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ORIGINAL ARTICLE

Use of Positron Emission Tomography in Surgery Follow-Up of Esophageal Cancer

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Abstract
Introduction Although the prognosis of patients with esophageal cancer has been improved by extended dissection, the incidence of recurrence still remains high. In esophageal cancer, positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) already demonstrated to be useful for initial staging and monitoring response to therapy. This prospective study compared the ability of FDG-PET and conventional imaging to detect early recurrence of esophageal cancer after initial surgery in asymptomatic patients.
Materials and Methods Between October 2003 and September 2006, 41 patients with esophageal cancer were included in a prospective study after initial radical esophagectomy. FDG-PET, thoracoabdominal computed tomography (CT), abdominal ultrasonography, and endoscopy were performed every 6 months after initial treatment.
Results and Discussion Twenty-three patients had recurrent disease (56%), mostly within the first 6 months after surgery (70%). Despite two false-positive scans due to postoperative changes, FDG-PET was more accurate than CT (91% vs. 81%, $p=0.02$) for the detection of recurrence with a sensitivity of 100% (vs. 65%), a specificity of 85% (vs. 91%), and a negative predictive value of 100% on a patient-by-patient-based analysis. For the detection of locoregional recurrence, FDG-PET was more accurate than CT (96.2% vs. 88.9%). FDG-PET was also more accurate than CT for the detection of distant metastases (92.5% vs. 84.9%), especially when involving either bones (100%) or liver (98.1%). A lower sensitivity of FDG-PET (57%) for the early detection of small lung metastases did not affect patient management (accuracy=92.5%).
Conclusion FDG-PET appears to be very useful for the systematic follow-up of asymptomatic patients after esophagectomy with an initial scan performed 6 months after surgery.

Keywords Esophageal carcinoma · FDG-PET · Positron emission tomography · Follow-up · Recurrence

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Introduction

Esophageal cancer is an aggressive gastrointestinal disease and surgery remains the main potential curative treatment. According to the two randomized trials published on the subject, neoadjuvant treatment before surgery may improve local tumor control but it does not increase overall survival compared to chemoradiation alone.[1,2] The use of preoperative radiotherapy (RT) failed to improve outcome,[3] most likely because of a high rate of distant metastasis, whereas the use of preoperative chemotherapy in US trials had little impact on either local failure or distant dissemination of disease. A recent meta-analysis did report a significant benefit for preoperative chemoradiotherapy,[4] but neoadjuvant radiochemotherapy is still debated in advanced esophageal cancer.[5] Although the prognosis of patients has been improved by extended dissection,[6,7] the incidence of recurrence still remains high with a reported rate in the range of 36% to 64%.[8–11] More than half of all recurrences occur within 12 months after surgery.[11] The early diagnosis of recurrence in esophageal cancer can be of potential interest. Until now, once recurrence occurs, some patients will receive chemotherapy or radiation therapy,[12] while some will only go through palliative treatment because of their poor general condition. In few cases, salvage surgery may be considered, since some authors reported a better associated outcome.[13–15] Although the management of a recurrence greatly depends on the pattern of recurrence and the general status of the patient, a consensus treatment strategy has not yet been established. Concerning the patients with distant metastasis, a recent issue of the Cochrane database tends to show that there is no statistically proven impact of the use of chemotherapy.[16] New targets are actually the subject of intensive research in the field of esophageal neoplasms. We have previously published the potential impact of epidermal growth factor receptor (EGFR) status in the management of surgically resected patients.[17] The use of anti-EGFR targets could be a good way for prospective trials in this type of patients. At present, one of the prerequisites in order to improve patient management is the detection of recurrences as early as possible based on the usual follow-up procedure that includes endoscopy, ultrasonography, and thoracoabdominal computed tomography (CT) every 3–6 months. Endoscopic examination is appropriate only for the detection of local recurrence or metachronous cancer of the gastroplasty that could be cured by minimal surgery.[18] Since CT is a morphological-based investigation tool, it is now well-known to be suboptimal in the diagnosis of nodal involvement, since nodal size is not an accurate parameter for predicting involvement. It is also suboptimal for the differentiation between posttreatment fibrosis and recurrence. Functional imaging may provide a promising alternative. Positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) permits the functional characterization of tissues by in vivo imaging glucose metabolism. In oncology, FDG-PET is successfully used for the assessment of tumor viability and the staging of many malignancies with increased glycolysis. In esophageal cancer, FDG-PET has been gaining acceptance for initial staging by improving the detection of unsuspected distant metastases.[19–21] Monitoring therapy response is the second major indication for FDG-PET in esophageal cancer.[22–25] Some authors have also suggested that FDG may have a predictive value of patient outcome in esophageal cancer,[26] as it has already been demonstrated for other types of malignancies including lung cancer, lymphoma, or head and neck cancer.[27–30]

