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Advances in Integrated Radionuclide Diagnosis and Therapy for Gastric Cancer: Targets, Tracers and Translational Applications

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1. Abstract

Gastric cancer (GC) remains one of the leading causes of cancer-related deaths worldwide. Although standard treatments including surgery, chemotherapy and immunotherapy have improved patient prognosis, the management of advanced disease and occult metastases continues to present a significant clinical challenge. The integration of nuclear medicine diagnostics and therapy represents a precision medicine model that combines molecular imaging with targeted radionuclide therapy (TRT), emerging as a promising strategy to overcome these limitations. TRT achieves precise delivery of radionuclides to lesions while avoiding non-targeted deposition by conjugating radionuclides with targeted carriers such as small molecules, peptides, or monoclonal antibodies. This approach enhances the efficiency and biological safety of tumor diagnosis and treatment. This review comprehensively summarizes the current status of nuclear medicine diagnostics for gastric cancer, detailing the evolution from metabolic imaging to novel targeted therapies targeting HER2, CLDN18.2, and fibroblast activation protein (FAP). Additionally, we conducted an in-depth analysis of the therapeutic potential of various radionuclides, explored synergistic combination therapy strategies, and outlined obstacles encountered during clinical translation-such as dosimetry and supply chain management—aiming to accelerate the application of these novel therapies in gastric cancer treatment.

2. Introduction

Gastric cancer (GC), as a common gastrointestinal cancer, ranks fifth among all tumours in terms of incidence and fourth in mortality worldwide [1]. It is reported that nearly one million new cases of GC are diagnosed annually globally, with over 650,000 deaths [2]. Major risk factors for GC include H. pylori infection, dietary habits, obesity, smoking, and genetic predisposition. Although endoscopy and contrast-enhanced CT remain the gold standard for diagnosis, their sensitivity is limited in detecting occult peritoneal metastases and micro metastatic lesions, which are crucial for accurate staging.

Positron Emission Computed Tomography/Computed Tomography (PET/CT), particularly when using 18F-FDG and FAPI imaging, enhances the accuracy of gastric cancer staging. However, its clinical utility is often compromised by physiological gastric uptake and the low glycolytic activity observed in certain histological subtypes, such as signet ring cell carcinoma and mucinous adenocarcinoma [3, 4].

In terms of treatment, the standard approach for advanced gastric cancer remains a combination of surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. However, treatment often faces challenges due to systemic toxicity, drug resistance, and the influence of the “cold” immune microenvironment commonly found in gastric tumours [5, 6]. Currently, radioisotope-based integrated diagnosis and therapy offers a

transformative approach. In 1941, 131I was first employed in the treatment of thyroid cancer, marking the beginning of research into radionuclide therapy (RNT) [7]. In recent years, this field has evolved from simple radioactive iodine therapy to complex targeted radionuclide therapy (TRT). TRT utilizes specific carriers—such as peptides, monoclonal antibodies (mAbs), or nanoparticles (NPs)-to deliver cytotoxic radionuclides (e.g., ^{177}Lu, ^{225}Ac) [8-10]. Directly to tumour cells [11-14]. This review explores recent advances in the field of integrated diagnosis and treatment for gastric cancer, focusing on emerging molecular targets and the strategic selection of radionuclides to improve patient prognosis.

3. Radionuclide-based Molecular Imaging of Gastric cancer

3.1. Molecular Imaging Limitations of 18F-FDG and the Cell Proliferation Marker 18F-FLT

Anaerobic glycolysis refers to the phenomenon where cancer cells rapidly supply energy to the body through glycolysis rather than relying on oxidative phosphorylation for energy production under aerobic conditions, and is considered a key characteristic of cancer [15]. Based on this feature, fluorodeoxyglucose (FDG), as a glucose analog, is widely used in the diagnosis, staging, and preoperative assessment of GC. However, although 18F-FDG exploits the “Warburg effect” of anaerobic glycolysis, its sensitivity for non-intestinal-type gastric cancer and peritoneal metastases is suboptimal [3, 16]. Meanwhile, approximately 20–30% of gastric cancers (such as early-stage gastric cancer, signet ring cell carcinoma, and mucinous adenocarcinoma) may yield false-negative results due to insufficient 18F-FDG uptake caused by low glycolytic activity [3, 17]. Additionally, benign lesions such as gastritis, leiomyomas, and polyps may yield false-positive results due to physiological uptake of 18F-FDG [4].

To solve this problem, researchers investigated the cell proliferation marker 18F-FLT. 18F-FLT is internalized and retained within cells via nucleoside transport, accumulating in proliferating tissues and malignant tumors, and is thus regarded as an indicator of tumour proliferation [18]. Herrmann et al. [19], demonstrated through their research that compared to 18F-FDG, 18F-FLT exhibits higher sensitivity in detecting locally advanced lesions, histological subtypes such as signet ring cell carcinoma, and regional lymph node metastases, and can be utilized for quantitative analysis [19]. This is primarily due to its lack of physiological uptake in the gastric wall. Staniuk et al. compared 18F-FLT PET with standard CECT in GC diagnosis, demonstrating for the first time the high sensitivity of 18F-FLT in identifying regional lymph node metastasis and distant metastasis in GC [20]. Using ROC curve, the sensitivity and specificity of FLT-PET/CT in metastatic regional lymph node assessment were higher than those of CECT. Therefore, 18F-FLT can effectively compensate for the detection limitations of 18F-FDG, enabling visualization analysis and efficacy assessment in gastric cancer [21, 22]. Notably, Honma et al. were the first to demonstrate that 18F-FLT exhibits extremely high sensitivity in identifying peritoneal dissemination [23]. Peritoneal dissemination is a common pattern of metastasis in gastric cancer recurrence, but its accumulation in the liver limits the assessment of liver metastases.

3.2. Tumor Microenvironment Imaging: FAPI and Hypoxia

The tumor microenvironment (TME) offers novel imaging targets, and molecular imaging techniques for gastric cancer have been further optimized. This advancement partially addresses the limitations of existing molecular diagnostic technologies, thereby enhancing the precision of gastric cancer diagnosis.

