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Research Article

Assessing the Clinical Impact of Lutetium-177 DOTATATE Peptide Receptor Radionuclide Therapy (PRRT) on Metastatic Neuroendocrine Tumors: A Multicenter Real-World Data from Türkiye

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Abstract

Objectives: This study aimed to evaluate the clinical outcomes, including progression-free survival (PFS), overall survival (OS), Objective Response Rate (ORR), and Disease Control Rate (DCR), in patients received Lutetium-177 (Lu-177) DOTATATE Peptide Receptor Radionuclide Therapy (PRRT) for metastatic neuroendocrine tumors. This study further stratified outcomes based on tumor grade, Ki-67 status, primary tumor localization, number of treatment cycles, and associated adverse effects.

Methods: We conducted a multicenter retrospective study analyzing the data of 73 patients with metastatic NETs across 17 different hospitals in various regions of Türkiye. A total of 73 metastatic NET patients underwent Lu-177 DOTATATE PRRT between December 2013 and March 2023.

Results: Over a median follow-up of 52.7 months, patients showed a median PFS of 13.7 months and OS of 51.2 months. The ORR was 29.6%, and the DCR was 66.2%. Grade 1 and 2 tumor patients had superior outcomes (PFS: 16.9 months, OS: 55.5 months) compared to grade 3 tumor patients (PFS: 8.5 months, OS: 29.5 months). Based on their Ki-67 status, those ≤ 20% had prolonged PFS (16.9 months) and OS (55.5 months) than those between 21 and 55% (PFS: 5.9 months, OS: 41.3 months). Regarding primary tumor localization, the PFS values were 13.1, 15.3, 13.7, and 8.6 months for pancreatic, GIS, lung, and unknown origin tumors, respectively. The OS across tumor types fluctuated between 41.1 and 54.1 months. Patients who received more than four cycles demonstrated significantly improved median PFS (22.4 months) and OS (90.3 months) compared to those who received ≤ 4 cycles (median PFS: 9.3 months; median OS: 41.8 months). Grade 3-4 adverse effects were observed in 21.9% of patients.

Conclusion: Our findings affirm that PRRT is a potent and well-tolerated treatment for metastatic NETs. Notably, patients who received more than 4 cycles of PRRT experienced a markedly improved median PFS and OS compared to their counterparts who received ≤4 cycles.

Keywords: Lutetium-177, neuroendocrine tumors, neuroendocrine neoplasm, peptide receptor radionuclide therapy, PRRT, radiolabeled somatostatin analogues

Neuroendocrine tumors (NETs) originate from diffuse neuroendocrine cells and can manifest anywhere in the body.[1-3] While many NETs remain asymptomatic and non-functioning, often identified incidentally during autopsies,[4] the incidence and prevalence of NETs—predominantly originating from the pancreas and gastrointestinal system—have been rising. Concurrently, with the advent of new treatment modalities, there has been a notable increase in the life expectancy of affected patients.[5-9] For those with metastatic or relapsed disease, a multidisciplinary treatment approach is imperative. Depending on the disease's extent, therapeutic options can range from peptide receptor radionuclide therapy (PRRT), everolimus, somatostatin analogues, and targeted therapies to temozolomide-based chemotherapy regimens, with the final decision resting upon the clinician's judgment.[10]

A distinguishing characteristic of most NETs is the expression of somatostatin receptors (SSTR). Due to this unique trait, radiopharmaceuticals have spearheaded innovative therapeutic developments for NETs.[11] Recent advancements in positron emission tomography (PET) have integrated diagnostic positron-emitting pharmaceuticals like 68Ga-DOTA peptides with therapeutic agents like Lu-177 DOTATATE peptide derivatives, paving the way for groundbreaking treatments.[12] PRRT has emerged as a targeted systemic therapy that harnesses radionuclide somatostatin analogues. This therapeutic approach combines somatostatin analogues (SSA) with ß-emitters, such as Yttrium-90 (90Y) and Lutetium-177 (Lu-177), directing them towards NET cells via cell surface somatostatin receptors (SSTR).[13]

The pivotal NETTER-1 trial has underscored PRRT's significance as an established therapeutic strategy for advanced GEP NETs.[7,14] Within this trial, patients with progressive midgut NET were introduced to a regimen combining Lu-177 DOTATATE with ongoing octreotide long-acting repeatable (LAR) therapy or received high-dose octreotide LAR alone. The primary endpoint of progression-free survival (PFS) was significantly superior in the PRRT group, registering a hazard ratio (HR) of 0.21 (95% CI: 0.14–0.33; $p<0.0001$). While the median overall survival was pegged at 27.4 months for the high-dose octreotide LAR group, it remained undetermined for the PRRT cohort as of the most recent data.[14] Importantly, observed toxicity was within acceptable limits, and enhancements in the quality of life (QOL) were reported.[7,14] Subsequent to the NETTER-1 trial's outcomes, the United States sanctioned the use of Lu-177 DOTATATE, a PRRT agent, for patients diagnosed with progressive, well-differentiated midgut NETs.[15] It is also stated in the European Neuroendocrine Tumor Society (ENETS) guidelines that PRRT is an effective therapy for metastatic NETs.[16] In a study conducted by Pusceddu et al. on 508 patients with enteropancreatic neuroendocrine tumors, it was stated that upfront PRRT was associated with significantly longer progression-free survival compared to upfront chemotherapy or targeted therapy in patients who experienced disease progression with SSA treatment.[17]

In the context of this study, our primary objective is to

delve into the efficacy and potential adverse reactions associated with PRRT in patients diagnosed with metastatic neuroendocrine tumors.

