

The diagnosis of differentiated thyroid cancer during pregnancy or in the first year post partum is a significant indicator of persistent disease

Vannucchi G, Perrino M, Rossi S, Colombo C, Vicentini L, Dazzi D, Beck-Peccoz P, Fugazzola L. Clinical and molecular features of differentiated thyroid cancer diagnosed during pregnancy. *Eur J Endocrinol* 2010;162:145-51.

SUMMARY

BACKGROUND

It has long been recognized that during pregnancy thyroid nodules or cancer may develop and that those with cancer may experience growth of their tumor. Though several theories have been proposed, the exact mechanism of this mitogenic effect is unknown. Estrogen has been an attractive candidate for this follicular growth because numerous studies have documented its neoplastic tendencies in thyroid tissues. The authors of this study sought to examine the role of estrogen in thyroid cancers during pregnancy by analyzing tumor immunohistochemical staining for estrogen receptor alpha (ER α). Patients were stratified into three groups based on timing of the diagnosis of thyroid cancer in relation to pregnancy to determine whether there was a relationship between patient outcomes and pregnancy.

METHODS

This is a retrospective study of 123 women followed between 1995 and 2006 at one institution in Italy. Patients were excluded if they were >45 years old at diagnosis, had a family history of thyroid cancer, or had a personal history of neck irradiation. All patients had been treated with total thyroidectomy; if clinically warranted, they also had cervical-

lymph-node dissection. Patients were divided into three groups based on the time of diagnosis of their thyroid cancer. Patients in group 1 were at least 1 year postdelivery (n =7). Group 2 patients had a diagnosis of thyroid cancer during pregnancy and underwent thyroidectomy during the second trimester (n = 11) or in the first year after pregnancy (n = 4). One patient was counted twice in this group, as she had a follicular carcinoma and was initially treated with lobectomy after her first pregnancy. Subsequently, papillary thyroid carcinoma (PTC) was diagnosed in the contralateral lobe during her second pregnancy. Group 3 patients were either nulliparous or their PTC was diagnosed and treated before pregnancy (n = 61).

Freedom from disease was based on the guidelines of the European and American Thyroid Associations for the management of differentiated thyroid cancer. Patients were deemed free of disease if they met all of the following criteria: undetectable thyroglobulin (Tg) while on levothyroxine therapy and after stimulation with recombinant human thyrotropin (rhTSH). In addition, patients had a negative thyroglobulin antibody (TgAb) level and a negative neck ultrasound (US). Persistent or recurrent disease was defined by a basal Tg >2 μ g/L on consecutive measurements or Tg >2 μ g/L after rhTSH stimulation, Tg >1 μ g/L after rhTSH stimulation on two consecutive measurements, neck US findings of malignancy, and/or uptake outside the thyroid bed on radioiodine scans, TgAb positivity for >4 years, or a rise in the TgAb levels.

Immunohistochemical analysis of 38 paraffin-embedded tissues (16 in group 1, 8 in group 2, and 14 in group 3) was performed to determine the presence of ER α in the PTC tumors. The tumors were classified as negative, weakly positive if there was a single area of positivity, or positive if there were multiple areas of positivity seen. Eleven tumors from patients in group 2 were evaluated for the presence of BRAF mutations.

RESULTS

Tumor–Node–Metastasis Tumor Staging, Patient Age, Treatment, and Follow-up in the Three Groups (Figures 1 and 2)

There were no significant differences between the groups in patient age at diagnosis, duration of follow-up, tumor size, or the presence of extrathyroidal invasion. Group 2 had a higher likelihood of lymph-node involvement, though this did not reach statistical significance. There was a significantly higher proportion of follicular carcinoma in group 2 as compared with the other two groups. There was no difference between the groups in terms of the use of remnant ablation or the amount of ¹³¹I administered (Figures 1 and 2).