FDG-PET has also been largely used for restaging symptomatic recurrent cancer. In esophageal cancer, Flamen et al. demonstrated that FDG-PET is highly sensitive for staging recurrent symptomatic patients.[31] In addition, Kato et al. reported in a retrospective study that PET has a better accuracy than CT in the follow-up of asymptomatic patients when PET is performed more than 1 year after surgery. It remains unknown whether repeated FDG-PET can be used earlier and systematically in the follow-up period, which would be of great interest in a disease such as esophageal cancer which is characterized by high potential of early recurrence.[32] Therefore, the main objective of our prospective study was to determine whether FDG-PET can provide more accurate information than CT in a routine follow-up procedure of patients with esophageal cancer early after surgery.

Materials and Methods

In this prospective study, we considered patients undergoing surgery in our institution whose follow-up was also performed in our institution in order to minimize variability in the procedures.

The required sample size for the comparison of PET and CT sensitivities was calculated with an α level of 0.05 and a type 2 error (β) of 0.1. Considering a hypothesized difference of 30%, the required sample size was 39 patients. So, 41 patients were included taking into account incomplete data (5%). The current study was carried out after an approval by the institutional ethical review committee.

Surgery and Initial Patient Management

Between October 2003 and September 2006, 41 consecutive patients with esophageal cancer were included in the present study after they underwent esophagectomy with curative intention. All procedures were performed by the

same surgical team. The vast majority of patients (90%) underwent a transthoracic esophagectomy (Ivor Lewis procedure). In one patient, an additional cervicotomy was performed in order to do the anastomosis in the neck after the reconstruction of the digestive tract using a gastric tube (Akiyama procedure). Three patients had a laparoscopic transhiatal esophagectomy. All surgical procedures were associated with traditional two-field lymphadenectomy (thoracic and abdominal). All suspect distant macroscopic lymph nodes visually depicted by the surgeon were removed for frozen histology. Tumor was present in margins in six patients (15%).

Nine patients received neoadjuvant chemoradiation before surgery because they had a locally advanced disease at presentation. Standard cisplatin and 5-fluorouracil-based chemotherapy regimens with concurrent radiation therapy were used. In addition, six patients received an adjuvant chemoradiation because of non-R0 resection.

Clinical Follow-Up

After initial treatment, each patient was monitored regularly every 4–6 months during the first 2 years and every year after the second year in case of no recurrence. Every follow-up evaluation included a complete clinical examination. Thoracoabdominal CT, abdominal ultrasonography, and endoscopy were performed every 6 months or more frequently depending on the clinical situation. FDG-PET examinations were added to this routine follow-up procedure, every 6 months during the first 2 years and every year after the second year. Comparative CT and PET scans were performed within 1 month from each other.

Positron Emission Tomography

All patients fasted for a minimum of 6 h before the PET examination. The blood glucose level was confirmed to be <9 mmol L^{-1} before injection of the ^{18}F-FDG. All FDG-PET examinations were performed using an Allegro dedicated PET scanner (Philips Medical Systems).[33] An emission whole-body scan was performed for each patient from thigh to head 60 min after the injection of a mean activity of 355 MBq of ^{18}F-FDG (5–6 MBq/kg). Emission scans were acquired for 3 min per bed position. Whole-body transmission scans using a ^{67}Cs source were also obtained for the purpose of performing attenuation correction. Emission data were corrected for scatter, random events, and dead time losses and images were reconstructed both with and without attenuation correction using a previously optimized 3D RAMLA reconstruction protocol.[34] Baseline PET images were reported by two experienced nuclear physicians unaware of the CT, endoscopic ultrasound findings, and histological results. Images were analyzed visually and semiquantitatively. Regional lymph node involvement and distant metastatic disease were assessed as present or absent. Lymph nodes and metastases were considered as FDG-positive if focal-prominent ^{18}F-FDG uptake compared to normal mediastinal activity was found at least in two consecutive transaxial slices. In identified lesions, the maximum standardized uptake values (SUVmax) corrected for the body weight of each patient were calculated performing region of interest analysis on the transaxial slice of the attenuation-corrected images in which the highest uptake was found.

