Chest CT and Whole-Body ^{18}F-FDG PET Are Cost-Effective in Screening for Distant Metastases in Head and Neck Cancer Patients

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The aim of the study was to define the cost-effectiveness of whole-body ^{18}F-FDG PET, as compared with chest CT, in screening for distant metastases in patients with head and neck squamous cell carcinoma (HNSCC). **Methods:** In a multicenter prospective study, 145 consecutive patients with high risk factors for distant metastases and scheduled for extensive treatment underwent chest CT and whole-body ^{18}F-FDG PET for screening of distant metastases. The cost data of 80 patients in whom distant metastases developed or who had a follow-up of at least 12 mo were analyzed. Cost-effectiveness analysis, including sensitivity analysis, was performed to compare the results of ^{18}F-FDG PET, CT, and a combination of CT and ^{18}F-FDG PET (CT + ^{18}F-FDG PET). **Results:** Pretreatment screening identified distant metastases in 21% of patients. ^{18}F-FDG PET had a higher sensitivity (53% vs. 37%) and positive predictive value (80% vs. 75%) than did CT. CT + ^{18}F-FDG PET had the highest sensitivity (63%). The average costs in the CT, ^{18}F-FDG PET, and CT + ^{18}F-FDG PET groups amounted to €38,558 (≈$57,705), €38,355 (≈$57,402), and €37,954 (≈$56,801), respectively, in the first year after screening. CT + ^{18}F-FDG PET resulted in savings between €203 (≈$303) and €604 (≈$903). Sensitivity analysis showed that the dominance of CT + ^{18}F-FDG PET was robust. **Conclusion:** In HNSCC patients with risk factors, pretreatment screening for distant metastases by chest CT is improved by ^{18}F-FDG PET. The combination of ^{18}F-FDG PET with CT is the most effective, without leading to additional costs.

Key Words: head and neck cancer; screening; distant metastases; CT; ^{18}F-FDG-PET; cost; cost-effectiveness

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Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5% of all malignant tumors worldwide. Early HNSCC can usually be managed successfully with either radiotherapy or surgery. However, two thirds of the patients with HNSCC present with advanced disease and are usually treated by a combination of surgery followed by chemotherapy or radiotherapy (*1*). Distant metastases usually occur late in the course of the disease. The lungs, bone, and liver are the most frequent sites. The presence of distant metastases at initial evaluation influences the prognosis and the treatment choice. No effective systemic treatment for disseminated HNSCC is currently available; patients with distant metastases are generally not considered curable and often receive only palliative treatment. Overall survival for patients with distant metastases detected at initial screening is significantly poorer than for patients with distant metastases missed during initial screening and detected during follow-up (*2*). Therefore, screening for distant metastases is important to avoid futile and often extensive treatments.

The overall incidence of clinically identified distant metastases in HNSCC at presentation varies from 2% to 18% (*2–5*) and is generally considered too low to warrant routine screening for distant metastases in all HNSCC patients (*3,6*). The detection is directly related to the stage of disease, particularly to the presence and extension of lymph node metastases and locoregional control, and depends on the applied diagnostic methods (*2,6–9*). Therefore, staging or screening of distant metastases using the best available diagnostic techniques in patients with high risk factors is considered worthwhile (*2,3,10*).

As most distant metastases are located in the lung, chest CT is the most often used technique to detect distant metastases in HNSCC. However, with chest CT several distant metastases and primary tumors are still missed. PET with ^{18}F-FDG is able to detect tumor deposits in the whole body. ^{18}F-FDG PET detects more distant metastases than does CT, but the combination of both techniques (CT + ^{18}F-FDG PET), as currently provided with hybrid PET/CT scanners, appears to be superior (*11,12*).

