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REVIEW

KSNM60 in Clinical Nuclear Oncology

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Abstract
Since the foundation of the Korean Society of Nuclear Medicine in 1961, clinical nuclear oncology has been a major part of clinical nuclear medicine in Korea. There are several important events for the development of clinical nuclear oncology in Korea. First, a scintillating type gamma camera was adopted in 1969, which enabled to perform modern oncological gamma imaging. Second, Tc-99 m generator was imported to Korea since 1979, which promoted the wide clinical use of gamma camera imaging by using various kinds of Tc-99 m labeled radiopharmaceuticals. Third, a gamma camera with single photon emission tomography (SPECT) capability was first installed in 1980, which has been used for various kinds of tumor SPECT imaging. Fourth, in 1994, clinical positron emission tomography (PET) scanner and cyclotron with a production of F-18 fluorodeoxyglucose were first installed in Korea. Fifth, Korean Board of Nuclear Medicine was established in 1995, which contributed in the education and manpower training of dedicated nuclear medicine physicians in Korea. Finally, an integrated PET/CT scanner was first installed in 2002. Since that, PET/CT imaging has been a major imaging tool in clinical nuclear oncology in Korea. In this review, a brief history of clinical nuclear oncology in Korea is described.

Keywords Korean Society of Nuclear Medicine · Nuclear oncology · Gamma camera · PET · PET/CT · SPECT

Introduction

Since the foundation of the Korean Society of Nuclear Medicine in 1961, clinical nuclear oncology has been a major part of clinical nuclear medicine in Korea. There are several important events for the development of clinical nuclear oncology in Korea [1]. First, a scintillating type gamma camera was adopted in 1969, which enabled to perform modern oncological gamma imaging. Second, Tc-99 m generator was imported to Korea since 1979, which promoted the wide clinical use of gamma camera imaging by using various kinds of Tc-99 m labeled radiopharmaceuticals. Third, a gamma camera with single photon emission tomography (SPECT) capability was first installed in 1980, which has been used for various kinds of tumor SPECT imaging. Fourth, in 1994, clinical positron emission tomography (PET) scanner and cyclotron with a production of F-18 fluorodeoxyglucose (FDG) were first installed in Korea. Fifth, Korean Board of Nuclear Medicine was established in 1995, which contributed in the education and manpower training of dedicated nuclear medicine physicians in Korea. Finally, an integrated PET/CT scanner was first installed in 2002. Since that, PET/CT imaging has been a major imaging tool in clinical nuclear oncology in Korea.

In this special review article, a brief history of clinical nuclear oncology in Korea is described, focusing on the published articles, and adoption of new equipment and radiopharmaceuticals, not including abstract only studies and case reports (Fig. 1). In addition, clinical nuclear oncology related to thyroid, endocrinology and neuro-oncology is not covered by this article in detail, which will be dealt with in other special review articles. To find published articles, web of science database (http://apps.webofknowledge.com/), Pubmed online database (https://pubmed.ncbi.nlm.nih.gov/), KoreaMed online database (https://www.koreamed.org/), and the website of the Korean Journal of Nuclear Medicine

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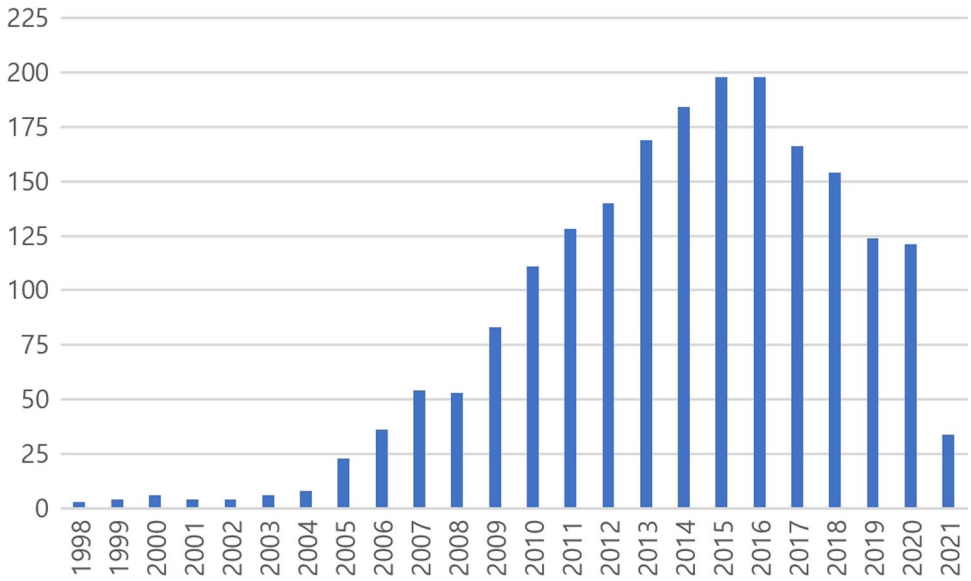