Methods

Patients

We executed a multicenter retrospective analysis spanning 17 distinct hospitals across various regions of Türkiye, evaluating 73 patients with metastatic-stage neuroendocrine tumors (NETs), either presenting de novo or as a relapse. These patients underwent PRRT between 2013 and 2022. To maintain the integrity and homogeneity of our dataset, we excluded patients diagnosed with neuroendocrine carcinoma (NEC) and those presenting grade 3 tumors with indeterminate Ki-67 levels. Consequently, only patients with confirmed NETs were included. Furthermore, to enhance the study's uniformity, patients exhibiting grade 3 tumors with Ki-67 levels surpassing 55% were excluded.

For a meticulous evaluation of treatment efficacy, patients were stratified based on their Ki-67 levels and tumor grade. The inclusion criteria encompassed patients aged 18 years or older with albumin levels exceeding 2.5 mg/dL, hemoglobin (Hb) levels ≥10 g/dL, white blood cell count (WBC) $\geq 3 \times 10^3$/L, platelet count (PLT) $\geq 90 \times 10^3$/L, calculated creatinine clearance (CrCl) greater than 40 mL/min, total bilirubin levels below 3.5 mg/dL, liver function test (LFT) results less than five times the upper limit, and an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1, or 2. All included patients must have completed at least one cycle of PRRT treatment and showcased radiologically measurable metastatic NET in line with the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 standards.

This study enrolled NET-diagnosed patients irrespective of whether PRRT was their first line of treatment or administered subsequent to multiple treatment lines. Previous treatments, including somatostatin analogs, 5-FU-based protocols, everolimus, or sunitinib, were permissible.

Treatment

All treatments were conducted in an inpatient setting. To safeguard renal function, patients were administered between 500 and 1000 ml of a solution containing 2.5% arginine and 2.5% lysine amino acids. This infusion started 30 minutes prior to the Lu-177 DOTATATE injection and continued over a duration of 4 hours. Additionally, 8 mg of ondansetron was given 30 minutes before the treatment to mitigate nausea. The Lu-177 DOTATATE was administered gradually over a span of 5 minutes. Post-treatment, it is imperative to conduct whole-body imaging for Lu-177 DOTATATE. This imaging process employs a "parallel hole medium energy collimator" set to a 208 keV energy peak and a 15% window width. While imaging can be undertaken anytime during the initial week post-treatment, it is recommended to be performed on the fourth day. If there is a need for a dosimetry procedure, a daily-prepared reference source encompassing 200 µCi of Lu-177, housed in a 20 mL vial, should be positioned in alignment with the patient's head for imaging purposes.

Furthermore, post-treatment monitoring entailed 60-minute interval observations spanning 5 hours, recording essential vital signs such as blood pressure, fever, and pulse rate. Any incidences of discomfort like pain, nausea, or vomiting were meticulously monitored for 24 hours, adhering to the established institutional protocols for all inpatient treatments.

Response Evaluation, Survival, and Toxicity

Response to Lu-177 DOTATATE treatment was gauged using [68Ga]Ga-DOTATATE PET combined with contrast-enhanced (ce) CT, carried out 4 weeks prior and 12-16 weeks subsequent to the treatment. The efficacy of the treatment was evaluated based on images from [68Ga]Ga-DOTATATE PET/CT and according to the RECIST 1.1 criteria,[17] leveraging the contrast-enhanced CT images sourced from the PET/CT. Follow-up [68Ga]Ga-DOTATATE PET/CT scans were scheduled every 12-18 weeks and continued until clinical progression or patient demise. Data entry included the Objective Response Rate (ORR), which included patients with Complete Response (CR) or Partial Response (PR). We calculated the Disease Control Rate (DCR) by adding patients with Stable Disease (SD) to PRRT to either the date of progression, death from any cause, or the last follow-up for patients without progression. The follow-up period was defined as the time from disease diagnosis to the last follow-up or date of death. Overall survival (OS) was calculated as the time from the first initiation of PRRT to either the date of the last follow-up or the date of death. The progression-free survival (PFS) was determined starting from the initial administration date of Lu-177 DOTATATE. Adverse events were duly documented three months post each Lu-177 DOTATATE treatment cycle, adhering to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 (Fig. 1).