^{18}F-FDG PET is a costly technique, and there are various clinical applications. Therefore, there is a need to use it for

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the most valuable applications to have the most efficient use of resources. We have performed a prospective, multicenter clinical trial determining the potential added value of whole-body ^{18}F-FDG PET in screening for distant metastases in HNSCC patients with risk factors to the best conventional imaging with CT. The clinical results are presented elsewhere (*11*). A prospective cost-effectiveness study was performed in close conjunction with the clinical trial to be able to assess the costs and benefits of ^{18}F-FDG PET in this patient group. We adopted a hospital perspective, in which only the direct costs of outpatient and inpatient diagnostic procedures and treatment are considered.

MATERIALS AND METHODS

The multicenter study was performed at 3 university medical centers in The Netherlands. Eligibility criteria were patients with HNSCC, candidates for extensive treatment with curative intent (surgery or radiotherapy, with or without chemotherapy), and patients at increased risk for distant metastases (i.e., ≥3 lymph node metastases [n = 20], bilateral lymph node metastases [n = 36], lymph node metastases of ≥6 cm [n = 30], low jugular lymph node metastases [n = 6], regional tumor recurrence [n = 10], and second primary tumors [n = 25]), as assessed by palpation, CT, MRI, or ultrasound-guided fine-needle aspiration cytology (*3*). The protocol was approved by the Medical Ethical Committee of the VU University Medical Center, and all patients gave written informed consent.

Imaging Techniques

All patients underwent chest CT and ^{18}F-FDG PET, in random order as dictated by logistics. Spiral CT scans were obtained with a fourth-generation Somaton Plus (Siemens AG) after the intravenous administration of contrast medium (Ultravist; Schering AG). ^{18}F-FDG PET was performed after patients had fasted for 6 h with ample access to water. At 60–90 min after the intravenous administration of 250–370 MBq of ^{18}F-FDG, the imaging of trajectory knee–skull base was performed using dedicated full-ring bismuth germinate PET scanners (in Amsterdam/Groningen, ECAT HR+ [CTI/Siemens]; in Nijmegen, ECAT EXACT [CTI/Siemens]). Any focal abnormality suggestive of malignancy was reported (*11*).

Data Analysis

The result of the clinical diagnostic work-up between presentation and a follow-up of 12 mo was used as reference standard, and patients were classified as positive or negative with respect to the presence of distant metastases. Follow-up was performed every 6 wk in the first year and consisted of visits to the outpatient clinic. During follow-up, the dates of the detection of distant metastases, second primary tumors, or death were recorded. Although the primary goal was screening on distant metastases, second primary tumors were also registered.

Cost Analysis

The hospital's perspective was considered. The cost analysis focused on direct medical costs. The base year was 2008. The costs of diagnosis and treatment were based on the total clinical consumption of all evaluable patients. For the most important items, unit costs were determined because these were a better estimator of the theoretic opportunity costs (*13,14*). These costs include not only the measurable costs of an intervention (e.g., radiotherapy, surgery, and imaging) but also the services that are not directly allocated to patient care, such as hospital overhead and administrative personnel. Therefore, all hospital costs can be assigned to the interventions given in the hospital. For the determination of these unit costs, the microcosting approach was used (*15*).

Table 1 shows the most important unit costs used in this analysis. The costs of ^{18}F-FDG PET scanning, hospital days, outpatient visits, and day-care treatments are composed of variable and overhead costs. The variable costs consisted of manpower (e.g., doctors, nurses) and materials (e.g., medication, supportive patient care, meals). The overhead costs were related to general hospital services and housing. The costs of radiotherapy covered the entire process, including preparation. When patients were subjected to chemotherapy, the costs of the chemotherapeutic agent were derived from the Pharmaceutical Compass (*16*) and included in the cost analysis; costs of administration are covered by hospitalizations and day-care treatment (*15*). For most laboratory and diagnostic tests, the Dutch tariff system was used as an approximation of unit costs.

Allocation of Resource Use and Details of Cost Analysis

Data on resource use were collected from the hospital information system, patient files, and the case report forms. Data on the numbers of hospital days, outpatient visits, day-care treatments, diagnostic activities, laboratory testing, radiation therapy sessions, surgical procedures, and medication were collected.