Fig. 1 Published articles by Korean authors related to oncological PET including PET/CT and PET/MR (Web of Science database, search date: Apr. 16th, 2021)

(https://www.ksnm.or.kr/journal/) were used. The published date was based on the formal date on printed version of the journals, not electronically published date except online-only journals.

Oncological Gamma Imaging and SPECT

There are several nuclear imaging methods by gamma camera in nuclear oncology including liver scan, bone marrow scan, bone scan, lymphoscintigraphy, Ga-67 citrate scan, Tc-99 m MIBI scan, and Tc-99 m tetrofosmin scan.

First study of liver scan for oncological indication by Korean authors was published in 1969, which showed I-131 Rose Bengal liver scintigraphy findings of various hepatic diseases including hepatoma, cirrhosis, and abscess by using a Transistorized Magnetic Scanner 500 (Picker, USA) [2]. However, liver scan is rarely used in Korea nowadays according to the development of other imaging modalities such as ultrasonography and magnetic resonance imaging. Figure 2 shows the liver scintigraphy of hepatoma.

First study of bone marrow scan for oncological indication by Korean authors was published in 1973, which showed Au-198 colloid bone marrow scan findings of various hematological diseases including leukemia and anemia by a Pho/Dot scanner (Nuclear Chicago, USA) [3]. However, bone marrow scan is rarely used in Korea nowadays according to the development of other imaging modalities such as FDG PET. Figure 3 shows bone marrow scan images of normal pelvis and pelvis with iron deficiency anemia.

Bone scan is the most common oncological gamma imaging in Korea. First study of bone scan for oncological indication by Korean authors was published in 1978, which reported Tc-99 m EHDP whole-body bone scan findings

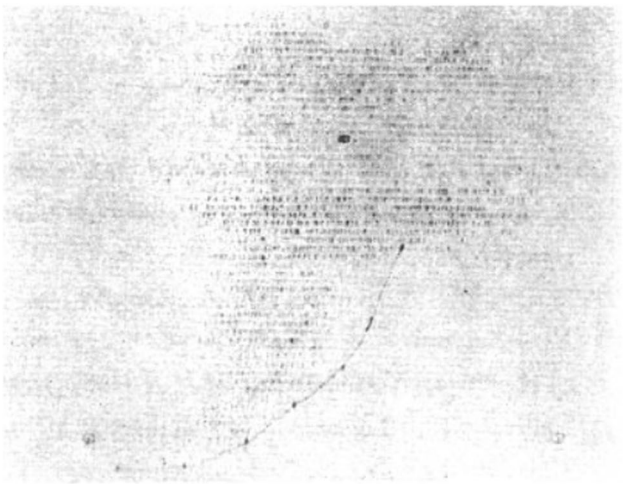

Fig. 2 Liver scintigraphy image of hepatoma (from ref. [2], permitted by the Korean Society of Nuclear Medicine). There is a photon defect in the right hepatic lobe corresponding to the hepatoma

of various kinds of bone diseases including primary bone tumors [4]. In 1979, first study for Tc-99 m methylene diphosphonate (MDP) whole-body bone scan findings of bone metastasis was published [5]. In 1995, the first original article for clinical nuclear oncology by Korean authors in an international journal was published, which dealt with the Tc-MDP bone scan findings in gastric cancer [6].

First study for lymph node imaging for caner by Korean authors was published in 1985, which showed the Tc-99 m phytate lymphoscintigraphy imaging of metastatic lymph nodes in gastric cancer [7]. Currently, lymphoscintigraphy for oncology has been used as preoperative sentinel lymph node imaging. First study for sentinel lymph node imaging was published in 2000 for breast cancer [8].

