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Article

Theranostics of Neuroendocrine Tumors: Bibliometric Study Based on Web of Science Database

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Simple Summary: Neuroendocrine tumors (NETs) are a rare and heterogeneous class of neoplastic lesions, but their prevalence has increased significantly over the past three decades. These tumors are sometimes difficult to treat. Improving diagnostic efficiency and treatment effectiveness is very important for patients with neuroendocrine tumors. Theranostic radiopharmaceutical approach combines diagnosis and treatment technology and has broad prospects in precision medicine, especially for the early diagnosis and treatment of tumors. Recently, researchers have discovered that radiolabeled somatostatin receptor (SSTR) antagonists have broad prospects in the diagnosis and treatment of neuroendocrine tumors. Through bibliometric analysis, we can understand the research trends and research hotspots in this field, and predict the development direction, which will be of great significance to the development of the discipline and clinical practice.

Abstract: Compared to agonists, radiolabeled somatostatin receptor (SSTR) antagonists have advantages in neuroendocrine tumors (NETs). Articles on radiolabeled somatostatin receptor agonists or antagonists in NETs were included by searching the Web of Science (WoS) database. The included literature has been subjected to data collection and bibliometric study. A detailed analysis of the included clinical articles was also performed. 123 publications were identified for bibliometric analysis. The number of publications on radiolabeled somatostatin receptor agonists and antagonists in the theranostics of NETs has increased significantly after 2014, with Germany publishing the most papers (39), followed by the United States (33) and Switzerland (28). The Swiss paper was cited the most, with 1783 quotations, followed by the USA (1338) and Germany (1330). The most common keywords were NETs (89), Peptide receptor-mediated radionuclide therapy (PRRT) (62), and antagonists (53). Antagonists had lower uptake in normal tissue and higher uptake in tumor tissue compared to agonists, with a high tumor-to-liver ratio. Research on radiolabeled somatostatin receptor agonists and antagonists in theranostics of NETs is increasing, with significant contributions from Europe and the United States. Radiolabeled somatostatin receptor antagonists are likely to be a hot topic in NETs theranostics.

Keywords: neuroendocrine tumors; theranostics; somatostatin receptor; agonists; antagonists; bibliometric study

1. Introduction

Neuroendocrine tumors (NETs) constitute a rare and heterogeneous group of neoplastic lesions that may originate from neuroendocrine cells distributed throughout the body. The gastroenteropancreatic region represents the most common site of origin. [1,2] The site of origin and the classification of these tumors result in distinctive behavioral and outcome characteristics. In addition to their histological features and anatomical location, tumors can be functional, triggering corresponding clinical symptoms through the secretion of a variety of biologically active compounds. Despite their relative rarity, NETs have seen a significant increase in prevalence over the past three

decades. This is due to improvements in awareness and diagnostic techniques. It appears that the majority of NETs are comparatively inert in comparison to other epithelial malignant neoplasms. It is noteworthy that these tumors can be aggressive and difficult to treat. [3–6]

The somatostatin receptors have high expression in tumors, whereas it is not significantly expressed in the majority of physiological tissues. Some human tumors derived from neuroendocrine and gastroenteropancreatic sources have been observed to express a range of SST mRNAs. Among these, SSTR2 has been identified as the most prominently expressed, providing feasibility for the utilization of radiolabeled somatostatin receptors in therapy and diagnosis. [7,8] The use of somatostatin receptors agonist-based theranostic radiopharmaceuticals, such as [^{90}Y]Y- or [^{177}Lu]Lu-DOTATOC, [^{177}Lu]Lu-DOTATATE, as well as [^{68}Ga]Ga-DOTATOC and [^{68}Ga]Ga-DOTATATE, in the diagnosis and management of patients with neuroendocrine tumors have previously been extensively promoted in clinical practice and play a pivotal role in both patient outcomes and quality of life. [9–16] An important factor of the utilization of agonists for theranostics of neuroendocrine tumors is their excellent capacity for internalization within tumor cells. Following high-affinity binding to the receptor, agonists commonly induce the internalization of the ligand-receptor complex and facilitate the accumulation of radioactivity. [8,17,18] The recent introduction of SSTR antagonists, such as [^{68}Ga]Ga-DOTA-JR11 [19], has resulted in notable advancements in the field of SSTR targeting. Unlike agonists, antagonists typically do not induce internalization. Rather, they bind to both activated and inactivated conformations of SSTRs, exhibiting a slower dissociation rate than agonists. As a result, the radioactivity accumulates on the surface of tumor cells, but with greater intensity than the agonists. In addition, SSTR antagonists benefit from a longer duration of action and stability in hydrophobic environments due to their greater chemical stability and hydrophobicity. Therefore, the SSTR antagonists show superior pharmacokinetic properties and improved tumor visualization (Figures 1 and 2). [20–23]

