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Review Article

RECENT DEVELOPMENT OF RADIONUCLIDE-BASED IMAGING IN DIAGNOSIS AND THERAPY OF LUNG CANCER: A REVIEW

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ABSTRACT

This review was conducted to review the recent development of radionuclides that potentially used in diagnosis and therapy of lung cancer. A comprehensive article search used a systematic review method based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The article search was conducted using online databases, such as PubMed, ScienceDirect, and Google scholar with inclusion criteria: studies are related to lung cancer and radiopharmaceuticals, contained clinical research results, and were published in the last five years. Five articles were selected and they were analyzed and summarized. Three studies have reported the preclinic data and two studies have reported the clinical data of a phase I study. Two of five studies showed the nuclides were potentially used for NSCLC, one of five studies showed the nuclide was potentially used for SCLC, and the other two studies showed their nuclides were potentially used for both NSCLC and SCLC. ^{131}I-Bevacizumab and ^{177}Lu-Satoreotide Tetraxetan are potential for therapy lung cancer which showed the reduction of tumor uptake, while ^{89}Zr-DFO-nimotuzumab, ^{68}Ga-3PTATE-RGD, and ^{89}Zr-DFO$_{PODS}$-^{DAR2}SC16-MB1 are potential for diagnosis because it showed high radioactivity concentrations in tumor-bearing mice. Based on five articles, the radionuclides in included articles have shown good results that indicate they are potential. However, some radionuclides still require further complement assessment research to improve their shortcomings.

Keywords: Lung cancer, Radiopharmaceutical, Radionuclide, Systematic review

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INTRODUCTION

Cancer is a disease that can be initiated in any organ or tissue of the body. When abnormal cells grow uncontrollably, cancer can invade contiguous parts of the organ. Metastasizing is the final process of cancer. This process becomes the major cause of death from cancer [1]. According to an estimate from The International Agency for Research on Cancer, Lung cancer has become the most cancer cause of death globally in 2020. It also became the second most commonly diagnosed cancer after breast cancer [2].

Lung cancer starts in the lungs. The lung is an organ located in right and left chest. The left lung has 2 lobes and the other side has 3 lobes. When we breathe, the air will enter our lungs through the trachea. The trachea typically divides into tubes called bronchi. Then, the bronchi divide into smaller bronchi. It also forms smaller branches called bronchioles. At the end of the bronchioles, there are tiny air sacs. It is called alveoli. Lung cancer particularly starts in the cells that lay the bronchi, bronchioles, and alveoli [3].

Lung cancer has divided into two main types: Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). Most lung cancers are NSCLC. There are some subtypes of NSCLC, such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. These subtypes have been grouped as NSLC because they usually have similarities in treatment and prognoses (outlook) even though they start from different types of lung cells [3]. SCLC is also known as oat cell cancer. This type of lung cancer tends to grow and spread faster than NSCLC. Only about 10% to 15% of all lung cancers are SCLC. About 70% of them are diagnosed when cancer has already spread. This cancer tends to respond well to chemotherapy and radiation therapy. However, cancer will return at some point for some people [3]. Therefore, it is important to well-timed diagnosis, has right treatment, and proper follow-up.

Recently, radiopharmaceuticals have attracted attention for cancer diagnosis and treatment. Radiopharmaceuticals are radionuclides bound to biological molecules that can target specific organs, tissues, or cells within the human body [4]. In this context, radionuclides are sent to tumor-targeted pharmaceuticals or bioactive molecules that predominantly accumulate in neoplastic cells within tumors into the tumor tissue [5]. Radionuclides involve radioactive elements with different emission properties.

Radiopharmaceutical Therapy (RPT) has become an effective and safe method for cancer treatment. RPT has also become the most preferred cancer treatment because of minimal invasive practices and the short duration of treatment. It also delivers a highly concentrated dose to the targeted tumor tissue and protects the normal tissue surrounding the tumor at the same time [6]. These advantages of RPT make it draw attention, including in the field of research in lung cancer.

Many researchers are interested to find a precision tool for diagnosing and treating lung cancer patients. It is proved by several studies of recent developments of new radionuclide for lung cancer that have been published. Therefore, the objective of this article is to review the recent development of radionuclides that are potentially used in the diagnosis and therapy of lung cancer.

METHODS

Design

The process of searching and selecting the articles for this review was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines of 2020. The PRISMA 2020 was an updated PRISMA to reflect recent advances in systematic review methodology and terminology. The PRISMA Guideline consists of an explanation step by step to do a systematic review, starting from searching for article data, screening articles, selecting article eligibility, and determining the selected articles. The PRISMA was designed to facilitate transparency and report sufficient detail of the methods and results of the systematic review so that users allow assess the trustworthiness and applicability of the review findings [7].