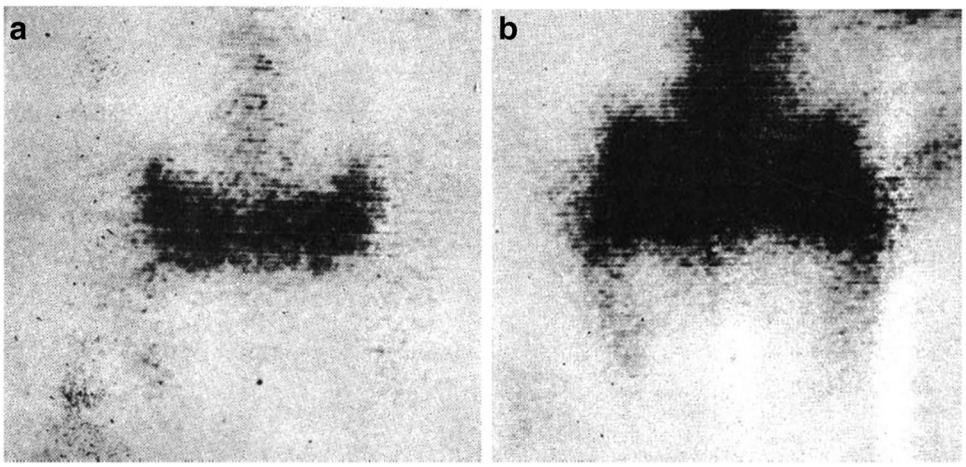

Fig. 3 Bone marrow scan images of normal pelvis (**a**) and pelvis with iron deficiency anemia (**b**) (from ref. [3], permitted by the Korean Society of Nuclear Medicine). There is significant increase of Au-198 colloid uptake in pelvis in case of iron deficiency anemia

First study for Ga-67 citrate scintigraphy for oncological indication by Korean authors was published in 1989, which showed the imaging findings of hepatocellular carcinoma correlated to angiography [9]. Another interesting published paper reported the comparative diagnostic results between Ga-67 planar and SPECT imaging in non-Hodgkin's lymphoma [10].

First study for Tc-99 m MIBI scan for oncological indication by Korean authors was published in 1994, which dealt with the diagnostic usefulness for localizing primary tumor and response to radiotherapy in non-small cell lung cancer [11]. Furthermore, in this study, SPECT is used for the first time in nuclear oncology in Korea. In the same 1994, a case report showing Tc-99 m MIBI uptake in simultaneous thyroid and lung cancers was published, which is the first study of clinical nuclear oncology by Korean authors in an international journal [12]. The first original article for tumor scan by Korean authors in an international journal was published in 1998, which dealt with Tc-99 m MIBI uptake in small cell lung cancer [13]. Figure 4 shows the Tc-99 m MIBI uptake in non-small cell lung cancer before and after radiation therapy.

Scintimammography is a kind of tumor scan for breast cancer, which has been clinically used in Korea until now. First study of scintimammography by Korean authors was published in 1999, which dealt with the comparative diagnostic results between Tl-201 and Tc-99 m MIBI planar and SPECT imaging for detecting breast cancer and metastatic