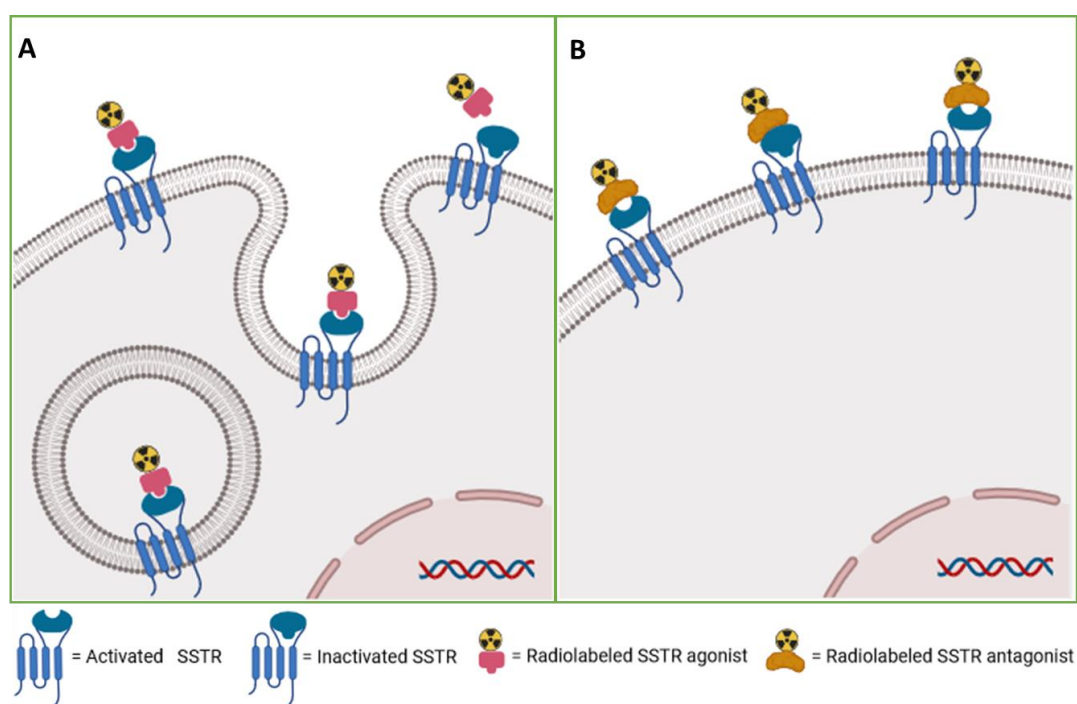


Figure 1. The pathway of the interaction of radiolabeled SSTR agonists and antagonists with the SSTR, a G protein-coupled receptor, overexpressed on GEP-NET cells, producing a radioactive signal for nuclear imaging and PRRT. A) Radiolabeled SSTR agonists interact with activated SSTR conformations and induce receptor internalization. The accumulation of radioactivity in tumor cells is utilized to generate both imaging signals and radiotherapeutic effects. B) A radiolabeled SSTR antagonist may interact with both activated and inactivated SSTR conformations, yet does not induce receptor internalization. As a result, a more intense radioactivity accumulates on the surface of tumor

cells, which can be utilized to generate both imaging signals and radiotherapeutic effects (therapeutic involving the use of PRRT).

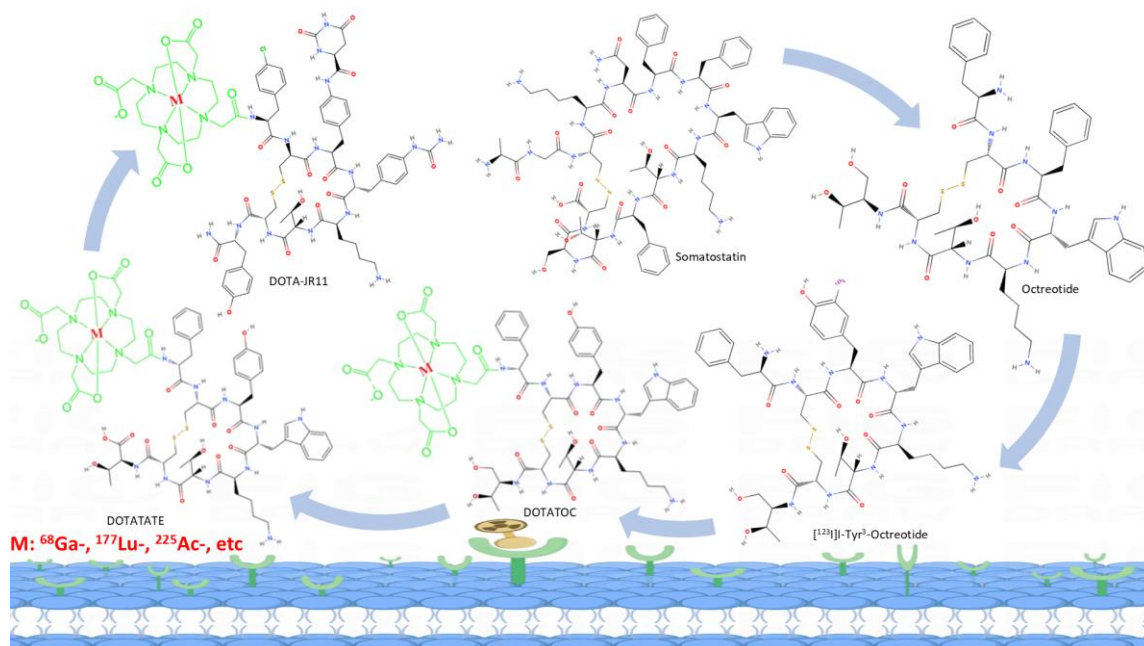


Figure 2. The figure presents an exemplary scheme for the development of somatostatin receptor-based theranostic agonist and antagonist radiopharmaceuticals, along with the chemical structure of the tracers.

A bibliometric study could provide researchers with a comprehensive overview of published literature. Through bibliometric analysis, we can understand the research trends and areas of interest within this field, as well as predict further development. This will be of significant value in advancing the discipline and clinical practice. [24,25] We used the Web of Science database to analyze the latest research on radiolabeled Somatostatin receptor agonists and antagonists in the theranostics of neuroendocrine tumors.

2. Materials and Methods

2.1. Literature Search Strategy

A comprehensive search of the Web of Science database was conducted. The following subject terms were employed in the search: (1) neuroendocrine tumors; (2) diagnosis or therapeutics or theranostics; (3) somatostatin receptor; (4) antagonists or inhibitors or agonists. The search was concluded on 30 July 2024.

The inclusion of published articles on radiolabeled somatostatin receptor agonists or antagonists for NETs was determined by two authors, who removed irrelevant literature by reading the title and abstract. In cases of doubt, a third author was invited to make a joint judgment on whether to include the article in the study. As this study did not involve human subjects, approval of the institutional review board statement was not required.

