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EDITORIAL

Imaging liver metastases—size *is* important

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All metastases start out small, and treatment is more likely to be effective if the disease is detected at an early stage, so the current focus of imaging is to improve our ability to find small lesions. Sixty years ago, the most effective instrument for detecting liver metastases was the surgeon's hand during laparotomy. J C Goligher, a former colleague in Leeds, followed up about 700 patients after resection of primary colorectal cancers, and found 31 whose livers appeared normal at surgery, but who came to autopsy within one month. Five of these (16%) were found to have unsuspected liver metastases. Forty years ago, Ozada & Pickren examined 150 autopsy livers containing metastases and found that in 11% of cases, the organs appeared normal to inspection and palpation but showed deep-seated tumours on sectioning. Twenty years ago, it became clear from follow up studies after resection of colorectal cancer that about one third of patients in whom the liver appeared normal at the time of laparotomy would develop detectable liver metastases within two years. Observation of tumour growth rates indicates that the lesions were almost certainly present in the liver at the time of surgical examination. During the last 20 years, non-invasive imaging techniques have improved to the degree that they are now at least as accurate as direct surgical examination of the liver, and even with the addition of intra-operative ultrasound (IOUS) it is now relatively uncommon for our surgical colleagues to discover lesions at the time of operation that were not already detected by earlier imaging. In a current study in my own department, 20% of patients undergoing liver resection with IOUS were found to have 'new' metastases on CT in within 6 months. All this suggests that surgical findings at laparotomy no longer represent a suitable standard of reference for measuring the accuracy of imaging. In order to show further improvements in imaging, we need a more sensitive reference standard.

The increasing use of surgical resection for liver metastases, particularly from colorectal primaries, gives us an opportunity to correlate imaging with histology in more detail, but there are still limitations here. Conventional pathologic examination of gross liver specimens involves slicing the organ at 1 cm intervals, but then employing the same methods as those used by the surgeons at laparotomy—visual inspection, and palpation. Pathologists may run into the same problem faced by the radiologist with CT and MRI—that of missing lesions which are smaller in size than the thickness of the slice. The obvious answer is to use thinner slices both in imaging and in pathologic examination. This could lead to a rather odd situation (which seems to be happening in my own institution) where we radiologists think we are detecting more and more small liver lesions, but the pathologist, using thinner slices to examine the resected liver segments, is also finding more smaller lesions, so our rates of detection are apparently not improving.

Until recently, studies describing the accuracy of imaging techniques did not usually indicate the size distribution of the lesions they found, so sensitivity could not be related to size. Recent work indicates that with colorectal liver metastases, careful MRI or CT should detect 95% or more of lesions larger than about 15 mm. The real issue now is the accuracy of detection for lesions smaller than this. One possible approach, which would be independent of the quality of the pathologic gold standard, would be to look at the distribution of sizes amongst the lesions detected. A presentation at the recent ESGAR/SGR meeting reported that almost 60% of colorectal liver metastases were smaller than 20 mm at the time of detection, and 30% were smaller than 10 mm. If we can further increase the proportion of lesions that are detected at this size range we can be confident that our imaging techniques are improving.

The next problem we run into is the relatively frequent incidence of small benign lesions in the liver. Studies

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dating back several years have shown that the majority of sub-centimetre lesions found on CT, even in patients with established malignant disease, remain stable over prolonged observation and appear to be benign, although pathologic confirmation is rarely obtained. With multi-slice CT we are finding more and more smaller and smaller lesions, which poses the same difficulty as that created by the introduction of lung CT over 20 years ago—most of these tiny lesions are benign, but their imaging characteristics are overlapping and in some cases indistinguishable from those of metastases. With MRI, benign features are often demonstrable, but even so, the prevalence of small benign malformations in the liver adds an extra level of difficulty to the recognition of sub-centimetre metastases. Although we will continue to improve the detection and characterisation of sub-centimetre lesions, there seems to be no prospect with current imaging methods of finding liver metastases smaller than about 2 mm. But do we need to?

Imaging is used not only to detect disease but also to localise it. The main objective of localisation (possibly the only objective) is to allow treatment by local measures—whether surgery, radiotherapy, or other forms of ablation. These types of treatment are only applicable to disease of macroscopic dimensions, so once we are dealing with sub-millimetre metastases, localisation may become unimportant and only detection is needed to allow systemic or regional chemo- or immuno-therapy. We already know that colorectal liver metastases, even when they are too small to be detected by surgical examination at laparotomy or by conventional imaging, produce changes in the relative proportions of arterial and portal venous inflow into the liver. This disturbance in liver perfusion was first shown 20 years ago by nuclear medicine techniques, and later by Doppler ultrasound. At the time, the mechanism for this blood flow disturbance was not known, but the more recent demonstration of angiogenesis in tumours of sub-millimetre size explains these early perfusion changes. So far, the perfusion techniques have not found wide usage, mostly because the original encouraging results have been difficult to reproduce in other centres. This is partly explained by the fact that as with other physiological measurements, the range of normal variation is enough to obscure small pathologic changes. Further, it is not clear how much tumour mass is needed to create the degree of perfusion disturbance which can be measured externally, so even if these approaches were reproducible and reliable, we still need to establish the size range of lesions which might be detectable.

Finally, the natural history of metastases at an even earlier stage of growth is gradually being unravelled. Experimental work on small animals many years ago showed that very large numbers of tumour emboli injected into the portal vein would produce only a few liver metastases, suggesting the presence of active biological defence mechanisms. Recent work from a group in Boston, summarised at ESGAR/SGR by Dr Kurskal, used an elegant technique of direct optical microscopy of the mouse liver *in vivo* to demonstrate the sequence of events at cellular level following the release of tumour cells into the portal circulation. In brief, they found that cancer cells were not mechanically trapped in portal venules, but were phagocytosed by Kupffer cells which then released cytokines, causing changes in the local vascular endothelium which allowed tumour cells to bind to and subsequently migrate through the vessel walls to establish invasive growth. Although further elaboration of the mechanisms involved is awaited, even these early results suggest new approaches for detection by molecular imaging techniques and for novel treatments.

In summary, we should now be able to detect, with careful use of current MRI and CT, the vast majority of colorectal liver metastases larger than 1–2 cm. In order for imaging to be equally effective for lesions in the 2–20 mm size range, we need to pursue further refinements in our existing technologies. Lesions in the size range of 0.2–2 mm are more likely to be treated by regional or systemic immuno- or chemo-therapy, so we don't need to worry about localising them, only about detecting their presence. This might best be achieved by exploiting the perfusion changes associated with tumour angiogenesis, but our techniques need to be more robust than they are at present, and we also need to explore the specificity of these vascular changes since similar perfusion disturbances occur in other forms of liver disease. For lesions at the earliest stage of growth (20–200 μ), it appears likely that detection will require the recognition of specific molecular or genetic markers and again it will be the specificity of these markers which determine the feasibility of detection by imaging, with PET being the most likely of our current techniques to contribute.