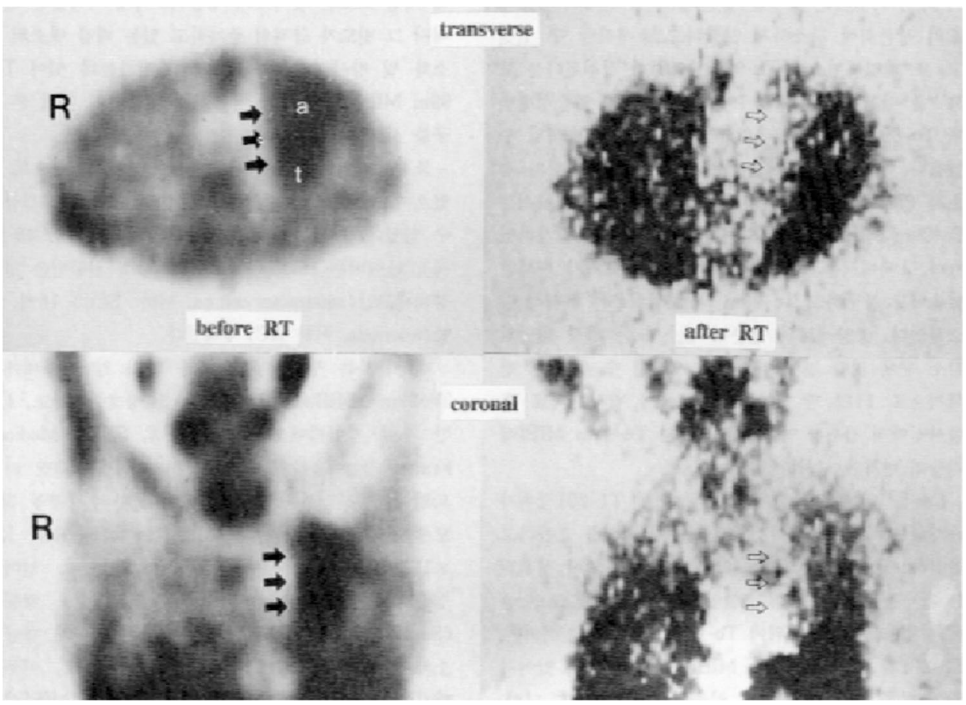

Fig. 4 Tc-99 m MIBI uptake in non-small cell lung cancer before (solid arrows) and after (empty arrows) radiation therapy (from ref. [11], permitted by the Korean Society of Nuclear Medicine)

axillary lymph nodes [14]. Scintimammography study by Tc-99 m tetrofosmin for detecting primary breast cancer was first published in the same 1999 [15]. In 2009, breast-specific gamma camera was introduced in Korea. The first clinical study for breast-specific gamma imaging (BSGI) was published in 2010, which showed that Tc-99 m MIBI BSGI had comparable diagnostic efficacy to conventional imaging modalities for detecting primary tumor and metastatic axillary lymph nodes [16].

Oncological FDG PET

Since clinical PET scanner and cyclotron with a production of FDG were first installed in Korea in 1994, FDG PET has been a major nuclear imaging modality in Korea. Figure 1 shows the number of published international articles by Korean authors related to oncological PET according to the published years. Until 2016, the number of published articles was continuously increased. Especially, a steep increase was found after 2005, which might be related to the national healthcare insurance coverage of FDG PET in Korea in 2005. However, after 2016, the numbers were decreased, which might be also related to the reduction of the national healthcare insurance coverage of FDG PET in Korea in 2015. Figure 5 shows the number of clinical PET scans in Korea according to the year. Similar to the published articles of Fig. 1, rapid increase was found since 2005, and rapid decrease between found between 2014 and 2015 was found, which might be related to the changes in the National Healthcare Coverage rules for FDG PET. The followings are key articles dealing with oncological FDG PET by Korean authors according to the oncological indications.

Diagnosis and Staging

Two original articles as the first clinical PET study by Korean authors were published at the same time in 1997, which dealt with the evaluation of solitary pulmonary nodules and soft tissue sarcoma by FDG PET, respectively [17, 18]. First clinical PET study published in an international journal in 1998 reported the diagnostic value of FDG PET in breast cancer [19].

In 2000, fist oncological Korean study dealing with nodal staging of FDG PET directly compared with contrast enhanced CT was published, which showed that FDG PET had significantly better sensitivity, specificity and accuracy for detecting metastatic lymph nodes than contrast enhanced chest CT in esophageal squamous cell carcinoma [20]. Another important 2 studies dealing with initial staging in gastric adenocarcinoma were published in 2005, which showed that FDG PET had significantly better specificity and accuracy than contrast enhanced abdominal CT for the first time in the world [21, 22]. In the same 2005, the first Korean clinical study regarding a dual-time point FDG PET was published, which reported that delayed PET had a better diagnostic efficacy than standard PET for diagnostic metastatic lymph nodes in non-small cell lung cancer [23].

