Clinical Value of a One-Stop-Shop Low-Dose Lung Screening Combined with ^{18}F -FDG PET/CT for the Detection of Metastatic Lung Nodules from Colorectal Cancer

Yeon-Hee Han¹ · Seok Tae Lim¹ · Hwan-Jeong Jeong¹ · Myung-Hee Sohn¹

Received: 20 September 2015 / Revised: 17 November 2015 / Accepted: 1 December 2015 / Published online: 17 December 2015
© Korean Society of Nuclear Medicine 2015

Abstract

Purpose The aim of this study was to evaluate the clinical usefulness of additional low-dose high-resolution lung computed tomography (LD-HRCT) combined with ^{18}F -fluoro-2-deoxyglucose positron emission tomography with CT (^{18}F -FDG PET/CT) compared with conventional lung setting image of ^{18}F -FDG PET/CT for the detection of metastatic lung nodules from colorectal cancer.

Methods From January 2011 to September 2011, 649 patients with colorectal cancer underwent additional LD-HRCT at maximum inspiration combined with ^{18}F -FDG PET/CT. Forty-five patients were finally diagnosed to have lung metastasis based on histopathologic study or clinical follow-up. Twenty-five of the 45 patients had ≤ 5 metastatic lung nodules and the other 20 patients had > 5 metastatic nodules. One hundred and twenty nodules in the 25 patients with ≤ 5 nodules were evaluated by conventional lung setting image of ^{18}F -FDG PET/CT and by additional LD-HRCT respectively. Sensitivities, specificities, diagnostic accuracies, positive predictive values (PPVs), and negative predictive values (NPVs) of conventional lung setting image of ^{18}F -FDG PET/CT and additional LD-HRCT were calculated using standard formulae. The McNemar test and receiver-operating characteristic (ROC) analysis were performed.

Results Of the 120 nodules in the 25 patients with ≤ 5 metastatic lung nodules, 66 nodules were diagnosed as metastatic. Eleven of the 66 nodules were confirmed histopathologically and the others were diagnosed by clinical follow-up. Conventional lung setting image of ^{18}F -FDG PET/CT detected 40 of the 66 nodules and additional LD-HRCT detected 55 nodules. All 15 nodules missed by conventional lung setting imaging but detected by additional LD-HRCT were < 1 cm in size. The sensitivity, specificity, and diagnostic accuracy of the modalities were 60.6 %, 85.2 %, and 71.1 % for conventional lung setting image and 83.3 %, 88.9 %, and 85.8 % for additional LD-HRCT. By ROC analysis, the area under the ROC curve (AUC) of conventional lung setting image and additional LD-HRCT were 0.712 and 0.827 respectively.

Conclusion Additional LD-HRCT with maximum inspiration was superior to conventional lung setting image of ^{18}F -FDG PET/CT for the detection of metastatic lung nodules from colorectal cancer ($P < 0.05$).

Keywords Colorectal cancer · Pulmonary nodule · F-18 FDG · Positron-emission tomography

Introduction

It is widely known that the lungs are the second most common site of metastasis from colorectal cancer after the liver. About 10–30 % of patients with colorectal cancer develop pulmonary metastases, and 2–4 % of patients with colorectal cancer have metastasis confined to the lungs [1–6]. After Thomford et al. [7] reported the principles of metastatic lung tumor resection in 1965, metastasectomy has been accepted by most surgeons as a potential curative option. Despite the development of novel chemotherapeutic and

✉ Seok Tae Lim
stlim@jbnu.ac.kr

¹ Department of Nuclear Medicine, Research Institute of Clinical Medicine, Chonbuk National University-Biomedical Research Institute, Chonbuk National University Hospital, Cyclotron Research Center, Molecular Imaging and Therapeutic Medicine Research Center, Chonbuk National University Medical School and Hospital, Jeonju, Jeonbuk, Republic of Korea

biologic agents, surgical resection is the most effective treatment for patients with pulmonary metastases [8]. While pulmonary resection for multiple or bilateral lesions remains controversial, the resection of solitary lung metastasis is generally accepted by physicians [9]. It is widely held that up to three metastatic lung nodules are resectable; however, more than three metastatic nodules are not considered an absolute contraindication. Furthermore, over past decades, the indications of surgery for metastatic lung nodules have been extended [9].