As a key component of the tumor microenvironment (TME), cancer-associated fibroblasts (CAFs) play a crucial role in the initiation and progression of cancer [24]. Fibroblast Activation Protein (FAP) serves as a specific marker for cancer-associated fibroblasts (CAFs), exhibiting high expression in various epithelial cancers. It is closely associated with tumor proliferation and progression [25, 26]. Based on the characteristics of FAPI, Researchers have developed a radiotracer based on FAPI (FAP inhibitor, which can specifically target and bind to FAP) for imaging various tumors [27]. Unlike 18F-FDG, FAPI visualizes tumors by highlighting CAFs within the tumor stroma and extracellular fibrosis [28]. Research has found that 50% of GC cases exhibit strong FAP expression [29]. Although gastric cancer exhibits lower uptake in FAPI PET compared to other gastrointestinal tumors, the relatively high tumor-to-background ratio in FAPI PET—due to the low physiological uptake of the gastric wall—enhances imaging performance. Consequently, FAPI PET holds considerable application potential for gastric cancer diagnosis [30]. Studies indicate that the metabolic parameters of ^{68}Ga-FAPI were higher than those of ^{18}F-FDG in the primary gastric cancer site, lymph nodes, and distant metastases., particularly small metastatic foci in the peritoneum, abdominal lymph nodes, liver, and bones [9,31-34]. Additionally, ^{68}Ga-FAPI demonstrates superior imaging performance compared to ^{18}F-FDG PET in subtypes such as signet ring cell carcinoma [35]. It is evident that compared to 18F-FDG, ^{68}Ga-FAPI is more advantageous for the auxiliary diagnosis and staging of gastric cancer, and can be used to evaluate treatment response and prognosis [36-43].

Tissue hypoxia is a common pathological state in cancer characterized by reduced oxygen supply. Leveraging this feature of cancer, researchers have developed multiple hypoxia PET probes [44, 45]. The first and most widely used radiolabeled hypoxia PET tracer in clinical practice is 18F-FMISO [46]. However, 18F-FMISO exhibits slow specific accumulation in tumors and high radioactive concentrations in the gastrointestinal tract, significantly limiting its clinical application. Currently, the primary next-generation hypoxia imaging PET agents include 18F-FAZA [47], 18F-FETNIM [48], 18F-FETA [49], 18F-HX4 [50] and 18F-EF5 [51]. Nario et al. [52], developed a novel radiotracer named 18F-FBNA, and found that compared to the aforementioned tracers, 18F-FBNA exhibits greater lipophilicity and is more readily captured by GC cells under hypoxic

conditions, resulting in higher cellular uptake[52]. In addition, researchers have identified ^{64}Cu-ATSM [53, 54]. They found that ^{64}Cu-ATSM exhibits greater lipophilicity than ^{18}F-FBNA and has been evaluated in multiple clinical trials. Furthermore, ^{64}Cu-ATSM also accumulates in tumors based on cellular redox potential and reactive oxygen species (ROS) types, making it an indirect biomarker for hypoxic PET imaging [55]. Additionally, researchers have developed a ^{64}Cu-ES PET agent, which has been validated to demonstrate superior therapeutic efficacy compared to other drugs such as ^{64}Cu-ATSM, making it a highly promising therapeutic and diagnostic agent for tumor treatment [56].

In summary, based on the metabolic and proliferative characteristics of GC cells, molecular imaging techniques for GC continue to be optimized and are expected to be further adopted in clinical practice, providing more accurate diagnostic tools for GC.

3.3. Novel Targeted Molecular Probes (Immune PET)

Currently, the detection of most GC target molecules primarily relies on techniques such as immunohistochemistry (IHC), which often present numerous limitations [57]. This procedure is often invasive, causing bodily damage while also potentially leading to cancer metastasis. More importantly, a single ex vivo sample may fail to reflect systemic expression patterns or the true status of target molecules within tumor tissue [57, 58]. Radioisotope labeling of GC target molecules combined with PET imaging has emerged as a novel diagnostic approach, demonstrating significant potential for non-invasive imaging and molecular expression detection.

HER2 is a transmembrane tyrosine kinase receptor belonging to the epidermal growth factor receptor (EGFR) family, and its overexpression is relatively common in GC [59]. As an anti-HER2 antibody, trastuzumab (TRZ) has been widely used in the targeted therapy of GC [60]. Guo et al. [60]. Constructed a ^{64}Cu-NOTA-trastuzumab probe by radiolabeling trastuzumab with ^{64}Cu for the specific detection of HER2 overexpression in GC patients [61]. Experimental results demonstrated that ^{64}Cu-NOTA-trastuzumab can detect primary GC lesions and liver metastases, exhibiting superior detection capability and stability compared to ^{18}F-FDG [61]. Reports have also evaluated ^{89}Zr-labeled trastuzumab [62], for the first time in esophagogastric adenocarcinoma (EGA). The study revealed that the ^{89}Zr-trastuzumab probe exhibits specificity for HER2+ EGA and demonstrates high contrast in visualizing both primary tumors and metastases [62]. Similarly, Zhou et al. developed ^{68}Ga-NOTA-MAL-MZHER2 for PET imaging of advanced GC [63]. They found that 68Ga-NOTA-MAL-MZHER2 can detect HER2 expression in GC patients at low doses during early-stage screening. Experimental findings indicate that GC patients exhibiting high affinity for the ^{68}Ga-HER2 affibody demonstrate significantly longer progression-free survival (PFS) compared to those with low affinity (4–9 months vs 2–3 months) [63]. In recent years, numerous PET imaging studies utilizing radionuclide-labeled HER2 have emerged, fully demonstrating the immense potential of HER2-targeted probes [64-67].