Response Evaluation

In 2004, the first FDG PET study dealing with the response to chemotherapy was published, which showed a possible role of FDG PET for predicting pathological response to neoadjuvant chemotherapy in breast cancer [24]. In 2005, the first FDG PET study dealing with the response to radiotherapy was published, which showed a possible role of FDG

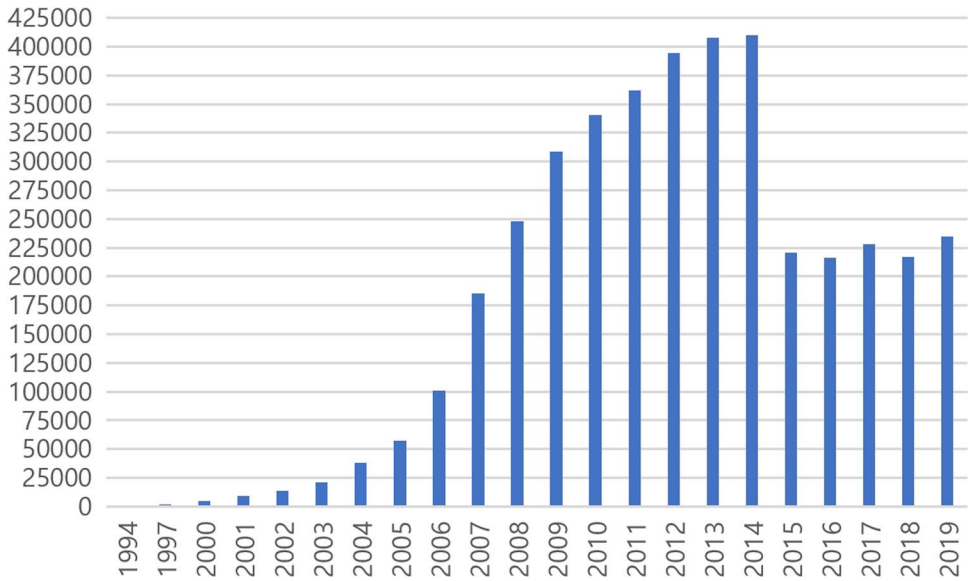

Fig. 5 The number of clinical PET scans performed in Korea according to the year

PET for early response to definitive radiotherapy in head and cancer [25].

Recurrence Evaluation

First clinical PET study for detecting recurrent tumors by FDG PET was published in 1998, which showed that FDG PET was useful to evaluate post-therapeutic recurrence in head and neck cancer [26]. In addition, this was the first multicenter clinical oncological PET study in Korea consisting of 2 institutes. In 2007, the first clinical FDG PET study for routine surveillance was published, which showed that routine surveillance FDG PET after completion of therapy was useful for detecting recurrence in head and neck cancer [27].

Prognosis Prediction

The first prognosis prediction study by baseline FDG PET was published in 2002, which showed that the maximum standardized uptake value (SUV_{max}) was one of significant prognostic factors in non-small cell lung cancer [28]. This study was also a kind of multicenter study consisting of data from 2 institutes. In 2004, another important Korean study dealing with prognostic role (in terms of overall survival) of FDG PET in cancer was published, which showed that tumor length by PET and number of PET-positive nodes were independent significant prognostic predictors for overall survival in multivariate analysis along with stage in esophageal cancer [29]. This study has a value that FDG PET findings were independent prognostic factors for the first time in the world in esophageal cancer. In 2010, the first clinical FDG PET study regarding the prognostic value of volume-based PET parameters by automatically generated volume-of-interest was published, which showed that the pretherapeutic metabolic tumor volume (MTV) of primary tumor adopting threshold SUV for tumor segmentation was an independent and better prognostic factor than SUV_{max} in esophageal carcinoma [30].

Others

In 2004, the first Korean study regarding radiogenomics in cancer was published, which correlated the FDG uptake in hepatocellular carcinoma (HCC) to gene expression profiles by an oligoDNA microarray [31]. In this study, FDG uptake was closely related to the highly expressed genes with cell survival, cell-to-cell adhesion or cell spreading, which could explain the aggressive biological behavior of HCC with high FDG uptake.

In 2005, the first Korean clinical FDG PET study adopting the concept of MTV and total lesion glycolysis (TLG) was published, which the TLG of recurrent tumors was significantly correlated with serum CEA level in colorectal cancer [32]. However, in this study, the VOI was manually drawn due to the limitation of software for the measurement.

In 2008, the first Korean clinical FDG PET study of cancer screening in asymptomatic subjects was published, which showed that the sensitivity, specificity, positive predictive value, and negative predictive value of PET for cancer screening were 52.5%, 95.9%, 20.6%, and 99.0%, respectively [33]. About 23% of detected cancers by the cancer screening program was detected by FDG PET only.

