Sensitive ultrasound to spot early-stage cancer

European researchers have developed highly sensitive ultrasound equipment that can detect tii quantities of reflective microbubbles engineered to stick to specific tumour cells. The technique should pick up tumours early and improve patients' chances of survival.

Most of the current diagnostic methods - biopsy analysis, biochemical tests and medical imaging - are not sufficiently sensitive. They frequently return a false negative; the tumour is only discovered when it is much bigger, and too late.

European researchers are developing a new technique that will help medical professionals visualise tiny quantities of pathological tissue in patients. The technology could localise tumours in their very earliest stages of development and help doctors begin treatments much earlier, giving patients a much better chance of survival.

The new approach uses medical ultrasound, a safe technology most commonly used for pre-natal visualisation of the foetus and the imaging of other soft tissues. A probe sends high-frequency acoustic waves into the body and detects how they bounce off the interfaces between different tissues.

To improve the sensitivity of this imaging technique, a sonographer may sometimes inject a so-called contrast agent into patients, which greatly increases the scattering of the acoustic waves back to the probe For ultrasound imaging, contrast agents are based on 'microbubbles', micron-sized gas-filled balls that sh up brightly on the ultrasound image.

Researchers in the EU-funded TAMIRUT project have developed a microbubble medium that can specifically target and bind to certain pathogenic cells in the body (such as endothelial cells of vessels lini the tumours). Combined with enhanced ultrasound equipment and signal processing capabilities, the syste can detect where microbubbles adhere to target cells, and reveal the presence of early-stage tumours.

Working with the pharmaceutical company Bracco Research S.A. in Switzerland, TAMIRUT researchers have developed a way to attach antibodies onto the surface of microbubbles. By selecting an antibody witl an affinity for marker molecules found only on target vascular cells, the microbubbles 'stick' only to the targ cells.

But it is not easy to pick up these hotspots on a scan. "We are looking at the very earliest stages of tumou growth, so there are not many cells present expressing the marker of interest," explains Alessandro Nencioni who coordinated the project.

"There may be only three or four microbubbles adhered to a site and current ultrasound equipment is not able to pick these up. Work on the hardware and signal processing is an essential aspect of this project as we seek to develop next-generation ultrasound imaging capabilities."

Strong signals

Esaote, an Italian manufacturer of medical imaging equipment, is working with several research partners a two SMEs: Vermon, a French manufacturer of medical imaging probes, and SignalGeneriX, a small firm based in Cyprus with expertise in signal processing. Their aim is to produce a scanner and a dedicated probe that can transmit and receive ultrasound waves across a wide range of frequencies and wave forms order to exploit (without any modification) the harmonic components caused by nonlinear scattering of the acoustic wave of the microbubbles.

The scanning equipment must have sufficient processing power to interpret the waves picked up by the probe, update the live image and adjust the transmitted waveforms in real time. Their detecting function is ensured by a specifically developed signal processing methods, able to detect a very limited number of microbubbles (down to a single bubble), to estimate their concentration, and to track their behaviour to get the diagnostic answer searched.

Originally, the project partners thought it would be possible to differentiate between bound and unbound microbubbles by the way they scatter particular ultrasound frequencies and wave forms. However, extensi simulations and laboratory testing have shown that this turns out to be very difficult. Instead, the scientists found a very simple answer: after 10 minutes, the microbubbles that are attached to target cells remain in place while the free microbubbles diffuse away.

The new probe will detect and calculate their local concentration and operators will be able to visualise any areas of high microbubble density within an entire organ. The repetition of this new imaging technique ove time could help medical staff to assess the evolution of a tumour, especially its vascularisation.

Using the engineered, targeted microbubble contrast agent, the improved ultrasound hardware and the signal processing, the TAMIRUT team has already demonstrated in simulations the potential of this approach for the early detection of prostate cancer.

"Our approach goes a long way to eliminating or strongly reducing the problem of false-negative diagnosis says Nencioni, "offering a second degree of evaluation after blood test screening. It is sensitive, specific and you are able to examine the whole organ, which is not possible by biopsy."

This ultrasound method improves accuracy, patient comfort and costs around half that of a biopsy. It could save European healthcare providers up to €250 million each year in biopsy costs alone.

The need for clinical trials of the targeted contrast agent and subsequent approval in humans means that t targeted microbubble agent is unlikely to be available for at least three years. But the improved signal processing algorithms will help to increase the sensitivity of ultrasound equipment, irrespective of the use these microbubbles.

Esaote is working with the other commercial partners to incorporate the new signal processing features int its medical imaging equipment by the end of 2009.

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