In colorectal cancer patients with only lung metastases, surgery provides a 5-year survival rate of 20–68 %, whereas patients with untreated lung metastasis show a median survival of less than 10 months with a 5-year survival probability of less than 5 % [10–15]. Therefore, the early detection and proper management of pulmonary metastasis are essential in patients with colorectal cancer.

In recent years, ^{18}F -fluoro-2-deoxyglucose positron emission tomography with computed tomography (^{18}F -FDG PET/CT) has been used as a promising tool for the detection of primary and metastatic lesions in the various types of malignancies, including colorectal cancer [16–22]. Most patients with colorectal cancer undergo spiral chest CT in addition to ^{18}F -FDG PET/CT for the surveillance of lung metastasis. However, this can be time-consuming and increase radiation exposure. Therefore, we evaluated the clinical advantages of additional low-dose high-resolution lung CT (LD-HRCT) combined with ^{18}F -FDG PET/CT over conventional lung setting image of ^{18}F -FDG PET/CT for the detection of metastatic lung nodules from colorectal cancer.

Materials and Methods

Patients

From January 2011 to September 2011, 649 patients with colorectal cancer were referred to our nuclear medicine department for ^{18}F -FDG PET/CT staging. All patients underwent additional LD-HRCT combined with ^{18}F -FDG PET/CT. Forty-five patients were finally diagnosed with lung metastasis. Final diagnosis was made based on histopathologic findings or clinical follow-up results. Twenty-five of the 45 patients had ≤ 5 metastatic lung nodules and the other 20 patients had >5 metastatic nodules. Finally, 120 lung nodules in the 25 patients with ≤ 5 metastatic nodules were enrolled in this study. This retrospective study was reviewed and approved by the institutional review board at our hospital (CUH 2014-12-025-002).

Imaging Acquisition

All patients fasted for at least 6 h prior to an intravenous injection of ^{18}F -FDG and blood glucose levels in all patients were <140 mg/dL. Approximately 5.5 MBq of ^{18}F -FDG per kilogram of body weight was administered intravenously. Scanning was performed about 45–60 min after ^{18}F -FDG administration. Images from the base of the skull to the proximal thigh were obtained using either a Biograph TruePoint 40 PET/CT scanner or a Biograph 16 PET/CT scanner (Siemens Medical Solutions, Knoxville, TN, USA). All patients were imaged in a supine position with normal shallow respiration. A CT scan was first obtained using continuous spiral

Table 1 Patients characteristics

Characteristics	No. of patients	Characteristics	No. of patients
Age		Lung metastasis only	6
Mean $\pm$ SD (years)	63.4 $\pm$ 9.9	Other metastasis	19
Range (years)	42–79	Liver	16
Sex		Peritoneum	5
Male	16	Adrenal gland	2
Female	9	Bone	2
Type of malignancy		Brain, chest wall, thyroid	3
Rectum	16	Histologic grade (19 patients)	
Rectosigmoid & sigmoid	6	Well differentiated	3
Ascending, transverse & descending colon	3	Moderate differentiated	15
TNM stage (18 patients)		Poorly differentiated	1
T2N1	1		
T3N0	7		
T3N1	5		
T3N2	3		
T4aN2 & T4bN1	2		

technique (120 kVp, 160 mA, 0.5 s rotation time), and a PET scan was then acquired in three-dimensional mode at 2–3 min per bed position. After the acquisition of the PET scan, additional LD-HRCT was performed at maximum inspiration (120 kVp, 120 mA, 0.5 s rotation time). The obtained PET data were reconstructed iteratively using an ordered-subset expectation maximization algorithm and initial CT data were used for attenuation correction.

Image Interpretation

Image analysis was performed by two nuclear medicine physicians. One hundred and twenty nodules in 25 patients were evaluated on conventional lung setting image of ^{18}F -FDG PET/CT and on additional LD-HRCT. Conventional lung setting image is the lung setting image of the CT portion of whole body PET/CT with normal shallow respiration and additional LD-HRCT is obtained at maximum inspiration. The sizes, numbers, locations, and shape of lung nodules were recorded and used to determine nodule status (benign or metastatic). Disagreements were resolved by consensus.