2.2. Bibliometric Analysis

The included literature has been subjected to data collection and cleaning, with information recorded including publication and citation counts, year of publication, H-index, country/region, affiliation, author, journal, reference, and author keywords. Before data analysis, a thesaurus file combined certain duplicates into a single term, fixed misspelled sections, and eliminated unnecessary words. VOSviewer 1.6.20.0 (Leiden University, The Netherlands) was used to analyze keywords and national contributions and to generate visualizations of these collaborative networks. Python 3.9.19

was used to draw line graphs and polar bar charts. VOSviewer uses the size of nodes to represent frequency and the lines between nodes to represent the total link strength. The color represents the average time of appearance in all included publications, with blue nodes corresponding to earlier appearances and yellow nodes corresponding to more recent appearances. A comprehensive examination of the clinical-type articles that compared antagonists and agonists was also conducted.

3. Results

A total of 555 articles were identified through the search strategy, and 123 documents were ultimately selected for bibliometric analysis and VOSviewer visualization based on the inclusion and exclusion criteria.

3.1. Global Trends in Publications

The number of publications on radiolabeled somatostatin receptor agonists and antagonists using a theranostic approach for neuroendocrine tumors has increased steadily and significantly since 2014 (Figure 3).

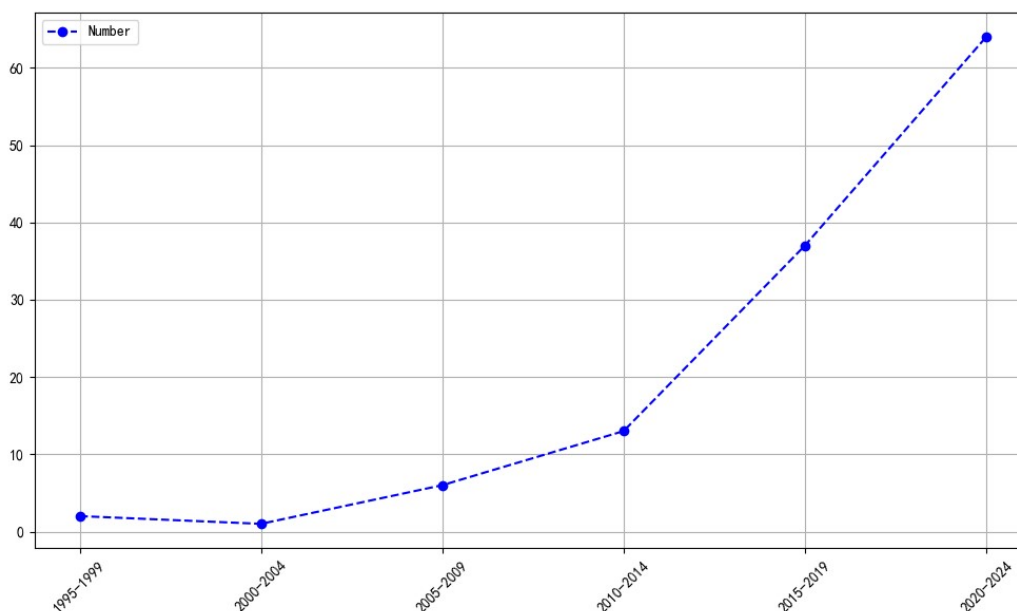


Figure 3. Trends in publications. The number of publications on radiolabeled somatostatin receptor agonists and antagonists using a theranostic approach has been exponentially increasing 1995-2024.

3.2. Analysis of Country Contributions

We analyzed the top 10 countries in terms of the number of publications and the top 10 countries in terms of the number of citations (Figure 4). Germany published the most articles (39), followed by the United States (33) and Switzerland (28). Switzerland's publications were cited 1783 times, which ranked first, followed by the United States (1338) and Germany (1330). Europe and the USA have the earliest research in this area and the highest number of publications (Figure 5).

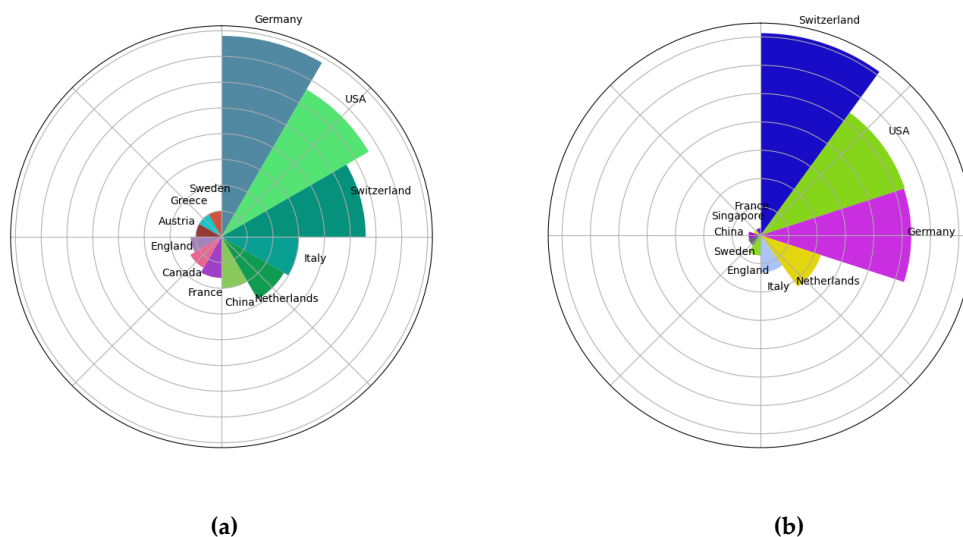


Figure 4. Polar bar charts. (a) Top 10 countries of publications; (b) Top 10 countries of citations.

