Safety and efficacy of combined Peptide Receptor Radionuclide Therapy and liver Selective Internal Radiation Therapy in a patient with metastatic neuroendocrine tumor

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Abstract. Nuclear medicine treatments of well-differentiated neuroendocrine tumors (NETs) are gaining increasing acceptance among clinicians. Peptide Receptor Radionuclide Therapy (PRRT) is an effective systemic treatment, providing a significant survival benefit and improving patients' quality of life. Loco-regional Selective Internal Radiation Therapy (SIRT) is a safe and effective treatment for unresectable NET liver metastases, providing good local tumor control and symptomatic relief. Few reports in literature examine the sequential use of PRRT and SIRT in metastatic NET**.** We report the case of a metastatic NET patient treated with sequential PRRT-SIRT achieving a long disease control interval without cumulative toxicity issues.

Keywords: neuroendocrine tumors – Peptide Receptor Radionuclide Therapy – Selective Internal Radiation Therapy – Trans-Arterial Radioembolisation – liver metastases – radionuclide therapy

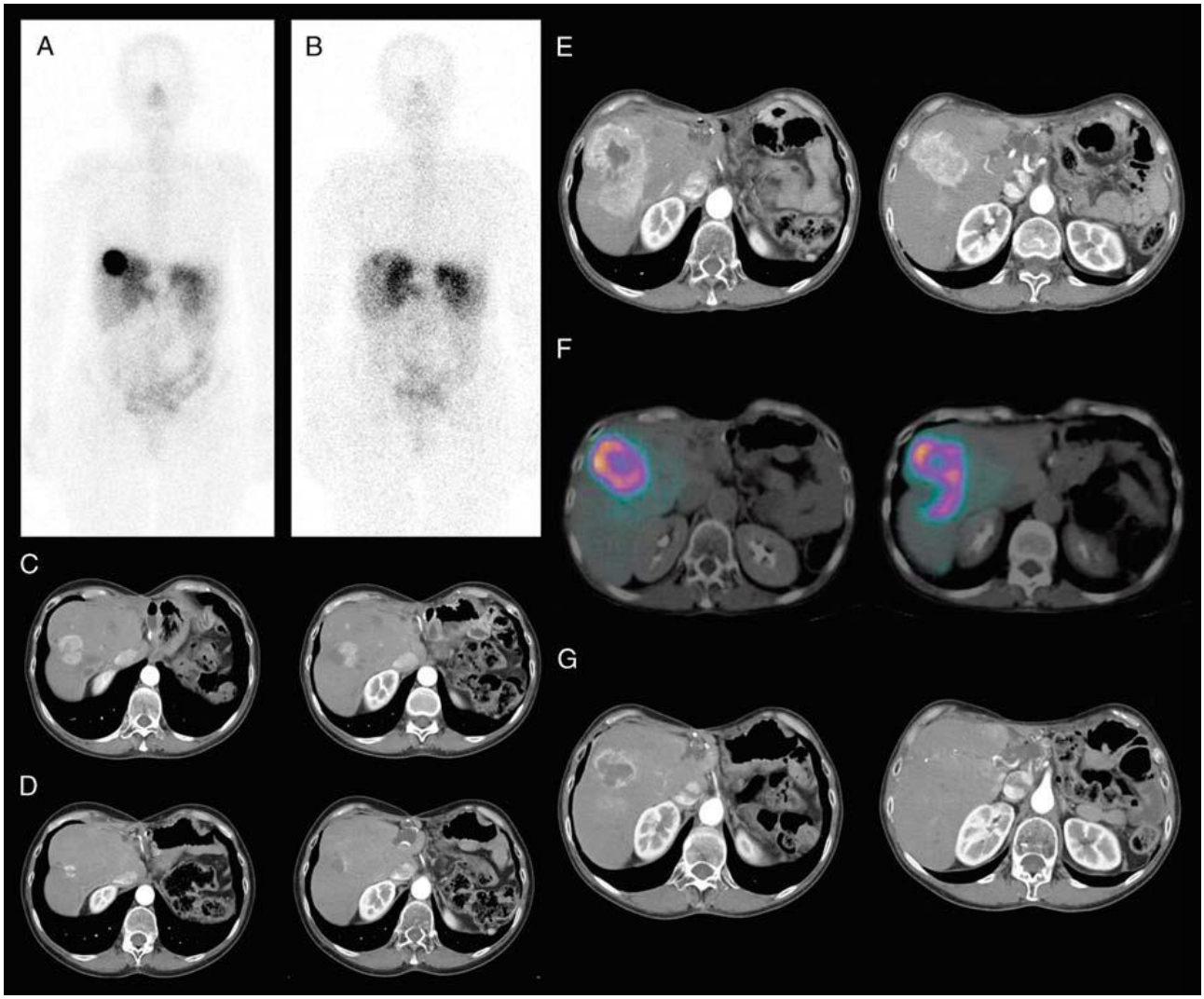

Figure 1. We report the case of a 43-year-old woman diagnosed with locally advanced pancreatic NET (Ki67 2%) in 2001. After neoadjuvant chemotherapy, pancreatic distal resection with subtotal gastrectomy and mesenteric lymphadenectomy was performed and somatostatin-analogue treatment started. In 2007, the occurrence of multiple liver metastases was observed and chemotherapy was rechallenged. In 2008 and 2010 liver S5-6 resection were performed (Ki67 22%), followed by liver-directed Trans-Arterial Chemo-Embolisation (TACE) in 2011 and Radio-Frequency Ablation (RFA) in 2012.

