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Efficacy and safety of ^{177}Lu-DOTATATE in lung neuroendocrine tumors: a bi-center study

Short rung title: ^{177}Lu-DOTATATE in lung NET

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ABSTRACT

To assess the efficacy and safety of ^{177}Lu-DOTATATE in patients with somatostatin receptor (SSR) positive lung neuroendocrine tumor (NET).

Methods: This is a retrospective review of the outcome of patients with typical carcinoid (TC) and atypical carcinoid (AC), treated with ^{177}Lu-DOTATATE at two ENETS Centres of Excellence. Morphological imaging (RECIST 1.1) and ^{68}Ga-DOTATATE PET/CT responses were assessed at 3 months after completion of ^{177}Lu-DOTATATE. Concordance between two response assessment methods was evaluated by Kappa statistics. Progression-free survival (PFS) and overall survival (OS) was estimated by Kaplan-Meier analysis and compared by Log-rank test. Treatment-related adverse events (AEs) were graded based on CTCAE version 5.

Results: Of 48 patients (median age, 63 years, 13 female), 43 (90%) had AC and 5 (10%) TC. Almost all patients (47, 98%) were treated due to progression. Majority (40, 83%) received somatostatin analogs and 10 patients (20%) had prior everolimus, chemotherapy or both. All patients had high SSR expression (≥ modified Krenning score 3) on pre-treatment ^{68}Ga-DOTATATE PET/CT. Patients received a median 4 (range 1-4) cycles of ^{177}Lu-DOTATATE (33% with concurrent radiosensitizing chemotherapy) to a median cumulative activity of 27GBq (range 6-43GBq). At median follow-up of 42 months, the median PFS and OS were 23 months (95% CI 18-28 months) and 59 months (95% CI 50-not reached [NR]), respectively. Of 40 patients with RECIST-measurable disease and 39 patients with available ^{68}Ga-DOTATATE PET/CT response categories were: partial response, 20% (95% CI 10-35%) and 44% (95% CI 30-59%); stable disease, 68% (95% CI 52-80%) and 44% (95% CI 30-59%) and progressive disease 12% (95% CI 5-27%) by both, respectively. There was a moderate concordance between response categories by RECIST and ^{68}Ga-DOTATATE PET/CT, weighted Kappa of 0.51 (95% CI 0.21-0.68). Of patients with stable disease by RECIST, those with partial response on ^{68}Ga-DOTATATE PET/CT had longer OS compared to those with no response, NR vs 52 months (95% CI 28-64), HR 0.2 (95% CI 0.1-0.6), p 0.001. Most grade 3/4 AEs were reversible and the most common was lymphopenia (14%) with no incidence of myelodysplasia/leukemia.

Conclusions: In patients with advanced progressive lung NET and satisfactory SSR expression, ^{177}Lu-DOTATATE is effective and safe with a high disease control rate and encouraging PFS and OS.

INTRODUCTION

Well-differentiated lung neuroendocrine tumor (NET) or “lung carcinoid”, classified into typical carcinoid (TC) and atypical carcinoid (AC), is a heterogeneous disease with variable clinical behavior and prognosis(*1*). TC rarely metastasizes and generally has a favorable prognosis, while AC is more likely to be metastatic at presentation and has a worse prognosis (*1*).

Surgery is the treatment of choice in patients with localized disease, while management of inoperable locally advanced and metastatic disease is complex and requires a multidisciplinary approach(*1*). For metastatic disease, the European Neuroendocrine Tumors Society (ENETS) guidelines recommend the mTOR inhibitor everolimus, as the first-line therapy for progressive lung NET, however, in patients with tumor of a low proliferative index, a somatostatin analog (SSA) can be considered as first-line therapy, especially when the uptake on somatostatin receptor (SSR) imaging is strongly positive (*2*). In the LUNA phase 2 trial, pasireotide (an agonist for SSR subtypes 1-3 and 5) alone or in combination with everolimus showed evidence of activity and safety (*3*). Chemotherapy is only considered in rapidly progressive metastatic pulmonary carcinoids and when no other treatment options are available. According to the National Comprehensive Cancer Network guidelines, platinum-based regimens or temozolomide can be used in stage IV AC with a high proliferation index (*4*).

Although lung NET frequently expresses SSR subtype 2 (SSR-2), the role of SSR-2 targeted peptide receptor radionuclide therapy (PRRT) with Lutetium-177 DOTA-0-Tyr3-Octreotate (^{177}Lu-DOTATATE) remains to be determined (*5*). Limited retrospective studies showed the efficacy of PRRT in lung NET, comparable to the results of the NETTER-1 trial, reflecting the generalisability of PRRT for any SSR positive NET (*6-8*). Due to lack of comparative studies, after progression on SSA, selection of the next systemic treatment modality including everolimus, chemotherapy or PRRT is at the discretion of physicians and depends on the access, expertise and practice patterns of different institutions in the world. Besides, the efficacy of ^{177}Lu-DOTATATE in patients previously untreated with either chemotherapy or everolimus is unclear. This dual-center study aims to assess the safety and efficacy of patients with lung NET who received ^{177}Lu-DOTATATE.

MATERIAL AND METHODS

Patients

This is a retrospective review of all consecutive patients with biopsy-proven, well-differentiated lung NET (TC or AC), who received PRRT. Data extracted from two ENETS centers of excellence, Peter MacCallum Cancer Centre (PMCC) in Melbourne, Australia and Hadassah-Hebrew University Medical Center (HHUMC), Jerusalem, Israel during the period from 2006 to 2019. This series shares a single patient with the Lim et al. series (*8*). This patient had PRRT at PMCC but was co-managed at another institution involved in that publication. We consider it valuable to include this patient's data given the additional response assessment analyses and longer follow-up in our series.

Eligibility criteria for ^{177}Lu-DOTATATE therapy included positive SSR imaging in all lesions, with either imaging progression or uncontrolled symptoms related to the unresectable disease. Positive Gallium-68 DOTA-0-Tyr3-Octreotate (^{68}Ga-DOTATATE) PET/CT scan or SSR imaging was defined as lesion uptake higher than liver and sub-grouped to less than spleen or higher than spleen based on tomographic imaging (modified Krenning score 3 and 4, respectively). Further eligibility criteria listed in the supplementary materials.

