



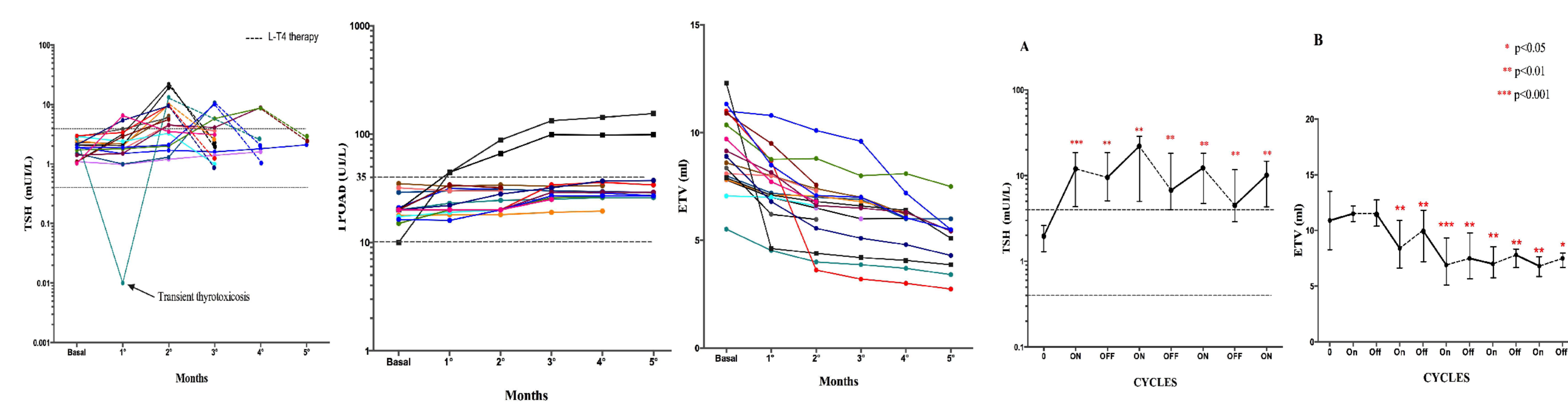
## Background

Regorafenib, a Tyrosine kinase inhibitor (TKI) recently approved for the treatment of metastatic colorectal cancer patients may, like others TKIs, produce hypothyroidism, but this effect has not been systematically evaluated so far.

