NANETS/SNMMI Consensus Statement on Patient Selection and Appropriate Use of ^{177}Lu-DOTATATE Peptide Receptor Radionuclide Therapy

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With the growing use of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT), there are many unanswered questions regarding patient selection. In this document, we review the literature on the use of ^{177}Lu-DOTATATE in neuroendocrine tumors (NETs) of different primary origin, discuss issues of controversy, and review potential contraindications to treatment.

The present consensus statement was developed collaboratively by the North American Neuroendocrine Tumor Society (NANETS) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI). NANETS is a multidisciplinary professional society of neuroendocrine specialists in North America that was founded in 2005. NANETS' mission is to improve NET disease management through increased research and educational opportunities. NANETS is committed to a multidisciplinary approach and consists of doctors and scientists involved in different specialties of NETs. SNMMI is an international scientific and professional organization founded in 1954 to promote the science, technology and practical application of nuclear medicine. In addition to publishing journals, newsletters, and books, the SNMMI also sponsors international meetings and workshops designed to increase the competencies of nuclear medicine practitioners and to promote new advances in the science of nuclear medicine.

MATERIALS AND METHODS

Systematic Review

To inform the development of these guidelines, a systematic review of evidence was performed. We followed the Preferred Reporting Items for Systematic Reviews and Metaanalysis (PRISMA) guidelines (*1*). A literature search of PubMed and the CENTRAL database resulted in 1,195 potentially relevant articles using the following search string: ("peptide receptor radionuclide therapy" OR "radioisotope therapy" OR "radionuclide therapy" OR "radiolabeled therapy" OR ^{90}Y OR ^{90}Y OR ^{90}Y OR "(90)Y" OR "Y(90)" OR "(177)Lu" OR "Lu(177)" OR ^{177}Lu OR ^{177}Lu OR ^{177}Lu OR PRRT) AND (neuroendocrine OR carcinoid OR paraganglioma OR pheochromocytoma OR neuroblastoma OR somatostatin). Papers that were excluded included those in non-NET patients, duplications, studies including ^{111}In, nonoriginal articles, and those without reported outcomes. After a review of the abstracts and titles, 153 articles were determined to meet the criteria for inclusion in this review. Given the focus of this work, reports using ^{177}Lu-DOTATATE were prioritized. Articles were then selected and grouped according to the primary site of tumor.

Scoring of Appropriateness

In developing these guidelines, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: "The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics." The workgroup scored each scenario as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9. Scores 7–9 indicate that the use of the procedure is appropriate for the specific scenario and is generally considered acceptable. Scores 4–6 indicate that the use of the procedure may be appropriate for the specific scenario. This implies that more research is needed to classify the scenario definitively. Scores 1–3 indicate that the use of the procedure is rarely appropriate for the specific scenario and generally is not considered acceptable.

Definition of Somatostatin-Receptor Positivity

^{177}Lu-DOTATATE PRRT should only be used to treat somatostatin receptor (SSTR)–positive tumors. Typically, positivity is defined as intensity of uptake in sites of disease that exceeds the normal liver, a threshold that was originally defined for use with ^{111}In-pentetreotide

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planar scintigraphy. Nevertheless, the same threshold is often applied to ^{68}Ga-DOTATATE PET imaging despite the fact that the PET scan tends to overestimate uptake compared with scintigraphy (*2*). Although the Food and Drug Administration (FDA) approval of ^{177}Lu-DOTATATE limits its use to gastroenteropancreatic (GEP)-NETs, there are other indications where SSTR-PRRT may be beneficial. Consideration of the site of primary tumor is important in determining if a patient should be treated with PRRT. Below we discuss the evidence for the use of ^{177}Lu-DOTATATE for the treatment of NET subtypes assuming that the disease is SSTR-positive on SSTR-PET or scintigraphy. SSTR-negative disease should not be treated using ^{177}Lu-DOTATATE.

