Safety of sentinel node biopsy in pregnant patients with breast cancer

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Background: Lymphoscintigraphy (LS) and sentinel lymph node biopsy (SLNB) have typically been contraindicated for pregnant patients diagnosed with breast cancer because they are considered unsafe.

Patients and methods: Twenty-six premenopausal non-pregnant patients who were candidates for LS underwent peritumoral injection of ~12 MBq of 99mTc-HSA nanocolloids. Static [15 min and 16 h post-injection (p.i.)] and whole-body (16 h p.i.) scintigraphic images were acquired. Activity concentration in the urine (0–2, 2–4, 4–8, 8–16 h p.i.) was evaluated by a gamma-counter. Activity in the bloodstream was measured at 4 and 16 h p.i. Thermoluminescent dosimeters (TLD) were placed, before tracer injection, on the injection site, between injection site and epigastrium (two points), and on the epigastrium, umbilicus and hypogastrium, and were removed before surgery.

Results: Scintigraphic images showed no radiotracer concentration except in the injection site and in the sentinel node. In all patients, the total activity excreted within the first 16 h was <2% of the injected activity. Activity in the blood pool was, at each time point, <1% of the injected activity. In 23 of 26 patients, all absorbed dose measurements were lower than the sensitivity of the TLD (<10 μGy); in the remaining three patients, the absorbed doses at the level of epigastrium, umbilicus and hypogastrium were in the following ranges: 40–320, 120–250 and 30–140 μGy, respectively.

Conclusions: According to our standard technique (12 MBq of 99mTc-HAS), LS and SLNB can be performed safely during pregnancy, since the very low prenatal doses from this diagnostic procedure, when properly performed, do not significantly increase the risk of prenatal death, malformation or mental impairment.

Key words: breast cancer, lymphoscintigraphy, pregnancy, radiation protection, sentinel node

Introduction

Sentinel lymph node biopsy (SLNB) has become a valid alternative to standard axillary dissection in patients with small breast carcinoma and a clinically negative axilla [1]. Dosimetric evaluations have demonstrated the safety of lymphoscintigraphy (LS) for sanitary personnel, and very low absorbed doses to the breast and normal tissues of patients [2]. So far, diagnosis of breast cancer during pregnancy has been considered a contraindication to LS and SLNB because of a lack of information regarding safety for the fetus [3], and axillary dissection is still routinely performed in these patients [4]. The aim of this study was to investigate safety of LS in terms of radiation risk and to estimate the possible absorbed doses to the fetus.

Patients and methods

We enrolled 26 young consecutive pre-menopausal, non-obese, non-pregnant women (mean age 36.7 years, range 25–44), who were candidates for LS for lymphatic mapping and SLNB. Patients signed written informed consent forms after the nature of the study was fully explained.

LS was performed according to our standard technique [5, 6]. Briefly, the procedure used consisted of a single peritumoral injection of 99mTc-labelled human albumin colloid particles (99mTc-HSA nanocolloids) in a volume of 0.2 ml 16–18 h before the surgical intervention. The net average injected activity was 12.1 MBq (range 9.0–16.6). Scintigraphic images were acquired 15 min and 16 h post-injection (p.i.) by a gamma camera (Starcam 600XR; GE Medical Systems, Milwaukee, WI, USA).
equipped with a low-energy, high-resolution collimator. Static left/right 40° anterior-oblique and anterior views were performed (256 × 256 matrix, zoom 1.33) collecting 100 kcounts. An additional whole-body scan was obtained 16 h p.i. to observe the possible diffusion of the radiotracer to other organs (e.g. kidneys, bladder or liver).

