with intermediate pretest probability who are at high risk for surgical complications (*3*). They note importantly that the cost-effectiveness of various diagnostic strategies depends critically on the pretest probability of malignancy.

The strength of the evidence required before a management decision is made will vary depending on the pretest likelihood of disease and the risk of a specific intervention. As Dr. Fisher indicates, a negative predictive value of a nodule with no uptake (i.e., "definitely benign" by our criteria) is 97% and is probably acceptable for adopting a watch-and-wait strategy, but a negative predictive value of a "probably benign nodule" (estimated standardized uptake value $>$ 0.6–0.8 but $<$ 1.5–2.0) is 87% and may not be convincing enough to avoid a biopsy, especially in a patient with a smoking history and other risk factors for malignancy (*2*). Although we dichotomized the 5 confidence levels of interpretation as described for determining sensitivity and specificity, we did develop interval likelihood ratios for each level of interpretation. In this regard, with our prevalence rate of 53% malignant nodules, a patient whose nodule was rated definitely benign by PET had a posttest probability of malignancy of only 3% as pointed out by Dr. Fisher. Similarly, a patient whose nodule was rated probably benign by PET had a posttest probability of 13%. In populations with lower prevalence rates, the pretest–posttest probability decrease would be shifted even further. For example, in a population with a 20% prevalence of malignancy, the posttest probabilities would be reduced to 1% and 4% in patients with definitely benign and probably benign interpretations, respectively.

We strongly agree with Dr. Fisher about the hazards of continuing to consider a binary cutoff of 2.5 for standardized uptake value as capable of reliably distinguishing benign from malignant nodules. We would instead encourage the adoption of a visual scoring methodology with a validated, more continuous scale that relates to interval likelihood ratios, such as described in our publication. In this manner, the clinical pretest likelihood of malignancy could be incorporated into the final estimate of the posttest likelihood of a malignant or benign nodule.

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Pregnancy Outcome After ^{131}I Therapy

TO THE EDITOR: We read with interest the article by Garsi et al. (*1*) concerning the pregnancy outcome and the health of offspring of women who had received ^{131}I for differentiated thyroid cancer. In this article, the authors evaluated 2,673 pregnancies from patients treated with ^{131}I and found 10.4% miscarriages before any treatment, 20% after thyroidectomy but before ^{131}I therapy, and 19% after ^{131}I therapy. There was no significant variation according to the cumulative ^{131}I dose. The incidences of stillbirths, preterm births, low birth weight, and congenital malformations were not significantly different before and after ^{131}I therapy. The authors concluded that there was no evidence that radioiodine therapy affected the outcomes of subsequent pregnancies and offspring.

Interestingly, we have reported a relatively similar study in a smaller number of patients. Our study predominantly examined the effect of ^{131}I therapy (3,700 MBq) on menstrual cycle or pregnancy in women less than 40 y old. Specifically, we evaluated 45 women with differentiated thyroid cancer who were treated with ^{131}I therapy and compared with 83 age-matched control women. We found menstrual cycle irregularities in 13.3% of patients before ^{131}I therapy but 31.1% after treatment. However, after ^{131}I therapy there were no subsequent pregnancy abnormalities such as premature births, miscarriages, or congenital abnormalities in the 7 children who were borne of 6 of the 45 patients (*2*). Another study, of 49 pregnancies from 76 patients who received ^{131}I therapy, found 10% miscarriages, 18% induced abortions, and no congenital malformations or first-year mortality (*3*). All these findings concur that ^{131}I therapy is safe regarding subsequent pregnancy outcome. However, our results suggest an increased incidence of menstrual cycle abnormalities after ^{131}I therapy. It will be interesting to see if Garsi et al. (*1*), in their large cohort of patients, noticed any such abnormalities induced by ^{131}I therapy.

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REPLY: We were interested to see the letter of Chrissa Sioka and Andreas Fotopoulos about our article (*1*). In addition to reporting results similar to ours, showing that ^{131}I therapy is safe regarding subsequent pregnancy outcome, with no increase in the risk of miscarriage, induced abortion, or congenital malformation, they added new data showing that ^{131}I therapy probably increases the incidence of menstrual cycle abnormalities (*2*).

To confirm these results, we analyzed the responses given by women in our series to similar questions. Of 2,190 women questioned about cycle abnormalities before and after their cancer and followed at least 2 y, we excluded 36 in whom another cancer had developed before thyroid cancer, 158 in whom another malignancy later developed, 263 who received external radiotherapy for thyroid cancer, and 137 who were treated with radioiodine for distant metastases. Of the remaining 1,866 women, 1,054 were

diagnosed with thyroid cancer at age 45 y or younger; 287 of these reported cycle abnormalities before the diagnosis, and 767 had no cycle abnormalities before the diagnosis. Of these 767 women, 326 received at least 1 radioiodine treatment with 3.7 GBq, and 441 did not. The majority of women were interviewed more than 2 y after radioiodine treatment. The proportion of women who reported cycle abnormalities after thyroid cancer was not significantly higher among women who were treated with ^{131}I ($n = 34$, 10%) than among those who were not treated with ^{131}I ($n = 41$, 9%). In a multivariate logistic regression taking into account year and age at menarche, at diagnosis, and at interview; weight; and smoking habit, we did not observe any increased risk of cycle abnormalities after thyroid cancer among women who had received ^{131}I therapy (odds ratio, 1.2 [95% confidence interval, 0.7–1.2]).