Statistical Analysis

Sensitivities, specificities, diagnostic accuracies, positive predictive values (PPVs), and negative predictive values (NPVs) were calculated using standard formulae. The McNemar test was performed to determine the significances of differences between the two modalities. Receiver-operating characteristic (ROC) analysis was performed to compare diagnostic performances. The significance of differences between areas under the two ROC curves was calculated using the Hanley and McNeil method. The analysis was performed using MedCalc software and statistical significance was accepted for P value <0.05 .

Results

Patient Characteristics

Patient characteristics are summarized in Table 1. Mean age was 63.4 (range, 42–79) years and 64 % of patients were male. Of the 25 patients with lung metastasis, 6 patients had metastasis confined to the lungs. The other 19 patients also had metastases to other organs such as liver, adrenal gland, bone, or brain. Based on colonoscopic and operative findings, 16 patients (64 %) had a rectal malignancy, 6 (24 %) had a rectosigmoid or sigmoid malignancy, and the other 3 (12 %) had an ascending, transverse, or descending colon malignancy. Most common TNM stage and histologic grade were T3N0 and moderate differentiation.

Fig. 1 Conventional lung setting image of ^{18}F -FDG PET/CT and additional low-dose high-resolution lung CT at maximum inspiration of a 61-year-old man with rectal cancer. Transverse (a) and sagittal (b) images of conventional lung setting images fail to depict any metastatic nodule. In contrast, transverse (c) and sagittal (d) images of additional low-dose high-resolution lung CT show a small nodule in the right lower lobe, which was confirmed as metastatic adenocarcinoma from rectal cancer histopathologically

Diagnostic Performances

Of the 120 nodules of the 25 patients, 66 were diagnosed as metastatic. Eleven of the 66 nodules were confirmed histopathologically and the others were diagnosed by clinical follow-up results. Conventional lung setting image detected 40 of the 66 nodules and additional LD-HRCT

Fig. 2 A 45-year-old woman with a history of lower anterior resection due to rectal cancer underwent ^{18}F -FDG PET/CT. A small nodule in the left upper lobe was hardly recognized by conventional lung setting image of ^{18}F -FDG PET/CT (a) because of an adjacent vessel. In contrast, the same nodule was identified in additional low-dose high-resolution lung CT (b). The nodule increased in size over 8 months (c) and was diagnosed as metastasis histopathologically

Table 2 Diagnostic performance

Lung nodules (<i>n</i> = 120)	Lesions				Diagnostic performance (%)				
	TP	FP	FN	TN	Sens	Spec	DA	PPV	NPV
Conventional lung setting	40	8	26	46	60.6	85.2	71.7	83.3	63.9
Low-dose high-resolution lung CT	55	6	11	48	83.3	88.9	85.8	90.2	81.4
<i>P</i> value					<0.001 ^a	0.087	0.015 ^a		

TP true positive, *FP* false positive, *FN* false negative, *TN* true negative, *Sens* sensitivity, *Spec* specificity, *DA* diagnostic accuracy, *PPV* positive predictive value, *NPV* negative predictive value

^a Statistically significant

detected 55 nodules. All 15 nodules missed by conventional lung setting image but detected by additional LD-HRCT were <1 cm in size. Figures 1 and 2 show the advantage of additional LD-HRCT over conventional lung setting image. The sensitivity, specificity, and diagnostic accuracy of the modalities were 60.6 %, 85.2 %, and 71.1 % for conventional lung setting image and 83.3 %, 88.9 %, and 85.8 % for additional LD-HRCT (Table 2). In ROC analysis, the areas under the curves (AUCs) of conventional lung setting image and additional LD-HRCT were 0.712 and 0.827 respectively and these values were significantly different (Table 3 and Fig. 3).

Discussion

Many studies have demonstrated the clinical usefulness of ¹⁸F-FDG PET/CT for the staging and surveillance of recurrence in patients with colorectal cancer [20–22]. However, although ¹⁸F-FDG PET/CT provides information regarding whole-body metastatic status, most patients with colorectal cancer undergo high-resolution or spiral chest CT for the evaluation of lung metastasis. In the present study, we attempted to determine the clinical value of additional LD-HRCT combined with ¹⁸F-FDG PET/CT for the detection of metastatic lung nodules from colorectal cancer. We enrolled patients with less than or equal to five metastatic lung nodules. Although, it is widely believed that three metastatic nodules are resectable, in recent years, more than three nodules have been treated by

metastasectomy when residual lung capacity can be preserved [9]. If pulmonary resection is planned for patients with lung metastases from colorectal cancer, it is critical that no nodule is missed and thus, image modalities with superior diagnostic performance are required.