As in all clinical studies concerned with diagnostic techniques, there are several possible diagnostic outcomes: true-positive, false-positive, true-negative, and false-negative. A positive test

TABLE 1. Costs of Hospital Days, Day-Care Treatment, Outpatient Visits, and ^{18}F-FDG PET Scan

Parameter	Outpatient visit		Day care		Normal care		Intensive care		^{18}F-FDG PET scan	
	Euros	Dollars	Euros	Dollars	Euros	Dollars	Euros	Dollars	Euros	Dollars
Specialist	23	34	20	30	28	42	41	61		
Nursing and administration	24	36	43	64	185	277	667	997	97*	145
Materials			33	49	42	63	137	205	295	441
^{18}F-FDG									294	440
Housing	6	9	72	108	102	152	180	269		
Overhead	12	18	36	54	77	115	237	354	241	360
Total	65	97	204	305	434	649	1,262	1,887	927	1,386

*Includes specialist costs.

outcome (distant metastases and [incurable] second primary tumor) results in palliative treatment, and a negative outcome (no distant metastases and [incurable] second primary tumor) results in curative treatment. In Table 2, all different test outcomes and treatment possibilities, together with the translation and consequence for the cost analysis, are presented. However, for the clinical decision making toward either curative or palliative treatment, other aspects are also of interest; these should be incorporated into the cost analysis as well. These aspects relate to the general condition of the patient, the patient's preferences, the cost implications of the clinical approach, and the possible use of second-line diagnostics to confirm or reject an initial test outcome. In addition, ^{18}F-FDG PET has proven its value in previous studies, and it would, therefore, be unethical to leave its test outcome out of the clinical decision. This decision to include ^{18}F-FDG PET resulted in several additional test outcome treatment combinations that had to be adjusted for in the cost analysis to be able to judge the added value of ^{18}F-FDG PET in screening for distant metastasis and synchronous primary tumors in HNSCC patients.

In the cost analysis, the following 3 diagnostic strategies are compared: CT alone, ^{18}F-FDG PET alone, and the combination of the 2 visually correlated. On the basis of the test outcomes and the aspects already mentioned, clinical experts determined the appropriateness of the clinical approach for each patient in the 3 diagnostic scenarios; subsequently, the consequences for the cost analysis were determined. These consequences were based on resource use in patients undergoing comparable interventions and on information from clinical experts who indicated what resource use was incorrectly withheld or used based on clinical characteristics of the patients. This resource use includes the costs of hospitalization, operations, radiotherapy, and revalidation and also includes the number of ancillary imaging techniques, hospitalizations, and interventions that would not have been applied in the absence of the ^{18}F-FDG PET scan. It was decided to exclude the impact on laboratory testing from the base case analysis because these are patient-specific and independent of further treatment.

Sensitivity Analysis

The estimation of resource use is associated with substantial uncertainty; because of patient variation, these are tested in multiple sensitivity analyses to determine the impact on the cost-effectiveness outcomes. Additionally, we performed a sensitivity analysis for which we included an estimation of the costs of laboratory testing associated with hospitalization for extensive treatment that was futile or that should have been performed based on the diagnostic test outcome.

RESULTS

Patient Characteristics

One hundred forty-five patients were entered in the study (*11*). After the exclusion of patients who were incorrectly included or had logistical problems, 111 patients remained. Because the reference standard for further data analysis was the detection of distant metastases or negative follow-up of 12 mo, we excluded 19 patients who died without distant metastases within this 12-mo follow-up. Therefore, we obtained evaluable data for 92 patients. For the cost-effectiveness analysis, the complete data for 80 patients were available. Of these 80 patients, 63 were men, and the mean age was 60 y (range, 40–81 y). Primary tumor sites were the oral cavity (n = 17), oropharynx (n = 24), hypopharynx (n = 16), larynx (n = 14), cervical esophagus (n = 3), and lymph node metastases of an unknown primary tumor (n = 18). Ten patients had more than 1 synchronous primary tumor. The patient characteristics in this study were comparable with the patient characteristics included in the clinical study.