Due to further liver disease progression, in 2013 the patient was referred for PRRT. A tandem, fractionated protocol was planned alternating fixed dose cycles of Lu-177-DOTATOC (5.55 GBq) and Y-90-DOTATOC (2.59 GBq) for a total of six administration at 6-8 weeks interval.[1] Post-therapeutic Lu-177-DOTATOC whole-body scintigraphy performed at 1st (A) and 3rd (B) PRRT cycle showed a significant decrease in radiopharmaceutical uptake in the right lobar lesion. Partial Response (according to RECIST 1.1) was confirmed by 3-months follow-up (D) CT scan compared to baseline (C).[2]

After a Progression-Free Survival (PFS) of 30 months from the first PRRT cycle, right liver progression was observed and a sequential SIRT treatment was planned.[3] The first SIRT was performed on the main lesion (S7-8, Y-90 activity 2.58 GBq, Absorbed Dose to target 519 Gy) in October 2015 (E-F). Six-months follow-up CT revealed a nearly complete regression of the target lesion (G). In October 2016, the second SIRT was performed targeting residual right lobe disease (Y-90 activity 3.92 GBq, Absorbed Dose to target 447 Gy). Three-months follow-up CT scan showed Partial Response of treated lesions.

After a cumulative PFS of 16 months from the first SIRT procedure, the patient started metronomic chemotherapy (capecitabine and temozolomide) for liver and bone progression, but the *exitus* was reported in November 2017.

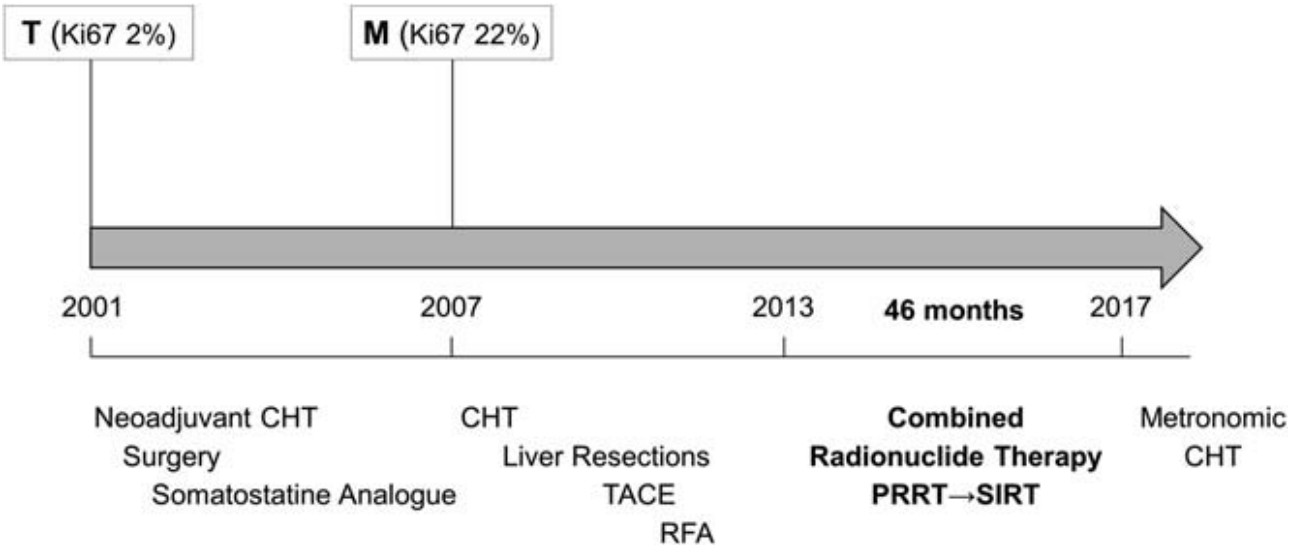

Figure 2. The complex therapeutic management of metastatic NET patients may involve a combination of systemic and loco-regional approaches.[4] Nuclear medicine treatments represent valid therapeutic options providing control of tumor growth and relief from disease-related symptoms. Peptide Receptor Radionuclide Therapy (PRRT) is an effective systemic treatment, providing a significant survival benefit and improving patients' quality of life.[5] Loco-regional Selective Internal Radiation Therapy (SIRT) is a safe and effective treatment for unresectable NET liver metastases, providing good local tumor control and symptomatic relief.[6] Only few reports in literature examine the sequential use of PRRT and SIRT in metastatic NET.[7,8]

In this heavily pre-treated patient, a combined therapeutic approach based on systemic PRRT followed by two sequential SIRT procedures showed a cumulative disease control interval of

46 months (Fig. 2). Both treatments were well-tolerated, without significant acute or delayed adverse effects. No potential cumulative toxicity to healthy liver parenchyma was observed.

Further studies are required to evaluate a combined approach with PRRT and SIRT in metastatic GEP-NET patients in terms of safety, tolerability and efficacy.

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