Prediction of ^{177}Lu-DOTATATE PRRT Outcome Using Multimodality Imaging in Patients with Gastroenteropancreatic Neuroendocrine Tumors: Results from a Prospective Phase II LUMEN Study

Our objective was to predict the outcome of peptide receptor radionuclide therapy (PRRT) using multimodality imaging and tumor dosimetry on gastroenteropancreatic neuroendocrine tumor (GEP-NET) lesions and patients. **Methods:** This prospective study included patients with progressive GEP-NETs. Treatment consisted of 4 cycles of 7.4 GBq of ^{177}Lu-DOTATATE. Imaging parameters were measured on ^{68}Ga-DOTATATE PET/CT ($SUV_{max/mean}$, somatostatin receptor [SSTR] tumor volume [TV], total lesion SSTR expression, and tumor-to-blood and tumor-to-spleen ratios), ^{18}F-FDG PET/CT ($SUV_{max/mean}$, metabolically active TV, and total lesion glycolysis), and diffusion-weighted MRI (apparent diffusion coefficient) in a maximum of 5 target lesions per patient at approximately 10 wk after each injection. Tumor dosimetry was performed using SPECT/CT at 3 time points for every cycle. Baseline imaging parameters, their relative changes after PRRT cycle 1 (C1), and the tumor-absorbed dose at C1 were correlated with lesion morphologic outcome. The average values of the imaging parameters and the minimal, maximal, and mean C1 tumor-absorbed dose in each patient were tested for association with progression-free survival (PFS) and best objective response (RECIST 1.1). **Results:** In the 37 patients, the median PFS was 28 mo. Eleven of the 37 (30%) achieved a partial response (RECIST 1.1). After a median follow-up of 57 mo, the median time to lesion progression had not been reached in 84 morphologically evaluable lesions, with only 12 (14%) progressing (size increase ≥ 20% from baseline). Patients receiving a minimal C1 dose of 35 Gy in all target lesions exhibited a significantly longer PFS (48.1 vs. 26.2 mo; hazard ratio, 0.37; 95% CI, 0.17-0.82; P = 0.02). Volumetric ^{68}Ga-DOTATATE PET parameters correlated with lesion and patient outcome: patients with an SSTR TV decrease of more than 10% after C1 had a longer PFS (51.3 vs. 22.8 mo; hazard ratio, 0.35; 95% CI, 0.16-0.75; P = 0.003). There was no statistical evidence of an association between other dosimetric or imaging parameters and the lesion or patient outcome. **Conclusion:** Minimal tumor-absorbed dose at C1 is predictive of outcome in patients with GEP-NETs treated with PRRT, providing a basis for personalized dosimetry-guided treatment strategies. An SSTR TV decrease after C1 could be

used for early therapy response assessment as a predictor of PRRT outcome.

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