Statistical Analysis

The continuous variables were summarized using the median (interquartile range (IQR) or range), and categoric variables were summarized using basic proportions. Data were analyzed using the SPSS 22.0 software. Chi-square analysis was employed to compare the effectivity of PRRT of the patients according to the primary site. The Kaplan–Meier

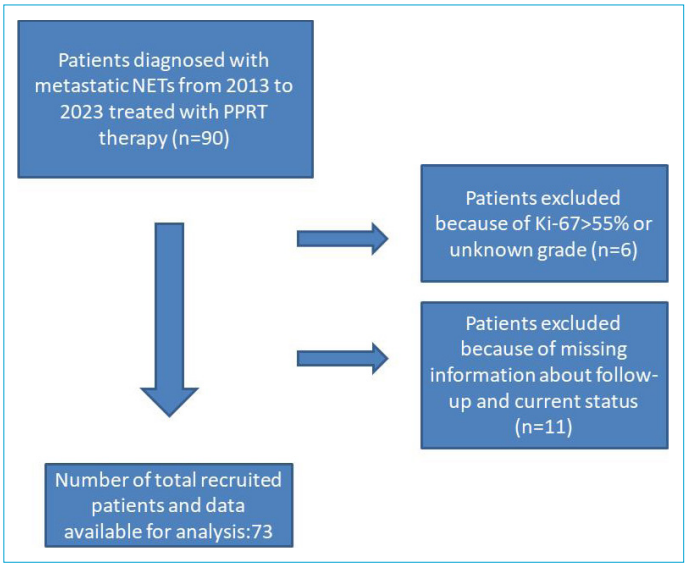

Figure 1. Flow diagram of patients identified and included in the final analysis.

method was utilized to estimate the median PFS and OS values of the patients and to compare these findings according to cycle number, histological grade, Ki-67 levels, and primary tumor localization. A p-value of less than 0.05 was considered statistically significant in all tests.

Results

A total of 73 metastatic NET patients underwent PRRT between December 2013 and March 2023. The median follow-up duration was 52.7 months (range: 8.1-157.2 months), with a median age of 54 years (range: 22-76 years). Patients received a median of 4 treatment cycles (range: 1-8). The clinicopathological details of the patients are summarized in Table 1.

The overall median PFS and OS were 13.7 and 51.2 months, respectively. The observed ORR was 29.6%, and the DCR was 66.2%. ORRs and DCRs based on the primary tumor location can be found in Table 2.

For patients with grade 1 and 2 tumors, the median PFS was 16.9 months, compared to 8.5 months for those with grade 3 tumors (p=0.01) (Fig. 2). For patients with grade 1 and 2 tumors, the median OS was 55.5 months, while it was 29.5 months for those with grade 3 tumors, demonstrating a significant difference (p=0.001).

In terms of Ki-67 status, patients with a Ki-67 value ≤20% had a median PFS of 16.9 months, whereas those with Ki-67 values between 21 and 55% had a median PFS of 5.9 months (p=0.003) (Fig. 3). The respective median OS durations were 55.5 and 41.3 months (p=0.04).

Regarding primary tumor localization, the median PFS was 13.1 months for pancreatic tumors, 15.3 months for gas-

Table 1. Patients and tumor characteristics of patients treated with ^{177}Lutetium

	All Patients, n (%)
Age median (min-max)	54 (22-76)
Gender	
Female	31 (42.5)
Male	42 (57.5)
Age groups	
<50	30 (41.1)
50-65	27 (37.0)
≥65	16 (21.9)
PS (ECOG)	
0	41 (56.2)
1	26 (35.6)
2	6 (8.2)
Site (Primary)	
Pancreas	30 (41.1)
GIS	26 (35.6)
Lung	12 (16.4)
Unknown	5 (6.8)
Tumor grade	
Grade 1	14 (19.2)
Grade 2	46 (69.9)
Grade 3	13 (11.0)
Prior surgery (curative)	
Yes	16 (21.9)
No	57 (78.1)
Metastatic sites	
Liver	31 (32.8)
Extra-liver	8 (17.5)
Liver and Extra-liver	34 (49.7)
Ki-67 (%)	
≤20	61 (83.6)
21-55	12 (16.4)
Which line PRRT?	
First	17 (23.3)
Second	30 (41.1)
Third	16 (21.9)
Fourth	8 (11.0)
Fifth	2 (2.7)
Previous treatment at metestatic stage, n (%)	
Somatostatin analogs	47 (64.4)
Cytotoxic chemotherapy	45 (61.6)
Everolimus	9 (12.3)
Sunitinib	3 (4.1)
No of cycles	
1	1 (1.4)
2	9 (12.3)
3	8 (11.0)
4	24 (32.9)
5	2 (2.7)
6	17 (23.3)
7	3 (4.1)
8	9 (12.3)

PRRT: Peptide Receptor Radionuclide Therapy; PS: Performance score; GIS: gastrointestinal system.

