Topic: SOMATIC ‘RET’ MUTATIONS IN SPORADIC MTC

Title: Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study.

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SUMMARY

Background: Medullary thyroid carcinoma (MTC) is a well-differentiated thyroid tumor that maintains the typical features of C cells. An advanced stage and the presence of lymph node metastases at diagnosis have been demonstrated to be the most important bad prognostic factors. Somatic RET mutations have been found in 40-50% of MTCs. Although a relationship between somatic mutations and bad prognosis has been described, data are controversial and have been performed in small series with short-term follow-up.

Objective: Aim of study was to verify the prognostic value of somatic RET mutations in a large series of MTCs with a long follow-up.

Methods: The authors studied 100 sporadic MTC patients with a 10.2 yr mean follow-up. RET gene exons 10-11 and 13-16 were analyzed. The correlation between the presence/absence of a somatic RET mutation, clinical/pathological features, and outcome of MTC patients was evaluated.

Results: A somatic RET mutation was found in 43 of 100 (43%) sporadic MTCs. The most frequent mutation (34 of 43, 79%) was M918T. RET mutation occurrence was more frequent in larger tumors (P=0.03) and in MTC with node and distant metastases (P<0.0001 & P=0.02, respectively). A significant correlation was found with a more advanced stage at diagnosis (P=0.004). A worse outcome was also significantly correlated with the presence of a somatic RET mutation (P=0.002). Among all prognostic factors found to be correlated with a worse outcome, at multivariate analysis only advanced stage at diagnosis and presence of RET mutation showed an independent correlation (P<0.0001 & P=0.01, respectively). Finally, the survival curves of MTC patients showed a significantly lower percentage of surviving patients in the group with RET mutations (P=0.006).

Conclusions: These findings demonstrate that the presence of a somatic RET mutation correlates with a worse outcome of MTC patients, not only for the highest probability to have persistence of the disease, but also for a lower survival rate in a long-term follow up. Interestingly, presence of somatic RET mutation correlates with the presence of lymph node metastases at diagnosis, which is a known bad prognostic factor for the definitive cure of MTC patients.

COMMENT

Medullary thyroid carcinoma (MTC) is a neoplasm of the calcitonin-secreting thyroid parafollicular ‘C’ cells and its origin makes it a separate entity from all the other differentiated thyroid carcinomas. MTC occurs sporadically or as a component of the inherited cancer syndrome of MEN type 2. RET Mutations found in MEN 2B (germline) are also found in the sporadic form of MTC (sporadic RET mutations), with a frequency of 40-50%. The RET proto-oncogene encodes for a trans-membrane receptor tyrosine kinase expressed in neural crest derived tissues. In sporadic MTC, the most frequent genetic anomaly is
a mutation affecting codon ‘918’ of exon ‘16’, substituting a methionine with a threonine (Met918Thr).
The M918T mutation has been reported in sporadic MTC as early as 1994-95. Because MTC is an aggressive cancer, with only a ~50% survival rate at 10-year follow-up, the cure and survival of these patients depend on early diagnosis and treatment. Therefore, to link somatic RET gene mutations with prognosis (and hence the extent of therapy) has been the quest of several groups of investigators with large experience in the care of MTC patients. In present study, the authors confirmed in a large series of patients with sporadic MTC that somatic RET mutations were frequent (43%) and associated with bad prognosis and outcome. As expected, the majority of RET mutations (79%) were located at codon 918 and corresponded to the M918T mutation. Patients with RET mutations had more frequent node involvement, distant metastases, more advanced stage of disease, more persistent disease, and there were more deaths from disease. The present findings validate the role of somatic RET mutations as a bad prognostic factor for MTC. These findings also have a practical implication because the RET mutations can now be determined by analyzing DNA extracted from the tumor at the time of early diagnosis by FNAB. Hence, the genetic information can be used to conduct more radical surgery. Also, in the era of development of new targeted therapies, the demonstration of RET mutations could be important for additional treatment using tyrosine kinase inhibitors. (Daniel Glinoer, M.D.; Ph.D.)

See Figures below (prevalence of somatic RET mutations in 100 patients and survival curves)