Clinical Study

Pretreatment screening identified distant metastases in 17 of 80 patients (21%; 95% confidence interval [CI], 15%−28%) and second primary tumors in 6 of 80 (8%; 95% CI, 3%−12%). All patients with distant metastases were treated palliatively. Half of the patients with a second primary tumor had disseminated lung cancer (lung or brain metastases), and they also received palliative treatment. The other 3 patients appeared to have limited-stage disease of their secondary primary and were treated with curative intent for both primary tumors. In 32 of 80 of the total group of patients (41%; 95% CI, 33%−50%), distant metastasis (33%; 95% CI, 25%−41%) or a second primary tumor (9%; 95% CI, 5%−15%) was detected during screening or within the 12 mo of follow-up.

^{18}F-FDG PET had a higher sensitivity (53% vs. 37%) and positive predictive value (80% vs. 75%) than did chest CT. The combination of CT and ^{18}F-FDG PET had the highest sensitivity (63%).

Details of the clinical study are presented elsewhere (*11*).

TABLE 2. Test–Treatment Combination and Consequence for Cost Analysis

Test–treatment combination	Consequence	Data source
True-positive → curative treatment	Adjustment for overestimation of costs	Average of resource use for curative intervention from patient file
True-positive → palliative treatment	None	—
False-positive → curative treatment	Adjustment for overestimation of costs	Average of resource use for curative intervention from patient file
False-positive → palliative treatment	None	—
True-negative → curative treatment	None	—
True-negative → palliative treatment	Adjustment for underestimation of costs	Average of resource use for similar curative intervention
False-negative → curative treatment	None	—
False-negative → palliative treatment	Adjustment for underestimation of costs	Average of resource use for similar curative intervention

Cost Analysis

The distribution of test outcomes and treatment options is presented in Figure 1. From this figure, it appears that in the CT-only scenario 11.25% of the patients were not treated in accordance with the test outcome. However, in 2.50% of these patients the positive test outcome related to an operable second primary, and therefore the curative operations were appropriate. In another 2.50%, a palliative approach was chosen, despite a negative test outcome, because of patient preference or clinical condition. As a consequence, 6.25% of these patients remained for whom a correction must be made for inappropriately withheld (3.75%) or given curative treatment (2.50%).

In the ^{18}F-FDG PET–only scenario, 16.25% of the patients were not treated according to their test outcome. Of these patients, 14% were curatively treated for an operable second primary tumor, and 7% were treated palliatively despite a negative test because of the patient's condition. In another 7% of these patients, the ^{18}F-FDG PET result raised questions that were answered with additional diagnostic testing; the ^{18}F-FDG PET result was, therefore, considered to be false-positive but this did not influence the treatment decision. Finally, 5% of the patients with a false-negative test outcome were treated palliatively; this had no impact on the cost analysis because the clinicians indicated there would have been no difference in curative and palliative treatments. Thus, 11.25% of the patients remained for whom a correction must be made for inappropriately withheld or given curative treatment.

In the third scenario, the combination of CT and ^{18}F-FDG PET, 13.75% received a treatment that was not in line with the test outcome. Of these patients, 16.75% were curatively treated for an operable second primary tumor, and 8.25% were treated palliatively, despite a negative test result because of the patient's condition. This scenario also included a patient for whom the ^{18}F-FDG PET result raised questions (these questions were solved with additional diagnostic testing) and a patient for whom the clinicians indicated that there was no difference in resource use between palliative and curative treatments. This scenario resulted in an adjustment for inappropriate resource use of the patients who were treated curatively despite a positive test outcome.

In 3 patients, the ^{18}F-FDG PET scan resulted in ancillary imaging or hospitalizations and interventions that would not have been applied in the absence of the ^{18}F-FDG PET scan; these resources were also defined and subtracted from the total resource use in the CT-only scenario. The results of the cost analysis for all diagnostic strategies are presented in Table 3. In this table, the difference in costs between treatment strategies and study-related diagnostic procedures (CT and ^{18}F-FDG PET) were included. A curative treatment cost approximately €41,369 (≈$61,912) and a palliative treatment €26,328 (≈$39,402).