Table 2. Best responses according to the PRRT treatment

Response category, n (%)	All Patients (n=73) n (%)	Site (Primary)				
		Pancreas (n=30)	GIS (n=16)	Lung (n=12)	Unknown (n=5)	p
Complete response (CR)	1 (1.4)	N/A	1 (3.8)	N/A	N/A	0.47
Partial response (PR)	20 (27.4)	11 (36.7)	5 (19.2)	4 (33.0)	N/A	
Stable disease (SD)	28 (38.4)	8 (26.7)	13 (50.0)	5 (41.7)	2 (40.0)	
Progressive disease (PD)	24 (32.9)	11 (36.7)	7 (26.9)	3 (12.5)	3 (60.0)	
Objective Response Rate (ORR) (CR+PR)	21 (28.8)	11 (36.7)	6 (23.1)	4 (33.3)	N/A	0.32
Disease Control Rate (DCR) (CR+PR+SD)	49 (67.1)	19 (63.3)	19 (73.1)	9 (75.0)	2 (40.0)	0.45

GIS: gastrointestinal system.

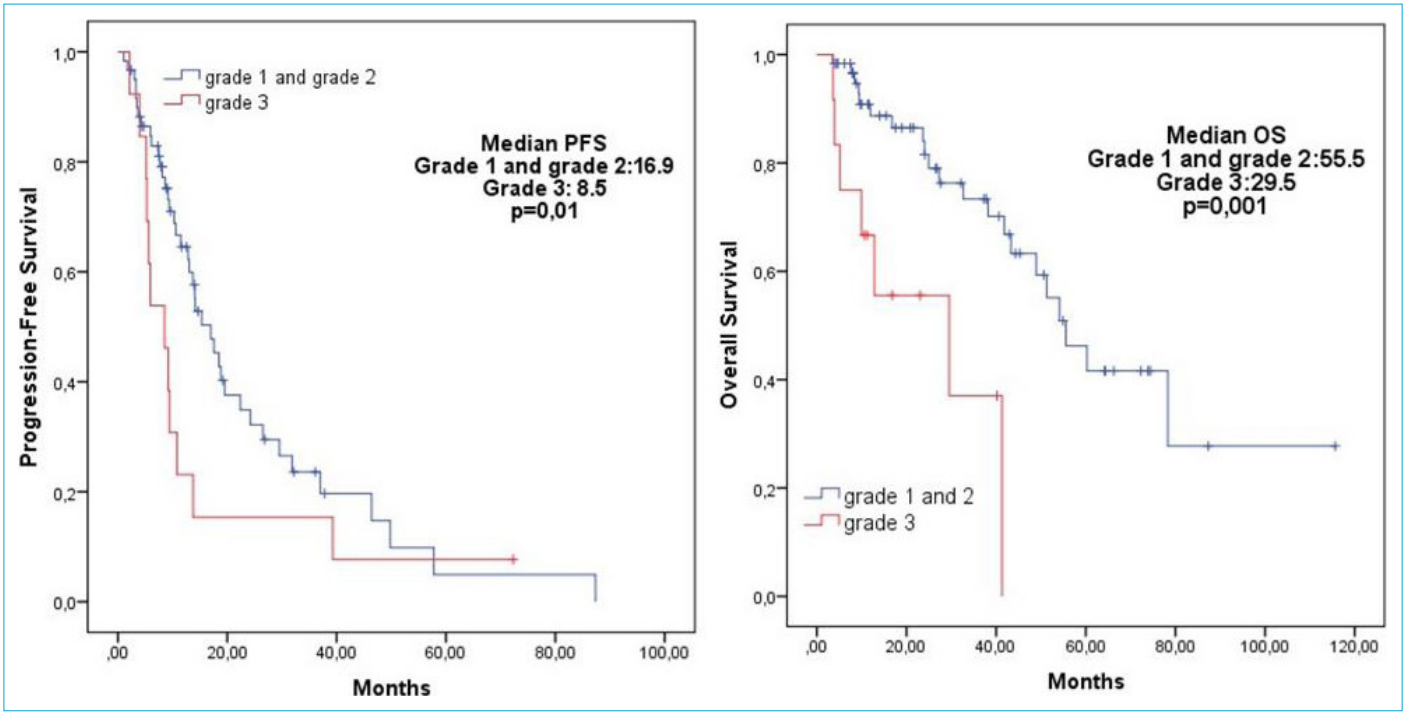

Figure 2. Survival analysis of patients treated with PRRT treatment according to the grade.

trointestinal system (GIS) tumors, 13.7 months for lung tumors, and 8.6 months for tumors of unknown origin. The differences in median PFS across tumor locations were not statistically significant (p=0.87). Similarly, OS did not significantly vary between pancreatic (51.2 months), GIS (54.1 months), lung (41.1 months), and unknown primary tumors (53.3 months) (p=0.94) (Fig. 4).

Patients who received more than four PRRT cycles demonstrated significantly longer median PFS (22.4 months) and OS (90.3 months) than those who received ≤4 cycles (median PFS: 9.3 months; median OS: 41.8 months) (Fig. 5).