As a highly specific tight junction protein exclusively present in gastric epithelial cells, CLDN18.2 exhibits strong positive expression in GC and becomes exposed during malignant progression. It is widely recognized as a potent therapeutic target for GC [68-70]. Hu et al. [71]. Constructed three anti-CLDN18.2 nano-recombinant antibodies and labeled them with ^{89}Zr [71]. They found that two types of ^{89}Zr-anti-CLDN18.2 antibodies (^{89}Zr-anti-CLDN18.2 VHH-ABD and ^{89}Zr-anti-CLDN18.2 VHH-Fc) can be stably and efficiently expressed for tumor uptake and liver accumulation, enabling dynamic monitoring, and quantitative analysis of CLDN18.2 expression in tumors and normal organs [71]. In subsequent clinical studies, researchers found that ^{89}Zr-anti-CLDN18.2 VHH-Fc demonstrated greater specificity and persistence compared to ^{89}Zr-anti-CLDN18.2 VHH-ABD [72]. In addition, Chen et al. constructed ^{89}Zr-DFO-TST001 by radiolabeling the monoclonal antibody TST001 against CLDN18.2 with ^{89}Zr [73]. They found that ^{89}Zr-DFO-TST001 demonstrated excellent specificity and high tumor accumulation at the cellular level [73]. And Wang et al. [74], further validated the excellent in vivo tracking capability of the radionuclide-labeled diagnostic PET probe for CLDN18.2+ GC in both mice and humans using the 124I-18B10 probe (TST001, derived from the humanized mouse-derived hybridoma antibody 18B10) [74]. Notably, 124I-18B10 successfully demonstrated the systemic distribution of CLDN18.2 protein in GC patients [74]. Meanwhile, several immuno-PET imaging tracers targeting CLDN18.2 have been demonstrated to be viable for PET imaging, such as immune tracers labeled with ^{68}Ga/^{64}Cu/^{18}F that target humanized nanobodies against CLDN18.2 [75, 76]. In addition, Zeng et al. [77]. Comprehensively evaluated the capabilities of the therapeutic radionuclide 177Lu radiolabeled and DOTA-conjugated TST001 in terms of cellular uptake, SPECT imaging, and biodistribution [77]. Results demonstrated that 177Lu-DOTA-TST001 exhibited specific and high tumor uptake in CLDN18.2+ GC mouse models. Furthermore, the study revealed enhanced tumor volume control, more pronounced tumor tissue destruction, stronger cell proliferation inhibition, and low biological toxicity and low biological toxicity for 177Lu-DOTA-TST001, suggesting strong potential for clinical translation [77].

Tropomyosin-2 (Trop2) is a cell surface glycoprotein naturally present in normal cells exhibiting stem cell-like properties [78]. However, its expression is significantly elevated in various cancers, including GC, and is strongly associated with lymph node metastasis and poor prognosis [79-81]. Reports indicate that two nanobodies developed against Trop2 were labeled with ^{68}Ga, yielding ^{68}Ga-NOTA-RTD98 and ^{68}Ga-NOTA-RTD01. The specificity of these probes for solid tumor immune PET imaging was validated [82]. Huang et al. pioneered the use of Trodelvy, an 89Zr-labeled antibody-drug conjugate (ADC) targeting Trop2, to conduct immune PET imaging studies of Trop2 expression in gastric and breast cancer model [83]. Results indicate that 89Zr-DFO-Trodelvy clearly delineates tumor morphol-

ogy, with tumor uptake increasing over time. They concluded that ^{89}Zr-DFO-Trodelvy exhibits specific, rapid, and sustained accumulation in tumors with high Trop2 expression, enabling non-invasive monitoring of Trop2 status [83].

Human hepatocyte growth factor receptor (c-MET) is a transmembrane tyrosine kinase normally expressed in epithelial cells [84]. c-MET can induce tumor proliferation and metastasis by activating the MAPK/PI3K pathway [85]. In GC, c-MET is overexpressed and is closely associated with tumor staging and poor prognosis [86]. Earlier studies reported that DN30, an anti-Met monoclonal antibody radiolabeled with ^{89}Zr and ^{124}I, enabled precise imaging of tumor-targeted tissues, suggesting the potential for physiological monitoring through radionuclide labeling of c-MET [87]. Hepatocyte growth factor (HGF) is the sole physiological activating ligand for c-MET [84]。Price et al. radiolabeled the c-MET-binding antibody AMG102 with ^{89}Zr and validated the selective accumulation of ^{89}Zr-DFO-AMG102 in tumor tissues with elevated local HGF protein levels in GC models, thereby indirectly reflecting c-MET expression levels [88]. Additionally, Klingler et al. constructed ^{89}Zr-DFO-Onartuzumab by labeling Onartuzumab (an anti-human c-MET monoclonal antibody) with ^{89}Zr [89]. Immune-PET imaging revealed that ^{89}Zr-DFO-Onartuzumab exhibited prolonged circulation time and specific tumor uptake in GC models, confirming its efficacy as a radioligand for the c-MET receptor in GC [89]。

Among GCs, there is another relatively rare category of tumors-neuroendocrine tumors (NETs). NETs often exhibit high somatostatin receptor (SSR) expression. Traditionally, SPECT imaging using 111In-labeled octreotide analogues has been employed to detect SSR-positive tumors. In recent years, PET-targeted probes utilizing ^{68}Ga-labeled SSR analogues (such as ^{68}Ga-DOTA-TATE) have significantly enhanced imaging sensitivity for NETs [90]. Concurrently, studies have demonstrated that ^{68}Ga-DOTA-TATE offers diagnostic advantages in detecting liver and distant metastases of NETs [91]. Among patients with NET liver metastases, the positive rate in initial pathology reports was 91.4%, while SSR-PET/CT achieved a positive predictive value of 95.5% for detecting NET liver metastases [91]. Furthermore, Ohlendorf et al. validated the diagnostic value of ^{68}Ga-DOTA-TATE in NETs through its application in staging assessments and monitoring treatment responses in NET patients [92]. In summary, the ^{68}Ga-labeled SSR-targeted tracer demonstrates distinct advantages for the qualitative diagnosis, clinical staging, pathological grading, and efficacy assessment of G1, G2, and certain G3 NETs, positioning it as a promising targeted probe [92-94].

In addition to the above targets that have been relatively well-studied, numerous potential targets remain unexplored in GC therapy (Table. 1). For example, ^{64}Cu-labeled PSMA-targeting ligand DKFZ-PSMA-617 [95], ^{8}Ga-labeled MG7 antibody [96], 64Cu/177Lu-labeled anti-CDH17 nanobody [10, 97], 68Ga/177Lu-labeled anti-CD47 nanobody C2 [98], and LNC1013 (a novel FAPI dimer) [99], 9Zr-labeled anti-human DR5 monoclonal antibody CTB006 [100], and ^{124}I-labeled trastuzumab and TREM2 probes [101, 102]. With the continuous advancement of research, numerous novel targeted molecular probes for GC have demonstrated promising results in animal models or preclinical trials, thereby advancing non-invasive detection and dynamic assessment of GC.