**Dosimetry**

Thermoluminescent dosimeters (TLD; 100 LiF chips; Harshaw, Thermo-electronic Corporation, Waltham, MA, USA) were placed, immediately before injection, on the injection site (TLD1), on two different sites between injection and epigastrium (TLD2–TLD3), and on the abdominal surface of the epigastrium (TLD4), the periumbilical area (TLD5) and the hypogastrium (TLD6), as shown in Figure 1. At each position, three different chips were placed. The measurement sites marked TLD4, TLD5 and TLD6 were considered representative for the evaluation of the possible committed absorbed dose to the fetus at the three different trimesters of pregnancy. TLDs were removed immediately before surgery (~16 h p.i.). The TLDs were properly calibrated before measuring the absorbed dose using standard procedures. After the exposure, each TLD readout was registered by a dedicated instrument (Mod. Toledo 656 Vinten, Sandy, UK) that converted the output signal into the absorbed dose by the appropriate calibration factor.

Urine samples were collected within established time intervals (0–2, 2–4, 4–8 and 8–16 h p.i.); two blood samples were taken at 4 and 16 h p.i. Activity concentration in biological samples was evaluated by a gamma counter (2 × 2 NaI crystal, well counter geometry), with 20% energy window for 99mTc centred at 140 keV.

**Results**

The average number of lymph nodes detected by scintigraphy was 1.3. In all patients scintigraphic images showed no diffusion of the radiotracer in the body; the injected activity was concentrated only in the injection site and in the lymph nodes, demonstrating negligible irradiation to other tissues and organs. Figure 2 shows the typical images obtained: the proper localisation of the radiotracer and its stability in the injection site and the lymph node only are confirmed in the static views at 15 min (Figure 2A) and 16 h p.i. (Figure 2B). The same anterior whole-body view at 16 h p.i. registered with two different greyscale settings, the standard (Figure 2C) and the maximally enhanced (Figure 2D), demonstrate the absence of radiotracer uptake in the pelvis. Imaging findings were confirmed by the measurement of the total activity excreted in the urine in the time interval between the injection and surgery (Figure 3). In all patients, the total activity excreted within the first 16 h was <2% of the injected activity (range 0.1–1.9%). The mean activity circulating in the blood pool, at each time
point, reached \( \sim 1\% \) of the injected activity (mean 0.9%; range 0.5–1.8%) and 1.0% (range 0.7–1.9%) at 4 and 16 h p.i., respectively.

The mean absorbed doses at the injection site (TLD1) and at the two points between injection and epigastrium (TLD2–TLD3) were 9.7, 0.5 and 0.2 mGy, respectively, in agreement with previously published data [2].

In 23 of 26 patients, all absorbed dose measurements over the surface of the abdomen at the supposed levels of the fetus were lower than the sensitivity of the TLD (<10 \( \mu \)Gy); in the remaining three patients, the absorbed doses to epigastrium, umbilicus and hypogastrium were in the following ranges: 40–320, 120–250 and 30–40 \( \mu \)Gy, respectively.

**Discussion**

In a review on breast cancer during pregnancy, it has been stated that ‘axillary dissection is preferred because nodal metastases are commonly found, nodal status affects the choice of adjuvant chemotherapy and SLNB poses an unknown risk to the fetus from the radioisotope’ [7]. The panel of the Consensus Conference on the role of SLNB in breast carcinoma advised against SLNB in pregnant women until more data were available [3].

On the other hand, Nicklas and Baker [8] suggested that ‘LS can be safely performed in pregnancy, with negligible risks to the fetus. In fact, only a minimal activity (13.5 to 16 MBq) of double-filtered \(^{99m}\)Tc sulfur colloid is injected at the site of the breast tumor and since the entire radioisotope remains trapped at the injection site or within the lymphatics, the exposure to the fetus is essentially zero.’ Morita et al. [9] stated that ‘pregnancy per se should not be a contraindication to studying patients with LS. Receiving a whole-body dose from activity 13.5 to 16 MBq in the breast, the dose of radiation exposure to the unborn child would be exceedingly low. In a worst-case scenario in which the entire dose entered the liver or the spleen, the dose to the ovaries would be 56 \( \mu \)Sv (37 MBq of colloid). With the activity injected into the breast or into the skin, the dose would be lower than that to the ovaries. With a developing fetus, the dose would be higher because of the closer proximity to the source but still low. In that case a lower dose to perform LS could be chosen.’ The authors also stated that with radioactive colloid there is no significant radiation dose from vascular absorption.