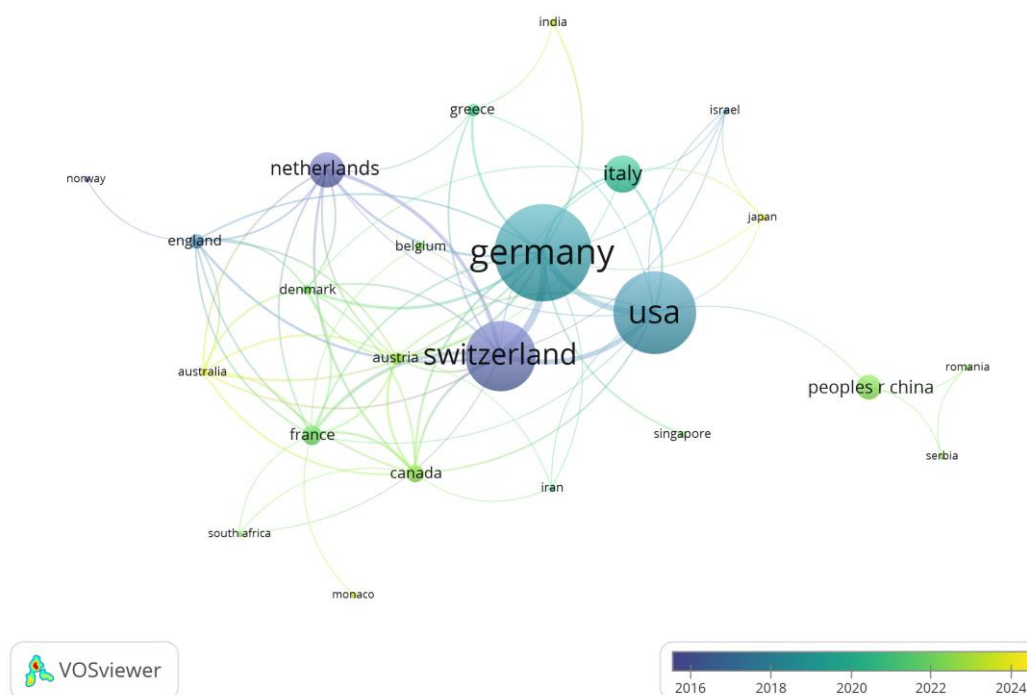


Figure 5. The visualization of countries and their respective cooperation networks is presented in this figure. It is evident that countries such as the USA and those in Europe have more pronounced networks and a greater propensity for collaboration, as evidenced by their higher number of publications compared to other countries.

3.3. Analysis of Keywords

The distribution of keywords was analyzed using the VOSviewer. Synonym merging was conducted prior to the analysis, and the minimum number of keyword occurrences was set to two. The keyword with the highest frequency was NETs (occurrences = 89), followed by PRRT (occurrences = 62) and Antagonists (occurrences = 53). [^{177}Lu]Lu-DOTATATE and [^{68}Ga]Ga-

DOTATATE are relatively more numerous studies, and somatostatin receptor antagonists are more recent (e.g., [^{68}Ga]Ga-DOTA-JR11, [^{177}Lu]Lu-satoreotide tetraxetan) (Figure 6).

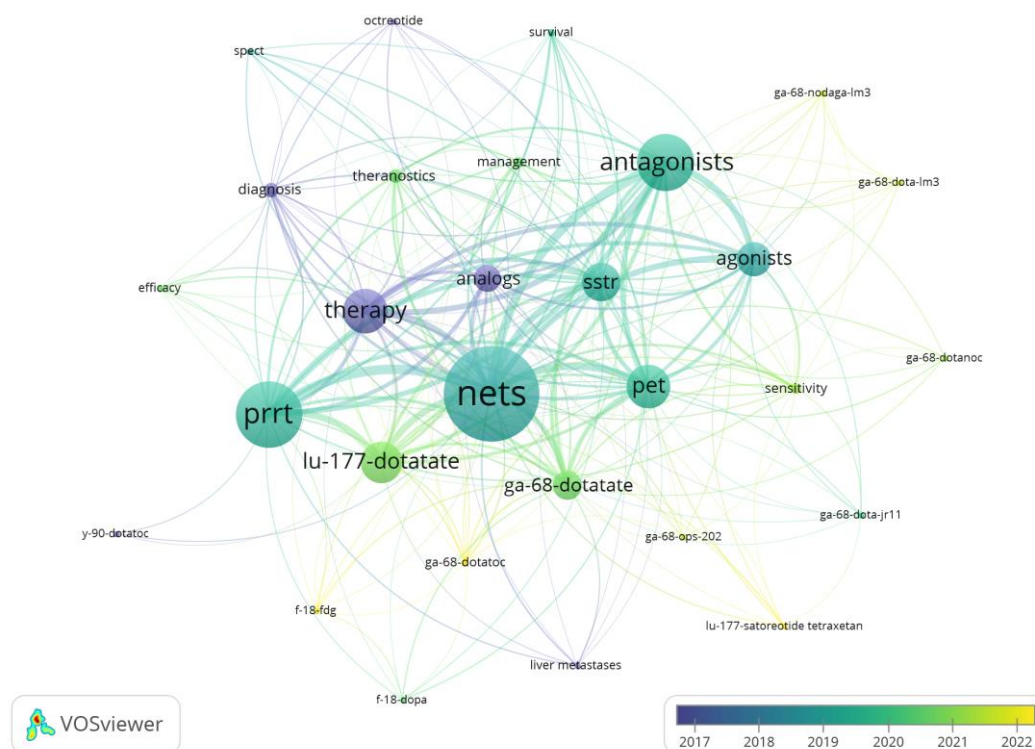


Figure 6. Keywords Visualization. The visualization of the keywords demonstrates a network of cooperation among them. The most frequently used keywords are NETs, PRRT, antagonists, SSTR, therapy, PET, [^{177}Lu]Lu-DOTATATE and [^{68}Ga]Ga-DOTATATE.

3.4. Analyses of Clinically Comparative Articles

3.4.1. Diagnosis of Neuroendocrine Tumors

We have summarized and analyzed clinical studies comparing antagonists and agonists to diagnose neuroendocrine tumors. Zhu, W. et al. [26], Liu, M. et al. [27], and Viswanathan, R. et al. [28] have shown that antagonist uptake is less than agonist uptake in normal tissues (e.g., spleen, renal cortex/kidney, adrenal glands, pituitary gland, stomach, liver, small intestine, pancreas, etc.) (Table 1).

Table 1. Comparison of the uptake values of the radiopharmaceuticals (agonists versus antagonists) in normal tissues.