Additional radiation exposure was calculated in all patients and it was found to range from 3.5 to 4.0 mSv (average, 3.84 ± 0.59 mSv). Because modern high-resolution CT (HRCT) units expose patients from 5.0 to 6.0 mSv, and thus, additional LD-HRCT with these units do not expose patients to excessive radiation.

In the present study, of the 25 patients with lung metastasis from a colorectal malignancy, 16 (64 %) had a rectal malignancy. This large portion of patients with a rectal malignancy appears to be related with venous drainage. Rectal malignancies more frequently give rise to pulmonary metastases because of the dual drainages of the inferior vena cava and portal

Table 3 ROC analysis

	Conventional lung setting	Low-dose high-resolution lung CT	Significance level
AUC	0.712	0.827	<i>P</i> value=0.004 ^a
95 % CI	0.622–0.791	0.748–0.890	

AUC area under the curve, *CI* confidence interval

^a Statistically significant

Fig. 3 ROC analysis of additional low-dose high-resolution lung CT and conventional lung setting image. The area under the curve (AUC) of the conventional lung setting image of ¹⁸F-FDG PET/CT and the additional low-dose high-resolution lung CT were 0.712 and 0.827, which represented a significant difference

venous system. This caval venous drainage can cause cancerous cells to enter the pulmonary arterial system, whereas venous drainage from other colonic regions is usually along the superior mesenteric and inferior mesenteric veins to the portal vein, which enters the liver first.

This study has several limitations. Firstly, it is limited by its retrospective design and by the relatively small number of patients enrolled. Second, only 11 of 66 lung nodules (16.7 %) were histopathologically confirmed and most nodules were diagnosed by clinical follow-up. Although not all lesions were histopathologically confirmed, we diagnosed nodules as benign or metastatic based on strict consensus, which defined benign nodule as one that remained unchanged in size, shape, and nature for at least 1 year. Another limitation is that we included patients with metastasis to other organs, such as liver, adrenal gland, bone, and brain. In these patients, finding metastatic lung nodules would not affect treatment protocol and might not influence overall outcome. Nevertheless, this pilot study is the first to investigate the potential benefits of additional LD-HRCT at maximum inspiration in addition to ^{18}F -FDG PET/CT.

Conclusion

A One-Stop-Shop additional LD-HRCT combined with ^{18}F -FDG PET/CT was found to be superior to conventional lung setting image of ^{18}F -FDG PET/CT for the detection of metastatic lung nodules in subcentimeter size from colorectal cancer. We believed that this diagnostic protocol could be time-saving and cost-effective and reduce radiation exposure for patients who are suspicious of lung metastasis compared with ^{18}F -FDG PET/CT combined with modern high-resolution CT or enhanced chest CT.

Acknowledgments This study was supported by a grant from the National R & D Program for Cancer Control, Ministry of Health, Welfare and Family Affairs, Republic of Korea (No. 0620220) and by a grant from the National Research Foundation of Korea (NRF) funded by the Korea government (MEST) (No. 2011–0028581).

Compliance with Ethical Standards

Conflict of Interest Yeon-Hee Han, Seok Tae Lim, Hwan-Jeong Jeong, and Myung-Hee Sohn declare that they have no conflicts of interest.

Ethics Statement This study was approved by ethics committee in our institution and was performed in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was waived because of the retrospective design of this study.

We declare that this paper is solely submitted to Nuclear Medicine and Molecular Image. The content has not been published or submitted for publication elsewhere. Final approval of the version to be published was done by all authors. All authors also meet the ICMJE Authorship Criteria.

