

## **Bone Metastases in Neuroendocrine Tumors: Molecular Pathogenesis and Implications in Clinical Practice**

Skeletal colonization is often regarded as a rare event in patients with neuroendocrine tumors (NETs) although both national registries and retrospective series report an incidence of bone metastases as high as 20% in subjects with advanced disease. While the biological mechanisms leading to bone metastatic colonization in NETs have been poorly investigated so far, key steps of osteotropic mechanisms, including the epithelial-to-mesenchymal transition, preparation of the premetastatic niche, migration of circulating tumor cells towards the bone marrow as well as the resulting alterations of the skeletal metabolism, are likely to operate also during the development of NET bone metastases. The skeleton involvement by NETs has a detrimental impact on both quality of life and patients' prognosis, leading to pain in the majority of symptomatic subjects. While it is currently unclear whether or not the earlier recognition of bone involvement by PET/CT imaging techniques employing <sup>68</sup>Ga-DOTA-conjugated peptides might improve outcomes through the exploitation of timely treatments, the management of bone-colonizing NETs is today based only on clinical experience from other osteotropic tumors. Here, we summarize the fundamental molecular mechanisms driving bone colonization and revisit both established and novel treatments for patients with bone metastatic NETs.

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