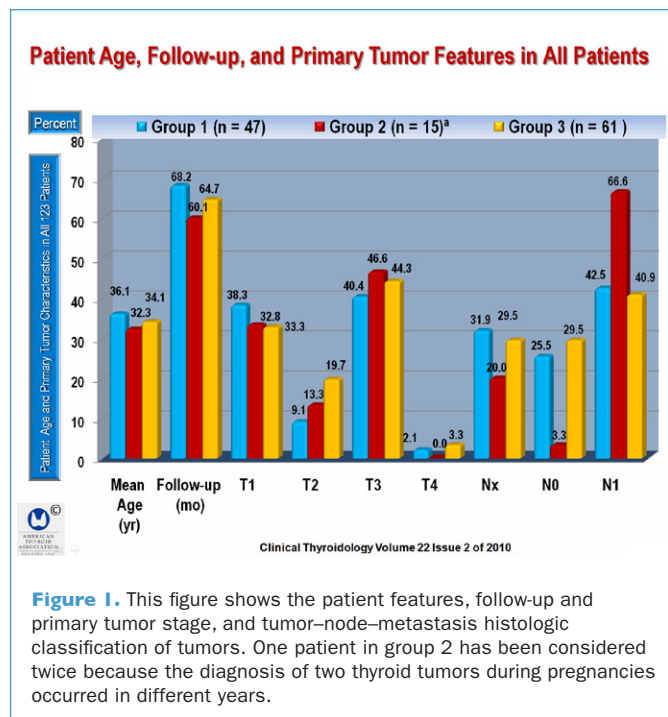


Figure 1. This figure shows the patient features, follow-up and primary tumor stage, and tumor–node–metastasis histologic classification of tumors. One patient in group 2 has been considered twice because the diagnosis of two thyroid tumors during pregnancies occurred in different years.

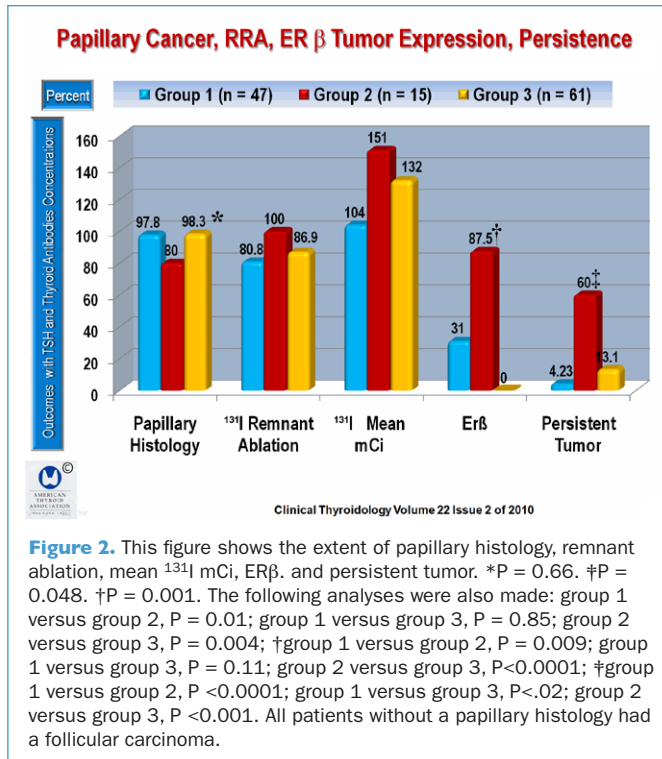


Figure 2. This figure shows the extent of papillary histology, remnant ablation, mean ¹³¹I mCi, ERβ, and persistent tumor. *P = 0.66. †P = 0.048. ‡P = 0.001. The following analyses were also made: group 1 versus group 2, P = 0.01; group 1 versus group 3, P = 0.85; group 2 versus group 3, P = 0.004; †group 1 versus group 2, P = 0.009; group 1 versus group 3, P = 0.11; group 2 versus group 3, P < 0.0001; ‡group 1 versus group 2, P < 0.0001; group 1 versus group 3, P < .02; group 2 versus group 3, P < 0.001. All patients without a papillary histology had a follicular carcinoma.

Tumor Features, Remnant Ablation, and ERα (Figure 2)

There was a significant difference in the expression of ERα among the three groups; it was identified in 31% of group 1 tumors, 87.5% of group 2 tumors, and none of the group 3 tumors (P = 0.01). The receptor was detected in multiple areas of the tumors in 35 to 40% of patients in groups 1 and 2 (Figure 2).

Analysis of Outcomes in the Three Groups (Figure 3)

Clinical outcomes varied significantly among the three groups. Persistent or recurrent disease was significantly more frequent in group 2 (60%) as compared with group 1 (4.2%) or group 3 (13.1%) (P < 0.0001). To rule out the possibility that the delay in surgery during pregnancy in group 2 patients was responsible for their worse outcome, a univariate analysis was performed. The variables of time until thyroidectomy and delay in remnant ablation after surgery were taken into account. Neither of these variables was significantly correlated with disease persistence or recurrence. Likewise, the increased incidence of follicular tumors in group 2 was not responsible for the worse prognosis, as two of these three patients are in remission. On stepwise logistic-regression analysis, pregnancy and the presence of lymph-node metastases were independent predictors of recurrent or persistent disease. Extrathyroidal invasion was not a statistically significant predictor of outcome, as the confidence interval of this association crossed unity (Figure 3). Neither the presence of a BRAF mutation nor follicular histology was responsible for the worse prognosis of group 2. All three patients with BRAF were in remission at the end of the study. Likewise, two of the three patients with follicular thyroid carcinoma were free of disease at the end of the study.