This study was conducted after receiving approval from the institutional ethics committee at the PMCC (Peter Mac Project No: 19/214R) and the HHUMC (approval number: 0072–16). Details of access to PRRT at respective institutions are summarized in supplementary materials.

Therapy

Each cycle of ^{177}Lu-DOTATATE was administered with premedication granisetron 2 mg, dexamethasone 8 mg, and renoprotective amino-acid infusion (25 g lysine and 25 g arginine in 1 L normal saline) commencing 30 min before ^{177}Lu-DOTATATE and continuing for 3 h thereafter(*9*). Dexamethasone was used as an antiemetic medication as per institutional protocol only at PMCC. The treatment regimen

typically included up to 4 cycles of ^{177}Lu-DOTATATE given 6–10 weeks apart. At PMCC ^{177}Lu-DOTATATE were usually given with radiosensitizing chemotherapy unless contraindicated, based on prior experiences showing enhanced efficacy without additional toxicity (*10-12*). Further details of radiosensitizing chemotherapy are described in supplementary materials. Patients at HHUMC did not receive concurrent chemotherapy.

Follow-up

Patients were clinically reviewed before, and after, each cycle of ^{177}Lu-DOTATATE and typically at 3 months following the last cycle of treatment. Evaluation at 3 months included assessment of symptoms, laboratory tests including full blood counts, renal function, hepatic function and serum chromogranin A (supplementary materials) as well as imaging by CT and/or ^{68}Ga-DOTATATE PET/CT with or without 2-[fluorine-18] fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET/CT. Ongoing follow-ups occurred at 3-6 monthly intervals. CT response was defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (*13*). Where available, contrast-enhanced CT images were directly compared. Otherwise, non-enhanced CT from PET/CT component of the study was assessed, using ^{68}Ga-DOTATATE uptake as a guide to follow the dominant lesions. RECIST response was used to define the outcomes while ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET response as exploratory outcome measures. Response assessments were performed blinded to the patient outcome.

A descriptor for pathologic uptake on ^{68}Ga-DOTATATE PET/CT scan has been adapted from a semi-quantitative visual scoring system originally designed for planar Indium-111 octreotide imaging known as the Krenning score, consisting of a scale from 0 to 4 as follows: 0 = no uptake; 1 = uptake < liver; 2 = lesion uptake similar to liver; 3 = uptake > liver and < spleen; 4 = uptake ≥ spleen(*14*). Response by ^{68}Ga-DOTATATE PET/CT is described in Table 1.

In patients who had baseline ^{18}F-FDG PET/CT, positive lesion is defined as uptake above the liver, metabolic responses were assessed on the ^{18}F-FDG PET images qualitatively according to the PMCC criteria (supplementary materials) (*15,16*).

Time to next treatment (TNT) has been included to capture the timing of the next treatment from start of ^{177}Lu-DOTATATE. All hematological and renal toxicities occurring from the time of the first ^{177}Lu-DOTATATE administration were recorded and defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

The continuous variables are summarized using the median (interquartile range [IQR] and/or range) or basic proportions for categorical variables. The concordance between RECIST and ^{68}Ga-DOTATATE PET/CT response was assessed by Cohen's kappa statistics. Fisher's exact was used to evaluate the difference between response rates in different groups. Progression-free survival (PFS) was calculated from the start of ^{177}Lu-DOTATATE to clinical or imaging progression, new oncologic treatment or death. Overall survival (OS) was recorded as the duration from the start of ^{177}Lu-DOTATATE to last follow-up or death. The patients who were alive at the last follow-up were censored on that date. The cut-off follow-up date was the 31st of August 2019. Log-rank test and Cox regression model were used to compare survival of different groups. Kaplan–Meier curve was used to depict the survival. Statistical analysis was performed using GraphPad Prism 8 (GraphPad Software, La Jolla, USA).

RESULTS

Patient Characteristics

Of 51 consecutive patients with lung NET (22 from PMCC and 29 from HHUMC), 3 patients were removed from the analysis as they received at least one cycle of Yttrium-90 -DOTATATE. Forty-eight patients were included for final analysis including 43 (90%) with AC and 5 (10%) with TC. The median Ki67 of the entire population was 10% (range 1%-30%) and most patients (90%) had metastatic disease in the liver, bone or multiorgan involvement. Majority (83%) received somatostatin analogs and 10

patients (20%) had prior everolimus, chemotherapy or both. Almost all patients (47/48, 98%) were treated due to radiographic disease progression, and one patient for uncontrolled symptoms (back pain correlated to sites of osseous metastasis). The majority (94%) demonstrated high avidity on SSR imaging with a Krenning score of 4. Of 25 patients who had a baseline FDG-PET/CT, 16/25 (64%) had concurrent FDG-avid disease (Table 2). The median cumulative activity of ^{177}Lu-DOTATATE was 27.4 GBq (range 7.1-43.4 GBq) administered over a median of 4 cycles (range 1-4). Sixteen patients (33%) had radiosensitizing chemotherapy (5FU or capecitabine with or without temozolomide) (Table 3).

Imaging Response

Of 40 patients with RECIST-measurable disease at 3 months, 8/40 patients (20%, 95% confidence interval [CI] 10-35%) had partial response and 27/40 patients (68%, 95% CI 52-80%) had stable disease resulting in disease control rate (DCR) of 88% (95% CI 73-95%). Five patients (12%, 95% CI 5-27) had progressive disease (Figure 1). Five patients were lost to follow-up, 1 died early and 2 had no available follow-up CT (Supplementary Table1).