Follow-up data concerning the 41 patients were prospectively collected in a database for further analysis. The current analysis was carried out after an approval by the institutional ethical review committee. Regional and distant recurrences were established by biopsy, if feasible, or by clinical follow-up and repeated examinations. Distant metastases could involve either distant organs or celiac lymph nodes for tumors of the lower thoracic esophagus or metastasis in cervical nodes for tumors of the upper thoracic esophagus according to the TNM system.[35]

Statistical Analysis

All semiquantitative data are presented as the mean±standard deviation (SD). In this study cohort, local recurrence was determined by endoscopic biopsy. The sensitivity, specificity, and accuracy of CT and PET were calculated using the standard definitions.[36] CT and PET performances were compared using a χ^2 Mac Nemar test for paired data and a statistically significant difference was defined as a p value ≤ 0.05.

Kaplan–Meier methods were used to estimate the survival distributions.[37] Survival was calculated from the date of initial diagnosis to the date of death or most recent follow-up in case of patients still alive.

Results

Patient characteristics are presented in Table 1. Thirty-eight were male (93%) and the mean age at the time of diagnosis was 60.7±9.4 years. Most of the tumors were squamous cell carcinoma (76%) and most of the patients had a well-differentiated or moderately differentiated tumor (90%). The majority of the tumors originated from the middle and lower esophagus (93%). In the population included in this study, 51% of the patients had an early stage disease (stage I or IIa), while 58% of the patients had a T3 primary lesion. Twenty patients (48%) had lymph node metastases (N1) at presentation.

At the time of the last follow-up, 31 patients were alive, 18 with no evidence of disease, and 13 with recurrence. The

Table 1 Patients Characteristics

Characteristics	All patients *N*=41 (%)
Gender	
Male	38 (93)
Female	3 (7)
Age at diagnosis	
Median	59
Range	43–83
Primary site	
Upper esophagus	3 (7)
Middle esophagus	20 (49)
Lower esophagus	18 (44)
Tumor cell type	
Squamous cell carcinoma	31 (76)
Adenocarcinoma	10 (24)
Histologic grade	
Well-differentiated	22 (54)
Moderately differentiated	15 (36)
Poorly differentiated	4 (10)
Treatment	
Surgery alone	25 (61)
Surgery+adjuvant CT±RT	7 (17)
Surgery+neoadjuvant CT+RT	9 (22)
Pathological stage	
I	6 (14)
IIa	15 (37)
IIb	5 (12)
III	15 (37)

RT radiotherapy, *CT* chemotherapy

recurrence rate was 56% and the mean time to recurrence was 8 months (5–39 months). With a mean follow-up of 46 months (30–55 months, median of 48 months), the median survival for all patients was 51 months. The 1- and 2-year survival rates were 80% and 65%, respectively, for patients with negative margins. The Kaplan–Meier curves on disease-free survival and overall survival are in presented in Figs. 1 and 2.

The mean time after surgery for the first PET scan was 6.3 months. It was positive for all six patients with involved margins. Two patients had regional nodal uptake and FDG-avid distant metastases (involving either the liver or vertebrae). Two patients had evidence of local recurrence and regional nodes on PET images; while for the two remaining patients, only local uptake evoking progressive residual disease was described. This first FDG-PET was considered as positive in 18 patients, demonstrating local recurrence in 13 cases and distant metastases in 12 cases. Seven of these patients had both local and distant lesions avid for FDG. In case of regional recurrence, 7 out of 18 patients had more than one abnormal foci corresponding to involved nodes. Confirmed distant metastases occurred in distant lymph nodes (five out of 12), bones (five out of 12), liver (three out of 12), lung (two out of 12), and adrenal

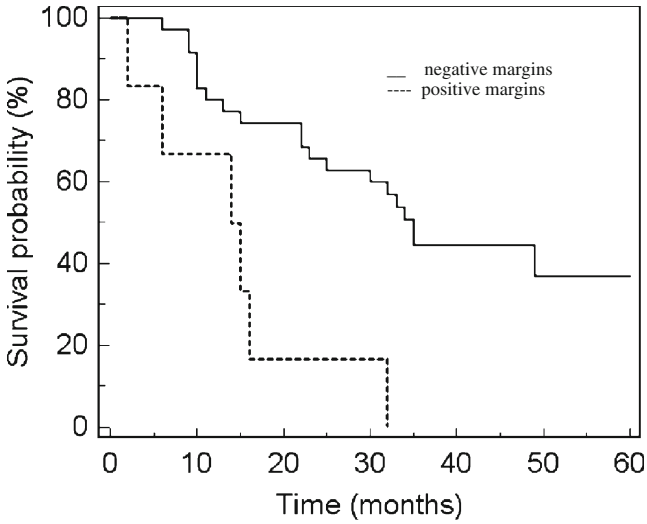

Figure 1 Kaplan–Meier analysis of the overall survival of esophageal cancer patients according to the margin status (negative of positive).

gland (one out of 12). Seven patients had more than one distant metastatic site.