Evidence for Use Based on Primary Site

Midgut NET. The NETTER-1 study is the only randomized phase III clinical study offering high level evidence of efficacy with ^{177}Lu-DOTATATE. This study was performed in midgut NETs and is discussed in more detail below. Additionally, numerous single-arm studies and clinical series provide additional data on risk and benefit, some in patients receiving only ^{177}Lu-DOTATATE (*3,4*) and others with combinations of ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC (Table 1) (*5,6*).

NETTER-1 Trial. The NETTER-1 trial, a double-blind, randomized, controlled study of ^{177}Lu-DOTATATE versus high-dose octreotide, enrolled grade 1 or 2 midgut NET patients with metastatic or locally advanced progressive tumors during treatment with octreotide (*7*). Of note, patients had well-differentiated histology with a proliferative index (Ki-67) of 20% or less and positive uptake on SSTR-scintigraphy. The NETTER-1 trial demonstrated an improvement of progression-free survival (PFS) for ^{177}Lu-DOTATATE compared with the control arm (8.4 mo for the control arm vs. not reached for ^{177}Lu-DOTATATE; hazard ratio of 0.21%–95% confidence interval, 0.13–0.33). Objective response rate with ^{177}Lu-DOTATATE was 18%, versus 3% with high-dose octreotide. Preliminary analysis of overall survival (OS) demonstrated a hazard ratio of 0.4 ($P = 0.004$) favoring ^{177}Lu-DOTATATE; final OS is pending. Analysis of health-related quality of life demonstrated that ^{177}Lu-DOTATATE significantly delayed decline in clinically relevant endpoints such as global health, physical functioning, role functioning, and in symptoms such as pain, fatigue and diarrhea (*8*). Overall, in patients with midgut NET, ^{177}Lu-DOTATATE should be considered in SSTR-positive patients at time of progression after treatment with first line somatostatin analog therapy (Appropriateness Score 9).

Pancreatic NET. Pancreatic NET (pNET) is the second most common site of origin for metastatic GEP-NETs, and several retrospective studies have reported results with ^{177}Lu-DOTATATE in this population. Compared with midgut NETs, pNETs appear to have a slightly higher overall response rate which ranges from 45%–60%, although OS and PFS are consistent with or slightly shorter than seen with midgut (Table 1) (*4–6,9,10*). Outside of the NETTER-1 trial, there are 2 prospective studies in pNETs: the first is the IEO phase 1–2 trial, which included 14 pNET patients and reported an overall response rate of 57% (8/14) (*11*), and the second is a study of 60 pNET patients with an overall response rate of 30% (18/60) (*12*). Based on registry data, the FDA included pNET within the indication for ^{177}Lu-DOTATATE, and PRRT should be considered for treatment of progressive pNET patients (Appropriateness Score 8).

Bronchial NET. Several papers have reported the use of PRRT in pulmonary NETs, treated with both ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE (Table 1). Overall response rates ranged from 13%–30%, whereas PFS ranged from 19–28 mo and OS ranged from 32–59 mo. Bronchial NETs are categorized into 2 groups, typical and atypical carcinoid tumors, which are considered distinct from the more aggressive large-cell and small-cell neuroendocrine carcinoma. Not unexpectedly, typical bronchial carcinoids appear to be more responsive to PRRT, although the majority of papers do not distinguish response rates between the subsets. One issue concerning bronchial NETs is the relatively small percentage of tumors which express sufficient somatostatin receptors to be candidates for therapy, although in one recent manuscript, 76% of 143 bronchial NETs were positive on somatostatin receptor scintigraphy (*13*). Although the literature is not definitive, there appear to be significantly higher levels of SSTR expression in typical bronchial carcinoids compared with atypical carcinoids (*14*). In patients with SSTR-positive tumors, ^{177}Lu-DOTATATE therapy can be considered as a potential therapeutic option after progression on everolimus (Appropriateness Score 7). Treatment with ^{177}Lu-DOTATATE before everolimus is considered less appropriate (Appropriateness Score 6).

