Evolving imaging technology: contrast-enhanced Doppler ultrasound is early and rapid predictor of tumour response

The article by Lassau et al. [1] on the use of contrast-enhanced Doppler ultrasound (Doppler US) for early and rapid assessment of tumour response after isolated limb perfusion (ILP) for locally advanced soft tissue sarcomas (STSs) of the extremities is an excellent example of the new opportunities that arise with rapidly evolving technologies in imaging. In the quest for early predictors and surrogate markers for response this technology represents a relatively simple, practical and cheap procedure.

In view of the large number of new drugs and treatment modalities that are under development, there is a great need for early reliable imaging indicators of tumour response. Of course this is also true for clinical management of patients in standard praxis. Many of these developments have been linked in particular to the evaluation of anti-angiogenic drugs, since the early signs of vascular shutdown, often in the absence of clinical responses, needed to be documented for these drugs to move up the clinical development pathway [2].

In the work reported by Lassau et al. [1] on the use of dynamic contrast-enhanced Doppler US (DCE-DUS, an acronym that may be practically analogous to DCE-MRI) or, as the authors have named it, Doppler ultrasound with perfusion contrast ((DUPC), the imaging technique is used to evaluate the tumour response after perfusion of an isolated limb with tumour necrosis factor (TNF) and melphalan (M). This procedure is now performed in cancer centres throughout Europe where staff have been trained in this procedure since the approval of TNF-based ILP for locally advanced soft tissue sarcomas to achieve limb salvage. Thus contrast-enhanced Doppler US is used here in the setting of standard patient management to predict tumour response quickly and therefore allow for early planning of resection of the tumour remnant in good responders, or allow for early planning of a second ILP or a different strategy in the management of early recognized poor responders. This is of great value in these patients to optimize the window of opportunity for limb salvage surgery [3]. Of course, the ability to adapt treatment strategies rapidly could be of similar value for patients with metastatic disease, and thus this procedure is of general importance despite its limitations at certain tumour sites. It should be realized that Doppler US in the ILP-setting is used to detect the vasodestructive effects on established and often very extensive tumour vasculature of high-grade STS after a TNF-based ILP. Therefore the post-treatment effects are often dramatic with massive necrosis, a situation that differs from the sometimes rather subtle decrease in flow rates in tumours, often followed by a small amount of necrosis, after the administration of anti-angiogenic drugs. However, Doppler US is apparently also performed in such conditions, as Lassau and colleagues [4, 5] have demonstrated in patients with in-transit melanoma metastases. Therefore it is possible that Doppler US may also be a promising imaging technique for tumour response assessment of visceral (metastatic) tumours outside the brain or thorax.

Lassau et al. have demonstrated the reliability of Doppler US to be as good as that of MRI. Obviously, the caveat here is that training and expertise are required, and that Doppler US is reliable in their hands.

The obvious advantage of Doppler US is that it is much simpler, more patient-friendly and cheaper than the ‘gold standard’ MRI. Moreover, it was demonstrated that a US performed as early as 1 day after ILP already has a good predictive accuracy, whereas MRI on the first day after surgery is a much less patient-friendly procedure.

When one compares Doppler US with other imaging techniques, reports in the literature show the following. The Rotterdam and the Berlin perfusion groups [6, 7] demonstrated a similar predictive reliability for phosphorus 31 magnetic resonance spectroscopy. This more complex imaging technique had very similar results in the range of about 94% predictive accuracy about a week after the ILP. In contrast, positron emission tomography (PET) scans have been reported to have a poorer performance in this setting, predicting response correctly in about 82% of cases [8, 9]. The main competitor in this field will be DCE-MRI. This technique can monitor the effectiveness of a variety of treatments, including chemotherapy, hormonal manipulation and radiotherapy, and novel therapeutic approaches, including antiangiogenic drugs, and there is clear evidence that DCE-MRI measurements correlate with immunohistochemical surrogates of tumour angiogenesis [10, 11], with many advances in experimental systems [12]. Analysis of the many measurements and the perfusion heterogeneity in tumours is extremely complex and, independent of what type of analysis is used, it is vital to achieve standardization among participating institutions for studies of this type. If this is complex for DCE-MRI it is of course also complex for DCE-DUS, because ultrasound procedures are operator dependent and training is required.

In conclusion, we can state that Doppler US is a welcome new relatively simple and practical procedure for the early assessment of tumour response. Many new technologies can be expected to reach the clinic over the next 5 years, each with their strengths, weaknesses and costs. Molecular imaging that will provide mechanistic insights into the antitumour effects at the molecular target level will be informative at the next level.
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References