

FDG-PET IMPROVES MANAGEMENT OF PATIENTS WITH COLORECTAL LIVER METASTASES ALLOCATED FOR LOCAL TREATMENT: A CONSECUTIVE PROSPECTIVE STUDY

M. Sørensen^{1,2}, F. V. Mortensen³, M. Høyer⁴, H. Vilstrup¹, S. Keiding^{1,2} and The Liver Tumour Board at Aarhus University Hospital*

¹ Department of Medicine V, ² PET Centre, ³ Department of Surgery L, ⁴ Department of Oncology D Aarhus University Hospital, Aarhus, Denmark

* H. Vilstrup and L. Astrup (Department of Medicine V), F.V. Mortensen and M. Rokkjær (Department of Surgery L), M. Høyer and F. Hansen (Department of Oncology D), D.T. Nielsen and S.M. Sørensen (Department of Radiology R), S. Keiding and M. Sørensen (Department of Medicine V and PET Centre), Aarhus University Hospital, Aarhus, Denmark

ABSTRACT

Background and Aim: Colorectal cancer is a common cancer in the Nordic countries and 50% of the patients develop liver metastases. Liver resection may result in long term survival. Proper staging is therefore essential and CT is the standard imaging modality. We examined whether additional FDG-PET improves therapeutic management of patients with colorectal liver metastases.

Patients and Methods: Fifty-four consecutive patients were enrolled. Each patient had a treatment plan made based on our standard evaluation. The patients then had a PET scan and the treatment plan was re-evaluated, taking these results into account.

Results: In 76% of the cases, PET did not change the treatment plan due to complete concordance with CT. In another 19% of the cases, the plan was altered due to finding of more liver lesions by PET than by CT (four patients), fewer or no liver lesions (three patients), and extrahepatic lesions not visible on CT (three patients). In 5% of the cases, non-concordance between PET and CT did not change the therapeutic plan.

Conclusion: Pre-treatment FDG-PET, used supplementary to CT, improved the treatment plan in one fifth of the patients with colorectal liver metastases.

Key words: Colorectal cancer; liver imaging; liver metastasis; positron emission tomography; surgery

There are 15,000 new cases of colorectal cancer in Finland, Sweden, Norway, Iceland, and Denmark each year (1). Twenty-five percent have synchronous liver metastases at the time of primary diagnosis and further 25% develop metachronous liver metastases

Correspondence:

Michael Sørensen, M.D.
PET Centre
Aarhus University Hospital
DK 8000 Aarhus
Denmark
Email: michael@pet.auh.dk
www.liver.dk

(1). For patients with metastases restricted to the liver, liver resection is considered the only potentially curative treatment with a 5-year survival of 25–40% (2–4). This procedure, however, has a peri-operative mortality and morbidity of 1–2% and 25–30%, respectively. Furthermore, liver resection does not improve the patient's chance of survival unless all tumour tissue is removed (4). Some patients, who have been deemed incurable by liver resection, can be offered other local treatments such as radiofrequency ablation, stereotactic radiotherapy or arterial chemo-embolisation, which may result in down-staging of the tumour, which subsequently may be suitable for liver

resection (5). Careful pre-treatment staging of each patient is therefore crucial.

At present, CT scanning is the most important imaging modality for detection of colorectal cancer metastases. Supplementary positron emission tomography scan, PET, after injection of the glucose analogue 2-[¹⁸F]-fluoro-2-deoxy-D-glucose, FDG, is increasingly used in all fields of oncology (6). This is based on the method's ability to depict highly metabolic active tissues, including cancer (7). Regarding patients with colorectal liver metastases, PET is reported to influence the clinical management in 20–50% of the cases, mostly due to detection of additional metastases not detected by CT (8–15). However, the management of and the basis of clinical decisions for such patients vary between institutions. Chest CT is for example routinely included in the diagnostic work-up in our institution.

In this prospective clinical study we evaluated the value of FDG-PET scan supplementary to our routine diagnostic procedures. The purpose was to evaluate whether the diagnostic accuracy could be significantly improved. The study included patients who, based on standard contrast enhanced CT-scan and clinical evaluation, were found suitable for local treatment of colorectal liver metastases.