Type of research

A systematic literature review was the type of research that was carried out in this study, which was conducted by identifying and interpreting all relevant results with a particular topic. A systematic review (SR) is a method to answer a particular research question by

synthesizing scientific evidence transparently while appraising the quality of the evidence. SR approach was done to summarize them objectively, appraise the quality of the included studies, reduce the risk of bias, and increase transparency at every stage of the review process [8].

Search strategy

The data was taken from several online databases, such as PubMed, ScienceDirect, and Google Scholar. Data was collected in Mei–July 2022. The study year range was 2017 to 2021. The keywords that were used to search the data were "Radiopharmaceutical", "Radionuclide", "Molecular Imaging", and "Lung Cancer". The conjunction used for these keywords was AND. After obtaining the appropriate keywords, it can be carried out on the database through the official website of each database. We used an automatic filter on each database and set them to include five years' latest articles and research article type.

Study selection

After the search was done, screening was carried out on each article obtained. The screening was done through the *Rayyan. ai* website. The first stage of screening was done by checking for duplication of search results. After separating the duplicate articles, proceed with sorting. Sorting includes the suitability of titles and abstracts with the topic of this research, namely the recent development of radionuclide in the diagnosis and therapy of lung cancer. Furthermore, the eligibility test was carried out. In the eligibility test, each article that has been screened from the title and abstract selection will be read in its entirety to see whether it is following the inclusion criteria that have been previously set.

Article's criteria

Inclusion criteria for this study are related to radiopharmaceuticals with the research subject (lung cancer). The article also contains radionuclide molecular imaging which is in clinical trials. Then, exclusion criteria are an article in another language except in English, study design, and publication type, such as systematic review, review papers/articles, conference abstract, case reports, editorials, and books.

Data extraction and summarized

The data were extracted and summarized independently in a table. The table contains the name(s) of the author(s), year of publication, the radionuclide that was developed, type of lung cancer target, type of decay, the clinical phase that the radionuclide was evaluated, and type of imaging modality.

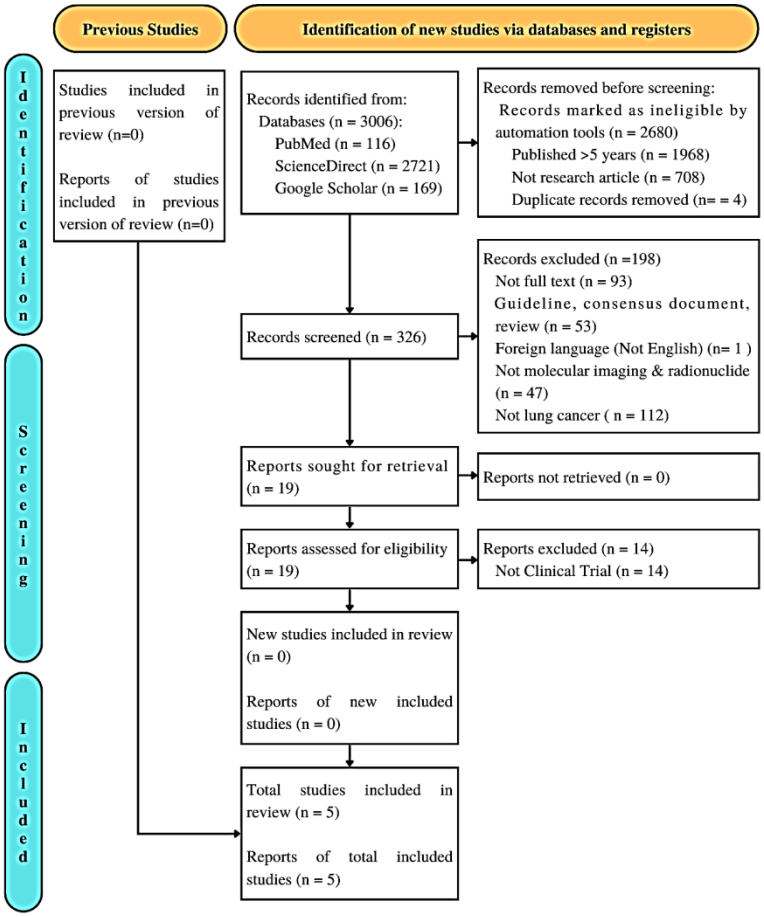

Fig. 1: Flow diagram of the study selection process following the preferred reporting for systematic reviews (PRISMA) guideline