References

1. Brister SJ, de Varennes B, Gordon PH, Sheiner NM, Pym J. Contemporary operative management of pulmonary metastases of colorectal origin. *Dis Colon Rectum*. 1988;31:786–92.
2. McCormack PM, Burt ME, Bains MS, Martini N, Rusch VW, Ginsberg RJ. Lung resection for colorectal metastases. 10-year results. *Arch Surg*. 1992;127:1403–6.
3. Turk PS, Wanebo HJ. Results of surgical treatment of nonhepatic recurrence of colorectal carcinoma. *Cancer*. 1993;71:4267–77.
4. Shirouzu K, Isomoto H, Hayashi A, Nagamatsu Y, Kakegawa T. Surgical treatment for patients with pulmonary metastases after resection of primary colorectal carcinoma. *Cancer*. 1995;76:393–8.
5. Goya T, Miyazawa N, Kondo H, Tsuchiya R, Naruke T, Suemasu K. Surgical resection of pulmonary metastases from colorectal cancer. 10-year follow-up. *Cancer*. 1989;64:1418–21.
6. Gonzalez M, Ris HB, Krueger T, Gervaz P. Colorectal cancer and thoracic surgeons: close encounters of the third kind. *Exp Rev Anticancer Ther*. 2012;12:495–503.
7. Thomford NR, Woolner LB, Clagett OT. The surgical treatment of metastatic tumours in the lung. *J Thorac Cardiovasc Surg*. 1965;49:357–63.
8. Younes RN, Abrao F, Gross J. Pulmonary metastasectomy for colorectal cancer: long-term survival and prognostic factors. *Int J Surg*. 2013;11:244–8.
9. Rena O, Casadio C, Viano F, Cristofori R, Ruffini E, Filosso PL, et al. Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. *Eur J Cardiothorac Surg*. 2002;21:906–12.
10. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. *Ann Thorac Surg*. 2007;84:324–38.
11. Riquet M, Foucault C, Cazes A, Mitry E, Dujon A, Le Pimpec Barthes F, et al. Pulmonary resection for metastases of colorectal adenocarcinoma. *Ann Thorac Surg*. 2010;89:375–80.
12. Lee WS, Yun SH, Chun HK, Lee WY, Yun HR, Kim J, et al. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. *Int J Colorectal Dis*. 2007;22:699–704.
13. Watanabe K, Nagai K, Kobayashi A, Sugito M, Saito N. Factors influencing survival after complete resection of pulmonary metastases from colorectal cancer. *Br J Surg*. 2009;96:1058–65.
14. Girard P, Ducreux M, Baldeyrou P, Rougier P, Le Chevalier T, Bougaran J, et al. Surgery for lung metastases from colorectal cancer: analysis of prognostic factors. *J Clin Oncol*. 1996;14:2047–53.
15. Vogelsang H, Haas S, Hierholzer C, Berger U, Siewert JR, Präuer H. Factors influencing survival after resection of pulmonary metastases from colorectal cancer. *Br J Surg*. 2004;91:1066–71.
16. Rosenbaum SJ, Stergar H, Antoch G, Veit P, Bockisch A, Kühl H. Staging and follow-up of gastrointestinal tumors with PET/CT. *Abdom Imaging*. 2006;31:25–35.
17. Bomanji JB, Costa DC, Ell PJ. Clinical role of positron emission tomography in oncology. *Lancet Oncol*. 2001;2:157–64.
18. Strauss LG, Klippel S, Pan L, Schönleben K, Haberkorn U, Dimitrakopoulou S, Strauss A. Assessment of quantitative FDG PET data in primary colorectal tumours: which parameters are important with respect to tumour detection? *Eur J Nucl Med Mol Imaging*. 2007;34:868–77.
19. Llamas-Elvira JM, Rodríguez-Fernández A, Gutiérrez-Sáinz J, Gomez-Rio M, Bellon-Guardia M, Ramos-Font C, et al. Fluorine-18 fluorodeoxyglucose PET in the preoperative staging of colorectal cancer. *Eur J Nucl Med Mol Imaging*. 2007;34:859–67.
20. Kitajima K, Murakami K, Yamasaki E, Domeki Y, Tsubaki M, Sunagawa M. Performance of integrated FDG PET/contrast-

- enhanced CT in the diagnosis of recurrent colorectal cancer: Comparison with integrated FDG PET/non-contrast-enhanced CT and enhanced CT. *Eur J Nucl Med Mol Imaging*. 2009;36: 1388–96.
21. Choi EK, Yoo IR, Park HL, Choi HS, Han EJ, Kim SH, et al. Value of surveillance ^{18}F -FDG PET/CT in colorectal cancer: comparison with conventional imaging studies. *Nucl Med Mol Imaging*. 2012;46:189–95.
22. Yoon HJ, Lee JJ, Kim YK, Kim SE. FDG-PET/CT is superior to enhanced CT in detecting recurrent subcentimeter lesions in the abdominopelvic cavity in colorectal cancer. *Nucl Med Mol Imaging*. 2011;45:132–8.