PATIENTS AND METHODS

PATIENTS AND STUDY DESIGN

Between October 2003 and April 2006 a total of 54 consecutive patients were included in the study. Patients who had been deemed suitable for local treatment of colorectal liver metastases based on CT and routine clinical decision making (CDM) were included. Patients who had had liver surgery within the preceding year were excluded. The study comprised 32 men and 22 women aged 41 to 77 years (median, 64 years); 23 patients had synchronous liver metastases and 31 patients had metachronous liver metastases.

A diagnostic and therapeutic plan was made for each patient at weekly conferences of the Liver Tumour Board at Aarhus University Hospital, viz. a multidisciplinary group comprising physicians from the fields of hepatology, liver surgery, radiology, PET, and oncology. The treatment plan was based on the individual case history, WHO performance status, standard liver biochemistry, CT-scan and percutaneous or laparoscopic ultrasound sonography, if warranted. Patients, who met the inclusion criteria for this study, were offered a supplementary FDG-PET examination. The PET examination was performed 1–18 days after CT, and the individual plan for the patient was then re-evaluated by the Liver Tumour Board, taking into account the result from the PET scan. It was noted for each patient if the CT- and PET results were concordant, and whether or not the clinical decision of diagnostic or therapeutic management was changed as a consequence of the supplementary FDG-PET (FVM and SK).

CT scanning was performed using a Philips Brilliance 64 multi-slice CT scanner (Philips Medical Systems, Eindhoven, The Netherlands). Scanning covered thorax and abdomen and included a separate scanning of the liver after intravenous injection of Visipaque (Nycomed Amer-sham) 270 mg/ml, 2 ml per kg body weight, with a 70 seconds delay. Interslice distance was 0.6 mm × 64.

PET scanning was performed using a Siemens ECAT EX-

ACT HR PET tomograph (CTI/Siemens, Knoxville, USA). FDG was produced at the PET Centre applying standard techniques and commercially available systems (General Electric, Uppsala, Sweden). The patient fasted overnight before the PET scan, but was requested to drink abundant of tap water. In each patient, blood glucose concentration was lower than 8 mmol/L (mean, 5 mmol/L). We injected 400 MBq FDG intravenously and the patient then rested for 1.5 hours to allow FDG to distribute and accumulate in malignant tissue. PET recordings covered the body from eyes to mid-thighs by moving the scanner bed in successive positions, comprising 14-cm transaxial fields of view. Scan time for each position was 11 minutes (a transmission scan of three minutes using external ⁶⁸Ge sources followed by an emission scan of 7 minutes). Recorded data were corrected for attenuation based on the transmission scan and for radioactive decay to start of the scan. Images were reconstructed using an iterative algorithm, resulting in three-dimensional images of the radioactivity concentrations. Each image consisted of voxels of 2.0 × 2.0 × 3.1 mm³, and the central spatial resolution was 6.7 mm FWHM (full-width at half-maximum). The PET images were examined by two PET physicians (SK, MS) for focal areas with an average lesion-to-surrounding tissue ratio of the radioactivity concentrations higher than 2 or the normalized radioactivity concentration, SUV, being 3.5 or higher (16). The only information available for the PET physicians was that the patients fulfilled the criteria for local treatment as evaluated by our standard diagnostic and staging work-up including abdominal and chest CT.

All procedures conformed to the recommendations stated in the Declaration of Helsinki of the World Medical Association (1964). The study was approved by the Ethics Committee for Aarhus County, and each patient approved the procedures.

RESULTS

In 19% (10/54) of the patients, therapeutic management was altered as a direct consequence of non-concordance between PET and CT (Tables 1–3). In another 5% (3/54) of the patients, non-concordance between the PET and CT results did not affect the therapeutic management.

In 76% (41/54) of the patients, supplementary PET did not affect the diagnostic or therapeutic management of the patient due to concordance with CT.

As shown in Tables 1 and 3, the reasons for changed therapeutic management was findings of more liver lesions by PET than by CT in four patients, fewer or no liver lesions in three patients, and extrahepatic lesions not visible on CT in three patients (two lymph nodes and one case of local recurrence of the colorectal cancer).

Among the four patients with more liver lesions found with PET than with CT, the PET findings were confirmed by histological examination of resected liver tissue in Patients ID-05 and ID-07. Follow-up CT confirmed rapid growth of liver lesions in Patient ID-09, and laparoscopic ultrasound sonography of the liver confirmed multiple liver lesions in Patient ID-01.