A second FDG-PET scan was performed within a mean delay of 12 months after surgery (12±2 months). One year after surgery, only one more patient, in comparison to the results of the first PET examination, had a true-positive scan for recurrence corresponding to locoregional disease without distant metastasis. For the third systematic evaluation, FDG-PET was performed with a mean delay of 19 months after surgery (19±1.6 months). In four patients, FDG-PET was abnormal, demonstrating local recurrence in one patient and both local disease and distant metastases in three patients. Those late scans were all confirmed to be true-positive findings (using the assessment criteria described in the "Positron Emission Tomography" section).

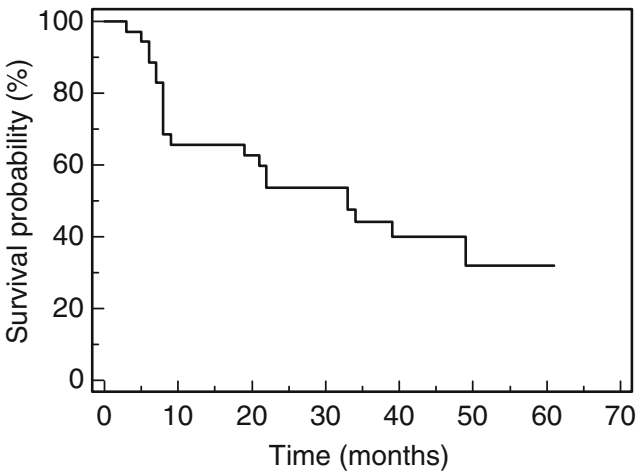

Figure 2 Kaplan–Meier analysis of the disease-free survival of esophageal patients with negative margins after initial surgery.

On a patient-by-patient analysis, sensitivity, specificity, and accuracy were, respectively, 65%, 91%, and 81% for CT and 100%, 85%, and 91% for FDG-PET (Table 2). The performance of the two modalities were statistically significantly different ($p=0.02$).

Local or regional recurrence was observed in 15 patients (seven with no distant metastases and eight with associated distant metastases). For the detection of locoregional recurrence, FDG-PET had a better accuracy than CT (96% vs. 89%, $p=0.05$) due to a higher sensitivity (93% vs. 60%) with similar specificity (97% vs. 100%; Table 2). There were two false-positive results on PET at 6 months, one in the gastroplasty and one in a perigastric node (abdominal). In both cases, abnormal uptake was moderate (SUVmax<3) and disappeared on the subsequent scans. False-positive results were confirmed based on a favorable outcome and no evidence of disease on the biopsy.

FDG-PET was globally more accurate than CT for the detection of distant metastases (92.5% vs. 84.9%, $p=0.002$; Table 2). Considering the different sites of recurrence, we found five false-negative PET results in the lung (two patients), liver (one patient), and in a celiac node (one patient). In all these cases, patients had substantial FDG-avid recurrence on other sites. Therefore, not detecting one small lesion (in the lung or liver) did not affect either the overall conclusion of the PET study or patient management.

For example, at 6 months, thoracoabdominal CT demonstrated small lung nodules in two patients confirmed to be lung metastases which were missed by the first FDG-PET scans corresponding to false-negative results in the lung. However, for both those patients, the lung nodules were associated to other metastatic foci correctly depicted by FDG-PET. Lung nodules became FDG-avid on the following PET examination as their size increased. On the other hand, PET allowed to discover distant metastases involving the lung, liver, or bones, which were not detected on CT in six patients (15%), leading to a change in the patient management.

No patient had a negative PET and a recurrence detected by another exploration. Therefore, considering a patient-by-patient analysis, we had no false-negative PET scan, corresponding to a 100% negative predictive value.

Of the 16 patients having a true-positive first PET examination, seven patients underwent additional chemotherapy and four patients underwent additional combined chemoradiotherapy. Because of poor medical condition, only a palliative regime was proposed to five patients with metastatic recurrence.

Discussion

To our knowledge, our study is the first report of a prospective repeated and systematic use of FDG-PET in the follow-up of asymptomatic esophageal cancer patients after surgery. Esophagectomy remains currently an option for the treatment of esophageal cancer. Several phase III trials have been conducted over the past 10 years to evaluate the potential interest of adding medical treatment prior to surgery. Recently, Tepper et al. have presented the final results of the CALGB 9781 study.[38] In this prospective phase III trial, 500 patients were targeted for enrolment and the primary endpoint was the overall survival. However, the final result of this trial cannot be conclusive due to poor recruitment rates (only 56 patients were finally included). Therefore, surgery alone remains today a valid option in the treatment of patients with squamous cell esophageal neoplasm. This explains the relative limited percentage among our patient population that underwent neoadjuvant chemoradiation.