2.4 Multimodal Fusion Imaging

The combination of functional and anatomical imaging enhances diagnostic reliability. Dual-tracer approaches, such as fusion imaging with ^{68}Ga-FAPI-04 and ^{18}F-FDG dual-tracer PET/CT, improve the detection rate of distant metastases. Additionally, researchers are exploring the integration of PET/MRI hybrid systems with MRI's high soft tissue contrast and molecular information to optimize preoperative T staging and assessment of response to neoadjuvant therapy.

Researchers have leveraged the unique features of different tracers to develop dual-tracer fusion imaging. For example, Miao et al. employed dual-tracer PET/CT using ^{68}Ga-FAPI-04 and ^{18}F-FDG for fusion imaging [103]. Although dual-tracer imaging did not outperform ^{68}Ga-FAPI-04 in detecting primary lesions and regional lymph node metastases, fusion imaging not only enhanced the sensitivity of detecting distant metastases in GC patients prior to surgery but also holds promise for improving treatment stratification [103]. Multimodal imaging combining CT and MRI better reflects tumor heterogeneity, aiding in the early identification of pathological response to neoadjuvant chemotherapy in locally advanced GC [104, 105]. Additionally, Wen et al. employed a micro-PET/CT system equipped with trastuzumab and a PET/MRI multimodal imaging technique labeled with ^{64}Cu or ^{124}I to quantitatively assess HER2 expression in a mouse GC model, thereby facilitating dynamic monitoring of monoclonal antibody (mAb) therapeutic efficacy [64]. Although current research remains limited, we believe multimodal fusion imaging technology holds significant potential for the diagnosis and treatment of GC.

Table 1: Radionuclide PET Imaging of Major Targets in GC.

Target	Expression Rate	Prognosis Relevance	Radionuclide Tracer	Publication Year	Publication
			^{64}Cu-NOTA-Trastuzumab	2018	[61]
HER2	12%-20%	+	68Ga-NOTA-MAL-MZHER2	2021	[63]
			^{89}Zr- Trastuzumab	2018	[62]
			89Zr-anti-CLDN18.2 VHH-ABD	2022	[71]

			89Zr-anti-CLDN18.2 VHH-Fc	2022	[71]
CLDN18.2	40%-50%	+	89Zr-anti-CLDN18.2 VHH-Fc	2022	[71]
			89Zr-DFO-TST001	2023	[73]
			^{124}I-18B10	2023	[74]
			177Lu-DOTA-TST001	2024	[77]
			^{68}Ga-NOTA-RTD98	2024	[82]
Trop2	56%	+	^{68}Ga-NOTA-RTD01	2024	[82]
			^{89}Zr-DFO-Trodelvy	20215	[83]
c-MET	5%-10%	+	89Zr-DFO-AMG102	2017	[88]
			89Zr-DFO-Onartuzumab	2020	[89]
SSR	65%	+	68Ga-DOTA-TATE	2022;2023	[91, 92]
PSMA	66%	-	^{64}Cu-DKFZ-PSMA-617	2017	[95]
MG7	94%	+	^{68}Ga-MG7 Antibody	2015	[96]
CDH17	50%-90%	+	^{64}Cu/^{177}Lu-Anti-CDH17 Nanobody	2020;2025	[10, 97]
CD47	50%	+	^{68}Ga-C2	2023	[98]
			LNC1013	2025	[99]
DR5	16%	-	^{89}Zr-CTB006	2021	[100]
TREM2	30%-60%	+*	^{124}I- Trastuzumab	2020	[101]

+ indicates prognostic relevance, - indicates no prognostic relevance.

*Specifically referring to macrophage expression.

Table 2: Comparison of Alpha Particle Therapy and Auger Electron (AE) Radioimmunotherapy (RIT).

Treatment Methods	Alpha Particle Therapy	Auger Electron Radioimmunotherapy
Fundamental Principles	Emitting alpha particles causes ionizing radiation	Emissions of Auger electrons trigger DNA damage
Particle Type	Helium nucleus (alpha particle)	Auger Electron
LET Value	High LET (~100 keV/μm)	Ultra-high LET (4–26 keV/μm, with locally higher energy deposition)
Range	Short range (50–100 μm, approximately 5–10 cell diameters)	Ultra-short range (<5 μm, single-cell level interaction)
Types of DNA Damage	Double-strand breaks predominate	Double-strand breaks + base damage composite damage
Penetration Depth	Unable to penetrate intact vascular/tissue barriers	Penetrates the blood-brain barrier (electronic cascade effect)
Therapeutic target	Cell membrane/cytoplasmic targeting (antibody-dependent localization)	Nuclear DNA targeting (requires NLS peptide for nuclear localization)
Applicable Lesion Size	Micrometastatic lesions (0.5–2 mm)	Residual cancer cells/submillimeter lesions
Treatment Cycle	Single-dose administration (due to high-energy rapid killing)	Multiple applications required (low penetration necessitates sustained action)
Clinical Advantages	Rapidly clear lesions and effectively target hypoxic cells	Precision targeting of single cells, capable of penetrating physiological barriers
Limitations	The production of radionuclides is challenging and not suitable for large-volume tumors	A verification system is required to prevent uneven dose distribution

.**Table 3**: Radioactive isotopes primarily used for gastric cancer treatment and their TRT

Radionuclide	Half-life	Energy (MeV)	Target	TRT	Development Stage	Publication Year	Publication
β-emitter							
^{64}Cu	12.7h	0.656	HER2	^{64}Cu-Trastuzumab	Preclinical studies	2019	[108]
			EGFR	^{64}Cu-Cetuximab	Preclinical studies	2022	[109]
^{67}Cu	61.9h	0.577	HER2	^{67}Cu-Trastuzumab	Preclinical studies	2025	[110]
^{131}I	8.1days	0.606	CLDN18.2	^{131}I-HLX58-Der	Preclinical studies	2025	[113]
				^{131}I-Zolbetuximab	Preclinical studies	2025	[114]
			E-cadherin	^{177}Lu -d9Mab	Preclinical studies	2011	[116]
			CLDN18.2	^{177}Lu-DOTA-TST001	Preclinical studies	2024	[77]
^{177}Lu	6.7days	0.479	ATPS	^{177}Lu-DOTA-ATPS mAb	Preclinical studies	2024	[8]
			CDH17	^{177}Lu-VHH-ABD	Preclinical studies	2025	[97]
			FAP	^{177}Lu-LNC1013	Phase II Clinical Trial	2025	[99]
α-emitter							
^{213}Bi	1h	2.6	E-cadherin	^{213}Bi-d9mAb	Preclinical studies	2005;2007	[120, 121]
^{212}Pb	10.6h	8.78	HER2	^{212}Pb-TCMC-Trastuzumab	Phase I Clinical Trial	2014	[122]
^{211}At	7.2h	7.45		^{211}At- Trastuzumab	Preclinical studies	2021	[124, 125]
Auger electrons							
^{125}I	59.6days	0.027	CLDN18.2	^{125}I-Zolbetuximab	Preclinical studies	2024	[136]
^{111}In	2.8days	0.24	HER2	^{111}In-Trastuzumab	Preclinical studies	2022	[137]

