study [2]. In all our LS studies [3], HSA Tc 99m nanocolloids are subdermally injected and the particles are rapidly trapped in the lymph node [4]. With this kind of radiopharmaceutical it is quite unlikely that the biokinetics of HSA nanoaggregates will vary and be influenced by hormonal biological changes during pregnancy. The lymphatic drainage of radiocolloids is inversely proportional to the particle size and 99–99.9% of the tracer is retained at the site of injection after subdermal or peritumoral administration [5]. This was recently confirmed in five patients who underwent SNP at different stages of gestation (2–7 months). The whole-body images showed no relevant differences from those of non-pregnant patients.

Moreover, a study addressing the same issue, evaluating safety of lymphatic mapping in pregnant patients, has recently been published [6]. The authors concluded that the risk to the embryo/fetus from breast lymphoscintigraphy with 92.5 MBq (2.5 mCi) of sulfur colloid Tc 99m (which is much higher than the 12 MBq used in our institute) is sufficiently small to validate SNB as an alternative to complete axillary lymph node dissection in pregnant women with breast cancer.

Therefore the real concern of Dubernard and colleagues is unclear to us: A radiation risk to the baby? Under-staging of the patients? In the series of 44 pregnant patients with breast cancer reported by Dubernard, 26 were N1 or N2 at the final pathological examination. In other words, 18 (40%) had node-negative disease.

Even if we accept that ‘pregnant breast cancer patients theoretically eligible for SNB are infrequent’ and that ‘the nodal involvement rate is high’, 40% of patients could still avoid axillary dissection, its side-effects, and, most importantly, the risks to the fetus related to the longer surgical and anaesthetic procedures. Thus we disagree with Dubernard and colleagues about the lack of justification for SNB in pregnant breast cancer patients. On the contrary, we believe that our LS technique and SNB may offer an important benefit to pregnant patients. So far, the only obstacle to application of SNB in pregnant women has been the absence of data regarding the safety of the fetus, and this has now been partially provided by Keleher et al. [6] and Gentilini et al. [7].

Dubernard and colleagues state twice that pregnant patients should not undergo SLNB outside clinical trials. We would like to remind them that the removal of axillary nodes is not curative but is performed with staging intent. Therefore it is not necessary to wait for the results of a prospective randomized trial in pregnant patients to validate the procedure. How many decades do we have to wait before providing pregnant patients with an alternative option to axillary staging? In our opinion, it might be less ethical to prevent pregnant patients, who have received adequate information, from choosing a staging procedure offering the important advantages given above with the same staging power as axillary clearance and much less morbidity.

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Hepatocellular carcinoma associated with acquired von Willebrand disease and extreme thrombocytosis

Reactive thrombocytosis (RT) is a common clinical condition and can be seen in patients with malignancies. On the other hand, acquired von Willebrand disease (AvWD) is a rare bleeding disorder and its occurrence in patients with solid tumors is even more unusual. Here we report a victim of hepatocellular carcinoma (HCC) who manifested both.

A 50-year-old man was referred for treatment of unresectable HCC. He presented with bleeding diathesis. His plasma thrombopoietin (TPO) level was extraordinarily high, while interleukin-6 level was low. Platelet aggregation tests showed mildly impaired capabili-
ties of aggregation with various agonists. No inhibitors of coagulation factors were detectable. Levels of von Willebrand factor (vWF) antigen and fibrinogen were high, but the functional property of vWF assessed by ristocetin cofactor activity (vWF:RCO) assay reached 30% of that of normal reference plasma only.

The possibility of inhibitor-induced AvWD was confirmed by a subsequent inhibition test. We mixed the patient’s plasma and pooled normal plasma in a 1:1 ratio, incubated it at 37°C for 2 h, and repeated the ristocetin cofactor activity assay. The mixture showed similarly decreased activity.

The patient then received therapy with epirubicin and interferon-alpha, with satisfactory response. Clinically, his bleeding diathesis abated. Laboratory work-up showed an improved hemostatic profile. His platelet count dropped dramatically without a concurrent fall of white cell count, which ruled out the possibility of marrow suppression effects of chemo-immunotherapy.

Our patient here exhibited two unique features: AvWD due to presence of vWF inhibitors and RT mediated by increased TPO production.

Non-hematological malignancies with coexisting AvWD are most commonly seen in patients with Wilms tumor. Other cancers sporadically reported include adrenocortical carcinoma, lung cancer, gastric carcinoma and primitive neuroectodermal tumor [1]. There have not been similar reports in patients with HCC. Generally, excessive tumoral adsorption of vWF was the pathogenesis of AvWD in cancer patients [1]. Nevertheless, we demonstrated vWF inhibitors as the underlying causes in our case.

Autoantibody-induced AvWD was typically associated with autoimmune or hematoproliferative disorders. In most patients, the antibody–vWF immune complexes were cleared from the circulation, which resulted in low levels of factor VIII and vWF antigen and reduced vWF:RCO activity [2]. Sometimes, these antibodies had restricted specificity, interfering with the binding of vWF to platelet glycoprotein Ib receptors without causing clearance of vWF antigen [3]. This could lead to normal antigen level with disproportionately reduced functional activity of vWF, as in our patient.

Various neoplasms have been associated with RT. The most widely accepted mechanism is that the endogenously increased IL-6 in cancer patients leads to excessive TPO production and resultant thrombocytosis [4]. Newer evidence has also revealed that tumor cells could over-express TPO. In a large series, thrombocytosis occurred in 2.7% of HCC patients and was the result of overproduction of TPO by HCC [5]. The contrast levels of IL-6 and TPO in our patient suggest a similar mechanism.

Both thrombocytosis and AvWD are rare paraneoplastic syndromes of HCC patients. Although RT rarely causes bleeding, hemorrhagic complications associated with AvWD could be problematic. When bleeding occurs, careful evaluation of hemostatic parameters is mandatory. If AvWD is documented, treatment must be planned accordingly.

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Limitations of Wright formula estimates of renal function

It was with interest that we read the publication by Marx et al. [1] who examined a number of formulae to estimate renal function in cancer patients over 70 years of age. They concluded that the Wright formula would provide an adequate estimation of glomerular filtration rate (GFR) in patients with a GFR within the normal range (50–120 ml/min). However, the key practical question relating to this work was not addressed, that is, the performance of the formulae in accurately predicting renal function for all patients across the full range of renal function, and particularly those with poor renal function (GFR <50 ml/min). This is an especially relevant issue for elderly patients, who were the patient group in this study. It would appear from the data that there were 40 patients with a GFR <50 ml/min; however, no details of the bias and precision of the Wright formula was presented for this group. Visual inspection of the data presented (Marx et al. [1], figure 1A) would indicate that the Wright formula significantly overestimates GFR in patients with poor renal function. The authors make no comment on the utility of the formula for this group of patients. It is worth noting also, that the original Wright paper did not provide an analysis for low levels of renal function [2].

In their paper, Marx et al. comment that our group have also shown the Wright formula to be superior over the