After esophagectomy with or without additional medical treatment, the overall 3-year survival rate of our patients was 56%. This result is compatible with those of previous reports (40% to 56%).[39–41] In addition, in our series, 23 of the 41 patients (56%) developed recurrent disease. This

Table 2 Comparison of Sensitivity, Specificity, and Accuracy of FDG-PET and CT for the Detection of Recurrence in Esophageal Cancer

Site of recurrence	PET				CT			
	Sensitivity (%)	Specificity (%)	Accuracy (%)	NPV (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	NPV (%)
All[a]*	100	85.3	90.7	100	65	91.2	81.5	81.5
Locoregional**	93.3	97.4	96.2	97.4	60	100	88.9	86.7
Distant*	100	89.4	92.5	100	66.6	92.1	84.9	87.5
Liver	75	100	98.1	98	50	96	92.5	96
Lung	57	97.9	92.5	93.8	71.4	95.7	92.5	95.7
Bone	100	100	100	100	33.3	100	92.5	92.3
Distant lymph node	88.9	95.5	94.4	97.7	55.5	100	92.5	91.8

NPV negative predictive value
*$p=0.002$; **$p=0.05$
[a] Patient-by-patient analysis

result is also similar to the rate reported by Chen and colleagues.[40] Recurrence of esophageal cancer is known to appear early after surgery, almost within the first year, justifying an early follow-up. Indeed, in this study, we were able to demonstrate that most of the recurrences (70%) were diagnosed very early after operation (16 patients at 6 months and one at 12 months). All six patients with non-R0 resection belonged to this early relapsing group and none of them is still alive at the time of the last follow-up. An additional ten patients also relapsed within the first 6 months after surgery. Those patients might have had micrometastatic disease beyond the area of extensive procedures at the time of resection and were unlikely to be cured by surgery alone. In our study, recurrence was classified as locoregional and/or distant recurrence. Half of recurrences (47%) were both distal and locoregional, and only one third (28%) were considered as only locoregional relapse. FDG-PET was more sensitive than CT in detecting recurrence on a patient-by-patient-based analysis (100% vs. 65%). For locoregional recurrence, FDG-PET was more accurate than CT.

Since FDG is not a tumor-specific tracer and is known to accumulate also in activated inflammatory cells, FDG-PET may fail to differentiate postoperative changes from recurrent tumor. As such, it is recommended not to scan patients immediately after surgery, which is why we began to perform FDG-PET only 6 months after surgery. For similar reasons, Kato et al., studying FDG-PET for postsurgery follow-up, only report on examinations performed a year after initial surgery in a retrospective series of 55 patients.[30] In our study, the performance of early scans, at an average 6 months after surgery, were not significantly compromised by postoperative changes. Only two false-positives were found due to moderate increased uptake in the gastric tube and a perigastric node. These findings, most probably due to postoperative inflammatory changes, disappeared in the second PET examination.

With regards to distant metastases, FDG-PET was also more accurate than CT on a patient-by-patient-based analysis. Only small lung nodules less than 1 cm, confirmed to be lung metastases based on the follow-up in three patients, were missed using PET. Those lesions became significant on the following scan after their size increased. This could also explain the miss of a small hepatic lesion and a celiac node. This lack of sensitivity for the detection of small lesions is a well-known technical limitation of FDG-PET due to partial volume effects as a result of limited spatial resolution leading to potential miss of small structures with moderate uptake. However, this limitation did not influence our results, since those small lesions have been always associated with other metastatic sites, leading to an overall positive for recurrence PET examination. Nevertheless, in case of small pulmonary lesions on CT without any evidence of recurrence on FDG-PET images, further investigation such as biopsy could be suggested since localized treatment could be considered.

For the detection of distant metastases elsewhere than in the lungs, FDG-PET was also more accurate than CT in our study. This is in accordance with data already available concerning the use of PET for the initial staging of esophageal cancer that can be explained by a larger field of view considered when scanning PET, generally from head to thigh. We found only one false-positive result due to a moderate uptake in the celiomesenteric area 6 months after initial surgery leading to a similar specificity with CT for distant metastases.