Tumors of Unknown Primary. Tumors of unknown primary are becoming less common since the introduction of SSTR-PET. To date, there are no studies performed only in patients with tumors of unknown primaries, although several studies report results for a subset of patients with unknown primaries (Table 1). Efficacy seems to be comparable to what is reported with a known gastrointestinal or pancreatic primary. Therefore, decisions to treat with PRRT in unknown primaries should mirror those in patients with GEP-NETs and ^{177}Lu-DOTATATE therapy should be considered in patients who progress despite treatment with first-line somatostatin analog therapy (Appropriateness Score 8).

Paraganglioma/Pheochromocytoma. Paraganglioma and pheochromocytoma (para/pheo) constitute a heterogeneous group of tumors with varying underlying genomic variations and variable SSTR expression. Succinate dehydrogenase subunit B–associated subtype has been well evaluated and has a high expression of SSTRs (*15*). There are several small single-center retrospective studies evaluating PRRT in para/pheo (some in the context of larger series including other NETs) that demonstrate overall response rate ranging from 7%–29% (*16,17*), with the highest reported response rate from a manuscript that described a combination of chemotherapy and PRRT (Table 1) (*18*). Currently there is an ongoing prospective clinical trial evaluating the efficacy of ^{177}Lu-DOTATATE in patients with advanced para/pheo (NCT03206060). It should be noted that ^{131}I-iobenguane (MIBG) was approved by the FDA for the treatment of MIBG-positive para/pheo (*19*). While ^{177}Lu-DOTATATE may be promising in this disease, treatment at this time should be limited to patients whose tumors are MIBG-negative (Appropriateness Score 7). Treatment of MIBG-positive patients with ^{177}Lu-DOTATATE in place of therapeutic ^{131}I-iobenguane is considered less appropriate (Appropriateness Score 6).

Special Circumstances

Renal Insufficiency. Clinical experience and trial evidence accumulated over the past 2 decades have demonstrated that PRRT with ^{177}Lu-DOTATATE is generally well-tolerated. Chronic and permanent toxicity affecting the kidneys is rare if necessary precautions and attention to specific risk factors are undertaken. Renal irradiation, and consequently the risk of toxicity, is significantly decreased when positively charged amino acids, such as lysine and arginine, are co-infused with the treatment, due to the competitive inhibition of reabsorption at the proximal tubule. Examining the outcomes of more than 2,500 patients (*20–27*), it is apparent that PRRT with ^{90}Y-peptides is associated with a significant risk for reduction of renal function. In subjects treated with ^{177}Lu-DOTATATE, the incidence of severe, end-stage renal damage is very rare, with only sporadic cases reported in the literature (*23,26*), mainly in patients with compromised renal function at baseline. Indeed, the NETTER-1 study demonstrated no evidence of clinically significant worsening of renal dysfunction among 11 patients with baseline mild renal dysfunction (GFR 50–59) and 13 patients with moderate renal dysfunction (GFR < 50) treated on the ^{177}Lu-DOTATATE arm of the study (*28*).

Severe renal dysfunction has generally been considered a contraindication to treatment with ^{177}Lu-DOTATATE. Many institutional series have required a minimum glomerular-filtration rate (GFR) of 50 cc/h. Based on available data, we do not consider a GFR < 50 to be a contraindication to ^{177}Lu-DOTATATE use. For patients with severe baseline renal dysfunction defined as GFR < 30, ^{177}Lu-DOTATATE should