As a final note, we were not able to confirm the results of Souza Rosário et al. (*3*), who reported transient abnormalities after ^{131}I therapy. However, our inability to confirm those results may be related to the long delay between treatment and interview in our patients, most of whom were not interviewed until more than 2 y after radioiodine treatment.

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A Proposition for the Use of Radioiodine in WDTC Management

TO THE EDITOR: Today, individualized treatments are increasingly at the forefront. Treatments tailored to tumor type and patient sensitivity are now possible. For example, breast cancer management is based mainly on menopausal status, histology, hormone receptor status, Neu status, histologic grade, and Ki67 expression rather than on TNM classification and stage. Therefore, the concept of one treatment for all (e.g., systematic radioiodine remnant ablation in patients with well-differentiated thyroid carcinoma [WDTC]) may be questioned because, as Hay et al. (*1*) maintain, the majority of patients are exposed to the risk from radiation for the theoretic benefit of a small minority. Thus, the viewpoint of Hay et al. is consistent with the current fashion. However, their perspective seems somewhat limited to me.

They state 3 goals of radioiodine remnant ablation: to increase the specificity of follow-up imaging using radioiodine, to attain undetectable thyroglobulin levels, and to decrease recurrence and increase disease-free survival by eliminating microfoci of carcinoma in the remaining tissue.

With regard to the first of these goals, increasing the specificity of follow-up radioiodine imaging, the future does not seem to lie in remnant ablation (which has other purposes) but in the use of SPECT/CT (*2*) or, especially and most recently with ^{124}I, PET/CT (*3*). These techniques may differentiate remnants from lymph nodes, and the sensitivity will increase substantially with the positron emitter isotope. In so doing, I agree that ablation of the remnant might be avoided, but postoperative metabolic imaging of the remnants and other iodine-avid metastatic foci must be applied and refined.

I do not completely agree with the authors when they report that "the administration of therapeutic ^{131}I without preceding scintigraphy to identify the target" is a "refinement in patient management." Although omitting scintigraphy before therapy may simplify management, in my opinion it does not represent progress. Postoperative and pretherapeutic imaging (as well as posttherapeutic imaging) also identify locoregional iodine-avid lesions (lesions in the nodes, indicating the need for repeated surgery) or distant iodine-avid lesions (metastatic lesions, which can be treated other than by radioiodine). When properly applied, pretherapeutic imagings also allow one to calculate the amount of activity required to destroy the remnants—an amount that is lower than the 3,700 MBq classically proposed—and fewer individuals are exposed to unnecessarily high doses of irradiation (*4*). In Europe, the administration of high activities requires one hospitalization of variable duration, with both financial and social implications.

Paradoxically, the second of these goals, undetectable thyroglobulin levels, is seen in up to 30% of patients undergoing surgery for thyroid carcinoma as a result of circulating antithyroglobulin antibodies. When these antibodies are present, remnant ablation is needed to destroy the normal thyroid tissue, eliminating any further source of antigenic stimulation and antibody production.

For the third goal of remnant ablation, eliminating microfoci, the most important prognostic factor for a patient with thyroid carcinoma is widely believed to be the surgeon (i.e., his or her ability to perform a complete or near-complete surgery and his or her willingness to operate again to remove lymph nodes). Unfortunately, what constitutes a remnant varies from surgeon to surgeon. Furthermore, some do not remove cervical nodes if the tumor is small, and some base pN status on an insufficient number of nodes. Kuffner et al. (*5*) recently found neck lymph node metastases for 6% of nanopapillary tumors 1 mm or smaller and 10% of micropapillary tumors 1 cm or smaller. These reported rates of metastasis are less than the 31% observed with larger papillary thyroid carcinomas (>1 cm). However, these findings suggest that patients older than 45 y and with small lesions but with pathologically positive nodes will be undertreated in the Hay et al. perspective (*1*).

In fact, before raising the question of remnant ablation, I would ask whether any thyroglobulin-producing normal remnants or thyroglobulin-producing tumor tissues are present. That question can be addressed by determining whether thyroglobulin is present after the operation or increases under thyroid hormone withdrawal or after treatment with recombinant human thyroid-stimulating hormone. The question can also be addressed by performing optimized scintigraphic imaging under endogenous or exogenous thyroid-stimulating hormone stimulation as part of the patient's postsurgical management.