RESULTS

The search of website databases yielded 3006 articles. After removing ineligible by using automation tools and duplicate articles, it remained 326 articles. After checking available full-text articles and screening the titles and abstracts, we found that 19 Articles were not available in full text, 53 articles were the wrong study design and publication type, one article was not available in English, 42 articles were not about molecular imaging or nuclide, and 112 articles were not related to lung cancer. Therefore, 19 articles remained. Then finally, 14 studies were excluded because they did not do clinical trial studies. In total, we have five articles assessed in this review. The process of selecting the article has been represented (fig. 1).

A detailed summary of the article included in this review has been provided (table 1). All studies have designed the radiolabel and

evaluated them in preclinical and clinic models for diagnostic and therapeutic applications. Three studies have reported the preclinic data [9, 11, 13]. The other two studies have reported the clinical data of a phase I study [10, 12]. Two of five studies showed their nuclides were potentially used for NSCLC [9, 10]. One of five studies showed its nuclide was potentially used for SCLC [13]. Two of five studies showed their nuclides were potentially used for both NSCLC and SCLC [11, 12].

Table 1: Radiopharmaceuticals potential for diagnosis and therapy of lung cancer

Author/year	Radionuclide	Type of lung cancer	Decay	Phase clinical trial	Purpose	Modality	Ref
Kameswaran *et al.*, 2017	^{131}I-Bevacizumab	NSCLC	β	Pre clinic	Therapy	-	[9]
Chekol *et al.*, 2018	^{89}Zr-DFO-nimotuzumab	NSCLC	γ	Phase I	Diagnosis	PET	[10]
Liu *et al.*, 2019	^{68}Ga-3PTATE-RGD	NSCLC and SCLC	γ	Pre clinic	Diagnosis	PET	[11]
Reidy-Lagunes *et al.*, 2019	^{177}Lu-Satoreotide Tetraxetan	NSCLC and SCLC	β	Phase I	Therapy	-	[12]
Sharma *et al.*, 2021	^{89}Zr-DFO$_{PODS}$-^{DAR2}SC16-MB1	SCLC	γ	Pre clinic	Diagnosis	PET	[13]

NSCLC: Non-Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; PET: Positron Emission Tomography.

The radiolabeled included in the study, such as ^{131}I-Bevacizumab, ^{89}Zr-DFO-nimotuzumab, ^{68}Ga-3PTATE-RGD, ^{177}Lu-Satoreotide Tetraxetan, and ^{89}Zr-DFO$_{PODS}$-^{DAR2}SC16-MB1. ^{131}I Bevacizumab and ^{177}Lu-Satoreotide Tetraxetan showed potential effects for the therapy of lung cancer that decay by beta emission (β). Whereas ^{89}Zr-DFO-nimotuzumab, ^{68}Ga-3PTATE-RGD, and ^{89}Zr-DFO$_{PODS}$-^{DAR2}SC16-MB1 are potentially used for diagnosing lung cancer that decay by gamma emission (γ). Positron Emission Tomography (PET) was used to develop a clinical grade of those radionuclides for imaging target expression.

DISCUSSION

This review displayed the current evaluation of potential radionuclides for diagnosis and therapy of lung cancer in preclinical and early-phase clinical trials. All of the studies had reported their radionuclide development. Kameswaran *et al.* (2017) develop radiolabeled Bevacizumab with I-131 to help therapy and provide antibodies in killing the tumor cells by utilizing the β-emitting radionuclide [9]. Bevacizumab is a humanized monoclonal antibody and the first angiogenesis inhibitor approved by the FDA [14]. It has been proven to be effective and safe in the treatment of many cancers, including NSCLC [15]. Radioactive ^{131}I was chosen to be labeled with Bevacizumab because it has many advantages, such as being more practical, easy to be labeled, plausible half-life, capable in imaging, and cost-effective. The half-life of ^{131}I is 8 d. It is suitable for the preparation of antibodies' localization properties and their transport [9].

In addition, ^{131}I-bevacizumab has been evaluated *in vitro* and *in vivo* in Kameswaran *et al.* study. ^{131}I-bevacizumab has demonstrated its specificity to Vascular endothelial growth factor (VEGF) expressing cells by binding and inhibiting its binding to the cell surface receptors significantly thereby preventing neovascularization and normalization of immature and abnormal blood vessels. Hence, It helps overcome hypoxia in the cancer cells and the chemotherapeutic drugs to reach their specific sites [16].