Oncological FDG PET/CT and PET/MR

Since integrated PET/CT scanners were first installed in Korea in 2002, it was replacing PET scanners rapidly and became a major nuclear imaging modality in Korea. Figure 6 shows the number of published international articles by Korean as main authors related to oncological FDG PET/CT according to the published years. This figure also shows the proportion of clinical indication of the studies. Diagnosis, staging, and prognosis prediction have been major clinical indications for published oncological FDG PET/CT. Until 2015, the number of published articles was continuously increased. However, after 2015, the numbers were decreased, which might be also related to the reduction of the national healthcare insurance coverage of FDG PET in Korea in 2015 as mentioned earlier.

In 2011, first PET/MR scanner for clinical oncology was installed in Korea, while this scanner does not allow simultaneous PET and MRI acquisition, it allows acquisition of automatically co-registered PET and MR images acquired sequentially. In 2012, first integrated PET/MR scanner allows simultaneous PET and MRI acquisition was installed in Korea. The implement of PET/MR system has led to oncological PET/MR study by Korean.

The followings are key articles dealing with oncological FDG PET/CT and PET/MR by Korean as main authors according to the oncological indications. Because of the limited space, it is impossible to deal with all published papers. Therefore, only several papers selected based on the historical importance of the paper, citation index (Table 1), and the journal's impact factor are described in this part.

Diagnosis and Staging

Since the implementation of integrated PET/CT scanner in Korea, numerous clinical FDG PET/CT studies by Koreans demonstrated a usefulness of PET/CT for diagnosing and staging in various tumors including non-small cell lung cancer [34–36] and head and neck cancer [36–43], cholangiocarcinoma [44, 45], uterine corpus cancer [46], ovarian cancer [47], gallbladder cancer [45], and esophageal cancer [48]. Korean studies dealt with diagnostic value of FDG