TABLE 1
Experience with PRRT by Site of Primary Tumor

Author	Year	Patients*	Treatment	ORR	PFS	OS
Midgut NETs (*grade 9*)						
Strosberg (*7*)	2017	116	^{177}Lu-DOTATATE	18%, 18/101	NR	NR
Sabet (*3*)	2015	61	^{177}Lu-DOTATATE	13%, 8/61	33	61
Hörsch (*5*)	2016	138	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	51	NR
Brabander (*4*)	2017	181	^{177}Lu-DOTATATE	31%, 57/181	30	60
Baum (*6*)	2018	315	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	22	69
Pancreatic NETs (*grade 8*)						
Baum (*6*)	2018	315	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	20	44
Hörsch (*5*)	2016	172	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	39	53
Brabander (*4*)	2017	133	^{177}Lu-DOTATATE	55%, 72/133	30	71
Ezziddin (*10*)	2014	68	^{177}Lu-DOTATATE	60%, 41/68	34	53
Sansovini (*53*)	2017	60	^{177}Lu-DOTATATE	30%, 18/60	29	NR
Garske-Román (*9*)	2018	48	^{177}Lu-DOTATATE	45%, 22/49	NR	NR
Bronchial carcinoid (before everolimus *grade 6*; after everolimus *grade 7*)						
Mariniello (*54*)	2016	114	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	13%, 15/114	28	59
Baum (*6*)	2018	75	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	11	40
Ianniello (*55*)	2017	34	^{177}Lu-DOTATATE	15%, 4/32	19	49
Brabander (*4*)	2017	23	^{177}Lu-DOTATATE	30%, 7/23	20	52
Parghane (*56*)	2017	22	^{177}Lu-DOTATATE	11%, 2/19	NR	40
Sabet (*57*)	2017	22	^{177}Lu-DOTATATE	27%, 6/22	27	42
Unknown primary tumor (*grade 8*)						
Baum (*6*)	2018	151	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	13	53
Brabander (*4*)	2017	82	^{177}Lu-DOTATATE	35% 29/82	29	53
Delpassand (*58*)	2014	7	^{177}Lu-DOTATATE	NR	11	NR
Bodei (*11*)	2011	3	^{177}Lu-DOTATATE	0% 0/3	NR	NR
Paraganglioma/pheochromocytoma (MIBG positive *grade 5;* MIBG negative *grade 7*)						
Forrer (*17*)	2008	28	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	7%, 2/28	NR	NR
Kong (*18*)	2017	20	^{177}Lu-DOTATATE	29%, 5/17	39	NR
van Essen (*16*)	2006	12	^{177}Lu-DOTATATE	17%, 2/12	NR	NR

*Only within NET subtype (n).
ORR = overall response rate; PFS = progression free survival (in months); OS = overall survival (in months); NR = not reported/reached.

be used only in exceptional circumstances. Of note, hydronephrosis represents a particular concern as it impairs renal excretion and increases exposure to radiation. As much as possible, hydronephrosis should be corrected before initiation of ^{177}Lu-DOTATATE treatment. Patients on dialysis may be treated with ^{177}Lu-DOTATATE but, as with other radiopharmaceutical therapies, this should be done very carefully, with consideration for dose reduction and dosimetry.

Prior Chemotherapy. It is still unclear whether prior cytotoxic chemotherapy increases risk of myelodysplatic syndrome (MDS) or acute leukemia (AL) associated with ^{177}Lu-DOTATATE. In one small series of 20 patients treated with an alkylating agent (primarily streptozocin) and subsequently treated with ^{177}Lu-DOTATATE, 4 cases of MDS/AL were observed (*29*). Compared with typical patients treated with PRRT in the same institution (*4*), these 20 patients had more cycles of chemotherapy, more cycles of alkylating agents, had experienced more frequent early high-grade hematotoxicity, and tended to more frequently have bone metastases. Conversely, the largest series of patients treated with ^{90}Y- or ^{177}Lu-peptides identified an incidence of 2.3% for MDS and 1.8% for leukemia (of which 75% evolved from MDS), with a median latency from exposure of 4.4 y (*26*). In these patients, only 29% of MDS and 22% of leukemia could be correlated to prior chemotherapy. Therefore, it remains uncertain whether prior chemotherapy, and temozolomide-based treatment in particular, is associated with increased risk of MDS/AL after ^{177}Lu-DOTATATE therapy or not.

Mesenteric and Peritoneal Disease. In certain clinical circumstances, we recommend caution before consideration of ^{177}Lu-DOTATATE. Mesenteric tumors are often characterized by substantial surrounding desmoplasia. There are theoretic concerns that radiation may exacerbate the desmoplatic process, thus leading to increase in symptoms. Similar theoretic concerns pertain to patients with extensive peritoneal carcinomatosis in whom radiation may lead to bowel obstruction. Certain centers prescribe short courses of prophylactic steroids (e.g., 1–2 wk) starting immediately after each dose of ^{177}Lu-DOTATATE.