In patient ID-10, biopsies from CT-lesions confirmed the negative PET findings, and close follow-up confirmed the negative PET results in patient ID-03.

TABLE 1
Patients with changed diagnostic or therapeutic strategy as a consequence of FDG-PET.

Patient ID age/ sex	CT and PET findings*	Pre-therapeutic validation of PET findings	Clinical consequence of PET	Post-therapeutic validation of PET findings
01 60/F	CT: 2 liver lesions PET: Multiple liver lesions	Laparoscopic ultrasound sonography: multiple liver lesions	Liver resection cancelled; patient treated with chemotherapy	
02 56/F	CT: 2 liver lesions PET: 2 liver lesions and 1 para-aortic lesion	Explorative laparotomy: malignant para-aortic lymph node	Liver resection cancelled; patient treated with chemotherapy	
03 76/F	CT: 1 liver lesion PET: 0 liver lesion	Per-operative ultrasound sonography: No liver lesions	Liver resection cancelled	No signs of disease after 1 year
04 72/F	CT: 1 liver lesion PET: 1 liver lesion and 1 lesion in ascending colon		Planned liver resection extended with resection of colon	Histology of resected colon confirmed PET
05 73/F	CT: no liver lesions PET: 3 liver lesions	Explorative laparotomy: 2 large liver lesions and several minor	Resection and per-operative RFA** of 3 malignant liver tumours	Histology confirmed malignant liver lesions
06 68/F	CT: 1 liver lesion, 2 lesions in right lung, 1 lesion in left lung PET: 1 liver lesion and 1 lesion below left clavicle	Fine needle aspiration from clavicular lymph node confirmed malignancy	SRT*** cancelled, patient down-staged with chemo- therapy and then RFA** of liver lesions	No signs of disease 2 years after PET
07 67/F	CT: 2 liver lesions PET: 3 liver lesions		Extended liver resection	Histology confirmed malignant liver lesions
08 60/M	CT: 1 liver lesion PET: No liver lesions		Liver resection cancelled	Alive with no signs of disease after 1 year
09 73/M	CT: 2-3 liver lesions PET: multiple liver lesions	New CT confirmed rapid growth of liver lesions	Liver resection cancelled; patient treated with chemo- therapy	
10 45/F	CT: 2 liver lesions PET: no liver lesions	Biopsies from CT-lesions were benign	Liver resection cancelled	Alive with no signs of disease after 8 months

Age is given in years. Sex: F = female, M = male.

* If not noted otherwise, neither CT nor PET depicted extrahepatic lesions.

** SRT = stereotactic radiotherapy.

*** RFA = radiofrequency ablation.

The findings of extrahepatic lesions by PET in three patients with no extrahepatic lesions on CT were confirmed by histology in each of the patients.

As shown in Table 2, diagnostic or therapeutic management was not changed in spite of PET findings of lung lesions in three patients. Patient ID-11 had multiple lung metastases seen at repeated CT performed three months after liver resection.

For patient ID-12 and ID-13, there were still no signs of lung disease after six and 12 months, respectively.

In Patient ID-14, synchronous liver metastases were suspected at the primary operation for a rectal cancer, but neither CT nor PET depicted any lesions. A laparotomy was accomplished as planned, and two 3-mm malignant liver lesions were removed (histology-proven). In this case, CT and PET were both false negative.

DISCUSSION

In the present prospective study, we investigated the impact of PET on the therapeutic management of a group of consecutive patients with colorectal liver

metastases, suitable for local treatment based on routine CDM and CT. The CT-investigation was the best possible CT of today's standard, using 64-sliced contrast-enhanced technique. As a direct consequence of findings by the supplementary PET, therapeutic strategy was changed in 19% (10/54) of the patients. This is comparable with previous studies, in which PET altered the management in 18 to 39% of the patients (8–15).

In 74% of the patients, there was concordance between PET and CT. In one patient (ID-05), CT failed to show liver metastases which were found during the primary operation for the colorectal cancer. PET found two liver lesions in this patient, and an explorative laparotomy confirmed two large liver lesions and several minor ones.