^{131}I-bevacizumab also has been confirmed significantly reduce the tumor cell uptake in animals co-injected with cold Bevacizumab. This was evidenced by the reduction of tumor uptake up to ~81% from 11.2±1.0%ID/g in mice injected to 2.1±0.4 %ID/g in the animals co-injected with ^{131}I-bevacizumab and unlabeled Bevacizumab at 24 h p. i. This result indicates that ^{131}I-bevacizumab is the potential to be a tumor-targeting agent. Moreover, ^{131}I-bevacizumab retained at>85% in both saline and serum at 37 °C for 5 d post iodination *in vitro* stability indicates it is potential for therapy. Accordingly, the positive laboratory results of ^{131}I-bevacizumab exhibited fulfill the radiopharmaceutical quality requirements. However, It still necessitates further studies for translation of ^{131}I-bevacizumab for therapy in the clinical setting [9].

Chekol *et al.*, (2018) showed the development of radiolabeled ^{89}Zr-DFO-nimotuzumab [10]. Nimotuzumab is one of the Epidermal Growth Factor Receptor I (EGFR) antibodies for treating different EGFR-positive cancers [17]. Non-Small Lung Cell (NSLC) is one of implicated overexpression of EGFR [10]. Nimotuzumab has affinity-optimized binding characteristics, thereby low binding to healthy tissues that express low EGFR [17]. Nimotuzumab was paired with radionuclide ^{89}Zr because it can ideally be paired with antibody vectors, as it has a long half-life (78.5 h) and the biological half-life of an antibody is on the order of 2–3 w. The only competent ^{89}Zr chelator available for radiolabeling and *in vivo* applications is desferrioxamine (DFO). It become the current "gold standard" chelator for zirconium-89 [18].

According to Chekol *et al.*, (2018) study, ^{89}Zr-DFO-nimotuzumab is known to have a fast distribution is 1.3 h and a slow clearance is 127.1 h. ^{89}Zr-DFO-nimotuzumab were injected 10-12 MBq 10–12 μg to tumor-bearing mice. It showed early high tumor uptake up to 6.2%IA/cc at 4 hp. i and persistently high at 168 hp. i where the highest uptake (18.3 %IA/cc) was performed in mice bearing EGFR-positive DLD01 xenograft [10].

The use of ^{89}Zr-DFO-nimotuzumab has been proven not to cause damage to the organ on histopathological examination of necropsy stained slices, even following 168-fold radioactivity injection and 25-mass dose excess of the projected human dose of the tracer–74 MBq 10 mg, meanwhile the effective dose was 37 MBq (10 mg). It indicates that ^{89}Zr-DFO-nimotuzumab is safe and secure, even though the effective dose of ^{89}Zr-DFO-nimotuzumab is more than three-fold lower than for similar immunePET imaging agents in clinical trials. Nonetheless, 89Zr-DFO-nimotuzumab has met the USP and Health Canada QC investigation agent requirements [10].

Liu *et al.* (2019) developed a ^{68}Ga-labeled PET tracer for dual-targeting capacity integrin receptor αvβ3 and somatostatin receptors 2 (SSTR2) [11]. High integrin αvβ3 and SSTR2 are expressed by neuroendocrine tumors (NET). Most lung cancer appertains to neuroendocrine tumors (NET) so that it is in line with most lung cancer cells, NSCLC and SLCL, which express integrin αvβ3 and SSTR2 [11]. According to theory, ^{68}Gallium (^{68}Ga) labeled Octreotate (TATE) or arginine-glycine-aspartic acid (RGD) showed good results and precision in the diagnosis of SLCL or NSCLC [19].

TATE is a somatostatin analog that can interact with SSTR2, while RGD is a tripeptide sequence that can interact with integrin αvβ3. ^{68}Ga-labeled RGD peptides and ^{68}Ga-labeled TATE peptides have been reported to be successful for imaging integrin αvβ3-expressing tumors and SSTR2-positive imaging. However, the tumor uptake of these tracers has been known suboptimal due to the single and relatively low binding affinity of this monomeric peptide and the imperfect pharmacokinetics [20, 21]. Therefore, the product that was developed by Liu *et al.* is ^{68}Ga-labeled Octreotate (TATE) and arginine-glycine-aspartic acid (RGD) (^{68}Ga-3PTATE-RGD) [11].