## Objective

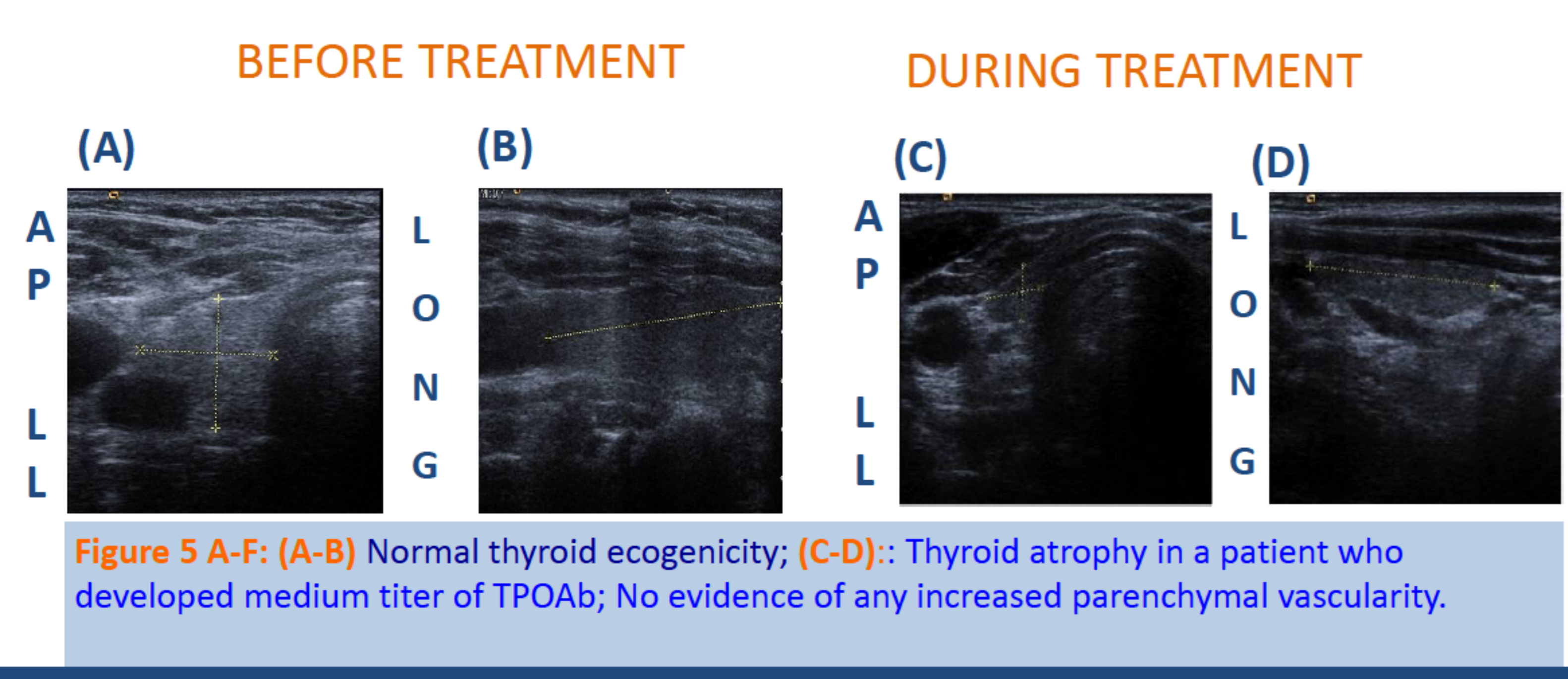
Prospective evaluation of thyroid function, autoimmunity and morphology during treatment with Regorafenib (Stivarga®). From November 2015, 18 consecutive patients (8 males and 10 females: mean age 64.9±8.1) with metastatic colorectal cancer with comparable tumor stage, normal thyroid function and no evidence of associated thyroid autoimmunity, were studied before and at monthly intervals (during ON and OFF period) after beginning Regorafenib at scheduled dose of 160 mg according to standard protocols. In all cases FT3, FT4, TSH and thyroid antibodies (TgAb and TPOAb) were measured together with clinical assessment and thyroid ultrasonography up to five months.

