The role of nuclear medicine in the staging and management of liver metastases has considerably evolved during the last decade. We have indeed definitively left the era of hepatic scintigraphy with technetium-labelled colloids that was poorly effective in detecting liver metastases. New tracers and metabolic concepts have been developed and are very useful tools in the hands of the clinicians.

**Positron emission tomography**

Positron emission tomography (PET) using the glucose analogue 2-[\(^{18}\)F]fluoro-2-deoxy-D-glucose (FDG) is regarded as the most important advance in medical imaging in oncology since the introduction of CT-scanning in the early eighties. Malignant tumours are characterized by an increase of glucose uptake. PET allows the detection of such foci of increased glucose metabolism and has proven very useful for diagnosis and staging of various malignancies (1-6).

PET-FDG has the unique capability to provide whole-body images in a single session, as opposed to conventional methods that focus on a specific region, eg liver or chest.

**PET-FDG for diagnosis of liver metastases**

PET-FDG is routinely used for the initial pretherapeutic staging of lung cancer (7-8), esophageal cancer (9) and pancreatic cancer (10). PET has proven effective in diagnosing liver metastases in all those indications, but its sensitivity is reduced for smaller metastases (below 1-cm) from pancreatic cancers (11). Some tumours are characterized by a low glucose uptake, such as well-differentiated prostate cancer (12) or neuro-endocrine tumours (13-14), which makes them bad indications for a PET-FDG.

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**PET-FDG for the preoperative staging of liver metastases**

PET-FDG has been most commonly used in patients with a known recurrence, mainly a liver metastasis, and who undergo evaluation for a possible resection. Studies on colorectal cancers have shown that PET results in upstaging of the disease in 30-35% of patients, and to change of the therapeutic option in 30% (21-25). In a recent study, ARULAMPALAM et al. reported that in 15 patients with known liver metastases (in a series of 42 patients), 11 had indeed extrahepatic disease that PET detected in all cases, as compared to CT that was positive only in 45% of cases (22). KALFF et al. recently evaluated the incremental value of PET-FDG over CT in 106 patients with recurrent CRC and reported that PET modified the management in 60 pts (59%) and in particular prevented surgery in 26 pts (24). In the same way, RUERS et al. studied 51 pts with suspected liver lesions and compared PET with conventional staging methods including spiral CT of chest, liver, abdomen and pelvis. They found that PET results upstaged 11 pts and downstaged 5 pts, resulting in a change in management in 10 pts (20%). Interestingly, they reported a lower sensitivity than usually reported for the detection of liver metastases by PET : 65% (23). As compared to other studies, the gold standard was histopathology or intraoperative ultrasound and the calculations were made on a lesion basis, as opposed to other studies using a patient-based analysis.

Two recent papers have compared PET to intraoperative ultrasound. RYDZEWSKI et al. reported on 120 pts out of whom 50 had PET and IOUS. 87 lesions were analyzed and the sensitivity for PET and IOUS were similar, 71%. They found that the positive predictive value for predicting the involvement of the hepatic section was 93% for PET and 87% for IOUS. As a result, IOUS changed the therapeutic option in only one patient (26). ROHREN et al. reported on 23 patients evaluated with both PET and IOUS. The lesion-based sensitivity was 79% for PET and they noted a correlation between the size of the lesion and the sensitivity that was significantly reduced for lesions below 1-cm. The lobar distribution of lesions was correctly evaluated by PET in 20 pts but the number and location of lesions were correct in 12 out of 22 pts with metastases (55%) (27).
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of a significant number of patients. This means that patient with a limited disease at PET have more chance of having truly resectable disease. In a recent study, we evaluated the ability of PET to predict the resectability of CRC recurrences in 79 patients with liver or other localizations (Fig. 1). We found that PET was significantly more performant than combined conventional imaging methods (CIM) in predicting the resectability or non resectability of the recurrence (82% vs 68%, p < 0.05). Indeed, out of 39 patients sent to operation on the basis of a PET + CIM suggesting operable limited disease, 31 could be operated on with curative intent (79%), which represents a major improvement as compared to the figures reported in the literature (28). In the group operated on with curative intent, the 3-yr survival rate was 78% (25).

Strasberg et al. have evaluated patients with liver metastases only. PET detected additional lesions in 10 pts. Interestingly, the 3-year survival rate was 77% in the group of patients operated on (29).