^{68}Ga-3PTATE-RGD was made by synthesizing a dual-target heterodimer NOTA-3PEG$_4$-TATE-RGD (3PTATE-RGD), including conjugating cyclic RGD, TATE peptides, and NOTA together with PEG$_4$ chains and glutamate linker [11]. NOTA was chosen as the chelating group because it is more suitable for complex formation with Ga^{3+} [22]. Based on the Liu *et al.* study, ^{68}Ga-3PTATE-RGD has also been evaluated *in vitro* and *in vivo*. It showed good pharmacokinetics. The half-life of ^{68}Ga is 68 min so that it is suitable

for the pharmacokinetics of peptidic radiopharmaceuticals. ^{68}Ga-labeled TATE peptide has demonstrated dual-targeting ability which its binding ability conformable to TATE for sstr2 binding and RGD for integrin $\alpha_v\beta_3$.

Another advantage of 3PTATE-RGD is the number of receptors can be increased for signal amplification. ^{68}Ga-3PTATE-RGD also showed good stability *in vitro* and *in vivo* against proteinases and metabolic enzymes. It also showed a high target (tumor) to non-target (T/NT) ratio and good images in two representative lung cell lines A549 (integrin $\alpha_v\beta_3$ positive) and H69 (sstr2 positive) tumor-bearing models. The xenografted tumor was delineated within 30 min after injection of ^{68}Ga-3PTATE-RGD with tumor uptake of 9.78±2.77 %ID/g and 6.46±0.59 %ID/g in H69 and A549 tumor-bearing mice. However, additional experiments are needed to confirm the ^{68}Ga-3PTATE-RGD dual-targeting ability in the detection both of sstr2 and integrin αvβ3-related carcinomas [11].

Reidy-Lagunes *et al.* (2019) study reported ^{177}Lu-satoreotide tetraxetan phase I clinical results. ^{177}Lu-satoreotide tetraxetan is a radioconjugate consisting of the somatostatin antagonistic peptide satoreotide tetraxetan (JR11). It is linked to the beta-emitting radioisotope lutetium (Lu) 177 via the chelating agent dodecanetetraacetic acid (DOTA) [23]. The somatostatin receptor (SSTR) affinity profile of ^{177}Lu-satoreotide tetraxetan is known similar to ^{177}Lu-DOTATATE, one of the SSTR agonists that bind the receptor as the natural ligand somatostatin. It binds to SSTR with a high affinity for SSTR2 that is present on the cell membranes of NET cells [24].

In Reidy-Lagunes *et al.* (2019) study, ^{177}Lu-satoreotide tetraxetan exhibited its capability in delivering a cytotoxic dose of beta radiation to SSTR-positive cells that present in large numbers on NETs with propitious tumor-to-normal organ dose ratios. ^{177}Lu-satoreotide tetraxetan has an effective terminal half-life ranging from 66 to 117 h with a median of 87 h. It is corresponding to its biological half-times ranging from 111 to 430 h with a median of 188 h [12].

Preliminary data indicated that one to two treatment cycles of ^{177}Lu-satoreotide tetraxetan gave a promising clinical response rate of 45% with a Progression-free survival (PFS) median was 21.0 mo, and 2 y PFS was 38% (20–73 mo). The high response rate is a result of high tumor radiation dose, which is caused by high tumor uptake and slow washout. These data support ^{177}Lu-satoreotide as a potential therapeutic in the treatment of NETs. However, radionuclide therapy with ^{177}Lu-labeled somatostatin ligands has reported some adverse effects, including nausea, vomiting, hair loss, asthenia, tremor, diarrhea, facial edema, lower extremity edema, and mucositis. It also reported unexpected severe hematologic toxicity, such as leukopenia, thrombocytopenia, anemia, or neutropenia. Nevertheless, hematologic toxicity can be reduced if the activity of treatment is reduced and intervals of treatment become longer while still preserving activity. Therefore, this study needs additional studies to determine the optimal therapeutic dose [12].

Sharma *et al.* (2021) study reported ^{89}Zr-radioimmunoconjugates as a potential radionuclide for aiding in disease burden assessment and facilitating suitable therapy selection for patients. In this study, they developed site-specifically labeled radioimmunoconjugates for Delta-like ligand 3 (DLL3)-targeted immunoPET. DLL3 is a tumor antigen expressed in SCLC. They synthesized ^{89}Zr-labeled radioimmunoconjugates by conjugating DFO to lysine residues within the immunoglobulin [13].