Of 39 patients with ^{68}Ga-DOTATATE PET/CT at 3 months, 17/39 patients (44%, 95%CI 30-59%) had partial response, 17/39 patients (44%, 95%CI 30-59%) had stable disease with DCR of 88% (95%CI 73-95%) (Table 4 and Figure 2). Five patients (12%, 95% CI 5-27%) had progressive disease. Of the 9 patients with no available ^{68}Ga-DOTATATE PET/CT, 5 were lost to follow-up, 1 died and 3 had Octreoscan as their post-treatment molecular imaging. In 39 patients with both RECIST-assessable disease and available ^{68}Ga-DOTATATE PET/CT, only a moderate concordance in response categories of the two modalities was noted, weighted Kappa of 0.51 (95% CI 0.21-0.68). Most patients with partial response or progressive disease by RECIST were also categorized similarly by ^{68}Ga-DOTATATE PET/CT, 4/5 (80%) and 7/8 (87%), respectively. The discordant response categories were noted in stable disease by RECIST: in this category, 10/26 patients were classified as partial response and 1 patient as progressive disease by ^{68}Ga-DOTATATE PET/CT due to the development of new avid lesions.

Follow-up ^{18}F-FDG PET/CT was available in 12/48 patients. While RECIST and ^{18}F-FDG PET/CT responses were in agreement in most cases, 3 cases with stable disease by RECIST were grouped as partial response by ^{18}F-FDG PET/CT.

In 30 patients from the AC cohort, although the rate of partial response was numerically higher in patients with Ki67 of >10%, compared to those with Ki67 of ≤10%, the difference did not reach statistical significance, 36% and 16%, respectively, p 0.4. Similarly, there was no significant difference in the rate of partial response in patients who received radiosensitizing chemotherapy, although a trend toward higher response rate was noted, 36% and 12%, respectively, p 0.1.

Survival Outcome

At a median follow-up of 42 months, there were 16 (33%) deaths. The median PFS and OS of the entire cohort were 23 months (95% CI 18-28 months) and 59 months (95% CI 50-not reached [NR]), respectively (Figure 3A-3B). The OS was not significantly different between the two institutions. The OS of the AC patients with Ki67 ≤ 10% versus Ki67 > 10% and patients who received radiosensitizing chemotherapy versus those who did not receive chemotherapy was not significantly different, p 0.7 and 0.4, respectively (Supplementary Figure 1A-1B).

Of patients with stable disease by RECIST, those with partial response on ^{68}Ga-DOTATATE PET/CT had longer OS compared to those with no response, NR versus 52 months (95% CI 28-65), hazard ratio (HR), 0.2 (95% CI 0.1-0.6), p 0.001 (Figure 4). Baseline ^{18}F-FDG PET/CT positive disease (available for 25/48 patients) and follow-up ^{18}F-FDG PET/CT response (available for 12/48 patients) did not correlate with OS, p 0.2 and 0.3, respectively.

During follow-up, 27 patients received further treatment. The median TNT was 23 months (range 7-56). Fifteen patients received further PRRT and 12 patients received other treatments, including everolimus (N=4), liver-directed therapy (N=3), change or increase the dosage of SSA (N=3) or chemotherapy (N=2). One patient who did show progressive disease at 3 months post PRRT received no

treatment but did not show any further progression up to 24 months, possibly indicating pseudo-progression.

Toxicity

^{177}Lu-DOTATATE was well tolerated with acceptable toxicity and the majority of CTCAE grade 3/4 hematological toxicity during treatment reversed to CTCAE grade 1/2 or baseline (Table 5). The most common hematological toxicity included thrombocytopenia and lymphopenia. There was no incidence of myelodysplasia/leukemia or renal toxicity on long-term follow-up.

DISCUSSION

PRRT is an effective treatment option for patients with advanced GEP NET with sufficient SSR expression who progressed on SSA (*4,7*). We have recently reported that only a proportion of lung NET expresses SSR at sufficient levels to potentially benefit from PRRT (*17*). Although lung NETs were not included in the NETTER-1 trial, limited clinical studies have shown promising results (*6,7*). By pooling the patients from two ENETs centers of excellence, we have shown that ^{177}Lu-DOTATATE is an effective and safe treatment modality in lung NETs with high SSR expression following progression on SSA with a radiographic response of 20%, DCR of 88%, and favorable median PFS and OS of 23 months and 59 months, respectively. This is largely consistent with previous studies indicating the efficacy of this treatment (Supplementary Table 2) (*8,18-27*).

Effective treatment options for advanced progressive lung NET are limited, with no available data to guide the sequencing of therapy. Furthermore, the limited patient tolerability remains of serious consideration when deciding on further lines of treatment with aim of preserving the quality of life. In the sub-cohort of 90 patients with lung NET in the RADIANT 4 trial, in 57 patients randomized to everolimus arm a 50% reduction in risk of disease progression or death was reported compared to placebo(*28*). Although 58% of the patients achieved any tumor shrinkage, only 2% were evaluated as partial response by RECIST. The median PFS was reported as 9.2 months (95% CI 6.8-10.9) with a 5.6-month

improvement compared to placebo (*28*). The phase II LUNA trial involving 112 patients, the majority with lung NET, supported the efficacy of pasireotide, everolimus or their combination, with radiographic DCR at 9 months of 39%, 33% and 58%, respectively(*3*). In line with the RADIANT-4 trial, the rate of partial response in the LUNA trial was 2% in all three groups. AEs requiring dose adjustment or interruption were reported in 24%, 52% and 61% of patients in the pasireotide, everolimus and the combination arm, respectively (*3*). Chemotherapy remains an option as palliative therapy in lung NET, with a combination of various chemotherapeutic drugs showed <30% objective response and median OS of 24.3 months in small retrospective series (*29*). Although PRRT is usually considered after progression on everolimus or chemotherapy, most patients (80%) in this study were untreated with either of those treatments. Although our result cannot be compared to prior trials or extrapolated to all patients with lung NET, the stringent patient selection based on sufficient SSR expression on pre-treatment scanning remains a major advantage of this targeted treatment. Furthermore, attention to tumor heterogeneity of SSR expression is important as we have recently shown that up to 50% of patients with lung NET may demonstrate inter and intra-patient heterogeneity on dual imaging by ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT(*17*).