Based on our PET results only, patient management has been modified in five patients with recurrences been treated using additional chemotherapy. However, this group of patients is currently too small in order to determine the impact on survival as a result of the observed changes in patient management based on PET. On the other hand, it is interesting to note that Raoul et al. demonstrated that early detection of recurrence is of great interest because more aggressive strategy can be considered leading to better outcome.[42] It is also by detecting recurrence earlier that patients will benefit from the inclusion in prospective trials using new therapeutic approaches as salvage surgery for single metastasis or new chemotherapy agents.[12–15] Consequently, a more accurate assessment of patient status will contribute to a better evaluation of such new therapeutic approaches. Based on our results, FDG-PET is more accurate than CT for this purpose as early as 6 months after surgery.

The major limitation of our study concerns the definition of the truth as commonly encountered in studies addressing the outcome of cancer patients. For obvious ethical and practical reasons, we could not biopsy all identified lesions. So, we designed our study as commonly done in such a case by establishing the truth based on different options: if a biopsy was feasible, then the truth was established by the pathologist; if the biopsy of a lesion was not feasible, the truth was established based on the follow-up. For example, a lesion was considered as a metastasis (true-positive) if it was found on repeated examinations and/or concordant on different modalities and if it was associated with an unfavorable outcome. Sensitivity, specificity, and accuracy values were calculated after the truth has been established as described. It is unsure whether we did depict all sites of recurrence by the different imaging modalities we have used. Most probably, it is not the case since it has been already demonstrated in a different and more favorable context of initial staging that none of the available imaging modalities has 100% sensitivity.[43] Therefore, the true incidence of recurrence is unknown and we can only try to estimate it by combining all available diagnostic tools as we did in this study.

This study has been performed using a dedicated PET scanner. Combined PET/CT devices are now widely available and increasingly used in clinical practice. Such facilities offer, in a single study, the best of each technology. Aside from the obvious gain of time, the gain of performance in the follow-up of asymptomatic patients after esophagectomy may be limited. Based on our results, the most likely benefit may concern a better definition of regional nodal involvement, since it is difficult to differentiate between one or many coalescent nodes based on PET images only. Combined PET/CT will, therefore, be useful in providing accurate anatomical information differentiating between nodal uptake and nodal station involvement with the potential impact of such distinction after initial surgery still to be determined.

Conclusion

Surgery remains a major option in the management of esophageal neoplasms. Early diagnosis of recurrence in asymptomatic patients could be a good way to improve the management of those patients. The present study is the first prospective study systematically using FDG-PET in the follow-up of surgically resected patients and it has shown that FDG-PET is accurate for the detection of early recurrence of esophageal cancer after initial surgery. Based on the presented results, FDG-PET could be included in the routine protocol for the evaluation of asymptomatic patients after surgery, as early as 6 months after the initial operative procedure. The use of FDG-PET in comparison with the use of endoscopy, CT scan, and/or echography remains to be demonstrated in terms of cost-effectiveness.