PET resulted in cancellation of planned surgery in 6% (3/54) of the patients due to extensive liver disease. PET revealed previously undetected extrahepatic disease in another 6% (3/54) of the patients, which resulted in extended surgery in two patients and down-staging by chemotherapy followed by radiofrequency ablation in one patient (ID-06). This directly improved the chance of curable surgery, since the surgery planned without PET might have left re-

TABLE 2

Patients who underwent liver resection in spite of non-concordance between CT and PET.

Patient ID age/ sex	CT and PET findings*	Follow-up
11 46/M	CT: 1 liver lesion PET: 1 multifocal liver lesion and 1 lesion in right mediastinum	Multiple lung lesions on CT after 3 months
12 63/M	CT: 2 liver lesions PET: 3 liver lesions and +1 lesion in right lung hilus	No signs of disease on CT after 6 months
13 67/M	CT: 1 liver lesion PET: 1 liver lesion and 1 lesion in right lung	No signs of disease on CT after 1 year

Age is given in years. Sex: F=female, M= male.

* If not noted otherwise, neither CT nor PET revealed any extrahepatic lesions.

sidual tumour in these patients. In other studies, detection of unsuspected extra-hepatic metastases by PET was the main reason for altered therapeutic management of patients with colorectal cancer, and the major consequence was cancellation of planned surgery (8–9, 11–12, 15, 17). The reason for this discrepancy may be that at our institution, chest CT is routinely performed when staging patients with suspected colorectal metastases. Since our study included patients deemed suitable for local treatment of colorectal liver metastases based on CT in particular, no patients with known lung metastases were included.

In the three patients with non-concordance between CT and PET (Table 2), CT of thorax was negative, whereas PET showed thoracic lesions. These lesions were small and considered non-specific, and it was consequently decided not to change the treatment. This decision was based on the fact that PET has a low specificity for small foci in the thoracic region (18). In two of our patients, follow-up did not reveal progression, whereas the third patient developed multiple lung metastases during follow-up. Another study (11) showed good agreement between the sensitivity of chest CT and FDG-PET, but unfortunately chest CT was not performed in all patients in that study.

It has recently been shown that the use of PET in pre-treatment evaluation of patients with liver metastases can substantially reduce overall costs and patient morbidity (19). This was also found by Fernandez et al. (20), who demonstrated a 5-year survival rate of 58% after resection of colorectal liver metastases in patients screened by pre-operative PET, compared to a median 5-year survival rate of 12–41%, when using staging modalities without PET. Strasberg et al. (14) found a 3-year survival rate of 77% for patients allocated for liver resection based on PET. The reduced costs and morbidity and the improved survival rates were mainly a result of a better selection and planning of patients for surgery, avoiding surgery of patients for whom the procedure was fu-

TABLE 3

Cases with non-concordance between CT and PET.

	Numbers
More liver lesions detected by PET than CT	4 (7.4%)
Fewer/no liver lesions on PET than on CT	3 (5.6%)
Extra-hepatic tumour detected by PET but not by CT	2 (3.7%)
Lymph node Local recurrence of primary colon cancer	1 (1.8%)

TABLE 4

Impact on treatment in the cases with non-concordance between PET and CT.

	Numbers
Surgery cancelled due to extensive disease	3 (30%)
Surgery cancelled due to no disease	3 (30%)
Extended surgery	3 (30%)
Down-graded by chemotherapy	1 (10%)

tile. Since PET, in other studies, has been shown to increase both sensitivity and specificity of local recurrence or the development of hepatic and extra-hepatic metastases (21–22), we decided to let the patients benefit from the PET results by including the results in a revised treatment plan.

The study was conducted using a PET camera without integrated CT. In the three patients with non-concordance between PET and CT, the use of a combined PET/CT scanner might have been helpful, since this improves the interpretation of both PET and CT images possible due to precise alignment of metabolic active lesions (PET) to well-defined anatomic structures (CT).

In conclusion, pre-treatment FDG-PET used supplementary to CT improved the treatment plan in one fifth of the patients with colorectal liver metastases. Consequently, PET is now included in our standard clinical work-up of this group of patients.

ACKNOWLEDGEMENTS

The work was supported by the Danish Medical Research Council (22-02-0337).