PRRT has also shown an acceptable safety profile with largely reversible short-term and limited long-term treatment-related AEs, with no cases of myelodysplasia or renal toxicity in our cohort, which is consistent with other studies (*18-21*). In a study by Sabet et al. grade 3 hematotoxicity was reported in 13.6% at 3-10 weeks after at least 1 cycle of PRRT with no grade 3 or higher nephrotoxicity (*19*). Mariniello et al. reported < 5% hematotoxicity following ^{90}Y-DOTATOC, and no hematological or renal AEs after ^{177}Lu-DOTATATE (*21*). In an Australian multicenter study Lim et al. reported 2/48 (4%) patients with acute myeloid leukemia following PRRT; one patient was heavily pre-treated including alkylating chemotherapy while the other patient treated with SSA only (*8*).

While previous studies and clinical trials have typically used CT or MRI for response assessment, it appears that the outcome of the patients with NET may not be adequately captured by RECIST 1.1 alone (*19-22,26,27,30*). In addition to standard RECIST, by combining the functional information provided by PET and morphologic change by CT, we also explored the use of ^{68}Ga-DOTATATE PET/CT for response assessment and found a moderate concordance between two modalities. Interestingly, the response by ^{68}Ga-DOTATATE PET/CT further stratified the OS of the patients who were otherwise

grouped as stable disease by RECIST (Figure 4). Such patients constituted almost two-thirds of our cohort. The recent update on appropriate-use criteria indicated the use of SSR PET as appropriate for restaging following completion of PRRT(*31*). Based on our experience, response should include the disappearance or significant reduction of ^{68}Ga-DOTATATE avidity such as a decline in the Krenning score of the known lesions without structural progression on CT or MRI. The response monitoring of non-measurable lesions such as osseous disease is also another advantage of SSR PET/CT. However, the exact role of ^{68}Ga-DOTATATE PET/CT in response monitoring remains to be determined without currently established or validated criteria but warrants further evaluation.

The retrospective nature of this study imposes some limitations including the potential selection bias which by combining the patients from two institutions we hope may have been mitigated. Despite relatively long follow-up time, death occurred only in around one-third of patients which limited the statistical power to robustly evaluate the prognostic implications of multiple clinical and imaging factors. In addition, the relatively low number of patients included further restricted the strength of statistical inference and precluded multivariate analysis. The use of different treatment protocols between the sites is also another limitation. For instance, dexamethasone was used as an antiemetic and most patients at PMCC also received concurrent radiosensitizing chemotherapy. However, this appears not to have had a major impact on outcomes with comparable survival at both centers. Lastly, 10% of patients had only locoregional disease which may have better outcomes compared to those with bone, liver or multiorgan involvement. We did not remove these patients from the analysis as this may have further reduced the statistical power of this study.

CONCLUSIONS

In patients with advanced progressive lung NET and satisfactory SSR expression, ^{177}Lu-DOTATATE is effective and safe with a high DCR and encouraging PFS and OS. Further prospective studies comparing ^{177}Lu-DOTATATE with other systemic options are warranted.

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KEY POINTS

QUESTION: What is the role of ^{177}Lu-DOTATATE in patients with somatostatin receptor (SSR) positive metastatic lung NET?

PERTINENT FINDINGS: In this retrospective study of 48 patients from two ENETS Centres of Excellence, ^{177}Lu-DOTATATE was safe and achieved a high tumor control rate with an objective response in one-fifth of patients. In patients who achieve stable disease by RECIST at three months following completion of ^{177}Lu-DOTATATE, the response by ^{68}Ga-DOTATATE-PET/CT may have prognostic implication.

IMPLICATIONS FOR PATIENT CARE: In patients with advanced progressive lung NET and satisfactory SSR expression, ^{177}Lu-DOTATATE should be considered as an early effective and safe treatment modality.

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FIGURES

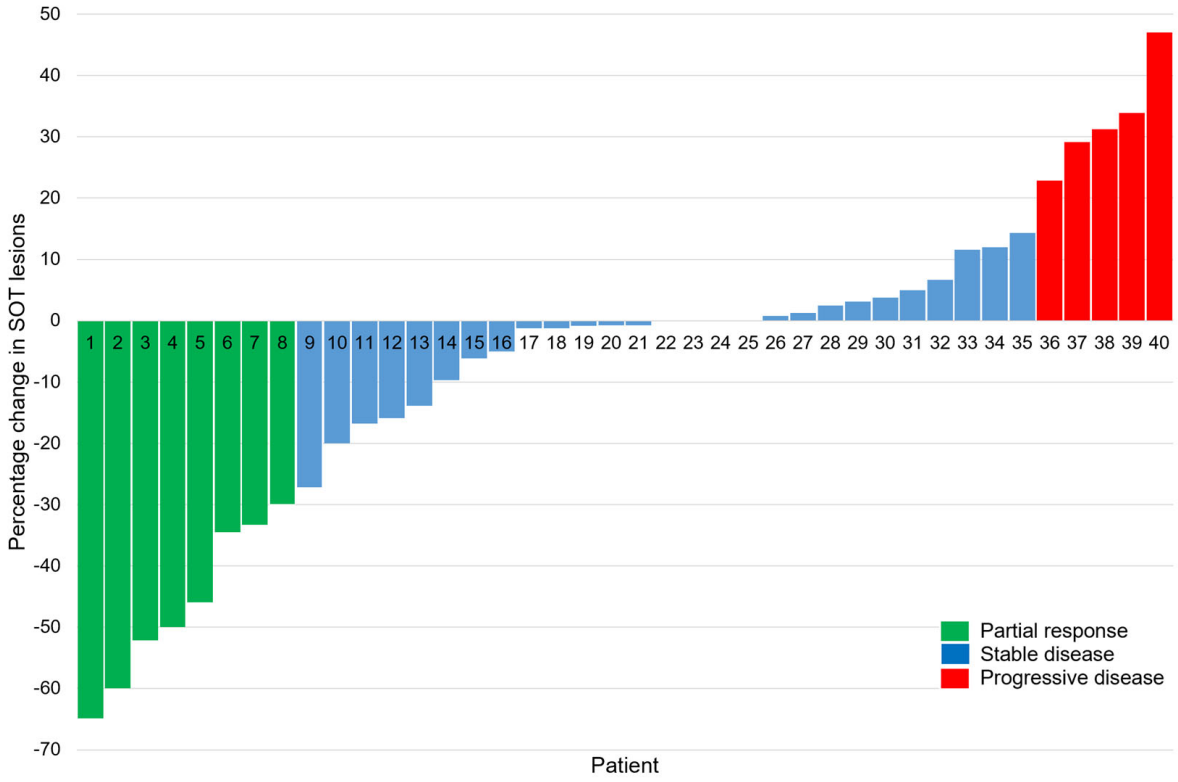


FIGURE 1. Waterfall plot of the RECIST response at three months post completion of PRRT