Comparing the diagnostic strategies, the most important changes are seen in the costs of hospital days, surgery, and radiotherapy. These changes are caused by the reduction of futile operations and curative radiotherapy in both the ^{18}F-FDG PET and the CT + ^{18}F-FDG PET scenarios versus the CT scenario (Table 3).

These reductions countered the introduction of additional diagnostic costs by ^{18}F-FDG PET testing and resulted in an average cost per patient of €38,558 (≈$57,705) in the CT-only scenario, €38,355 (≈$57,402) in the ^{18}F-FDG PET–only scenario, and €37,954 (≈$56,801) in the CT + ^{18}F-FDG PET scenario. The differences between these scenarios are small; the introduction of ^{18}F-FDG PET led to a cost reduction between €203 (≈$303) and €604 (≈$903).

Sensitivity Analysis

The costs of hospitalizations, operations, radiotherapy, and diagnostic imaging are the main cost drivers in

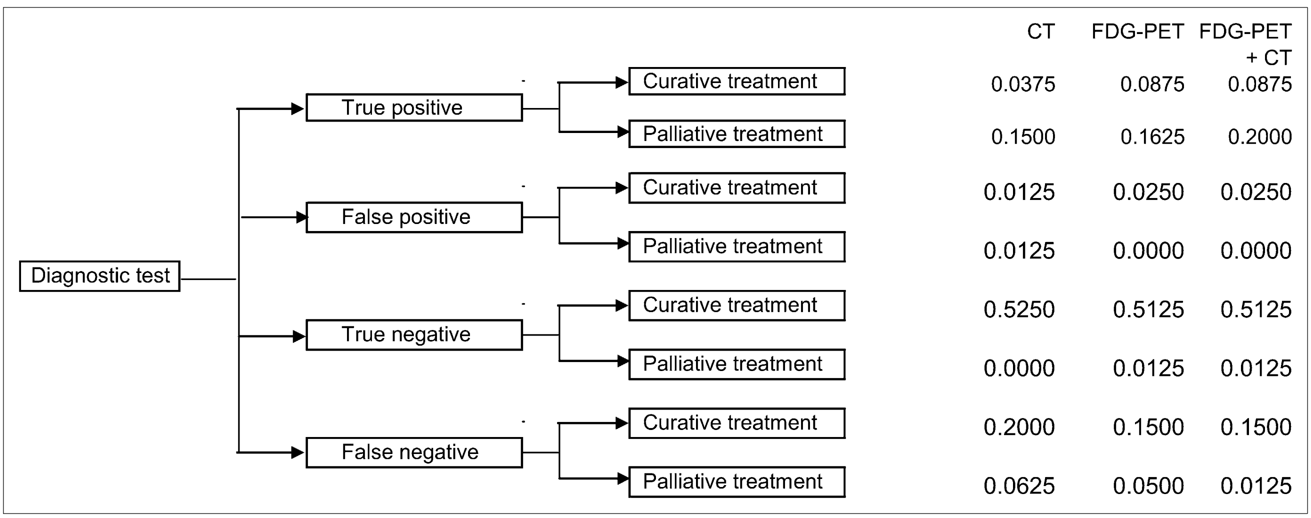

FIGURE 1. Distribution of patients over test outcome and treatment approach.