Conclusion

PET-FDG has proven effective in the pretherapeutic initial staging of tumours that usually metastasize to liver, such as pancreatic, esophageal or lung cancers.

In the follow-up of cancer, PET-FDG is highly effective for the diagnosis and staging of liver metastases from colorectal cancer. To date studies are lacking in other types of cancer although the sensitivity of PET has been shown high for detecting recurrent breast cancer to the liver (30). In CRC, PET is more accurate than conventional techniques for the staging of disease and is a better predictor of resectability. Its uses results in a better selection of patients for surgical exploration. More studies are now needed to confirm that the survival will be increased in the group with PET-confirmed limited disease.

Nuclear Medicine in neuroendocrine tumors

The development in the early nineties of radiolabelled somatostatin analogs enabled noninvasive evaluation of tumors displaying a high density of somatostatin receptors, especially the subtype 2 (31). These receptors are abundant in several tumor types derived from the APUD system, in particular, gastroenteropancreatic neuroendocrine tumors (GEP) such as carcinoid tumors and islet-cell carcinomas. The mostly used tracer is $^{111}$In-pentetreotide, an octapeptide derivative of somatostatin that can be used for gamma camera imaging. This technique has proven highly sensitive to detect primary tumors as well as metastases of GEP tumors. The detection rate of patients with GEP was on aggregate 89% but as high as 95% after exclusion of insulinomas, a tumor type that inconsistently shows somatostatin receptor subtype 2 (32). Based on these findings, $^{111}$In-pentetreotide is now currently used in the workup of patients with GEP tumors. Its role in the management of liver metastases is specific in view of the exquisite sensitivity of the state of the art MRI and CT-scan techniques. First, it can be used to detect liver metastases in patients with a known extrahepatic tumor, e.g. an ileal carcinoid. In this indication, $^{111}$In-pentetreotide scintigraphy has proven effective in detecting liver metastases or extrahepatic gastrinomas in up to 70% of patients with a Zollinger-Ellison syndrome as compared with 19%, 38% and 45% by ultrasonography, CT-scan and MRI respectively (33). In a series of 47 patients with GEP tumors we were able to detect 21/22 liver metastases whereas various conventional imaging modalities detected 20/22 (34). Table 1 shows the summarized results of these studies. In the latter series however the major contribution of $^{111}$In-pentetreotide scintigraphy was to demonstrate 27 extrahepatic lesions that were not previously shown by a detailed imaging workup. This is probably the major diagnostic contribution that can be expected in patients with neuroendocrine liver metastases: the demonstration of extrahepatic lesions is of course of considerable importance in the decision to resect liver metastases. In an elegant study, Leibani et al. demonstrated among 90 patients without previously known metastases, the presence of hepatic and extrahepatic metastases in 7 and
25% of the patients. Third, 111 In-pentetreotide scintigraphy had an impact on the surgical decision in 2% of patients. By semi-quantitatively showing the somatostatin receptor density, 111 In-pentetreotide will be essential to identify such patients to redirect the therapy using 90 Y or 177 Lu-labelled somatostatin analogs. CIM + only 2% 5% 10% 4% SRS + 36% 9% 20% 12% SRS + 98% 95% 58% 92% SRS + only 36% 9% 20% 12% CIM + only 2% 5% 10% 4% 18 patients, respectively whereas they showed extrahepatic metastases in 13 patients out of 59 with known liver metastases (35). In this series, 111 In-pentetreotide scintigraphy had an impact on the surgical decision in 25% of the patients. Third, 111 In-pentetreotide scintigraphy by showing the expression of somatostatin receptors is also able to noninvasively identify those tumors that become less differentiated, especially carcinoids, and may therefore be a good indication for chemotherapy (36). Although this occurrence is relatively rare, it is essential to identify such patients to redirect the therapeutic option. Finally, the recent development of peptide-based radiotherapy using beta-emitter labelled somatostatin analogs requires a well-controlled selection of the patients. By semi-quantitatively showing the somatostatin receptor density, 111 In-pentetreotide will be essential to appropriately select patients when such treatment becomes implemented in clinical practice (37). It is currently advised that the uptake of 111 In-pentetreotide by tumor lesions should be at least equal but ideally higher than the liver uptake to anticipate any benefit from therapy using 18F or 17Lu-labelled somatostatin analogs.

References