Author	Zhu, W.		Liu, M.		Viswanathan, R.	
Year	2020		2024		2024	
Radiopharmaceuticals	[^{68}Ga]Ga-DOTA-JR11	[^{68}Ga]Ga-DOTATATE	[^{18}F]AlF-LM3	[^{68}Ga]Ga-DOTATATE	[^{68}Ga]Ga-DATA5m-LM4	[^{68}Ga]Ga-DOTANOC
Administration activity(MBq)	155 ± 52	148 ± 52	288 ± 28	148 ± 18	150	92.5
Spleen	3.2 ± 1.3	22.5 ± 8.0	6.9 (2.8-12.1)	20.2 (9.7-29.7)	6.6 (4.0-9.7)	11.3 (7.2-18.3)

	p < 0.001		p < 0.01		p < 0.0001	
Renal cortex/kidney	6.7 ± 1.6	14.6 ± 3.8	10.3 (7.7-12.8)	12.2 (9.5-14.8)	9.8 (6.6-13.8)	6.1 (4.1-9.6)
	p < 0.001		p = 0.04		p = 0.0004	
Adrenal glands	2.1 ± 0.8	11.3 ± 4.4	11.6 (5.9-17.0)	16.3 (9.7-25.1)	4.1 (2.4-6.1)	5.4 (1.6-6.6)
	p < 0.001		p < 0.01		p = 0.695	
Pituitary gland	2.1 ± 1.6	7.7 ± 3.2	8.8 (3.4-10.9)	11.1 (7.6-26.3)	2.1 (1.2-3.5)	1.7 (0.8-2.5)
	p < 0.001		p < 0.01		p = 0.025	
Stomach	1.9 ± 0.6	7.1 ± 4.2	2.7 (2.0-3.4)	6.2 (3.2-8.8)	-	-
	p < 0.001		p = 0.02		-	
Liver	2.8 ± 0.9	9.7 ± 3.0	2.9 (2.3-3.8)	6.2 (3.6-9.9)	2.5 (1.7-3.8)	3.5 (2.4-5.3)
	p < 0.001		p < 0.01		p = 0.01	
Small intestine	1.9 ± 0.5	6.1 ± 1.8	2.6 (2.0-3.6)	5.8 (3.6-10.9)	-	-
	p < 0.001		p < 0.01		-	
Pancreas	1.7 ± 0.6	4.3 ± 1.9	1.8 (1.4-2.3)	2.8 (1.8-4.3)	-	-
	p < 0.001		p < 0.01		-	
Value	SUVmax		SUVmax		SULpeak	

In certain comparative studies of antagonist and agonist uptake in tumor tissue, antagonists have been found to be as prominent as, if not more so than, agonists. For example, Nicolas, G. P. et al. [29] conducted a comparison between [⁶⁸Ga]Ga-OPS202([⁶⁸Ga]Ga-NODAGA-JR11, 15 µg peptide) with [⁶⁸Ga]Ga-DOTATOC (15 µg peptide), and [⁶⁸Ga]Ga-OPS202 (50 µg peptide) with [⁶⁸Ga]Ga-DOTATOC (15 µg peptide), there was no significant difference in all lesion uptake parameters (p > 0.05). However, the antagonists demonstrated superior performance compared to the agonists in terms of tumor-to-background ratio. The liver ratio, [⁶⁸Ga]Ga-OPS202 (15 µg peptide) and [⁶⁸Ga]Ga-OPS202 (50 µg peptide) were superior to [⁶⁸Ga]Ga-DOTATOC (15 µg peptide) with p-values of 0.004 and 0.008, respectively. Zhu, W. et al. [26] presented that antagonists were significantly superior to agonists for uptake in liver lesions (p < 0.001) and antagonists were also significantly superior in tumor-to-liver ratio (p < 0.001). Also Liu, M. et al. [30] compared four ⁶⁸Ga-labelled antagonists with [⁶⁸Ga]Ga-DOTATATE. The comparison of the antagonists revealed no notable differences in lesion uptake parameters when compared to [⁶⁸Ga]Ga-DOTATATE (p = 0.772). When each of the four ⁶⁸Ga-labelled antagonists was compared with [⁶⁸Ga]Ga-DOTATATE, [⁶⁸Ga]Ga-NODAGA-LM3 demonstrated superior performance compared to [⁶⁸Ga]Ga-DOTATATE (p < 0.001). However, [⁶⁸Ga]Ga-DOTA-JR11 was inferior to [⁶⁸Ga]Ga-DOTATATE (p = 0.001), [⁶⁸Ga]Ga-NODAGA-JR11 and [⁶⁸Ga]Ga-DOTA-LM3 did not exhibit a significant difference in comparison with [⁶⁸Ga]Ga-DOTATATE. Therefore, both the four ⁶⁸Ga-labelled antagonists, when considered collectively and individually in comparison with [⁶⁸Ga]Ga-DOTATATE showed a notable superiority of antagonists over agonists in terms of tumor-to-liver ratio (p < 0.001).

In addition, Liu, M. et al. [27] conducted another study demonstrating a significant advantage of [¹⁸F]AlF-NOTA-LM3 over [⁶⁸Ga]Ga-DOTATATE in terms of tumor-to-liver ratio (p < 0.001). The study by Viswanathan, R. et al. [28] comparing [⁶⁸Ga]Ga DATA^{5m}-LM4 with [⁶⁸Ga]Ga-DOTANOC similarly demonstrated a significant advantage of both antagonists over agonists in terms of tumor-to-liver ratio (p = 0.008) (Table 2).

Table 2. Comparison of uptake values of the radiopharmaceuticals (antagonists and agonists tracers) in normal tissues.