Grade 3-4 side effects occurred in 16 patients (21.9%), with hematological and renal effects being the most prevalent (Table 3). These side effects led to treatment discontinuation in 5 patients. No deaths were attributed to the treatment. Information on the duration and recovery of cytopenias was not gathered.

Discussion

Our study presents a comprehensive retrospective, multicenter analysis across 17 centers, focusing on the efficacy and safety of PRRT treatment in 73 patients diagnosed with metastatic neuroendocrine tumors (NETs) originating from diverse primary sites. The overall findings revealed a median progression-free survival (PFS) of 13.7 months and a median overall survival (OS) of 51.2 months for the entire cohort. The objective response rate (ORR) was identified at 29.6%, with a disease control rate (DCR) of 66.2%. A de-

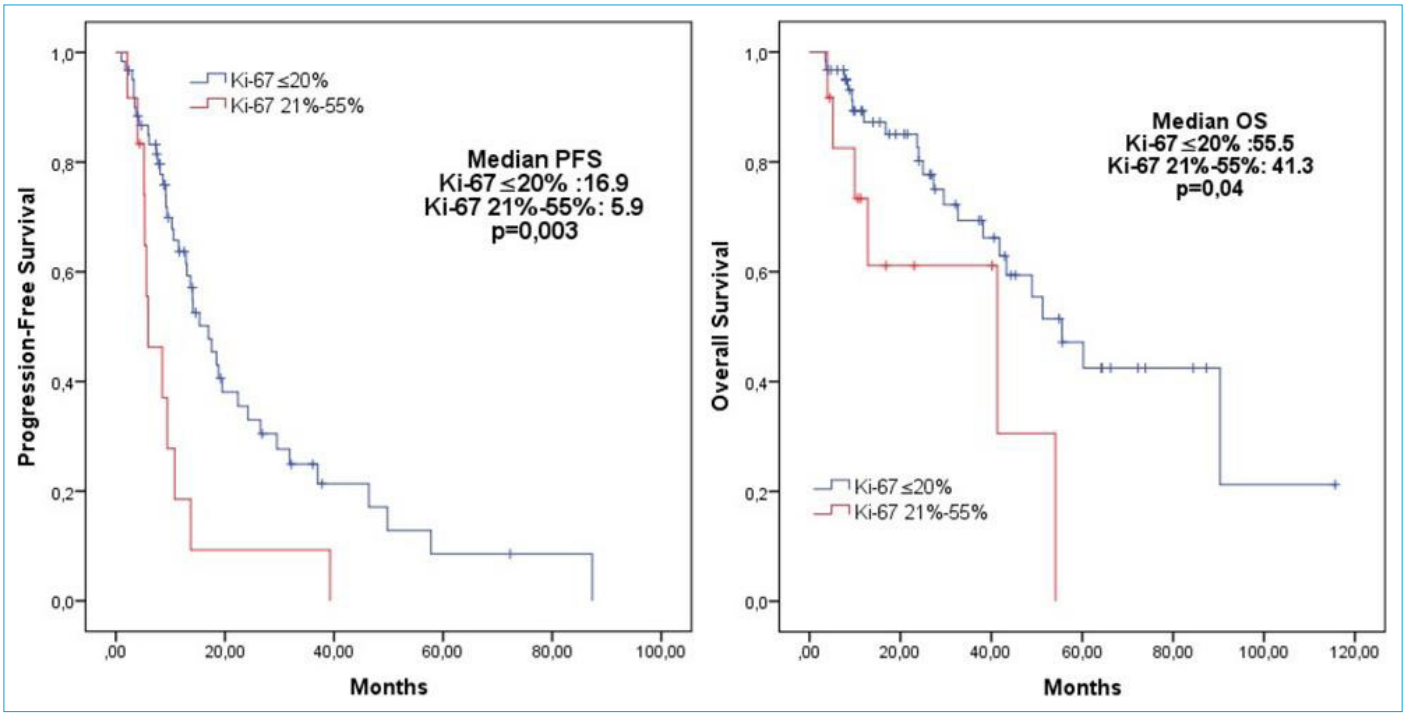

Figure 3. Survival analysis of patients treated with PRRT treatment according to the Ki-67 groups (≤20%, 21-55%).