SOT lesions, sum of the target lesions diameters

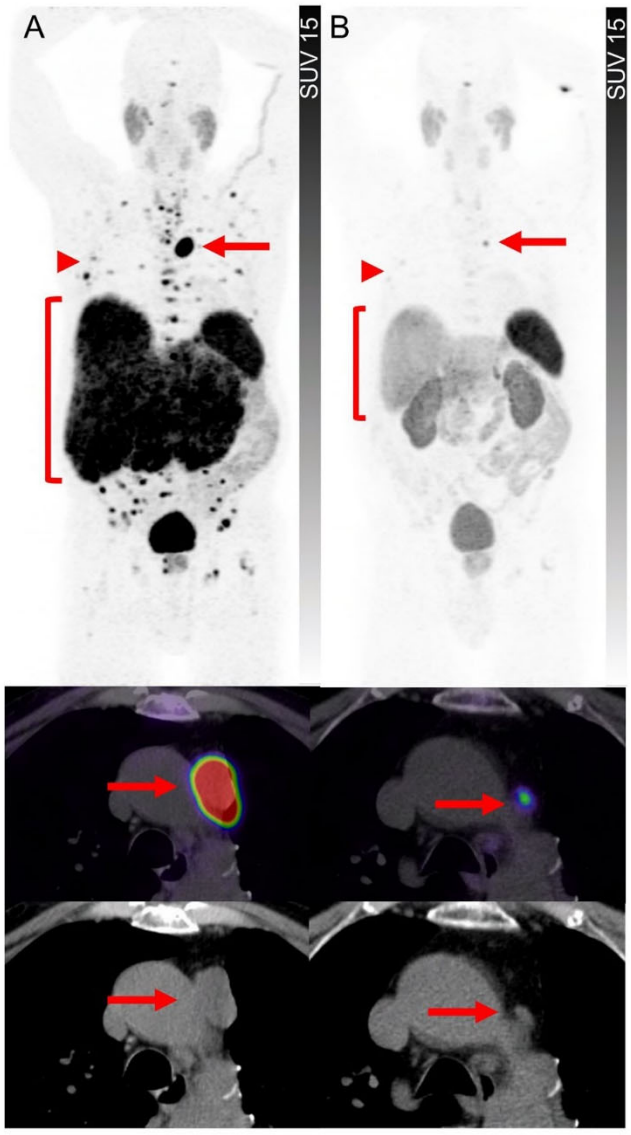


FIGURE 2. A representative patient with metastatic atypical lung carcinoid with partial response on ^{68}Ga-DOTATATE PET/CT and CT at 3 months post PRRT. Maximum intensity projection PET, PET/CT and CT at baseline (A) and three months follow-up (B) show marked response to treatment in the liver (brackets), bones (arrowheads) and lymph nodes (arrows)

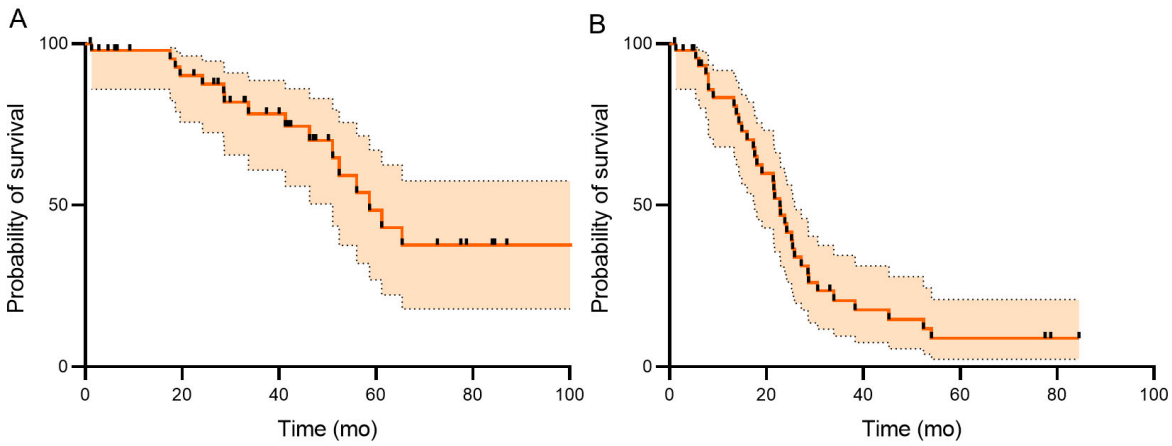


FIGURE 3. Kaplan Meier plot depiction of the overall survival (A) and progression-free survival (B) of the entire cohort