References

1. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005;23:2310–2317. doi:10.1200/JCO.2005.00.034.
2. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, Pezet D, Roullet B, Seitz JF, Herr JP, Paillot B, Arveux P, Bonnetain F, Binquet C. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160–1168. doi:10.1200/JCO.2005.04.7118.
3. Kleinberg L, Forastiere AA. Chemoradiation in the management of esophageal cancer. J Clin Oncol 2007;25:4110–4117. doi:10.1200/JCO.2007.12.0881.
4. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 2007;8:226–234. doi:10.1016/S1470-2045(07)70039-6.
5. Triboulet JP, Mariette C. Oesophageal squamous cell carcinoma stade III. State of surgery after radiochemotherapy (RCT). Cancer Radiother 2006;10:456–461. doi:10.1016/j.canrad.2006.08.002.
6. Baba M, Aikou T, Yoshinaka H, Natsugoe S, Fukumoto T, Shimazu H, Akazawa K. Long-term results of subtotal esophagectomy with three-field lymphadenectomy for carcinoma of the thoracic esophagus. Ann Surg 1994;219:310–316. doi:10.1097/00000658-199403000-00012.
7. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 1994;220:364–372. doi:10.1097/00000658-199409000-00012.
8. Matsubara T, Ueda M, Takahashi T, Nakajima T, Nishi M. Localization of recurrent disease after extended lymph node dissection for carcinoma of the thoracic esophagus. J Am Coll Surg 1996;182:340–346.
9. Bhansali MS, Fujita H, Kakegawa T, Yamana H, Ono T, Hikita S, Toh Y, Fujii T, Tou U, Shirouzu K. Pattern of recurrence after extended radical esophagectomy with three-field lymph node dissection for squamous cell carcinoma in the thoracic esophagus. World J Surg 1997;21:275–281. doi:10.1007/s002689900228.
10. Hulscher JB, van Sandick JW, Tijssen JG, Obertop H, van Lanschot JJ. The recurrence pattern of esophageal carcinoma after transhiatal resection. J Am Coll Surg 2000;191:143–148. doi:10.1016/S1072-7515(00)00349-5.
11. Mariette C, Balon JM, Piessen G, Fabre S, Van Seuningen I, Triboulet JP. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. Cancer 2003;97:1616–1623. doi:10.1002/cncr.11228.
12. Yamashita H, Nakagawa K, Tago M, Nakamura N, Shiraishi K, Ohtomo K. Salvage radiotherapy for postoperative loco-regional recurrence of esophageal cancer. Dis Esophagus 2005;18:215–220. doi:10.1111/j.1442-2050.2005.00502.x.
13. Komatsu S, Shioaki Y, Ichikawa D, Hamashima T, Kan K, Ueshima Y, Koide K, Lee CJ, Ikeda E, Mutoh F, Kurioka H, Oka T, Yamagishi H. Survival and clinical evaluation of salvage operation for cervical lymph node recurrence in esophageal cancer. Hepatogastroenterology 2005;52:796–799.
14. Kubota K, Kato H, Tachimori Y, Watanabe H, Yamaguchi H, Nakanishi Y, Iinuma G. Surgical therapy for recurrent esophageal cancers at anastomoses after esophagectomy. Hepatogastroenterology 2001;48:1364–1367.
15. Natsugoe S, Okumura H, Matsumoto M, Uchikado Y, Setoyama T, Uenosono Y, Ishigami S, Owaki T, Aikou T. The role of salvage surgery for recurrence of esophageal squamous cell cancer. Eur J Surg Oncol 2006;32:544–547. doi:10.1016/j.ejso.2006.02.014.
16. Homs M, v d Gaast A, Siersema P, Steyerberg E, Kuipers E. Chemotherapy for metastatic carcinoma of the esophagus and gastro-esophageal junction. Cochrane Database Syst Rev 2006;18:CD004063H.
17. Vidal O, Soriano-Izquierdo A, Pera M, Elizalde J, Palacin A, Castells A, Pique J, Volant A, Metges J. Positive VEGF immunostaining independently predicts poor prognosis in curatively resected gastric cancer patients: results of a study assessing a panel of angiogenic markers. J Gastrointest Surg 2008;12:1005–1014. doi:10.1007/s11605-007-0336-3.
18. Atmani A, Topart P, Vandenbroucke F, Louzi A, Ferrand L, Lozac'h P. Metachronous cancer of gastroplasty after esophagectomy. Dis Esophagus 2006;19:512–515. doi:10.1111/j.1442-2050.2006.00623.x.
19. Flamen P, Lerut A, Van Cutsem E, De Wever W, Peeters M, Stroobants S, Dupont P, Bormans G, Hiele M, De Leyn P, Van Raemdonck D, Coosemans W, Ectors N, Haustermans K, Mortelmans L. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol 2000;18:3202–3210.