High-Grade Disease. ^{177}Lu-DOTATATE has been studied almost exclusively in patients with low or intermediate-grade neuroendocrine neoplasms (NENs). Consequently, there is limited evidence to support the use of ^{177}Lu-DOTATATE in grade 3 disease (*30–32*). Several studies demonstrate that very high proliferative indices (i.e., Ki-67 $>$ 35%–55%) are associated with inferior outcomes. Zhang, et al. reported the largest retrospective study to date of 69 patients with SSTR-expressing G3 NENs with a Ki-67 $>$ 20% who received PRRT (*33*). The median PFS was 9.6 mo and median OS was 19.9 mo. Notably, patients with Ki-67 $>$ 55% had the shortest survival (PFS 4 mo, OS 7 mo). Due to the potential heterogeneity of disease in this patient population, confirmation of SSTR expression across all metastases is essential. Additional imaging with ^{18}F-FDG PET may also be of use to fully characterize all sites of disease.

Pediatric Patients. NETs are rare in pediatric patients (*34*). In addition to NETs, PRRT may be useful in neuroblastoma and paraganglioma/pheochromocytoma, particularly if ^{131}I-MIBG therapy is not an option or if patients have progressed after MIBG therapy. However, there are limited data on PRRT in children. The largest study to date evaluated ^{90}Y-DOTATOC in 17 patients with various NETs and demonstrated minimal or partial response in 41% of patients (*35*). Two smaller studies which included a total of 10 patients demonstrated efficacy, but also demonstrated marrow toxicity in those patients previously treated with MIBG (*36,37*). In patients with neuroblastoma, it is not clear whether ^{177}Lu-DOTATATE should be used given the extensive experience with MIBG. Overall, PRRT appears promising in pediatric patients with NETs and neuroblastoma, although at this time ^{177}Lu-DOTATATE use should be limited to tumors that are negative on MIBG imaging.

Timing of Treatment

In nearly all cases described in the literature, patients treated with ^{177}Lu-DOTATATE had already progressed on a first-line somatostatin analog (SSA). While progression is typically defined radiographically, select patients may be treated based on symptomatic progression. Due to the long-term safety and efficacy of SSAs, first-line treatment with ^{177}Lu-DOTATATE is generally not appropriate. Certain exceptions to this rule include patients with very high tumor burden where any further growth would entail significant risk. The decision to treat with ^{177}Lu-DOTATATE, in the second-line or beyond, needs to be considered in the context of the larger systemic treatment landscape.

For patients with typical, hormone-secreting midgut NETs, systemic treatment options beyond first-line SSA are limited. In this population, the RADIANT-2 study compared everolimus combined with octreotide to placebo plus octreotide and did not demonstrate a significant improvement in PFS (*38*). Therefore, ^{177}Lu-DOTATATE should be considered the second-line systemic treatment of choice for most patients with functional somatostatin-receptor positive midgut NETs.

In advanced nonfunctioning gastrointestinal and bronchial NETs, everolimus was shown to significantly improve PFS compared with placebo (*39*). Decisions regarding sequencing of ^{177}Lu-DOTATATE versus everolimus must be individualized, with SSTR expression levels factored into the decision, although in bronchial NETs everolimus should be considered before ^{177}Lu-DOTATATE.

For patients with pancreatic NETs, multiple systemic treatment options exist including everolimus, sunitinib, and capecitabine/temozolomide chemotherapy. The latter is likely most appropriate for patients with relatively aggressive or symptomatic tumors, irrespective of SSTR expression. Further research is needed to develop evidence-based recommendations on sequencing of ^{177}Lu-DOTATATE with respect to these alternative treatment options.