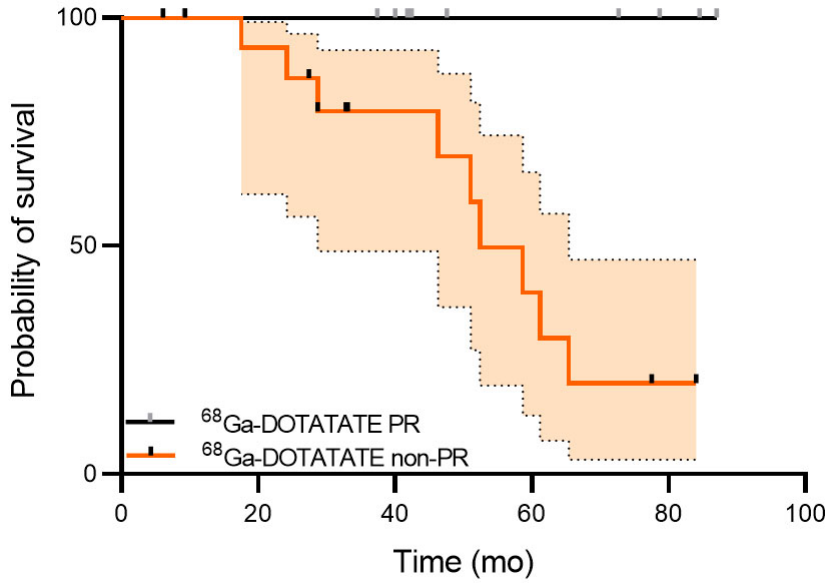


FIGURE 4. Of the patients with stable disease by RECIST, those with partial response (PR) on ^{68}Ga-DOTATATE PET/CT had longer overall survival compared to non-responders (non-PR) on ^{68}Ga-DOTATATE PET/CT, as demonstarted by Kaplan Meier plot

TABLES

TABLE 1. ^{68}Ga-DOTATATE PET/CT response criteria

Complete response	Disappearance of all tracer-avid lesions or If residual anatomical abnormality on CT with tracer uptake indistinguishable or less than background physiologic uptake
Partial response	Reduction in intensity of uptake by one modified Krenning score* in at least one tumor site associated with decrease/stable in size on CT (if measurable) or PET (if non-measurable on CT) or Reduction in size of tracer-avid lesions on CT (if measurable) regardless of intensity of uptake
Stable disease	Not partial response or progressive disease
Progressive disease	Development of new tracer-avid lesions or Increase in the size of the tracer-avid lesions on CT (if measurable) or on PET (if non-measurable on CT) regardless of intensity of uptake†

*Modified Krenning score, 0 = no uptake; 1 = uptake < liver; 2 = lesion uptake similar to liver; 3 = uptake > liver but < spleen; 4 = uptake ≥ spleen

†Rarely an increase in the size of the lesion can be seen in responsive lesions. This may be associated with an increase in central hypodensity/necrosis on CT and a decrease in peripheral tracer uptake on PET. In this circumstance, a confirmatory follow-up study or correlation with other imaging modalities may be required.

TABLE 2. Patient characteristics

Characteristics	**Number (%)**
Gender, male: female	35:13 (73: 27)
Median age in years (range)	63 (25-84)
Type	
Typical carcinoid	5 (10)
Atypical carcinoid	43 (90)
Ki67	
≤ 2%	3 (6)
3%-20%	34 (71)
> 20 %	3 (6)
Unknown	8 (17)
Dominant site of disease	
Local/loco-regional	5 (10)
Liver	10 (21)
Bone	3 (6)
Multi-organ	30 (63)
SSR expression by ^{68}Ga-DOTATATE (modified Krenning score)	
Score 3	3 (6)
Score 4	45 (94)
Baseline ^{18}F-FDG PE/CT	
No uptake	3 (6)
≤ liver	6 (12)
> liver	16 (33)
Not available	23 (48)
Prior treatments	
SSA	40 (83)
Surgery	25 (52)
Chemotherapy	5 (10)
Everolimus	3 (6)
Everolimus and chemotherapy	2 (4)
Radiotherapy	2 (4)
Liver-directed therapy	2 (4)
None	1 (2)

SSA: Somatostatin analog; SSR: somatostatin receptor

TABLE 3. Treatment parameters

Parameters	Number
Indication of ^{177}Lu-DOTATATE (N=48)	
Disease progression	47
Uncontrolled symptoms	1
Number of cycles	
1	3
2	6
3	13
4	26
Cumulative ^{177}Lu-DOTATATE activity in GBq (range)	27 (6-43)
Radiosensitizing chemotherapy (N=16)	
1 cycle	3
2 cycles	3
3 cycles	4
4 cycles	6
Chemotherapy regimen	
5FU	4
Capecitabine	8
Combined capecitabine and temozolomide	4

TABLE 4. Response to treatment

Modality	Response	Number (%, 95% CI*)
CT-RECIST	Complete response	0
	Partial response	8/40 (20, 10-35)
	Stable disease	27/40 (68, 52-80)
	Progressive disease	5/40 (12, 5-27)
	Not available	8
^{68}Ga-DOTATATE PET/CT	Complete response	0
	Partial response	17/39 (44, 30-59)
	Stable disease	17/39 (44, 30-59)
	Progressive disease	5/39 (12, 5-27)
	Not available	9
^{18}F-FDG PET/CT	Complete response	0
	Partial response	5/12 (42)
	Stable disease	3/12 (25)
	Progressive disease	4/12 (33)
	Not available	36

