Lymphoscintigraphy in pregnant patients with breast cancer: is it really safe?

In their recent study, Gentilini et al. [1] investigated the safety of lymphoscintigraphy and sentinel node biopsy in pregnant women with breast cancer. After peritumoral injection of 12 MBq 99mTc-HSA nanocolloids, static and whole-body scintigraphic images were acquired. Concentration of radioactivity in the urine and bloodstream was measured using a gamma counter. Scintigraphic images showed radiotracer concentration at only the injection site and the sentinel node. Total activity was excreted via the urine within 16 h and activity in the blood pool at each time point was <2% and <1% of the injected activity, respectively. Gentilini et al. concluded that, according to their standard technique, lymphoscintigraphy and sentinel lymph node biopsy can be performed safely in pregnant women with breast cancer. However, this conclusion is fairly questionable.

As pointed out by Gentilini et al., their study was of non-pregnant women. The distribution and excretion of 99mTc-HSA nanocolloids in pregnant women are not known, and it is not logical to investigate the pharmacodynamics of 99mTc-HSA nanocolloids (due to radioactivity of 99mTc-HSA non-colloids) in pregnant women. The uterus is located next to the urinary bladder; therefore, the accumulation of the gamma radiation of 99mTc, which has high penetration activity, could possibly be harmful to the fetus. It is therefore difficult to apply the results of an article studying non-pregnant women to pregnant women.

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Reference


doi:10.1093/annonc/mdi108
Published online 2 February 2005

Optimised lymphoscintigraphy in pregnant patients with breast cancer is safe

We agree with Dr Tek and colleagues in that research involving radiation exposure of pregnant patients should be discouraged. However, their statement that ‘it is hard to translate the results of a study conducted in non-pregnant women into pregnant women’ is questionable. As no specific information exists regarding the changes in the kinetic behaviour of radiopharmaceuticals during pregnancy, the assumption that no changes occurred was postulated. However, this assumption is fully justified in our paper [1] and strengthened by a wide list of references. Our conclusions are further supported by the following considerations. (i) Due to our optimised technique and the type of radiopharmaceutical used, there is no evidence to suggest that the biokinetics of HSA should be influenced by hormonal biological changes during pregnancy. (ii) Recently, in our institute, five patients underwent sentinel node biopsy at different stages of gestation (between 2 and 7 months). The biodistribution documented by the images did not evidence any relevant difference from non-pregnant patients and the newborns are beautiful and healthy babies. (iii) Other authors evaluated the radiation risks for the foetus from nuclear medicine diagnostic procedures [2–4] and Steenvoorde et al. [5] stated that ‘the best approximation of the foetal dose is still the calculation of the dose delivered to the uterus’. (iv) In the worst hypothesis, in which all the injected radioactivity entered the blood pool and reached the urinary bladder, the absorbed doses are conservatively estimated to be 0.11 mGy to the uterus of the non-pregnant woman, 0.08 mGy to the foetus of the 3-month pregnant woman and 0.03 mGy to the foetus for the 6- and 9-month pregnant woman. It is noteworthy that the resultant doses are progressively lowered as the pregnancy stage increases, being highest for the uterus of the non-pregnant patient. (v) Publications 60 and 84 of the ICRP [6, 7] state that ‘...the pregnant patient has the right to know the magnitude and type of potential radiation effects that might result from in-utero exposure. Communication should be related to the level of risk. However, communication that risk is negligible is adequate for very low dose procedures (<1 mGy to the foetus).’ Overall circumstances, including the most conservative, indicate that the absorbed doses to the foetus are much lower than 1 mGy, well below the negligible risk threshold.

Finally, it is important to remember that the analysis of risks and benefits is one of the three essentials principles of radiation protection to be applied to any medical procedure involving radionuclides. In our described lymphoscintigraphic technique, the proposed benefits to the mother substantially exceed the possible detriment to the child. Anxiety and uncertainty to the patient must be avoided.

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Human papilloma virus (HPV) testing and sentinel node biopsy both represent significant advances in the diagnosis and management of cervical cancer. In the June 2004 issue of *Annals of Oncology*, two papers draw attention to these techniques. Dannecker et al. [1] showed that self-testing may be a facile means of sampling in cervical cancer screening, and Barranger et al. [2] illustrated the potential of sentinel node biopsy applied to cervical cancer. Although both of these papers contribute significantly to the current knowledge and opinion regarding the diagnostic options available for cervical cancer, I believe that both techniques will eventually be largely circumvented by DNA microarrays.

Cytology is essentially a 19th century technology. Despite refinements including the Pap stain, its overall potential has not changed vastly since the resolving power of the light microscope reached the physical limit. Cervical cytological screening has reduced the incidence and mortality of cervical cancer. However, it has a relatively low sensitivity and reproducibility [3]. The interpretation of cervical cytology is a subjective visual recognition skill rather than a specific laboratory test. It is limited by cellular sampling, human error and, most of all, by its reliance purely on the appearance of the cellular phenotype to predict diagnosis.

HPV testing may be a useful adjunct to cervical cytological screening as it has the potential to be used as an objective diagnostic assay. However, despite this, the majority of cervical HPV infections resulting in dysplasia resolve. Therefore, HPV testing cannot provide the sole solution to cervical cancer screening and diagnosis.

DNA microarrays have been shown to be capable of diagnosing a variety of cancers and to provide diagnostic and prognostic information that is unavailable from cytopathology or histopathology [4]. Beyond diagnosis of cancer, DNA microarrays have been shown to have the ability to predict metastasis. In particular, DNA microarrays have been shown to predict lymph node metastasis, for example in breast cancer [5]. Therefore, patients could have the benefit of accurate diagnosis as well as the avoidance of minimally invasive but not risk-free sentinel node biopsy. With the advent of global human genome DNA microarrays such as the Affymetrix® Hu U133 Plus 2.0 GeneChip®, it is likely that even greater diagnostic accuracy will be attained.

Limitations of DNA microarrays include the cost and the labile nature of RNA, which is subject to degradation, as well as transcriptome variations secondary to artefacts including hypoxia-induced gene induction. The answer to these limitations may be either to use defined protocols with agents such as RNAlater® combined with a cheaper, focused DNA microarray with probes for several hundred key genes. Alternatively, the solution may be to develop a protein-based diagnostic assay using a panel of protein markers developed from DNA microarray research, perhaps ultimately in the form of a protein microarray. Biomarkers have already been identified in cervical cancer using DNA microarrays [6]. I look forward to the results of further DNA microarray studies on cervical cancer in the current era of high-throughput technologies.

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