## Results

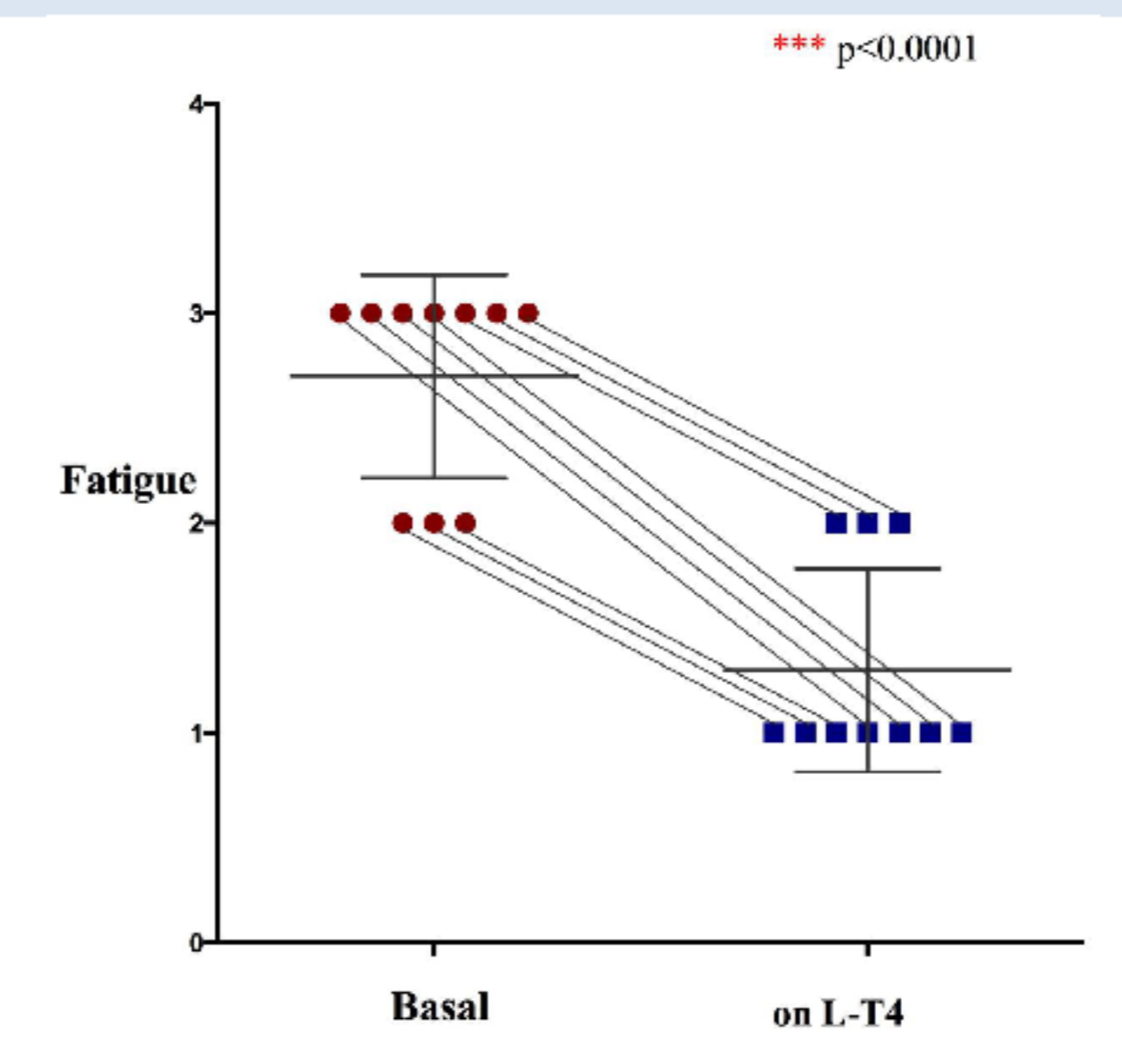


**Figure 1:** Individual course of all TSH treated with L-T4 therapy; **Figure 2:** Individual course of all TPOAb; **Figure 3:** Individual course of ETV. **Figure 4 A-B:** A: Variation of TSH during ON and OFF period without L-T4 therapy; B: Variation of ETV during ON and OFF period.

**Figure 1-4:** 10/18 (55%) patients developed variable degree of hypothyroidism (**Fig.1**); 2/18 (12%) patients developed detectable TPOAb (**Fig.2**); 11/18 (61%) patients displayed a marked decrease of estimated thyroid volume (ETV); (**Fig.3**); A: Significant increase of TSH during ON period and decrease up to normal values during OFF period; B: Significant reduction of ETV during ON period and increase during OFF period (**Fig.4 A-B**).



**Figure 5 A-F:** (A-B) Normal thyroid echogenicity; (C-D): Thyroid atrophy in a patient who developed medium titer of TPOAb; No evidence of any increased parenchymal vascularity.



**Figure 6:** Significant reduction of the score of fatigue after L-T4 therapy in 10 hypothyroid patients. G1= Low; G2= medium; G3=high.

**Figure 6:** Variations of fatigue before and after L-T4 therapy.

## Conclusions

These preliminary data indicate that Regorafenib, similarly to other TKIs Inhibitors, may rapidly cause hypothyroidism in about one half of patients, and probably trigger thyroid autoimmunity. An early diagnosis and management of hypothyroidism is therefore mandatory for an effective clinical control of fatigue in most of the cases, in order to prevent unnecessary dose reductions and modifications. Further studies are needed to characterize longer-term effects on thyroid function-autoimmunity and to assess whether hypothyroidism may have a prognostic value as a biomarker of clinical response.