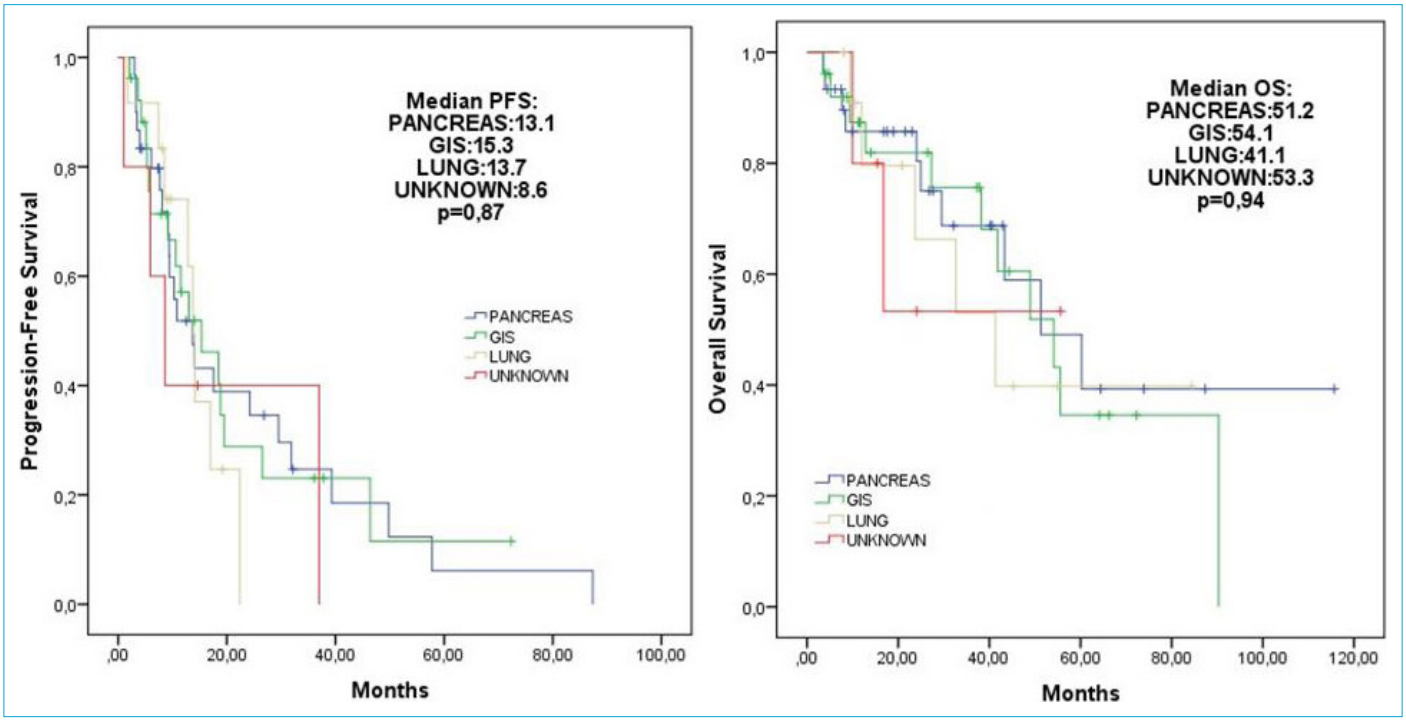

Figure 4. Survival analysis according to the primary site.

tailed sub-analysis indicated that the median PFS and OS were notably higher in NET patients of grade 1-2 than in grade 3. Similarly, patients with Ki-67 ≤ 20% displayed superior median PFS and OS compared to their counterparts with Ki-67 ranging between 21% and 55%. Furthermore, patients who received more than four cycles demonstrated significantly improved median PFS and OS compared to those who received ≤ 4 cycles. In a bid to evaluate the influence of primary tumor location on treatment outcomes, we categorized the 73 patients into specific groups based on the origin of the tumor, namely, pancreas, gastrointestinal tract, lung, and unknown. Intriguingly, our analysis did not