TABLE 3. Average Costs per Treatment Strategy and Overall Costs

						Diagnostic strategy					
	Costs		Diagnostic strategy			CT		^{18}F-FDG PET		^{18}F-FDG PET+CT	
Strategy	Euros	Dollars	CT	^{18}F-FDG PET	^{18}F-FDG PET + CT	Euros	Dollars	Euros	Dollars	Euros	Dollars
Average costs											
Curative treatment											
Hospital days	14,667	21,927	0.7875	0.725	0.6875	11,550	17,268	10,634	15,897	10,084	15,075
Day care	124	185	0.7875	0.725	0.6875	98	146	90	134	85	127
Consults	1,575	2,355	0.7875	0.725	0.6875	1,240	1,854	1,142	1,707	1,083	1,619
Surgery	10,388	15,530	0.7875	0.725	0.6875	8,181	12,230	7,531	11,259	7,142	10,677
Radiotherapy	5,074	7,585	0.7875	0.725	0.6875	3,995	5,973	3,678	5,499	3,488	5,215
Chemotherapy	1,243	1,858	0.7875	0.725	0.6875	979	1,463	901	1,347	855	1,278
Imaging											
^{18}F-FDG PET	0	0	0.7875	0.725	0.6875	0	0	927	1,386	927	1,386
CT	0	0	0.7875	0.725	0.6875	173	259	0	0	173	259
Other	2,626	3,926	0.7875	0.725	0.6875	2,068	3,092	1,904	2,846	1,805	2,699
Other diagnostics	5,942	8,883	0.7875	0.725	0.6875	4,679	6,996	4,308	6,440	4,085	6,107
Total	41,639	62,250	0.7875	0.725	0.6875	32,963	49,280	31,115	46,517	29,727	44,441
Palliative treatment											
Hospital days	7,678	11,479	0.2125	0.275	0.3125	1,632	2,439	2,111	3,157	2,399	3,587
Day care	124	185	0.2125	0.275	0.3125	26	39	34	51	39	58
Consults	1,575	2,355	0.2125	0.275	0.3125	335	500	433	648	492	736
Surgery	1,359	2,031	0.2125	0.275	0.3125	289	432	374	559	425	635
Radiotherapy	4,418	6,605	0.2125	0.275	0.3125	939	1,404	1,215	1,817	1,381	2,064
Chemotherapy	2,606	3,896	0.2125	0.275	0.3125	554	828	717	1,071	814	1,217
Imaging											
^{18}F-FDG PET	0	0	0.2125	0.275	0.3125	0	0	927	1,386	927	1,386
CT	0	0	0.2125	0.275	0.3125	173	259	0	0	173	259
Other	2,626	3,926	0.2125	0.275	0.3125	558	834	722	1,080	821	1,227
Other diagnostics	5,942	8,883	0.2125	0.275	0.3125	1,263	1,888	1,634	2,443	1,857	2,776
Total	26,328	39,361	0.2125	0.275	0.3125	5,768	8,623	8,167	12,210	9,328	13,945
Overall costs (including cost of CT, ^{18}F-FDG PET, or both)											
Hospital days						13,182	19,707	12,745	19,054	12,483	18,662
Day care						124	185	124	185	124	185
Consults						1,575	2,355	1,575	2,355	1,575	2,355
Surgery						8,469	12,662	7,905	11,818	7,566	11,312
Radiotherapy						4,934	7,377	4,893	7,316	4,869	7,279
Chemotherapy						1,533	2,291	1,618	2,419	1,669	2,495
Imaging											
^{18}F-FDG-PET						0	0	927	1,386	927	1,386
CT						173	259	0	0	173	259
Other						2,626	3,926	2,626	3,926	2,626	3,926
Other diagnostics						5,942	8,883	5,942	8,883	5,942	8,883
Total						38,558	57,644	38,355	57,341	37,954	56,741

this patient population. The results of several sensitivity analyses on these main cost drivers are presented in Table 4.

The cost differences now ranged between €110 (≈\$164) and €697 (≈\$1,043). Variation in resource use and costs affected the differences between the strategies. Furthermore, the results still remained robust in favor of the CT + ^{18}F-FDG PET scenario.

DISCUSSION

We presented the results of the cost and cost effectiveness analyses for 3 diagnostic strategies in screening for distant metastasis and synchronous primary tumors in HNSCC patients. We showed that ^{18}F-FDG PET with or without CT was a valuable diagnostic tool in these patients; its addition resulted in both a reduction of futile operations and an increase in appropriate curative interventions, without leading to additional costs. There are a few aspects of the cost analysis that deserve some attention.