4. Targeted Radionuclide Therapy (TRT) of GC

With advances in radioimmunotherapy (RIT) technology, an increasing number of radionuclides have been discovered for cancer treatment. Therapeutic radionuclides can be categorized into three types: beta emitters, alpha emitters, and Auger electron emitters (Figure 1). Targeted radionuclide therapy (TRT) involves labeling radionuclides that emit alpha particles, beta particles, or Auger electrons onto carriers with specific binding capabilities, and attaching specific chelating agents. This approach enhances compound stability while enabling radionuclide bind to specific tumor targets [106]. The energy released by radionuclides can specifically irradiate tumor tissues and produce biological effects, leading to cellular senescence and death within the irradiation field, thereby achieving precise targeted therapy.

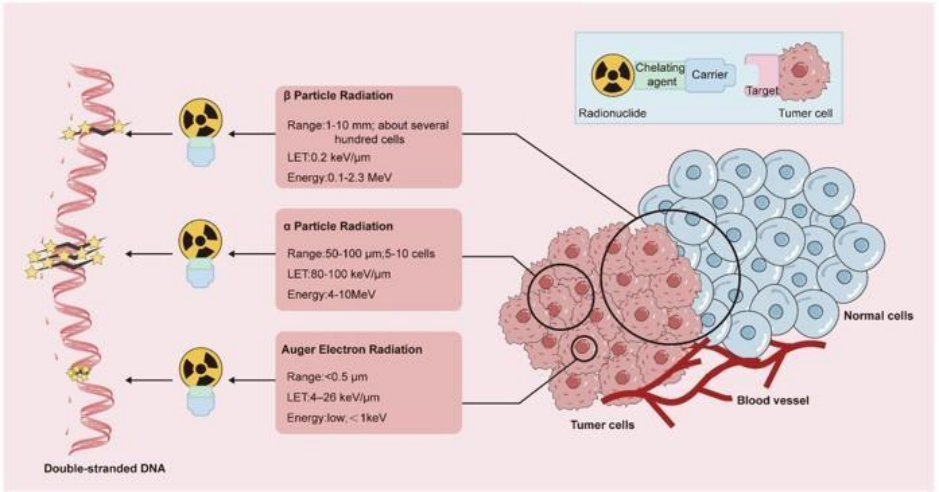

Figure 1: Schematic of targeted radionuclide therapy (TRT).

4.1. Beta-Emitting Radionuclide Therapy

Beta nuclides are one of the most commonly used types of radionuclides in TRT for clinical applications. Beta rays can directly act upon cells, inducing single-strand breaks in DNA. Simultaneously, due to the bystander effect and cross-beam effect associated with β rays, the therapeutic efficacy of β nuclide therapy is often quite significant.

Copper primarily functions as a diagnostic radionuclide. However, some studies indicate that copper may also play a role in the treatment of GC [107]. Zaheer et al. [108]. Conducted experiments using ^{64}Cu-labeled trastuzumab co-administered with paclitaxel in a GC nude mouse model [108]. Results indicated that while the presence or absence of ^{64}Cu did not affect the efficacy of TRZ, radionuclide facilitated deep penetration and uniform distribution of mAbs within the tumor microenvironment (TME). This approach reduced drug toxicity and enhanced protection of surrounding normal tissues [108]. Additionally, reports describe the use of ^{64}Cu-labeled cetuximab in combination with vorinostat (a radiosensitizer) for intraperitoneal radioimmunotherapy (ipRIT) in GC [109]. Results demonstrated that intraperitoneal injection of ^{64}Cu-cetuximab achieved higher and faster drug accumulation at peritoneal metastatic sites, significantly prolonging survival in mouse models. This indicates that ^{64}Cu-cetuximab may represent a potential therapeutic approach for treating peritoneal metastases in GC [109]. Pineau et al. conducted a study using 67Cu-labeled trastuzumab for HER2-positive GC treatment. Results demonstrated significant and dose-dependent inhibition of tumor growth without observed toxicity, indicating its potential as a promising therapeutic agent for GC [110].

Antibody-drug conjugates (ADCs) achieve targeted delivery by chemically linking chemotherapy drugs to specific tumor-associated proteins or antigens through binding to designated target molecules [111]. Due to their high specificity, strong selectivity, favorable clinical efficacy, and lower toxicity risk, ADCs have emerged as an innovative therapeutic approach for various cancers [112]. HLX58 （the CLDN18.2-specific antibody） labeled with 125I can be employed for PET imaging of CLDN18.2+ tumors [113]. Liu et al. combined 131I with the cytotoxic drug Deruxtecan (DXd) and targeted HLX58 to synthesize a radiolabeled antibody-drug conjugate (RADC), namely 131I-HLX58-Der [113]. The average tumor volume in the 131I-HLX58-Der treatment group decreased by 12.15-fold, while that in the HLX58-Der monotherapy group decreased by 4.80-fold. Experiments confirmed that the combination of 131I-induced precise internal radiation therapy and Der's cytotoxic effects delivers a dual-pronged attack against GC [113]. Similarly, Wang et al. evaluated the therapeutic response and toxicity of 131I-Zotuximab in CLDN18.2+ GC mice by preparing the radioligand. Results demonstrated that 131I-Zotuximab exhibited significant therapeutic efficacy and low toxicity [114]. Moreover, with increasing doses, CLDN18.2 expression in tumor tissues significantly decreased, indicating substantially enhanced therapeutic efficacy and survival rates. This further validates the therapeutic potential of 131I-Zotuximab [114].