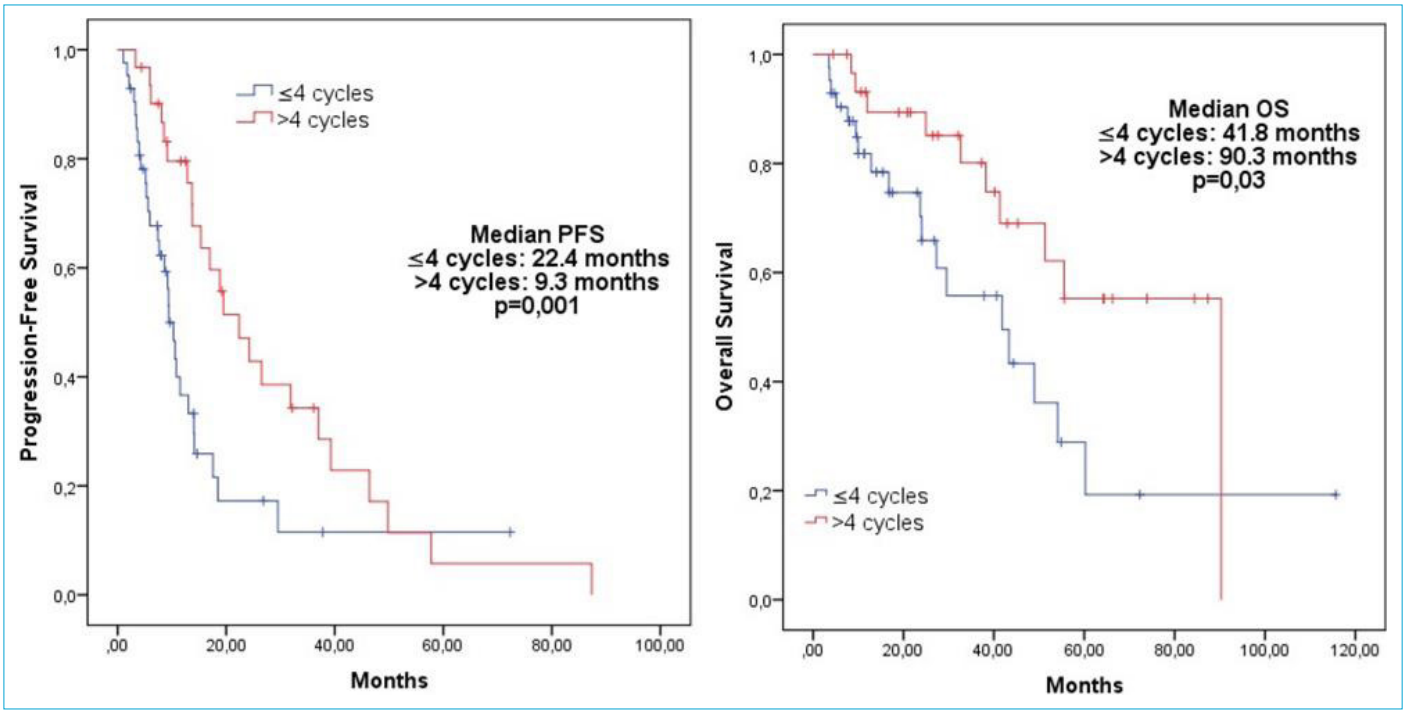

Figure 5. Survival analysis according to the ≤4 cycles vs >4 cycles.

discern any significant disparities in median PFS and OS among these classifications. On the safety front, grade 3-4 adverse effects were evident in 21.9% of the participants, reinforcing the notion that the PRRT regimen is generally well-tolerated.

The existing literature offers data that are somewhat challenging to compare due to the heterogeneity of studies in terms of tumor type, risk factors, prior treatments, and established endpoints.[18] Raj et al., in a study conducted at the Memorial Sloan Kettering Cancer Center involving high-grade metastatic NET patients, reported a median PFS of 13.7 months and a DCR of 72.0% associated with PRRT treatment.[19] Another study by Baum et al. involving 56 metastatic NET patients determined that the ORR following PRRT treatment was 34.0%, with a DCR of 66% and a median PFS of 17 months.[20] The prospective P-PRRT trial, which incorporated 52 patients with metastatic NET, identified a median PFS of 16 months and an ORR of 36.0%.[21] Furthermore, the prospective phase I-II IDEO trial revealed an ORR of 29.0% for metastatic NET.[22] Our findings align closely with the extant literature, presenting a median PFS of 13 months, a median OS of 55 months, an ORR of 29%, and a DCR of 66% (Table 2). In contrast, Ezziddin et al., in their research on 74 metastatic NET patients, identified a median PFS of 26 months, an ORR of 37.0%, and a DCR of 89.0%. The heightened PFS, ORR, and DCR in their study compared to ours may be attributed to the higher proportion of patients with a Ki-67 level of ≤10%.[23] In a meta-analysis encompassing 15 studies, the pooled analysis, specifically from the 13 studies that utilized the RECIST criteria, revealed a DRR of 27.58% (95% confidence interval (CI) 21.03–35.27%) and a DCR of 79.14% (95% CI 75.83–82.1%).[24] The influence of the Ki-67 index and tumor grade as robust predictors of survival is increasingly acknowledged. Recent research involving 74 patients underscored the pivotal role of the Ki-67 index in predicting the outcomes after PRRT, with the G1/G2 gastroenteropancreatic NET showing promising response and survival rates.[23] Garske-Román et

Table 3. PRRT toxicity

	Any grade, n (%)	Grade 1,2, n (%)	Grade 3,4, n (%)
Hematological	40 (54.7)	28 (38.3)	14 (19.1)
Renal	20 (27.3)	18 (24.6)	2 (2.7)
Gastrointestinal	38 (52.0)	36 (49.3)	3 (4.1)
Hepatic	10 (13.6)	8 (10.9)	2 (2.7)
Other (Alopecia, cough, flushing, headache)	16 (21.9)	16 (21.9)	0 (0.0)

al. noted that patients with a Ki-67 >20% had a reduced median PFS and OS compared to their counterparts with Ki-67 ≤20%.[18] Consistent with this, our findings indicated that patients with Ki-67 ≤20% exhibited an enhanced median PFS and OS relative to those with Ki-67 ranging between 21% and 55% (Fig. 3). Additionally, grade 1-2 patients demonstrated a longer PFS and OS compared to grade 3 patients (Fig. 2). In another study, it was stated that PPRT was as effective in grade 2 tumors as it was in grade 1 tumors in metastatic small bowel tumors.[25] Well-differentiated grade 3 NENs have demonstrated responsiveness to PRRT when patients are judiciously selected.[26-28] Current guidelines suggest that PRRT might be a viable therapeutic option for SRI-positive NET G3, although robust data to support this assertion remain scarce.[29] Interestingly, PRRT might hold therapeutic promise for NEN G3 as SRI positivity has been documented in both NET G3 and NEC cases.[30,31] At present, two pivotal Phase 3 trials, namely, NETTER-2 and COMPOSE, are underway, focusing on G2 and G3 NETs.[32] The outcomes of these trials are eagerly awaited.