20. Heeren PA, Jager PL, Bongaerts F, van Dullemen H, Sluiter W, Plukker JT. Detection of distant metastases in esophageal cancer with (18)F-FDG PET. J Nucl Med 2004;45:980–987.
21. Kole AC, Plukker JT, Nieweg OE, Vaalburg W. Positron emission tomography for staging of oesophageal and gastroesophageal malignancy. Br J Cancer 1998;78:521–527.
22. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA, Eloubeidi MA. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. J Thorac Cardiovasc Surg 2005;129:1232–1241. doi:10.1016/j.jtcvs.2004.12.042.
23. Brucher BL, Weber W, Bauer M, Fink U, Avril N, Stein HJ, Werner M, Zimmerman F, Siewert JR, Schwaiger M. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Ann Surg 2001;233:300–309. doi:10.1097/00000658-200103000-00002.
24. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, Lorenzen S, Schuster T, Wieder H, Herrmann K, Bredenkamp R, Hofler H, Fink U, Peschel C, Schwaiger M, Siewert JR. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol 2007;8:797–805. doi:10.1016/S1470-2045(07)70244-9.
25. Weber WA, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, Meisetschlager G, Busch R, Siewert JR, Schwaiger M, Fink U. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol 2001;19:3058–3065.
26. Cheze-Le Rest C, Metges JP, Teyton P, Jestin-Le Tallec V, Lozac'h P, Volant A, Visvikis D. Prognostic value of initial fluorodeoxyglucose-PET in esophageal cancer: a prospective study. Nucl Med Commun 2008;29:628–635.
27. Wong RJ, Lin DT, Schoder H, Patel SG, Gonen M, Wolden S, Pfister DG, Shah JP, Larson SM, Kraus DH. Diagnostic and prognostic value of [(18)F]fluorodeoxyglucose positron emission tomography for recurrent head and neck squamous cell carcinoma. J Clin Oncol 2002;20:4199–4208. doi:10.1200/JCO.2002.02.590.
28. Haioun C, Itti E, Rahmouni A, Brice P, Rain JD, Belhadj K, Gaulard P, Garderet L, Lepage E, Reyes F, Meignan M. [18F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood 2005;106:1376–1381. doi:10.1182/blood-2005-01-0272.
29. Hellwig D, Groschel A, Graeter TP, Hellwig AP, Nestle U, Schafers HJ, Sybrecht GW, Kirsch CM. Diagnostic performance and prognostic impact of FDG-PET in suspected recurrence of surgically treated non-small cell lung cancer. Eur J Nucl Med Mol Imaging 2006;33:13–21. doi:10.1007/s00259-005-1919-4.
30. Sasaki R, Komaki R, Macapinlac H, Erasmus J, Allen P, Forster K, Putnam JB, Herbst RS, Moran CA, Podoloff DA, Roth JA, Cox JD. [18F]fluorodeoxyglucose uptake by positron emission tomography predicts outcome of non-small-cell lung cancer. J Clin Oncol 2005;23:1136–1143. doi:10.1200/JCO.2005.06.129.
31. Flamen P, Lerut A, Van Cutsem E, Cambier JP, Maes A, De Wever W, Peeters M, De Leyn P, Van Raemdonck D, Mortelmans L. The utility of positron emission tomography for the diagnosis and staging of recurrent esophageal cancer. J Thorac Cardiovasc Surg 2000;120:1085–1092. doi:10.1067/mtc.2000.110464.
32. Kato H, Miyazaki T, Nakajima M, Fukuchi M, Manda R, Kuwano H. Value of positron emission tomography in the diagnosis of recurrent oesophageal carcinoma. Br J Surg 2004;91:1004–1009. doi:10.1002/bjs.4595.
33. Surti S, Karp JS. Imaging characteristics of a 3-dimensional GSO whole-body PET camera. J Nucl Med 2004;45:1040–109.
34. Visvikis D, Turzo A, Gouret S, Damien P, Lamare F, Bizais Y, Cheze-Le Rest C. Characterisation of SUV accuracy in FDG PET using 3D RAMLA and the Philips Allegro PET scanner. J Nucl Med 2004;45:103P.
35. Greene F, Page D, Flemming I. AJCC cancer staging manual. New York: Springer, 2002.
36. Beck JR. Likelihood ratios. Another enhancement of sensitivity and specificity. Arch Pathol Lab Med 1986;110:685–686.
37. Kaplan E, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81. doi:10.2307/2281868.
38. Tepper J, Krasna M, Niedzwiecki D, Hollis D, Reed C, Goldberg R, Rich T, Kiel K, Mayer R. Superiority of trimodality therapy to surgery alone in esophageal cancer: results of CALGB 9781. J Clin Oncol 2006;24:4012.
39. Nakagawa S, Kanda T, Kosugi S, Ohashi M, Suzuki T, Hatakeyama K. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. J Am Coll Surg 2004;198:205–211. doi:10.1016/j.jamcollsurg.2003.10.005.
40. Chen G, Wang Z, Liu XY, Liu FY. Recurrence patterns of esophageal cancer after Ivor-Lewis esophagectomy—a report of 196 cases. Ai Zheng 2006;25:96–99.
41. Rouvelas I, Zeng W, Lindblad M, Viklund P, Ye W, Lagergren J. Survival after surgery for oesophageal cancer: a population-based study. Lancet Oncol 2005;6:864–870. doi:10.1016/S1470-2045(05)70347-8.
42. Raoul JL, Le Prise E, Meunier B, Julienne V, Etienne PL, Gosselin M, Launois B. Combined radiochemotherapy for postoperative recurrence of oesophageal cancer. Gut 1995;37:174–176. doi:10.1136/gut.37.2.174.
43. Luketich JD, Friedman DM, Weigel TL, Meehan MA, Keenan RJ, Townsend DW, Meltzer CC. Evaluation of distant metastases in esophageal cancer: 100 consecutive positron emission tomography scans. Ann Thorac Surg 1999;68:1133–1136. doi:10.1016/S0003-4975(99)00974-1.