177Lu is not only used for tumor imaging but also plays a crucial role in tumor therapy. The β particles emitted by 177Lu effectively target tumor tissue while sparing surrounding healthy tissue, making it one of the most promising therapeutic radionuclides. Currently, 177Lu-DOTA-TATE and 177Lu-PSMA-617 have been approved for the treatment of NETs and prostate cancer, respectively [115]. A study evaluated the therapeutic efficacy of 177Lu-labeled d9Mab (a monoclonal antibody targeting the transmembrane glycoprotein E-cadherin) in a GC nude mouse model [116]. Results demonstrated that 177Lu-d9Mab effectively prolonged survival and exhibited significant efficacy in treating GC via intraperitoneal radiolabeled immunotherapy (ipRIT)[116]. Zeng et al. validated the favorable efficacy and low toxicity of 177Lu-DOTA-TST001 in a CLDN18.2+ GC mouse model, suggesting the potential for personalized RNT based on molecular subtyping [77]. Mao et al. constructed 177Lu-VHH-ABD by labeling CDH17 with a nanobody using 177Lu [97]. In a mouse GC model, 177Lu-VHH-ABD demonstrated prolonged circulation times with increased and sustained tumor accumulation, significantly inhibited tumor growth, offering a promising therapeutic approach for CDH17-overexpressing GCs [97]. In addition, Wang et al. demonstrated for the first time the diagnostic and therapeutic efficacy of 68Ga/ 177Lu-LNC1013 (a novel FAPI dimer) in GC patients. Results showed that 68Ga-LNC1013 effectively accumulated in FAP+ tumors and demonstrates higher detection rates across multiple lesion types, including primary tumors, liver metastases, and peritoneal metastases. It also exhibits superior uptake and image contrast compared to ^{18}F-FDG in specific lesions [99]. Simultaneously, they compared the therapeutic efficacy of 177Lu-LNC1013 with that of 177Lu-FAPI-46 (a monomeric FAPI analogue), finding that both radiotracers significantly inhibited tumor growth [99]. However, 177Lu-LNC1013 exhibited longer tumor retention time and demonstrated a more pronounced inhibitory effect [99].

In summary, β-rays can directly induce single-strand breaks in cellular DNA due to their potent tissue penetration and radiation range. Furthermore, owing to the presence of cross-radiation and bystander effects, β-emitting radionuclide-targeted drugs can irradiate neighboring cells and enhance therapeutic efficacy. Most antibodies labeled with β-emitting radionuclides have demonstrated favorable antitumor efficacy and low toxicity, offering a highly promising approach for precision treatment and improved prognosis in gastric cancer.

4.2. Targeted Alpha Therapy (TAT)

Alpha particles are high-energy, highly charged particles with a relatively short range (50–100 μm), but they possess high linear energy transfer (LET) (80 keV/μm) [117]. Compared to βparticles (0.2 keV/μm, 0.05–12 mm), alpha particles release substantial energy over extremely short distances, causing intense, irreversible localized damage to tumor cell DNA [117].

The characteristics of α particles make them an effective radiation modality for eliminating circulating malignant cells (such as leukemia cells in blood or bone marrow) or small cell clusters (such as disseminated disease and micrometastatic lesions in solid tumors [118]. Targeted α therapy (TAT) leverages the unique properties of α particle to precisely locate and target cancer cells while minimizing cross-irradiation effects on healthy tissues [119].

Reports have indicated that localized low-dose radioimmunotherapy using 213Bi-radiolabeled antibodies targeting mutant E-cadherin significantly prolongs the median survival time of mice with advanced gastric cancer, reduces CEA levels, and effectively inhibits peritoneal metastasis of GC [120, 121]. It has also been reported that 212Pb can be used in the treatment of HER2+ tumors patients by radiolabeling trastuzumab [122]. 211At is a potential candidate nuclide for TAT due to its chemical properties being suitable for labeling targeting carriers, and its release of only one α particle per decay, which helps control off-target effects [123]. Kodaira et al. performed TAT on HER2+ GC by labeling trastuzumab with 211At [124]. Within the body, 211At-trastuzumab binds to cancer cells and emits α particles, which repeatedly strike the tumor cells along their trajectory. Through high linear energy transfer (LET) and short range, it efficiently kills tumor cells while minimizing collateral damage [124]. Furthermore, additional reports have further validated the antitumor effects of 211At-trastuzumab in HER2+ liver metastatic GC (LMGC), indicating that the TAT of 211At-trastuzumab holds significant potential in GC treatment [125].

In addition to 213Bi and 211At, numerous other radionuclides are being explored for targeted α particle therapy in GC. Currently, α particles commonly used in cancer treatment include 212Pb, 223Ra, and 225Ac. Although current research on the role of these α particles in GC remains insufficient, these radionuclides have been applied in the treatment of various neoplastic diseases, including prostate cancer [126], pancreatic cancer [127], ovarian cancer [128], breast cancer [129], multiple myeloma [130] and NETs [131]. In the future, TAT based on the aforementioned radionuclides will also continue to advance in the field of GC treatment.

4.3. Auger Electron Radioimmunotherapy (AE-RIT)

Auger electrons (AEs) are low-energy electrons emitted when radionuclides undergo internal conversion or electron capture decay. The LET value for Auger electron emission ranges from 4 to 26 keV/μm, exceeding that of beta particles. Furthermore, the range of Auger electrons is shorter than that of α particles (<0.5 μm) (Table 2). Therefore, Auger electrons can directly target the lesion site without damaging surrounding cells [132]. Compared to α particle therapy, which primarily targets small cell clusters, AE-RIT is more suitable for treating micrometastatic lesions and individual cells [133]. Most research on RNT utilizing Auger electrons has employed ^{111}In and ^{125}I. Since the lethal damage Auger electrons inflict on DNA depends on their proximity to nuclear DNA, nuclear localization sequences (NLS) are often required to facilitate the transport of substances-such as antibodies labeled with Auger electron-emitting radionuclides-to specific targets within the tumour cell nucleus [133, 134].

Yang et al. [135]. Investigated the effects of different doses of radioactive 125I on the growth of GC in mice. The results indicated that Auger electrons emitted by 125I significantly inhibited GC cell growth and effectively promoted the expression of pro-apoptotic factors such as Bax, caspase-3, and caspase-8 within tumour cells [135]. Wang et al. demonstrated the targeting efficacy and therapeutic effect of 125I-labeled Zolbetuximab against CLDN18.2-overexpressing GC [136]. Additionally, Li et al. [137]. Constructed two types of ^{111}In-trastuzumab-NLS for AE-RIT studies in a GC mouse model by radiolabeling trastuzumab with ^{111}In and modifying it with two NLS peptides of differing lengths [137]. Results indicated that both 111In-trastuzumab-NLS variants transported the radionuclide more efficiently into the cell nucleus and demonstrated superior nuclear uptake and intracellular transport in tumor cells compared to 111In-trastuzumab alone [137].