They modified two thiol-reactive variants of DFO with a DLL3-targeting antibody SC16-MB1 cysteine-engineered variant using maleimide moiety (Mal-DFO) and phenyloxadiazolyl methyl sulfone group (PODS-DFO). Therefore, it resulted in six kinds of immunoconjugates, such as DFO_{Mal}-^{TCEPhigh}SC16-MB1, DFO_{Mal}-$^{TCEPl\ ow}$SC16-MB1, DFO_{Mal}-^{DAR2}SC16-MB1, DFO_{PODS}-^{DAR2}SC16-MB1, DFO_{Mal}-^{DAR2}hIgG1-MB1, and DFO_{PODS}-^{DAR2}hIgG1-MB1 that were radiolabeled with ^{89}Zr [13].

Based on the study, the quartet of ^{89}Zr-labeled SC16-MB1 radioimmunoconjugates showed comparable and high radioactivity concentrations in the DLL3-positive H82 tumors with range uptake values from 19.2±3.5 to 23.3±4.8 %ID/g at 120 h p. i. Injection of PODS ^{89}Zr-labeled-control radioimmunoconjugate to H82-bearing mice exhibited ~40% lower radioactivity in the kidneys than maleimide-based administered. ^{89}Zr-DFO_{PODS}-^{DAR2}SC16-MB1 produced a 30% lower kidney uptake compared to ^{89}Zr-DFO_{Mal}-^{DAR2}SC16-MB1 [13].

In the end, the result of the study demonstrated that radioimmunoconjugates synthesized using PODS offer quicker reaction, cleaner, irreversibly with thiol, high stability, and better *in vivo* performance, and also ^{89}Zr-DFO_{PODS}-^{DAR2}SC16-MB1 is a stronger candidate for clinical translation than other radioimmunoconjugates. In addition, the study suggests that DAR2 radiopharmaceutical may be suitable for the clinical immunoPET of DLL3-expressing cancers because it is stable and well-defined [13].

We found similar studies to this current review. Telo *et al.* (2020) and Theodoropoulos *et al.* (2020) studies also discussed radiopharmaceuticals for lung cancer [25, 26]. Telo *et al.* (2020) study included articles that were published up through 2018 and Theodoropoulos *et al.* (2020) study included articles that were published from 2015 to 2020, while this current review included articles that were published from 2017 to 2021 [25, 26]. Nevertheless, the radionuclides that were mentioned in this current review have not been mentioned in previous review studies, with the result that this is a strength of this review that could be a complement and update review.

In addition, those previous review studies were focused on PET/CT imaging. They used the "positron emission tomography" keyword in the process of searching and selecting articles. This current review did not limit the modality imaging, even though all the included articles used PET in their development process.

LIMITATION

There are several limitations of this review. First, the process of searching for studies may not have been sufficiently comprehensive due to time limitations. We conduct a review because we wrote this paper in order to join the 2nd Bandung International Teleconference on Pharmacy event, which was restricted by time constraints. Second, we used only three databases as our sources. As a consequence, some articles might be missed. Third, some articles might be missed because we used Medical Subject Headings (MeSH) terms or keywords and limited our search by including only studies conducted in English. Therefore, this might have led to missing relevant studies in other languages.

CONCLUSION

Recent studies have evaluated radionuclides and radiopharmaceutical agents that are the potentially for diagnosis and therapy of lung cancer. To have an advanced diagnosis of lung cancer, radiolabel ^{89}Zr-DFO-nimotuzumab, ^{68}Ga-3PTATE-RGD, and ^{89}Zr-DFO_{PODS}-^{DAR2}SC16-MB1 appear high radioactivity concentrations in tumor-bearing mice, thus it is potential for diagnosis of SLCL or NSCLC. In the treatment of advanced lung cancer, ^{131}I-Bevacizumab and ^{177}Lu-Satoreotide Tetraxetan showed positive laboratory results, which were observed the reduction of tumor uptake up to ~81% in the animals co-injected with ^{131}I-Bevacizumab and unlabeled Bevacizumab and the clinical response rate of 45% with PFS median was 21.0 mo in patients with one to two treatment cycles of ^{177}Lu-satoreotide tetraxetan. However, ^{131}I-Bevacizumab, ^{68}Ga-3PTATE-RGD, and ^{177}Lu-Satoreotide Tetraxetan studies still need further research for a complimentary assessment to warrant ^{131}I-Bevacizumab and ^{68}Ga-3PTATE-RGD ability for therapy and diagnosis and determine the optimal therapeutic dose of ^{177}Lu-Satoreotide Tetraxetan.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors do not have any conflicts of interest.

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