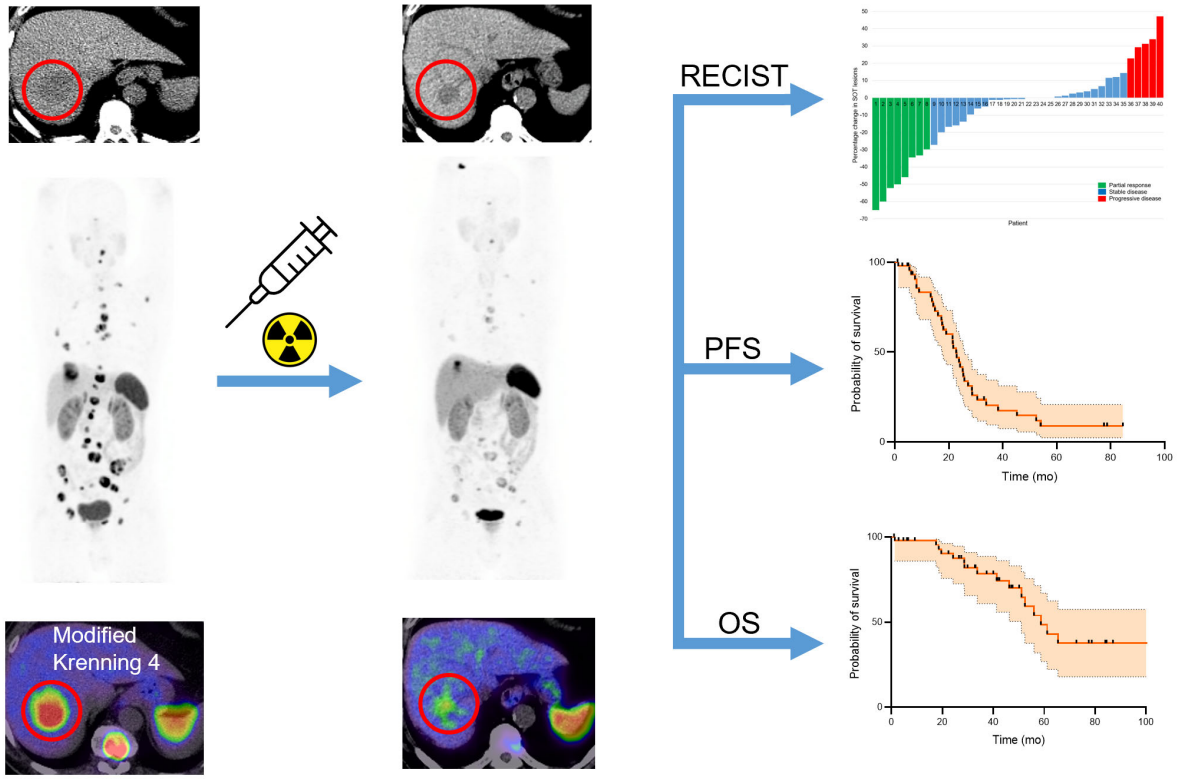
*Not calculated for the sample sizes of < 30

TABLE 5. Hematological adverse events of ^{177}Lu-DOTATATE

	During treatment (%)				**3 months post-treatment (%)**			
CTCAE Grade	1	2	3	4	1	2	3	4
Anaemia	22 (43)	4 (8)			26 (51)	1 (2)		
Leukopenia	10 (20)		1 (2)	1 (2)	8 (16)	1 (2)	1 (2)	
Neutropenia	5 (10)	2 (4)		1 (2)	4 (8)			
Lymphopenia	9 (18)	13 (25)	6 (12)	1 (2)	11 (22)	12 (24)	1 (2)	
Thrombocytopenia	13 (25)	1 (2)		1 (2)	12 (24)			

CTCAE: common terminology criteria for adverse events

Graphical Abstract



Supplementary material

MATERIALS AND METHODS

Patients

Patients were deemed unsuitable for ^{177}Lu-DOTATATE if disease demonstrated low avidity SSR imaging (uptake equal to or less than liver activity), hypoalbuminemia (albumin level ≤ 25 g/L), thrombocytopenia (platelet count < 50 × 109/L at PMCC and < 70 ×109/L at HHUMC), pancytopenia (hemoglobin level < 10 g/dL and white cell count < 3 × 109/L for the Israeli center), Eastern Cooperative Oncology Group (ECOG) performance score of 4, expected survival < 3 months, or confirmed pregnancy.

Ethical Approval

All patients at PMCC were treated on compassionate grounds under the Special Access Scheme (SAS), which allows treatment of patients with life-threatening diseases with experimental therapies that have demonstrated efficacy in other studies. The use of SAS provisions was approved by the institutional ethics committee (Peter Mac Project No: 19/214R) and all patients provided written informed consent to undergo treatment and follow-up. The Israeli Ministry of Health approves PRRT treatment for patients with metastatic progressive NETs and the study was approved by the HHUMC institutional ethical committee (approval number: 0072–16).

Therapy

At PMCC radio-labelling and administration of ^{177}Lu-DOTATATE was performed under local institutional protocol as previously published(*1*). Radiolabelling of ^{177}Lu-DOTATATE at HHUMC was also published previously (*2*).

At PMCC, an earlier protocol used infusional fluorouracil (5-FU) as a radiosensitizer (typically 200 mg/m2 daily, starting 2 days before ^{177}Lu-DOTATATE for 2 weeks in total). With the availability of oral capecitabine, a 5FU prodrug, this substituted 5FU at the dosage of 825 mg/m2 twice daily commencing 2 days before ^{177}Lu-DOTATATE for 2 weeks. At the discretion of the oncologist following discussion at the multidisciplinary team meeting, if temozolomide was combined with capecitabine, this was administered at 100mg/m^2 twice daily for 5 days commencing on the day of ^{177}Lu-DOTATATE for 5 days.

Follow-up

Chromogranin A (CgA) assessment at baseline and follow-up was not included in the manuscript due to the different reference ranges of the two institutions' laboratories and to avoid any possible flaws related to the inter and intra-laboratory variations and also several interfering factors with CgA levels.

^{18}F-FDG PET/CT response was based on PMCC criteria and grouped : complete response (^{18}F-FDG–avid lesions revert to the background of normal tissues in which they are located), partial response (significant reduction in tumor uptake), stable disease (no visible change in metabolic activity of tumors), progressive disease (increase in intensity or extent of tumor metabolic activity or new sites) (*3,4*).

Supplementary Table 1. Imaging response of all patients

Patient	^{68}Ga-DOTATATE PET/CT response	^{18}F-FDG PET/CT response	RECIST 1.1 response
1	Partial response	na	Partial response
2	Partial response	na	Partial response
3	Partial response	Partial response	Partial response
4	Partial response	na	Partial response
5	Partial response	na	Partial response
6	Stable disease	na	Partial response
7	Partial response	Partial response	Partial response
8	Partial response	na	Partial response
9	Partial response	Partial response	Stable disease
10	Partial response	na	Stable disease
11	Partial response	na	Stable disease
12	Partial response	na	Stable disease
13	Partial response	na	Stable disease
14	Partial response	Partial response	Stable disease
15	Stable disease	na	Stable disease
16	Partial response	na	Stable disease
17	Stable disease	na	Stable disease
18	Stable disease	na	Stable disease
19	Partial response	na	Stable disease
20	Stable disease	na	Stable disease
21	Partial response	Stable disease	Stable disease
22	Stable disease	na	Stable disease
23	Stable disease	Stable disease	Stable disease
24	Stable disease	Partial response	Stable disease
25	Stable disease	Stable disease	Stable disease
26	Stable disease	na	Stable disease
27	Stable disease	na	Stable disease
28	Stable disease	na	Stable disease
29	Stable disease	na	Stable disease
30	Stable disease	na	Stable disease
31	Partial response	na	Stable disease
32	na	na	Stable disease
33	Stable disease	na	Stable disease
34	Progressive disease	na	Stable disease
35	Stable disease	na	Stable disease
36	Progressive disease	na	Progressive disease
37	Progressive disease	Progressive disease	Progressive disease
38	Progressive disease	Progressive disease	Progressive disease