Auger electron radiotherapy holds promise as a potential precision medicine approach due to its narrow energy deposition range and high linear energy transfer (LET) value. This energy deposition minimizes cytotoxicity to healthy cells [138]. By using NLS to co-localize targeting molecules with cell nuclei, energy deposition can be concentrated near DNA, thereby enhancing the efficacy of AE-RIT [139]. Consequently, AE-RIT proves more effective in treating postoperative residual tumours, circulating tumour cells, or micro metastatic lesions in disseminated cancers (Table 3).

4.4. Combination Therapy Strategy

Targeted radionuclide therapy has demonstrated unique potential in the treatment of GC. Most current research focuses on the combination of radionuclides with monoclonal antibodies (mAbs), aiming to hinder tumor progression through the dual effects of RNT and targeted therapy. In addition, nuclide therapy can be combined with radiation therapy, immunotherapy, and other treatment measures to achieve synergistic effects through dual mechanisms, thereby doubling the therapeutic outcomes.

As previously mentioned, the combination therapy of ^{64}Cu-cetuximab and radiotherapy effectively prolonged the survival in GC mouse models compared to monotherapy with ^{64}Cu-cetuximab [109]. Rao et al. discovered that combining 177Lu-trastuzumab with statins enhances HER2 expression on cell surfaces and increases tumour uptake of radiation from 177Lu-trastuzumab. This significantly improves the therapeutic efficacy of 177Lu-trastuzumab in gastric cancer, thereby achieving the objectives of inhibiting tumor growth and prolonging survival [140]. Furthermore, statins exhibit radioprotective effects, reducing radiation toxicity in GC mice receiving combined statin and RNT, demonstrating considerable clinical potential [140]. Park et al. combined the 177Lu-radiolabeled anti-ATP synthase mAb (177Lu-DOTA-ATPS mAb) with the anti-angiogenic drug sunitinib, synergistically enhancing suni-

tinib's therapeutic efficacy. Experiments demonstrated that the combination of 177Lu-DOTA-ATPS mAb with sunitinib resulted in more pronounced tumour volume regression compared to monotherapy, effectively inhibiting tumour progression [8]. Additionally, reports indicate that the combination therapy strategy of 177Lu-labeled LNC1004 (a radiopharmaceutical targeting FAP) with anti-PD-L1 immunotherapy demonstrates promising efficacy for patients with FAP+ tumours [141]. Meanwhile, Simon et al. demonstrated the feasibility of combining 177Lu-DOTA-TATE with photothermal therapy for treating somatostatin receptor (SSR)-positive tumours [142]. Additionally, reports have explored the potential for combination therapies involving TAT alongside external beam radiation therapy (EBRT), immunotherapy, cytotoxic chemotherapy (CCT), and brachytherapy (BT) [143].

Compared to the systemic toxicity associated with drug therapy, TRT significantly reduces the burden on the patient's body. Combining radiotherapy, immunotherapy, and other treatments with targeted radionuclide therapy enables precise delivery of radionuclide-carrier complexes to target sites via delivery systems. This approach achieves dual benefits: delivering targeted treatment while synergistically enhancing therapeutic efficacy, thereby maximizing results with minimal effort.

5. The Integration of Radionuclides in GC Diagnosis and Treatment

Over the past few decades, radionuclides have made remarkable strides, introducing novel concepts for cancer diagnosis and treatment. And the concept of integrating diagnostic imaging with therapeutic intervention is gaining increasing recognition. Using chelating agents to simultaneously deliver diagnostic and therapeutic radionuclides, PET imaging is combined with RIT. This approach enables tumour treatment while allowing real-time monitoring of treatment response, facilitating timely adjustments to the therapeutic regimen.

Wen et al. evaluated the imaging efficacy and therapeutic effects of Her-PEG-dMNPs-nanoprobes loaded with trastuzumab and labeled with ^{64}Cu and ^{124}I [64]. Zhang et al. developed ^{68}Ga-NOTA-C2 by using a ^{68}Ga-radiolabeled nanobody C2 targeting CD47 to explore its diagnostic value [98]. Simultaneously, they fused C2 with the albumin-binding domain (ABD) to synthesize ABDC2. ABDC2 was labeled with ^{68}Ga, ^{89}Zr, and ^{177}Lu, respectively, to evaluate the diagnostic and therapeutic value of these radionuclides [98]. Through experiments, they validated the real-time monitoring capability of ^{68}Ga/^{89}Zr and the antitumor efficacy of ^{177}Lu [98]. Additionally, reports have evaluated the diagnostic and therapeutic capabilities of radionuclides by simultaneously administering LNC1013 with ^{68}Ga and ^{177}Lu [99]. Specifically, ^{68}Ga-LNC1013 demonstrated excellent performance in achieving real-time FAP imaging, while ^{177}Lu exhibited stable and sustained antitumor efficacy in the FAP + GC mouse model [99]. This makes ^{68}Ga/^{177}Lu-LNC1013 a highly promising diagnostic and therapeutic solution for FAP-targeted imaging and simultaneous treatment [99].

Furthermore, the same radionuclide offers inherent advantages in pharmacokinetics and biosafety. The use of a single radionuclide for both imaging and treatment of GC represents a significant advancement in radionuclide technology. For example, there are reports on the use of ^{64}Cu and ^{67}Cu for research into the diagnosis and treatment of GC [110]. Based on the diagnostic capabilities of ^{64}Cu-trastuzumab PET imaging and the therapeutic effects of ^{67}Cu-trastuzumab, a novel diagnostic-therapeutic dual-purpose radiopharmaceutical has been developed. It has demonstrated promising efficacy in both the diagnosis and treatment of HER2+ GC [110].

