

Thyroid hormone ratio and clinical outcome: results from the Treador Study

From a physiopathological point of view patients with advanced solid cancer and neoplastic cachexia might be associated, in some way, with frail older patients, a well-known and extensively described multi-factorial clinical condition, characterized by increased catabolism and marked muscle wasting. Interestingly, some studies documented a possible association between peripheral thyroid hormone levels and physical performance and/or survival of older patients, especially those with frailty. In details, higher levels of FT₄ may predict poor outcome of older patients while, higher FT₃ levels may be inversely related to better physical performance.

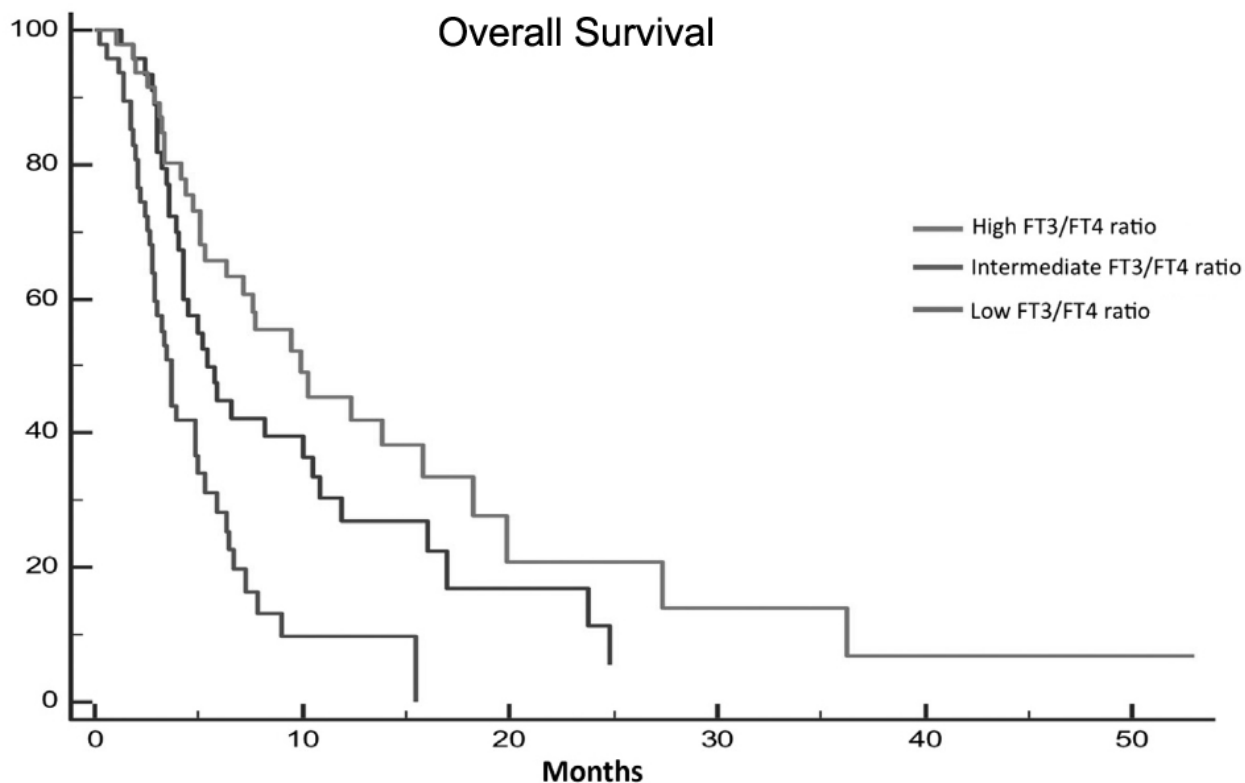


Fig. 1. Overall survival of metastatic colon rectal cancer patients according to FT₃/FT₄ tertiles (Modified from Schirripa et al. Clinical Colorectal Cancer 2018).

Given that both FT₃ and FT₄ peripheral concentration may, at least partially, depend on peripheral thyroxin deiodination, catalysed by deiodinase enzymes (isozyme D1, D2, and D3), some authors suggested that the FT₃/FT₄ ratio may reflect the complex metabolic alterations observed in specific clinical settings such as those related to frailty. In this regard, a previous study in hospitalized

geriatric patients showed a significantly shorter survival in patients with the lowest quartile of FT_3/FT_4 ratio. Thus, the rationale of our work relied on the similarity between this clinical condition (frail syndrome), characterized by extreme muscle wasting (sarcopenia), and neoplastic cachexia. On this basis, we tried to document the potential predicting value of FT_3/FT_4 ratio in cachectic cancer patients.

We selected a retrospective cohort of patients (n=68) affected by advanced mCRC (stage IV) who underwent regorafenib treatment. Our results were subsequently challenged by means of a robust multivariate model which included many factors already known as prognostic in this setting. The population was chosen for the homogeneity of the oncologic disease and for the availability of basal thyroid function data (FT_3 , FT_4 , TSH) given the thyroid toxicity of regorafenib. Our results were strengthened by an external confirmation on an independent pool of patients (n=73) from another Italian Cancer Centre.

In our study, as well as in sarcopenic older patients, the FT_3/FT_4 ratio independently predicted patient survival and outperformed the measurement of the single free hormone (FT_3 or FT_4) or TSH in predicting mortality. In particular, mCRC patients with the lowest tertile of the FT_3/FT_4 ratio presented a significant worse prognosis in term of overall survival (Fig. 1) and progression free survival.

In this experience, we only documented an association between FT_3/FT_4 ratio and survival in mCRC patients without analyzing possible bio-molecular mechanisms. Interestingly, many authors suggested that FT_4 peripheral conversion is mainly carried out by D1 in the liver. At the same time, some evidences highlighted the role of D2, which is mostly expressed in muscle cells. In our study, we cannot rule out that both processes are involved given that many of our patients presented either an extensive liver involvement or clinical cachexia with reduced overall muscle mass. In conclusion, we identified FT_3/FT_4 ratio as a new prognostic factor in advanced mCRC patients receiving regorafenib. Specific studies are warranted to clarify the biological mechanisms of our findings in order to open the possibility for therapeutic targeting of FT_3/FT_4 ratio.

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Publication

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