€13.230	€236
Moblie PET	€12.921	€13.230	−€309
PET/CT academic setting	€12.905	€13.230	−€325
PET/CT non-covered academic setting	€13.574	€13.230	€344

vs versus

Table 5 Influence of prevalence on the mean costs in euros per patient

Mean costs per patient PET sensitivity = 1 and varying prevalence and specificity											
Prevalence specificity	0.1	0.2	**0.233**	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
0.1	12.750	13.415	13.637	14.080	14.746	15.411	16.076	16.742	17.407	18.073	18.738
0.2	12.619	13.299	13.526	13.979	14.659	15.339	16.019	16.698	17.378	18.058	18.738
0.3	12.489	13.183	13.415	13.878	14.572	15.266	15.961	16.655	17.349	18.044	18.738
0.4	12.359	13.067	13.304	13.776	14.485	15.194	15.903	16.612	17.320	18.029	18.738
0.5	12.228	12.952	13.193	13.675	14.398	15.122	15.845	16.568	17.291	18.015	18.738
0.6	12.098	12.836	13.082	13.574	14.311	15.049	15.787	16.525	17.262	18.000	18.738
0.7	11.968	12.720	12.971	13.472	14.224	14.977	15.729	16.481	17.233	17.986	18.738
0.8	11.837	12.604	12.860	13.371	14.138	14.904	15.671	16.438	17.205	17.971	18.738
0.83	11.803	12.574	**12.831**	13.344	14.115	14.885	15.656	16.426	17.197	17.967	18.738
0.9	11.707	12.488	12.749	13.269	14.051	14.832	15.613	16.394	17.176	17.957	18.738
1	11.577	12.372	12.638	13.168	13.964	14.760	15.555	16.351	17.147	17.942	18.738

Mean costs per patient direct laryngoscopy Sensitivity and Specificity 1,0 and varying prevalence											
	0.1	0.2	0.233	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
T+	1.822	3.643	4.251	5.465	7.287	9.108	10.930	12.752	14.574	16.395	18.217
T−	10.540	9.369	8.979	8.198	7.027	5.856	4.685	3.513	2.342	1.171	0
Total	12.362	13.013	13.230	13.663	14.314	14.964	15.615	16.265	16.916	17.566	18.217

T+ costs of patients with recurrent tumour, *T−* costs of patients without recurrent tumour

quality of life of patients was not taken into account, although there were probably more negative side effects in the conventional strategy. As in all diagnostic imaging techniques, there is an interobserver variability in reporting the scans. This may influence the overall cost-effectiveness of ^{18}FDG-PET. A calculation of this was not performed in this study.

The ^{18}FDG-PET-based strategy in this study showed no false-negative test results. Therefore, no patients would have been wrongly denied further diagnostics and eventual therapy. Although the patientgroup was originally included consecutively, some patients were lost in retrospect because not enough data were available to calculate the costs. This led to a group with a coincidental high sensitivity of ^{18}FDG-PET of 100%. In a systematic review by Brouwer et al. [22] the pooled sensitivity was 89% and this is a more valid number than 100%. False negative results in a ^{18}FDG-PET strategy will carry the risk of missing recurrent disease at the earliest possible stage. Such delay may potentially adversely affect prognosis and reduce the possibility for laryngeal preservation treatment. It may also induce extra costs.

The results of this study though, are in agreement with the results of a study by Terhaard et al. [12]. They concluded that a^{18}FDG-PET scan should be the first diagnostic step when a local recurrence is suspected after radiotherapy and in case of a negative ^{18}FDG-PET scan no direct laryngoscopy with taking of biopsies is needed.

In this study the prevalence was only 23%. However, in a study by Brouwer et al. [3] the prevalence was 45%. Differences in prevalence between studies are commonly found. In the present study half of the patients had advanced primary tumours. The probability of recurrence in advanced primary tumours is considered higher. There is a tendency to treat advanced laryngeal cancer with concomitant radiotherapy and chemotherapy. If the percentage of patients treated for advanced primary tumours would have been higher, the prevalence of recurrent disease would be higher and consequently the ^{18}FDG-PET-based strategy would have been less cost effective. On the other hand, in a previous study, it was shown that patients with advanced stage laryngeal carcinoma needed most direct laryngoscopies [3]. From that point of view it can be anticipated that patients with advanced primary tumours may particularly benefit from an ^{18}FDG-PET based strategy.

Another reason for the different prevalence may be the inclusion criteria. In the retrospective study of Brouwer et al. [3] all patients who underwent direct laryngoscopies were included. Because of the retrospective nature of this study it was not possible to analyse the degree of suspicion. Probably also patients were included in whom recurrence was obvious and direct laryngoscopy was only performed for histopathological proof and treatment planning. In these patients PET has no additional value. In the present study only patients with some degree of suspicion were included, and no clear recurrences. In our ongoing prospective randomized multicenter study, the degree of suspicion is

scored when a patient is included [3]. Patient selection on degree of suspicion will influence the prevalence and consequently the cost-effectiveness. If patients with clear recurrences are included the costs of a ^{18}FDG-PET based strategy will be higher.

Since both the conventional and the ^{18}FDG-PET-based strategy showed no false-negative test results in this study, these pathways are absent in the decision model used. An estimation of the costs and the effects of false-negative findings can not be made. Second, because of the absence of false-negative ^{18}FDG-PET scans, the influence of sensitivity of ^{18}FDG-PET can therefore not be tested in a sensitivity analysis.

As previously stated, cost-effectiveness studies differ in terms of evaluation and costing. The costs of an ^{18}FDG-PET scan depends, e.g. on the number of ^{18}FDG-PET studies per PET camera, type of PET camera, number of bed positions, time per bed position, costs of ^{18}FDG, number of technologists and nuclear physicians. For an ^{18}FDG-PET scan of the head and neck two bed positions were scanned with a total time of 15 min per patient. ^{18}FDG-PET as whole-body technique may be performed when screening for distant metastases is indicated in patient with risk factors [23]. Because of the different indications a whole-body ^{18}FDG-PET was not used in this study. If a whole-body scan is used, there is a possible risk that false-positive lesions are found elsewhere in the body. This would induce extra costs for further investigation. Since a whole-body scan was not used in this study, these costs were not calculated. The extra costs of false-positive results within the larynx were included.

For the delivery of ^{18}FDG there is only one distributor in The Netherlands. Probably the price of ^{18}FDG can be reduced when more distributors enter the market, resulting in a lower price per ^{18}FDG-PET scan.

Although there are differences between health systems between countries, we think that our findings could largely be generalised to other countries. The results largely depend on the price of ^{18}FDG-PET scan or ^{18}FDG-PET-CT scan and the costs of follow-up treatment. In this respect, we calculated with real cost prices instead of using tariffs. The used prices are therefore do not depend on a health care financing system.

Since non-surgical treatments with salvage surgery in reserve are being popularised, the clinical problem of detecting recurrent laryngeal carcinoma after radiotherapy is increasingly important. Therefore, cost-effectiveness is also one of the endpoints in an ongoing randomised multicentre trial [24].

In conclusion, ^{18}FDG-PET seems to be effective and not costlier in selecting patients for direct laryngoscopy under general anaesthesia to detect recurrent laryngeal carcinoma after radiotherapy. These findings have to be confirmed in a prospective randomised clinical trial.

Acknowledgment The authors like to thank A.J.G.A. van Heiningen for critical review of the manuscript.

Conflict of interest statement The authors declare that they have no conflict of interest.

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