39	Stable disease	Progressive disease	Progressive disease
40	Progressive disease	Progressive disease	Progressive disease
41	na	na	na
42	na	na	na
43	na	na	na
44	na	na	na
45	na	na	na
46	na	na	na
47	na	na	na
48	na	na	na

na: not available

Supplementary Table 2. Summary of the studies of PRRT in lung neuroendocrine neoplasia (carcinoid)

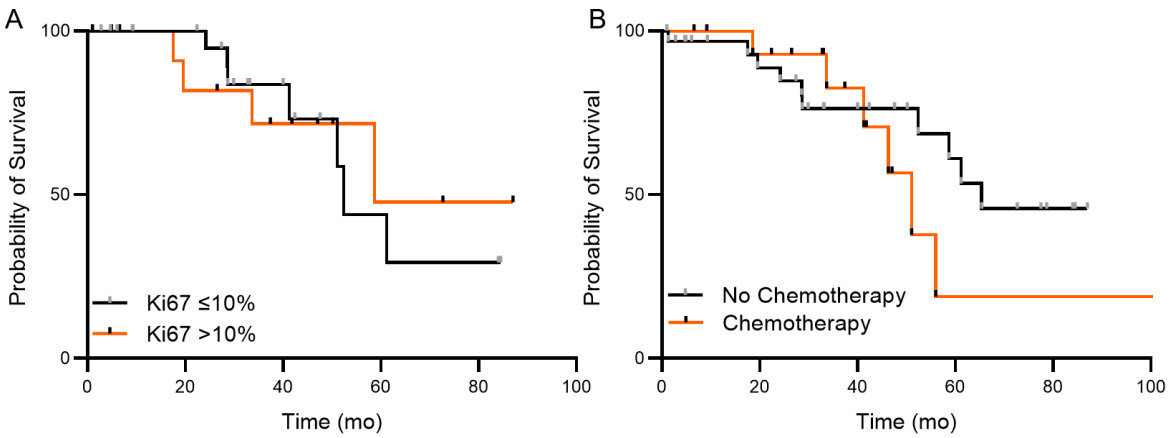
Reference	Study	n (TC: AC)	Therapy	Response Criteria	CR n (%)	PR n (%)	SD n (%)	Progressive disease n (%)	Follow-up (mo)*	PFS mo (95% CI)*	OS mo (95%CI)*
Current study	Retrospective	48 (5:43)	^{177}Lu	RECIST	0	8/40 (20)	27/40 (68)	5/40 (12)	42	23 (18-28)	59 (50-NR)
(*5*)	Prospective	34 (15:19)	^{177}Lu	SWOG	1 (3)	4 (12)	16 (47)	13 (38)	29	18 (13-26)	49(26-69)
(*6*)	Retrospective	22 (5:17)	^{177}Lu	RECIST	0	6 (27)	9 (41)	7(32)	54	27 (9-45)	42 (25-59)
(*7*)	Retrospective	22 (13:8) 1 SCLC	^{177}Lu	RECIST	1/19 (5)	1/19 (5)	11/19 (58)	6/19 (32)	NS	NS	40
(*8*)	Retrospective	48 (15:32) 1 unknown	^{177}Lu	Review of notes/radiology reports/correspondence	0	16 (33)	24† (50)	8 (17)	33	NS	43
(*9*)	Retrospective	114 (34:40) 40 NOS	^{177}Lu or ^{90}Y or combined	RECIST	0	15 (13)	61 (54)	38 (33)	45	28	59
(*10*)	Retrospective	23‡	^{177}Lu	RECIST	0	7 (30)	7 (30)	6 (26)	64	20	52 (49-55)
(*11*)	Retrospective	9 (4:5)	^{177}Lu	SWOG	0	5 (56)	3† (33)	1 (11)	20	31	NS
(*12*)	Prospective	13	^{177}Lu or ^{90}Y or combined	Functional response on PET/CT	0	8 (62)	3 (23)	2 (15)	NS	NS	NS
(*13*)	Prospective	5	^{177}Lu	RECIST	0	2 (40)	3† (60)	0	29	NS	NS
(*14*)	Retrospective	6	^{177}Lu or ^{90}Y or combined	RECIST	0	1 (17)	3 (50)	2 (33)	17	NS	NS
(*15*)	Prospective	6	^{177}Lu	RECIST	0	1 (17)	5 (83)	0	31	NS	NS

*Figures have been rounded off

† minor response is grouped as stable disease

‡ Including 3 not evaluable patients

AC: atypical carcinoid; CI: confidence interval; CR: complete response; ^{177}Lu: ^{177}Lu-DOTATATE; n: number of patients; NR: Not reached; NS: not stated; NOS: Not otherwise specified; OS: overall survival; Progressive disease: progressive disease; PR: partial response; RECIST: response evaluation criteria for solid tumors; SCLC: small cell lung carcinoma; TC: typical carcinoid; SWOG: Southwest Oncology Group; ^{90}Y: ^{90}Y-DOTATATE



Supplementary Figure 1. Kaplan Meier plot of atypical carcinoid showing no significant difference in OS of the patients with Ki67≤10% compared to those with Ki67>10% (A). No significant difference in OS of the patients treatment with concurrent chemosensitizing chemotherapy and those without chemotherapy (B).

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