In summary, by utilizing radiopharmaceuticals or mAb-conjugated nanoparticle carriers to simultaneously deliver diagnostic and therapeutic radionuclides, it is possible to achieve tumour treatment while performing targeted molecular imaging. Moreover, the real-time imaging capability of diagnostic radionuclides enables dynamic monitoring of treatment efficacy, facilitating timely adjustments to therapeutic regimens and achieving seamless integration of diagnosis and treatment. Simultaneously, targeted PET imaging can guide the delineation of radiotherapy target areas, further clarify irradiation boundaries, and reduce irradiation errors. This approach helps minimize bodily damage and enhances treatment precision.

6. Controversies and Future Horizons

The convergence of nuclear medicine, molecular theory, and related multidisciplinary fields has significantly expanded the strategic boundaries of radionuclide therapy, providing powerful tools for precise early warning and treatment of gastric cancer. With its exceptional biological targeting capability and low toxicity to normal tissues, TRT demonstrates tremendous clinical potential as a systemic therapeutic strategy [144]. However, despite significant progress in relevant basic research, radionuclide diagnostics and therapeutics still face unprecedented challenges on the path to clinical translation. A gap remains between scientific achievements and clinical application that urgently requires bridging.

Firstly, enhancing targeted uptake and reducing therapeutic toxicity are core challenges in clinical translation. In terms of diagnosis, the primary challenge facing radionuclide-labeled imaging agents lies in the nonspecific uptake by non-tumorous lesions. For example, radionuclide-labeled FAPI imaging agents may yield false positives due to uptake in inflammatory conditions such as gastritis, thereby compromising the imaging detection of GC lesions [28, 145]. Therefore, it is necessary to further enhance the affinity between the radionuclide and the targeting ligand to improve lesion uptake. Based on differing levels of radionuclide expression, precise localization of tumour lesions and inflammatory lesions can be achieved. In therapeutic applications, to achieve precise delivery of radionuclides to target sites and minimize biological toxicity, a series of strategies have been implemented, including the development of antibody fragments, recombinant proteins, and pre-targeting approaches. Notably, pre-targeting approaches achieve precise and efficient

targeted delivery by first using unlabeled antibodies to target tumour cells, followed by administering the radionuclide-labeled antibody conjugate to the body [146, 147]. This strategy has been validated in tumour models such as colorectal cancer, breast cancer, and neuroblastoma. Additionally, the "mask-release" technology, which masks the binding sites of targeted antibodies using peptide molecules and relies on protease activation within the tumour microenvironment, has also demonstrated potential for reducing off-target tissue toxicity. Its application in the pharmaceutical field remains in the exploratory stage [148].

Secondly, technological innovation and platform optimization will further drive the advancement of precision diagnostics. With progress in multi-omics, artificial intelligence, and surface analysis technologies (for antibodies and other targeted therapies), the ability to identify biomolecules and signaling pathways associated with GC will undergo a qualitative leap. Therefore, the discovery of novel targets is imminent. Meanwhile, high-affinity carriers play a crucial role in TRT. By leveraging the potent inhibitory properties of mAbs and integrating them with novel carriers such as nanoparticles, we can not only further enhance radionuclide enrichment efficiency but also prolong the in vivo half-life of radionuclides and improve penetration. This approach ultimately increases tumor uptake and retention time [149]. As the primary demand for radionuclides has gradually shifted from diagnostic imaging to targeted therapy, α emitters with short range and higher energy deposition are gaining significant attention as highly promising therapeutic radionuclides. Alpha particles such as 211At, 212Pb, and 225Ac have been evaluated in patients with various cancers and have demonstrated potent anticancer effects in clinical trials [150, 151]. Currently, most alpha-emitting radionuclides used for therapeutic purposes remain in the preclinical stage. 233Ra-Cl_2 is the only alpha-emitting radiopharmaceutical currently approved [152]. For α particles, high production costs and low output remain insurmountable challenges. Currently, high-energy proton irradiation of 223Th can be used to produce large quantities of 225Ac, but the 225Ac extracted through this method remains suboptimal and insufficient to meet widespread therapeutic demands [153]. Recent reports explore the potential for mass-producing α particles using proton accelerators or photoneutron reactions, aiming to reduce production costs while increasing yield [154].

Thirdly, combining TRT with immunotherapy and other approaches to enhance efficacy through sound mechanisms will also be a key area of future research. Numerous reports have demonstrated the use of diagnostic radionuclides such as ^{64}Cu and ^{68}Ga alongside therapeutic radionuclides like ^{131}I and ^{177}Lu to achieve simultaneous diagnosis and treatment of GC [99]. Meanwhile, there are also reports exploring the possibility of using different isotopes of the same element for diagnostic and therapeutic purposes [110]. In the future, the integration of diagnostic and therapeutic applications of radionuclides will be further advanced [155, 156].

Finally, drug safety, dosimetry, and supply chain management form the foundation for ensuring clinical application. Quality control and safety are paramount, particularly when selecting metal chelators (such as DOTA chelators), where a balance must be struck between labeling efficiency and the drug's lipophilicity and charge characteristics [157]. To address carrier stability damage caused by recoil effects from α-nucleus decay [126, 158], employing carrier molecules with higher affinity and faster internalization rates [159], or encapsulating nuclides within nanoparticles and liposomes, can mitigate damage to healthy organs from free nuclides[160]. At the same time, individualized dosing (dose titration) should not be overlooked [161]. Treatment plans should be tailored to each patient based on the distribution and structure of metastatic lesions. Compared to single-dose administration, fractionated dosing allows for an increased total dose while providing recovery time between doses, thereby helping to reduce systemic toxicity and improve clinical efficacy [147]. Furthermore, given the rapid decay and stringent regulatory requirements of therapeutic radionuclides, establishing globally coordinated regulatory standards, refining the entire supply chain encompassing production, containment, sealed assembly, transportation, and clinical delivery, and developing GMP-compliant large-scale production strategies are essential steps for achieving the key clinical translation of radionuclides [162, 163].

In summary, the integration of radionuclide diagnosis and therapy offers a novel perspective and approach for the early diagnosis of gastric cancer, the removal of micrometastases, and precision treatment. TRT achieves precise targeting by combining radionuclides with carrier molecules, effectively destroying tumours while protecting surrounding healthy tissues. Despite the challenges that persist, ongoing technological advancements and in-depth research will drive further breakthroughs in radionuclide diagnosis and therapy, accelerating its clinical translation. Future progress in radionuclide diagnosis and therapy for gastric cancer requires sustained efforts and research to expedite its clinical application.

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