Author	Year	Radiopharmaceutic als	Administratio n activity(MBq)	All lesions		Liver lesions	Tumor-to-liver ratio	value		
Nicolas, G. P.	2018	[⁶⁸ Ga]Ga-OPS202 (15 µg peptide)	161 ± 21	12.3 (9.9- 16.9)	p = 0.88	10.9 (9.5- 20.7)	p = 0.54	5.3 (2.9- 5.7)	p = 0.00	SUVmax
		[⁶⁸ Ga]Ga- DOTATOC (15 µg peptide)	161 ± 11	12.4 (12.0 - 14.5)	-	11.8 (10.6 - 14.0)	-	1.9 (1.4- 2.9)	-	-
		[⁶⁸ Ga]Ga-OPS202 (50 µg peptide)	172 ± 14	14.4 (9.6- 16.3)	p = 0.96	12.6 (9.6- 19.9)	p = 0.65	4.3 (3.4- 6.3)	p = 0.00	-
		[⁶⁸ Ga]Ga- DOTATOC (15 µg peptide)	161 ± 11	12.4 (12.0 - 14.5)	-	11.8 (10.6 - 14.0)	-	1.9 (1.4- 2.9)	-	-
Zhu, W.	2020	[⁶⁸ Ga]Ga-DOTA- JR11	148 ± 52	-	-	18.6 ± 12.5	p < 0.00	7.7 ± 5.4	p < 0.00	SUVmax
		[⁶⁸ Ga]Ga- DOTATATE	155 ± 52	-	-	27.3 ± 15.4	-	3.4 ± 2.0	-	-
Liu, M.	2024	[⁶⁸ Ga]Ga- NODAGA-LM3	200 ± 11	57.4 ± 38.5	p < 0.00	-	-	10.4 ± 8.2	p < 0.00	SUVmax
		[⁶⁸ Ga]Ga- DOTATATE	-	40.0 ± 22.8	-	-	-	4.4 ± 3.6	-	-
		[⁶⁸ Ga]Ga- NODAGA-JR11	-	39.7 ± 26.5	p = 0.10	-	-	10.3 ± 9.9	p < 0.00	-
		[⁶⁸ Ga]Ga- DOTATATE	-	34.3 ± 23.9	-	-	-	5.3 ± 5.3	-	-
		[⁶⁸ Ga]Ga-DOTA- LM3	172±21	38.9 ± 32.1	p = 0.85	-	-	14.1 ± 13.2	p < 0.00	-
		[⁶⁸ Ga]Ga- DOTATATE	155±52	37.2 ± 22.1	-	-	-	5.3 ± 5.2	-	-

		[⁶⁸ Ga]Ga-DOTA-JR11	148±52	28.9 ± 26.1	p = 0.00	-	-	12.0 ± 10.6	p < 0.00	
		[⁶⁸ Ga]Ga-DOTATATE	155±52	44.0 ± 25.7		-		5.5 ± 3.8		
		All antagonists	-	40.1 ± 32.5	p = 0.77	-	-	12.1 ± 10.8	p < 0.00	
		[⁶⁸ Ga]Ga-DOTATATE	-	39.4 ± 23.8		-		5.2 ± 4.5		
Liu, M.	2024	[¹⁸ F]AIF-NOTA-LM3	288±28	22.1 (10.2-49.6)	p = 0.61	32.7 (12.7-50.9)	p = 0.71	12.1(4.8-24.3)	p < 0.00	SUVmax
		[⁶⁸ Ga]Ga-DOTATATE	148±18	17.1 (10.0-48.1)		31.4 (15.6-60.0)		4.9 (1.6-9.8)		
Viswanathan, R.	2024	[⁶⁸ Ga]Ga-DATA ^{5m} -LM4	-	-	-	15.7 (8.3-25.7)	p = 0.48	7.71 (3.3-14.4)	p = 0.00	SULpeak
		[⁶⁸ Ga]Ga-DOTANOC	-	-		14.7 (7.3-20.9)		4.1 (1.9-6.4)		

The study by Wild D. et al. [21] compared the diagnostic efficacy of [⁹⁰In]In-DOTA-BASS and [¹¹¹In]In-DTPA-octreotide based on the total lesion level, with 25/28 lesions detected by [¹¹¹In]In-DOTA-BASS and 17/28 by [¹¹¹In]In-DTPA-octreotide. All lesions visible on [¹¹¹In]In-DTPA-octreotide scans were also seen on [¹¹¹In]In-DTPA-BASS, whereas 8 lesions on [¹¹¹In]In-DTPA-BASS were not seen on [¹¹¹In]In-DTPA-octreotide. Bone lesions were undetectable in both [¹¹¹In]In-DOTA-BASS and [¹¹¹In]In-DTPA-octreotide scans. Nicolas, G. P. et al. [29] compared [⁶⁸Ga]Ga-OPS202 with [⁶⁸Ga]Ga-DOTATOC based on overall lesion levels and showed that both [⁶⁸Ga]Ga-OPS202 (15 µg peptide) and [⁶⁸Ga]Ga-OPS202 (50 µg peptide) had significantly better sensitivity than [⁶⁸Ga]Ga-DOTATOC (50 µg peptide). Zhu, W. et al. [26] showed that [⁶⁸Ga]Ga-DOTA-JR11 was superior to [⁶⁸Ga]Ga-DOTATATE in the detection of liver lesions and [⁶⁸Ga]Ga-DOTATATE was superior to [⁶⁸Ga]Ga-DOTATOC in the detection of bone lesions in both patient-based and lesion-based studies. Liu, M. et al.[30] reported that patient-level comparisons between antagonist imaging (all tracer combinations including [⁶⁸Ga]Ga-NODAGA-LM3, [⁶⁸Ga]Ga-DOTA-LM3, [⁶⁸Ga]Ga-NODAGA-JR11, and [⁶⁸Ga]Ga-DOTA-JR11) and [⁶⁸Ga]Ga-DOTATATE were comparable in patient-level sensitivity, specificity, and accuracy, with no statistically significant differences observed. Patient-level sensitivity, specificity, and accuracy were significantly higher for [⁶⁸Ga]Ga-NODAGA-LM3 compared to [⁶⁸Ga]Ga-DOTATATE. The sensitivity of [⁶⁸Ga]Ga-DOTA-JR11 was poor compared to [⁶⁸Ga]Ga-DOTATATE. Liu, M. et al.[27] also reported that [¹⁸F]AIF-NOTA-LM3 was superior to [⁶⁸Ga]Ga-DOTATATE in the detection of liver and lymph node metastases, both on a per-patient level and on a per-lesion level.