Liver Targeted Therapy. Hepatic arterial embolization is a common approach to patients with unresectable, liver-dominant midgut NETs. Metaanalyses suggest a radiographic response rate of approximately 50%, with a higher rate of symptomatic response. There are no completed clinical trials comparing various embolization modalities, and thus significant controversy exists regarding the optimal embolic approach: bland embolization versus chemoembolization or ^{90}Y-radioembolization. However, despite the lack of prospective evidence, liver embolization remains an appropriate, guidelines-endorsed alternative to ^{177}Lu-DOTATATE in patients with liver-dominant metastases, and offers the potential for rapid symptom palliation among patients with carcinoid syndrome or other secretory symptoms (*40,41*).

There exist some concerns regarding interaction between ^{177}Lu-DOTATATE and prior liver-directed therapies. In one small series, increased hepatotoxicity with PRRT was observed in patients who had undergone prior liver-directed therapy (*42*). Of particular concern is the risk of cumulative hepatic radiation toxicity in patients who have undergone prior radioembolization, a procedure itself associated with risk of long-term radiation-induced hepatic injury. Patients with extensive hepatic disease are potentially at risk of developing radiation hepatitis, although there is little evidence of chronic hepatic toxicity with ^{177}Lu-DOTATATE, even among patients with high liver tumor burden (*43*).

Surgery. Surgical resection of the primary tumor and subtotal resection of metastatic disease plays an important role in NET patients. Limited retrospective data suggest that debulking before PRRT can result in improved response to PRRT and PFS (*44*).

Overall Considerations. Due to lack of trials comparing the numerous treatment options, selection and sequencing of treatments are not evidence based and must be made based on cross-trial comparisons and assessments of risk versus benefit in individual patients.

FUTURE DIRECTIONS

With the clinical approval of ^{177}Lu-DOTATATE, there are many possibilities for future research and optimizing clinical care with

PRRT. These include optimizing the number of therapy cycles and administered activity, consideration of repeat therapy, delivering the therapy intraarterially, the use of different radionuclides, and using novel peptides to bind SSTRs.

Although the NETTER-1 trial used 4 treatments at a fixed activity, optimizing the number of treatments or the administered activity of each administration may allow for decreased toxicity and improved efficacy. By measuring treatment effect during therapy or measuring lesional/organ dose, it may be possible to adjust the treatment schedule to increase efficacy. Currently, it is unclear how and even whether one should use patient specific dosimetry to adjust the administered activity, and many feel that giving a fixed activity works well for the majority of patients.

This idea of repeat PRRT has been evaluated in retrospective studies (*45–47*). If a patient responds well to one complete course of ^{177}Lu-DOTATATE, then it is reasonable to conclude that they may respond well to another course of ^{177}Lu-DOTATATE when they subsequently progress. These studies showed that repeat PRRT is safe and effective, although the PFS is not as long compared with the initial PRRT course.

Many patients have liver-dominant disease, and in these patients intraarterial ^{177}Lu-DOTATATE administered via the hepatic artery has been proposed (*48,49*). In theory, this provides higher delivery to the tumor, while reducing the systemic circulation and associated side effects.

Both ^{90}Y and ^{177}Lu have been used for PRRT, and each may provide different benefits given their different physical properties (*50*). The electron emitted from ^{90}Y has a higher energy and would be beneficial for bulkier tumors. Conversely, the longer pathlength of ^{90}Y will also have a greater bystander effect on normal tissues such as the bone marrow and kidneys resulting in higher toxicity. The relative benefits of ^{90}Y vs. ^{177}Lu have not been studied. Similarly, the use of α-emitters is another area of active research.

DOTATATE is an SSTR analog, which becomes internalized after activating the receptor. SSTR antagonists have been developed that have a higher binding specificity to the SSTR such that even though they do not activate the receptor nor get internalized into the cell, they potentially deliver a high dose of radiation (*51,52*).

CONCLUSION

The decision to initiate ^{177}Lu-DOTATATE therapy in a patient with progressive NET is complex and should be made within the setting of a multidisciplinary discussion. ^{177}Lu-DOTATATE should be considered when treating GEP-NETs, and tumors of unknown origin, generally after progression on somatostatin analog. In patients with bronchial carcinoids, ^{177}Lu-DOTATATE should be considered after everolimus, and in patients with para/pheo, therapy should be limited primarily to patients with MIBG-negative disease.

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