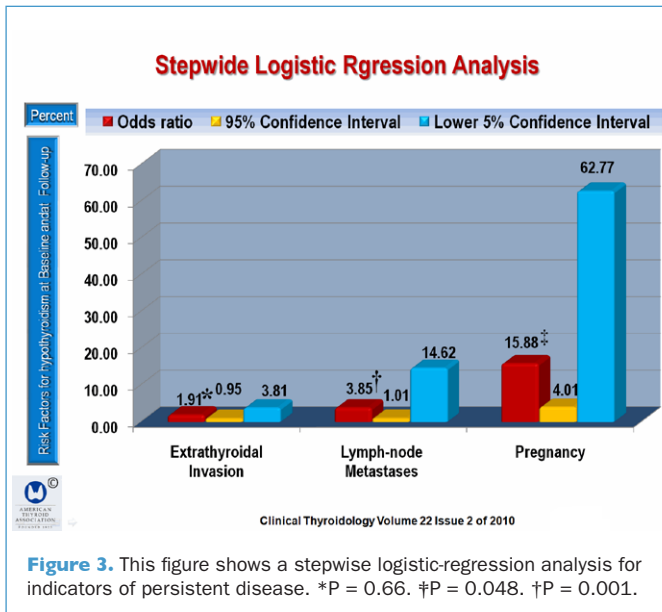


Figure 3. This figure shows a stepwise logistic-regression analysis for indicators of persistent disease. *P = 0.66. †P = 0.048. ‡P = 0.001.

CONCLUSIONS

Patients with thyroid cancer detected during pregnancy are more likely to have persistent or recurrent disease as compared with women whose tumors were diagnosed before pregnancy or more than a year after pregnancy. Estrogen may play a role in these poorer outcomes; immunohistochemical staining for ERα was significantly more prevalent in the tumors diagnosed during pregnancy.

COMMENTARY

Although it has been routinely reported that both thyroid nodules and cancer may grow or develop during pregnancy (1,2), there is a relative paucity of data regarding the long-term outcome of patients diagnosed with thyroid cancer during pregnancy. This important study by Vannucchi et al. seeks to clarify this cloudy picture. Two prior studies have examined the outcome of patients diagnosed with thyroid cancer during pregnancy (3,4). The study by Moosa and Mazzaferri (4) determined that outcomes were similar when surgery was performed during or shortly after pregnancy. This study was important in that lengthy follow-up (median, 22.4 years) was available and that there was no difference in overall survival or recurrence rates between women diagnosed during pregnancy and age-matched controls. The limitation of the study, however, was that diagnostic whole-body scans were the norm for detection of residual disease at the time and there were no data on thyroglobulin. Armed with the knowledge that these scans are burdened with a high false negative rate (5), Vannucchi et al. sought to investigate whether patients will fare equally well when using the modern criteria for determination of remission (6). The higher recurrence rates in pregnant women seen in the study by Vannucchi et al. are in contrast with those of Moosa and Mazzaferri. It is likely that this difference reflects the modern use of more sensitive testing for recurrent disease with thyroglobulin assays and

cervical ultrasonography. However, it should be noted that with the long follow-up in the study by Moosa and Mazzaferri, one would expect the latent small tumors unable to be seen initially with diagnostic scans would eventually come to clinical detection after so many years. Additional long-term studies may be beneficial in clarifying this discrepancy.

In an attempt to explain this poorer prognosis among women diagnosed with thyroid cancer during pregnancy, the authors performed immunohistochemical studies of ER α expression in tumors from all three groups. Thyroid cancer is three times more common in women than in men. This sex difference, coupled with the findings of increased tumor growth during pregnancy prompts the question of the etiologic mechanism of these phenomena. Estrogen is the logical culprit; it has been implicated in the growth of benign and malignant thyroid tissue through the activation of the mitogen-activated protein kinase pathway (7). Indeed, the cell proliferation appears to be mediated through estrogen-mediated upregulation of ER α levels in thyroid cells (8). Thus, the findings by Vannucchi et al. of increased ER α in tumors diagnosed during pregnancy reinforce these conclusions of cell-line studies and add further evidence that estrogen may be at least partially responsible for the increased growth of thyroid tumors during pregnancy.

— Jennifer A. Sipos, MD

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