[¹⁸F]AIF-NOTA-LM3 was the first SSTR analog to show an advantage in detecting lymph node lesions compared to [⁶⁸Ga]Ga-DOTATATE. Research by Viswanathan, R. et al.[28] dedicated a significant advantage of [⁶⁸Ga]Ga-DOTA^{5m}-LM4 over [⁶⁸Ga]Ga-DOTANOC in both liver metastases and bone metastases based on a lesion-level comparison.

3.4.2. Radiotherapeutics for Neuroendocrine Tumors

Wild, D. et al. found that [22], [¹⁷⁷Lu]Lu-DOTA-JR11 and [¹⁷⁷Lu]Lu-DOTATATE had similar blood clearance: alpha half-life (distribution phase) 8 ± 6 minutes versus 10 ± 6 minutes and beta half-life (elimination phase) 8.8 ± 1.4 hours versus 7.8 ± 2.5 hours. The α -phase half-life shows how long it takes for the two radiopharmaceuticals to reach organs or tissues. The β -phase half-life shows how long they stay in the body. [¹⁷⁷Lu]Lu-DOTA-JR11 showed a longer intra-tumor residence time and a higher tumor uptake rate (residence time 1.3 to 2.8 times longer, tumor uptake rate 1.1 to 2.6 times higher) than [¹⁷⁷Lu]Lu-DOTATATE, resulting in a 1.7 to 10.6 times higher tumor dose. The study by Baum, R. P. et al. [31] also found a higher uptake and longer effective half-life of [¹⁷⁷Lu]Lu-DOTA-LM3 in systemic, renal, splenic, and metastatic tumors compared to the agonist [¹⁷⁷Lu]Lu-DOTATOC. The dose of radiopharmaceuticals absorbed by organs and tumors was also compared in both studies (Table 3).

Table 3. Radiation absorbed dose by organs and tumors after administration of [¹⁷⁷Lu]Lu-DOTA-LM3 and [¹⁷⁷Lu]Lu-DOTATOC.

Author	year	Radiopharmaceuticals	Absorbed dose by organs and tumors(Gy/GBq)				
			whole body	kidney	spleen	tumor	liver metastases
Wild, D.	2014	[¹⁷⁷ Lu]Lu-DOTA-JR11	0.13 ± 0.031	1.8 ± 0.44	3.0 ± 2.3	7.0 (5.7–16)	-
		[¹⁷⁷ Lu]Lu-DOTATATE	0.083 ± 0.021	1.2 ± 0.35	2.5 ± 1.5	2.0 (1.2–4.6)	-
Baum, R. P.	2021	[¹⁷⁷ Lu]Lu-DOTA-LM3	0.12 ¹	2.3	3.4	51	93
		[¹⁷⁷ Lu]Lu-DOTATOC	0.04	0.6	0.8	10	12

¹ This article only showed the mean value.

There were no serious adverse effects in either study, but in the study by Wild, D. et al. [22] one patient experienced transient flushing after injection of [¹⁷⁷Lu]Lu-DOTA-JR11, and a patient experienced grade 3 thrombocytopenia, which recovered completely within 8 weeks. In the study by Baum, R. P. et al. [31], mild nausea without vomiting was observed in five patients, and three patients also developed grade 3 thrombocytopenia but did not show unusual and did not require platelet transfusions.

3.4.3. Paired Theranostic

Paired imaging/therapy with radiolabeled somatostatin receptor antagonists is a novel approach to neuroendocrine tumors. In a portion of a prospective clinical trial reported by Krebs, S. et al. [32], 20 patients suffering from progressive, histologically-confirmed, unresectable NET underwent PET/CT imaging using [⁶⁸Ga]Ga-DOTA-JR11 and SPECT/CT with [¹⁷⁷Lu]Lu-DOTA-JR11 imaging. The results of this study on the correlation between ⁶⁸Ga- and ¹⁷⁷Lu- labeled antagonist (the same precursor DOTA-JR11), respectively, showed that both imaging revealed positive lesions in all 20 patients with metastatic NETs. The correlation between SUV and tumor-to-normal tissue ratios on PET and SPECT also demonstrated that [⁶⁸Ga]Ga-DOTA-JR11 PET/CT could be used as a tool for patient selection and then PRRT with [¹⁷⁷Lu]Lu-DOTA-JR11 ([¹⁷⁷Lu]Lu-satoreotide tetraxetan). Similar good biodistribution on [⁶⁸Ga]Ga-DOTA-JR11 PET/CT and [¹⁷⁷Lu]Lu-satoreotide tetraxetan

SPECT/CT images with minimal or mild uptake in uninvolved livers aid in the detection of lesions. The tumor lesion SUV_{peak} uptake ratio of [¹⁷⁷Lu]Lu-satoreotide tetraxetan to [⁶⁸Ga]Ga-DOTA-JR11 was high in all patients, especially as even patients with tumor lesions with low SSTR expression may benefit from [¹⁷⁷Lu]Lu-satoretin tetracycline treatment.

4. Discussion

To the best of our knowledge, this is the first systematic investigation into the utilization of somatostatin receptor agonists and antagonists in the theranostics of neuroendocrine tumors.

The results of this study demonstrated that there has been a rapid increase in the number of publications in this area, particularly following 2014, when the growth rate accelerated obviously (Figure 3). The analysis included published articles by researchers in 29 countries. However, it should be noted that the majority of these publications originate from Europe and the United States. In terms of quantity, visibility and impact, publications from Germany, the US, and Switzerland have the greatest global impact (Figure 4, 5). This may be attributed to two factors: Primarily, the economic base of these countries is capable of sustaining their output in research, [33] and secondly, the development of novel radiopharmaceuticals for theranostic purposes, requires state-of-the-art facilities and an interdisciplinary team. [34,35] For example, Professor Helmut Maecke [36–38] and his research group are pioneering experts in the field of radiolabeled SSTR analogs. They are renowned for their contributions to this area of research. His notable contributions to the development of peptide receptor radionuclide therapy (PRRT) have significantly advanced the field of PRRT. In particular, DOTATOC (DOTA-[Tyr3]-Octreotide) [39] represents a significant innovation in neuroendocrine tumor therapy, as it has been instrumental in improving both targeting and therapeutic efficacy in tumors that express the growth inhibitory receptor. It provides a more efficacious treatment option for patients with inoperable or metastatic neuroendocrine tumors. In recent years, a number of Asian countries, including China, Singapore, Iran, Japan, and India, have become engaged in research activities within this field. Of these countries, China has made the most significant contributions (Figure 5).