REFERENCES

- Hakama M, Hoff G, Kronborg O, Pahlman L: Screening for colorectal cancer. *Acta Oncol* 2005;44:425–439
- Fong Y: Surgical therapy of hepatic colorectal metastasis. *Cancer* 1999;49:231–255
- Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D: Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. *Association Francaise de Chirurgie. Cancer* 1996;77:1254–1262
- Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M: Surgical resection of hepatic metastases from colorectal cancer: A systematic review of published studies. *Br J Cancer* 2006;94:982–999

5. Vauthey JN, Zorzi D, Pawlik TM: Making unresectable hepatic colorectal metastases resectable – does it work? *Semin Oncol* 2005;32(6 Suppl 9):S118–122
6. Reske SN, Kotzerke J: FDG-PET for clinical use. Results of the 3rd German interdisciplinary consensus conference, “Onko PET III” 21 July and 19 September 2000. *Eur J Nucl Med* 2001; 28(11):1707–1723
7. Warburg O: The metabolism of tumours. Richard Smith. New York, 1931, pp. 129–169
8. Arulampalam THA, Francis DL, Visvikis D, Taylor I, Ell PJ: FDG-PET for the pre-operative evaluation of colorectal liver metastases. *EJSO* 2004;30:286–291
9. Böhm B, Voth M, Geoghegan J, Hellfritsch, Petrovich A, Scheele J, Gottschild D: Impact of positron emission tomography on strategy in liver resection for primary and secondary liver tumors. *J Cancer Res Clin Oncol* 2004;130:266–272
10. Boykin KN, Zibari GB, Lilien DL, McMillan RW, Aultman DF, McDonald JC: The use of FDG-positron emission tomography for the evaluation of colorectal metastases of the liver. *Am Surg* 1999;65(12):1183–1185
11. Imdahl A, Reinhardt MJ, Nitzsche EU, Mix M, Dingeldey A, Einert A, Baier P, Farthmann EH: Impact of 18F-FDG-positron emission tomography for decision making in colorectal cancer recurrences. *Langenbeck's Arch Surg* 2000;385:129–134
12. Rosa F, Meimarakis G, Stahl A, Bumm R, Hahn K, Tatsch K, Dresel St: Colorectal cancer patients before resection of hepatic metastases. Impact of 18F-FDG PET on detecting extra-hepatic disease. *Nuklearmedizin* 2004;43:135–140
13. Ruers TJM, Langenhoff BS, Neeleman N, Jager GJ, Strijk S, Wobbes T, Carstens FHM, Oyen WJG: Value of positron emission tomography with [F-18]Fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. *J Clin Onc* 2002;20:388–395
14. Strasberg SM, Dehdashti F, Siegel BA, Drebin JA, Linehan D: Survival of Patients Evaluated by FDG-PET Before Hepatic Resection for Metastatic Colorectal Carcinoma: A Prospective Database Study. *Ann Surg* 2001;3:293–299
15. Vitola J, Delbeke D, Sandler MP, Campbell MG, Powers TA, Wright K, Chapman WC, Pinson W: Positron emission tomography to stage suspected metastatic colorectal carcinoma to the liver. *Am J Surg* 1966;171:21–26
16. Delbeke D, Martin WH, Sandler MP, Chapman WC, Wright jr. JK, Pinson CW: Evaluation of benign vs malignant hepatic lesions with positron emission tomography. *Arch Surg* 1998;133:510–516
17. Zealley IA, Skehan SJ, Rawlinson J, Coates G, Nahmias C, Somers S: Selection of patients for resection of hepatic metastases: improved detection of extra-hepatic disease with FDG PET. *RadioGraphics* 2001;21:55–69
18. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K, Uno K: Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. *Lung Cancer* 2004;45:19–27
19. Zubeldia JM, Bednarczyk EM, Baker JG, Nabi HA. The economic impact of 18FDG positron emission tomography in the surgical management of colorectal cancer with hepatic metastases. *Cancer Biother Radiopharm* 2005;20:450–456
20. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg S: Five-years survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). *Ann Surg* 2004;240:438–450
21. Delbeke D, Martin WH: PET and PET-CT for evaluation of colorectal carcinoma. *Semin Nucl Med* 2004;34:209–223
22. Wiering B, Krabbe PFM, Jager GJ, Oyen WJG, Ruers TJM: The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases. A systematic review and metaanalysis. *Cancer* 2005;104:2658–2670

Received: December 11, 2006

Accepted: March 28, 2007