In a study by Kunikowska et al. that evaluated the 10-year long-term outcomes of metastatic NET patients treated with PRRT, it was observed that survival rates did not differ significantly between patients with bowel cancers and those of pancreatic origin.[33] In our investigation, when we considered the primary tumor location, no statistically significant difference was identified in ORR, DCR, and survival analyses (Table 2, Fig. 4). In the study by Brabender et al. encompassing 610 metastatic NET patients, the ORR and DCR values, when assessed in relation to primary tumor location post-PRRT, did not show any significant disparities.[34] Zandee et al. reported a median PFS of 18 months with PRRT treatment in a cohort of 34 metastatic pancreatic NET patients.[35] Similarly, Ianniello et al., in a prospective study involving 34 metastatic lung NET patients, determined a median PFS of 19 months.[36] Lim et al. documented an ORR of 33% and an OS of 49 months in their research on 48 metastatic lung NET patients treated with PRRT.[13] Notably, available data on the significance of PRRT in patient treatment remains scant, primarily because recent studies have mainly focused on GEP-NETs.[25,29,37] In a comparison made by Swiha et al. between GEP-NET and NON-GEP-NET patients, it was observed that GEP-NET patients exhibited superior survival rates. However, it is essential to note that only 23% (or 8 patients) in their cohort had non-GEP-NETs.[38] More expansive research is crucial to assess the efficacy of PRRT in non-GEP-NETs relative to GEP-NETs.

One of the salient findings in our study was the significant improvement in PFS and OS for patients who underwent more than four cycles of treatment compared to those who had four or fewer cycles (Fig. 5). This observation aligns with the literature that uses a cutoff of four treatment cycles to evaluate efficacy.[18,39] Garske-Roman and colleagues, in their study on 200 metastatic NET patients, drew comparisons between the survival outcomes of patients who received more than four cycles and those who received four or fewer cycles. Intriguingly, a considerable majority (68.5%) underwent more than four cycles, aiming to achieve an absorbed dose to the kidneys of 23 Gy. Among the patients still alive during the study's analysis, a majority (56.4%) had received more than four cycles, whereas among the deceased, a smaller proportion (43.6%) had undergone more than four cycles.[18] Moreover, PFS was observed to be superior in this group. Another study, centered on the effectiveness of PRRT in metastatic gastrinoma patients, revealed that although serum gastrin levels did not decline after the initial four treatment cycles, there was a significant decrease in the levels in the subsequent cycles.[40]

In our analysis, 16 patients (21.9%) experienced grade 3–4 renal or hematological toxicity. This rate is congruent with findings from other comprehensive retrospective studies on PRRT.[41,42] However, in the NETTER-1 study, no renal adverse effects were noted in patients treated with Lu-177.[7] Five patients opted to discontinue the therapy, all of whom had previously undergone multiple lines of chemotherapy and other treatments. In the phase 1/2 prospective study in Japan and in the phase 1 prospective study in Korea, it was stated that PPRT was a safe treatment.[42,43]

Limitations

The retrospective design of our study carries inherent limitations, such as potential selection bias. We have endeavored to mitigate this by amalgamating data from 17 distinct institutions. By relying on each patient's treating physician for data collection, we sought to ensure the highest level of accuracy, given the retrospective nature of our analysis. Our study exhibits a limitation in not incorporating renal dosimetry in the treatment with Lu-177 DOTATATE, a factor that could potentially provide a deeper understanding of the treatment's efficacy and safety profile.[44] Moreover, the relatively modest sample size may curtail the robustness of our statistical inferences. Another limitation to consider is the variability in treatment protocols across the participating centers.

Conclusion

The rising global incidence of cancer, coupled with increased mortality rates for certain malignancies, underscores the persistent challenges faced by clinicians.[45] The frequency of neuroendocrine tumors is also not negligible, highlighting the need for continuous research and effec-

tive therapeutic interventions. Our research offers a thorough multicenter retrospective evaluation spanning 17 institutions, delving into the efficacy and safety of PRRT in treating 73 patients with metastatic neuroendocrine tumors (NETs) from various primary sites. Our findings affirm that PRRT is a potent and well-tolerated treatment for metastatic NETs. Notably, patients who received more than four cycles of PRRT experienced a markedly improved median PFS and OS compared to their counterparts who received ≤4 cycles. The ongoing advancements in PRRT indicate a potential expansion of radionuclide therapies to address various targets and tumor types in the future.

Disclosures

Ethics Committee Approval: Ethics committee approval was obtained from İstanbul Bilgi University. (project number: 2023-40162-085). It is performed in accordance with the Declaration of Helsinki. All patients were informed, and consent forms were signed.

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