Keywords reflect the core of scientific research. Commonly used keywords focus on neuroendocrine tumors, diagnosis and treatment, and radiopharmaceuticals. Radiopharmaceuticals used for diagnosis are mainly [⁶⁸Ga]Ga-DOTATATE, and those used for treatment are mainly [¹⁷⁷Lu]Lu-DOTATATE, both of which belong to somatostatin receptor agonists (Figure 6). Although [⁶⁸Ga]Ga-DOTATOC is the first FDA-approved ⁶⁸Ga radiopharmaceutical for PET imaging, it appeared earlier than [⁶⁸Ga]Ga-DOTATATE. [40] However, this study is different. The keyword VOSviewer of [⁶⁸Ga]Ga-DOTATOC has a smaller weight and appears later than [⁶⁸Ga]Ga-DOTATATE. This may be because the concept of somatostatin receptor antagonists for imaging/treating neuroendocrine tumors emerged later than agonists, and in the past researchers have not used agonists as keywords when discussing PRRT or diagnosis but rather analogs. Another reason is that [⁶⁸Ga]Ga-DOTATATE has a better affinity for human SSTR2 than [⁶⁸Ga]Ga-DOTATOC, and researchers preferred to compare it with [⁶⁸Ga]Ga-DOTATATE when interpreting antagonists. [41,42]. The same phenomenon was confirmed in our analysis of clinical research articles, where only one study chose [⁶⁸Ga]Ga-DOTATOC as a control group when comparing antagonists and agonists [29]. The gradual emergence of some somatostatin receptor antagonists in recent years, such as [⁶⁸Ga]Ga-OPS202, [⁶⁸Ga]Ga-NODAGA-LM3, [⁶⁸Ga]Ga-DOTA-JR11, [¹⁷⁷Lu]Lu-DOTA-JR11, [¹⁷⁷Lu]Lu-DOTA-LM3, etc. (Figure 6), and these radiopharmaceuticals respond to the fact that research in this field has now made some progress and has a better outlook.

Since its emergence, somatostatin receptor radioligands have received sustained attention from a wide range of scientific researchers, greatly contributing to the development of peptide radiopharmaceuticals. [43,44] The application of somatostatin receptor radiopharmaceuticals in clinical practice has undoubtedly improved the diagnostic and therapeutic efficacy of patients with neuroendocrine tumors, as well as the quality of life and survival rate of patients. [45,46] Since antagonists can bind to more tumor targets than agonists, a paradigm shift in binding from internalizing SSTR2 agonists to antagonists is feasible. [20,47,48] Therefore, antagonists have a wider

clinical indication. Our investigation has continued that the majority of current antagonists have good clinical performance, especially in normal tissues where uptake is significantly lower than that of agonists (Table 1). The tumor-to-liver ratio of antagonists has an obvious advantage over agonists, which would help in the detection of liver metastases from NETs (Table 2). In addition, the ^{177}Lu labeled somatostatin receptor antagonists used for treatment were also superior to agonists in terms of dose absorbed by tumors, especially in liver metastases compared to agonists (Table 3). Clinical studies of paired imaging/therapy of neuroendocrine tumors with radiolabeled somatostatin receptor antagonists are also currently underway, with a study by Krebs, S. et al. [30] demonstrating the feasibility and efficacy of sequential imaging with radiolabeled same precursor DOTA-JR11 (^{68}Ga]Ga-DOTA-JR11 and [^{177}Lu]Lu-DOTA-JR11) for neuroendocrine tumors.

There are several limitations to this study. First, although WoS is a very powerful and authoritative database for bibliometric analyses, there may be unavoidable omissions when retrieving relevant articles. Secondly, therapeutic diagnostics is an emerging field in medicine and as we focused only on somatostatin receptor agonists and antagonists in neuroendocrine tumors, the number of publications retrieved and ultimately included in the analysis was relatively small. However, we believe that 123 articles are sufficient to identify the current status and trends in the field. The adoption rate of keywords may vary considerably between fields, as the limitations of the search strategy may affect the time of these keywords appear in the literature, resulting in a discrepancy between public perception and academic use. Alternatively, this may reflect the fact that changes in the focus of researchers may also lead to changes in keywords, resulting in differences between public perception and academic use. Taken together, these factors explain why the frequency and time of keywords in our dataset may not be entirely consistent with those commonly expected.

5. Conclusions

This study analyzed the literature in the WoS core database on the use of somatostatin receptor agonists and antagonists in the theranostics of neuroendocrine tumors. The number of relevant publications in this area is increasing, with countries such as Europe and the US contributing significantly both in terms of quantity and quality of literature. It is anticipated that somatostatin receptor antagonists will remain a prominent area of investigation in the field of neuroendocrine tumor theranostics in the future. A small number of clinical trials comparing antagonists and agonists have already appeared, and antagonists have shown exciting results in both diagnostic and therapeutic aspects. When employed for diagnostic purposes, antagonists demonstrate a lower uptake than agonists in normal (non-target) tissues and exhibit a higher tumor-to-liver ratio than agonists. This would be advantageous for neuroendocrine diagnosis, particularly the detection of liver metastases.

In the context of therapeutic applications, it was observed that the radiation dose of antagonists to tumor tissue was higher than that of agonists, particularly in cases of liver metastases. Furthermore, the feasibility of an antagonists-paired PET/SPECT imaging has been demonstrated, which may aid patient selection and therapy management.

These results demonstrate considerable potential for antagonists in the domain of neuroendocrine theranostics. However, the current number of studies is relatively limited, though it is increasing. Further research will be required to more comprehensively compare the effects of antagonists with those of agonists in the diagnosis and treatment of neuroendocrine tumors, as well as to conduct additional imaging therapy-matching studies with antagonists.

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