Some papers [10, 11] have reported data on the use of radionuclides in pregnant patients and the placental transfer of radiopharmaceuticals. The estimated absorbed dose to the fetus/embryo per unit activity of \(^{99m}\)Tc-HSA administered intravenously to the mother is 5.1 \( \mu \)Gy/MBq (in the early phases of the gestation; for the other stages the dose decreases). Taking into account that we inject locally 12 MBq, the overestimated dose to the fetus of 61 \( \mu \)Gy is negligible.

These hypotheses have been confirmed by our evaluation. The biological pharmacokinetic data show that a very small amount of the injected activity is circulating in the blood pool and excreted by the urinary system (<2%). Considering the physical decay of the radiotracer (\( t_1/2 = 6\) h), we can confirm that the level of radioactivity in the body is absolutely negligible at each time point studied after the administration, proving that there is a negligible risk to the fetus.

With this study, performed in non-pregnant women, we provide evidence that, according to our standard technique [12], LS can be safely performed during pregnancy, as specific radiation protection evaluations do not indicate significant risk for the fetus in any phase of a potential gestation. These conclusions are consistent with the relationship between dose for stochastic effects and threshold values for deterministic effects. Radiation-induced malformations have a threshold of 100–200 mGy or higher and are associated with central nervous system problems. Fetal dose in excess of 100 mGy can result in some reduction of intelligence quotient [13]. With a fetal dose of 10 mGy, the risk of leukaemia and cancer may be as high as 1.4 (40% increase over normal incidence). For an individual exposed in utero to 10 mGy, the absolute risk of cancer at ages 0–15 years is about one excess cancer death per 1700 [13].

However, we would like to emphasise that there is wide variety in LS techniques and injected activity. Results are strictly dependent on administered activity and size of colloids, and therefore LS performed using a different technique might lead to different results from a radiation protection point of view.

Some practical recommendations might be given in order to further minimise the exposure of the fetus such as avoiding contact with other nuclear medicine patients (e.g. by scheduling pregnant patients as the first procedure of the day, and keeping the patient in a single-bed room), and reducing time interval between LS and surgery, with a consequent possible reduction of the administered activity. Thus, in pregnant patients, SLNB can be performed within 2–3 h p.i. with 3–5 MBq of \(^{99m}\)Tc radiocolloids.

It has to be underlined that, especially during pregnancy, treatment of breast cancer has to be planned taking into account the patient’s preference after providing adequate information and after a careful discussion of all the possible scenarios. Nevertheless, the decision-making process regarding adjuvant treatment in pregnancy is limited. In fact, even though anecdotal use has been reported [14], tamoxifen and other endocrine agents are generally not recommended [15] and some drugs such as metotrexate are strongly contraindicated during pregnancy, whereas anthracyclins can be administered during the second and the third trimester [4]. From this standpoint, axillary staging gives important prognostic information and allows better local control, but does not influence the type of adjuvant treatment during pregnancy.

Minimising surgical treatment with SLNB also has the advantage of decreasing surgical morbidity and reducing the period of postoperative recovery. This might allow an earlier start of adjuvant chemotherapy which in young premenopausal (non-pregnant) patients with non endocrine-responsive tumours, as frequently occurs during pregnancy, might improve outcome [16].
One suitable option, in selected cases, might be to perform breast-conserving surgery and SLNB under local anesthesia in order to further reduce the risk of preterm labour and spontaneous miscarriage, which is increased in pregnant patients undergoing surgery [17]. Even if this approach results in an increased percentage of second operations, the sentinel lymph node could be examined with permanent sections, reducing operative time, and the patient might subsequently begin systemic treatment, with eventual completion of the local treatment postponed after delivery in cases of sentinel lymph node metastases.

**Conclusions**

According to our standard technique, LS and SLNB can be safely applied during pregnancy, since prenatal doses from this diagnostic procedure, when properly performed, are low enough that they do not significantly increase the risk of radioactive-induced effects such as prenatal death, malformation or mental impairment. LS and SLNB represent a suitable option for patients with breast cancer during pregnancy whenever axillary nodes are clinically negative.

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**References**