Although the cost estimates are sensitive to changes in the main cost drivers in these patients, the differences remain small. Furthermore, it is not likely that these variations will lead to a cost increase with the introduction of ^{18}F-FDG PET because we estimated the savings associated with the reduction in futile operations conservatively. We, for instance, did not include the laboratory and pathology costs associated with the prevented operations and hospitalizations.

TABLE 4. Results of Sensitivity Analysis

	CT		^{18}F-FDG PET		^{18}F-FDG PET + CT		^{18}F-FDG PET vs. CT		^{18}F-FDG PET + CT vs. CT	
Cost of...	Euros	Dollars	Euros	Dollars	Euros	Dollars	Euros	Dollars	Euros	Dollars
Hospital days 10% higher	39,876	59,615	39,630	59,247	39,202	58,608	−247	−369	−674	−1,008
Hospital days 10% lower	37,240	55,674	37,081	55,436	36,706	54,875	−159	−238	−534	−799
PET 10% higher	38,558	57,644	38,355	57,341	37,954	56,741	−203	−303	−604	−903
PET 10% lower	38,558	57,644	38,355	57,341	37,954	56,741	−203	−303	−604	−903
Surgery 10% higher	39,405	58,911	39,146	58,523	38,711	57,873	−259	−388	−694	−1,038
Surgery 10% lower	37,711	56,378	37,565	56,159	37,197	55,610	−146	−219	−514	−768

During the last decade, the costs for radiotherapy in HNSCC have increased because of the implementation of 3-dimensional conformal radiotherapy, intensity-modulated radiation techniques, stereotactic radiotherapy, and combination with chemotherapy (*17,18*). The introduction of these new techniques implies that the savings with ^{18}F-FDG PET could be higher.

Additionally, there is 1 difference between the cost and the clinical analysis. One patient had a lesion in the liver that would have been missed on a conventional CT–thorax scan. However, the result for this patient was scored positive because of the extension of the scanning range to the abdomen. The results for this patient were scored true-positive for the cost analysis and false-negative for the clinical study. This, again, was a conservative estimation because an adjustment for the underestimation of resource use in this patients based on test outcome was not necessary. Thereby, the difference between the ^{18}F-FDG PET and the CT scenarios was underestimated.

Previous studies in fewer patients with advanced head and neck cancer also found that savings from futile extensive operations exceeded the costs of ^{18}F-FDG PET (*2,18*). This study replicates these findings in a much larger number of patients. Additionally, we were able to demonstrate the effect of combining the test results of independently performed ^{18}F-FDG PET and CT tests. It is likely that integrated ^{18}F-FDG PET and CT will further improve efficiency (*19*).

Generalization of the results to other countries is not straightforward, because health-care organization and prices differ. However, the outcomes of this study mainly depend on the sensitivity and specificity of ^{18}F-FDG PET ± CT and the costs of ^{18}F-FDG PET ± CT. Especially the prices of ^{18}F-FDG PET and hospital days could differ between countries. In general, these cost prices are higher in other countries, especially in the United States. In the sensitivity analysis, the higher cost prices of ^{18}F-FDG PET still result in savings (with thresholds of €1,130 [≈$1,691] for the ^{18}F-FDG PET and €1,530 [≈$2,289] for the ^{18}F-FDG PET + CT scenarios). The higher prices of hospital days always result in savings in the ^{18}F-FDG PET scenarios. The most important value of ^{18}F-FDG PET lies in offering patients a better (and more efficient) diagnostic strategy.

CONCLUSION

^{18}F-FDG PET is a valuable diagnostic tool when screening for distant metastasis and synchronous primary tumors in HNSCC patients. The use of ^{18}F-FDG PET results in both a reduction of futile operations and an increase in appropriate curative interventions in these patients, without leading to additional costs.

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