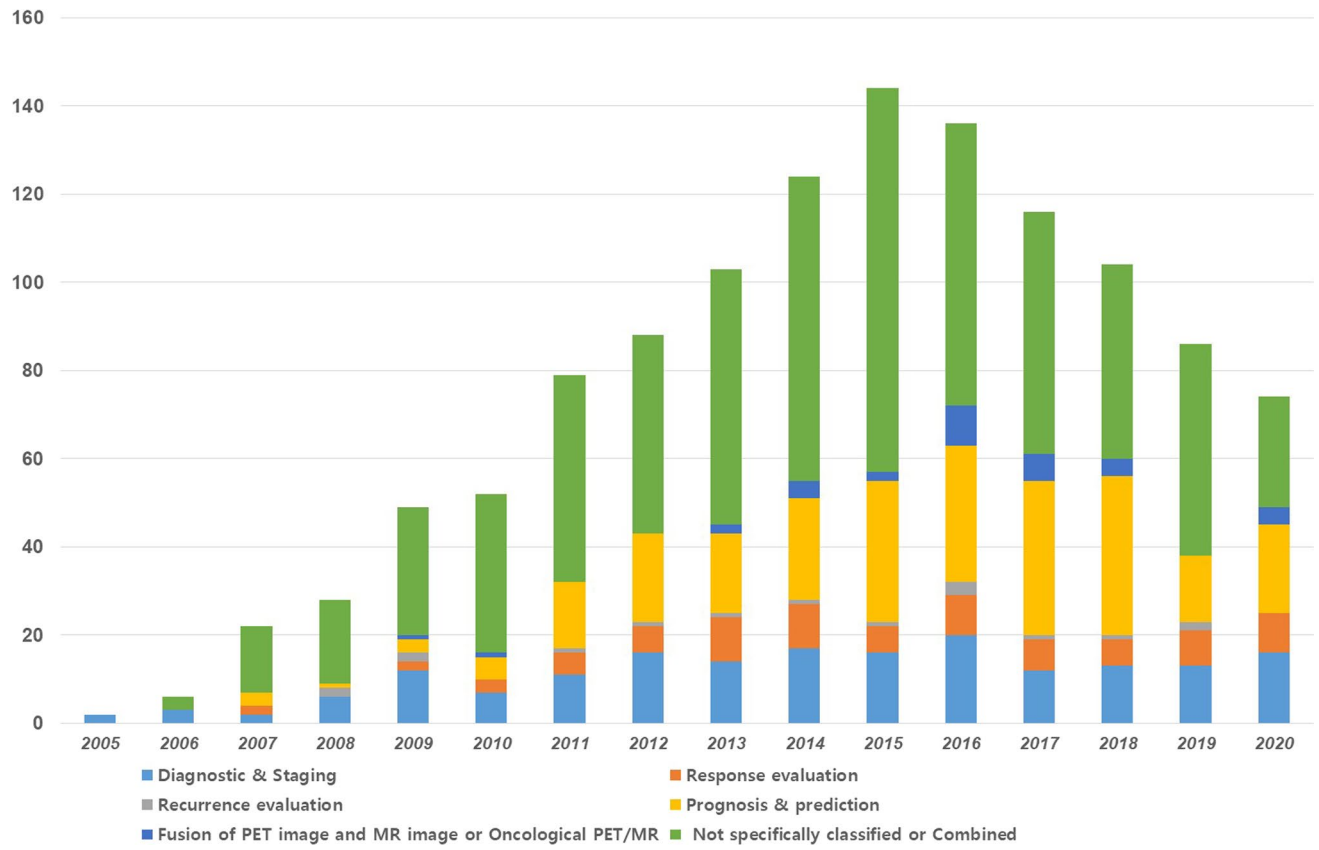

Fig. 6 Published articles by Korean as main authors related to oncological FDG PET/CT according to clinical indications (Web of Science database, search date: Apr. 16th, 2021)

PET/CT also showed that PET/CT is useful in differentiating benign from malignancy among pulmonary nodules [49], musculoskeletal tumors [50], pancreas lesion [51], and in detecting primary site in unknown primary tumors [52, 53].

In 2005, two original articles as the first oncological PET/CT study by Korean as main authors were published in international journal, which dealt with the value of preoperative staging in non-small cell lung cancer and detection of second primary cancer in initial tumor staging, respectively [54, 55].

In 2006, a prospective study of FDG PET/CT directly compared with magnetic resonance imaging (MRI) was published, which reported that PET/CT was more sensitive for detecting metastatic lymph nodes than MRI in uterine cervix cancer [56]. Another important prospective study dealing with nodal staging in non-small cell lung cancer was published, which showed that FDG PET/CT has high specificity and positive predictive value of mediastinal nodal staging [57]. In the same 2006, clinical FDG PET/CT study regarding thymic epithelial tumors was published, which reported a usefulness of PET/CT for staging the extent of the disease [58].

In 2011, clinical FDG PET/CT studies by Korean regarding a dual-time point were published in international journal [59–61]. Delayed scan had a better diagnostic efficacy than standard scan for the detection of hepatic metastasis in colorectal cancer [60], and of axillary lymph node metastasis in breast cancer [61].

Response Evaluation

In 2007, two original articles as the first FDG PET/CT study dealing with the value of PET/CT in assessing treatment response were published in international journal, which showed the feasibility of PET/CT after radiotherapy in head and neck squamous cell carcinoma and the predictive value of PET/CT after neoadjuvant chemoradiotherapy in esophageal cancer, respectively [62, 63].

In 2009, the prospective study to evaluate the role of PET/CT as a tool for early response predictor in advanced non-small cell lung cancer was published, which showed that metabolic response on early assessment was useful in identifying the patients who would have progressive disease [64]. In the same 2009, another important study regarding the chemotherapy response based on FDG PET/CT was published, which reported that PET/CT might be a valuable tool for evaluating the response to neoadjuvant chemotherapy

Table 1 List of top 10 original articles in terms of citation number in clinical oncological PET including PET/CT and PET/MR by Korean authors (Web of Science database, search date: Apr. 16th, 2021)

No	Title	Journal/year	Citation
1	Non-small cell lung cancer: prospective comparison of integrated FDG PET/CT and CT alone for preoperative staging [54]	Radiology. 2005 Sep;236(3):1011–9	326
2	Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study [56]	Cancer. 2006 Feb 15;106(4):914–22	226
3	A prospective evaluation of ^{18}F-FDG and ^{11}C-acetate PET/CT for detection of primary and metastatic hepatocellular carcinoma [132]	J Nucl Med. 2008 Dec;49(12):1912–21	163
4	Metabolic tumor volume of [18F]-fluorodeoxyglucose positron emission tomography/computed tomography predicts short-term outcome to radiotherapy with or without chemotherapy in pharyngeal cancer [80]	Clin Cancer Res. 2009 Sep 15;15(18):5861–8	158
5	Non-small cell lung cancer staging: efficacy comparison of integrated PET/CT versus 3.0-T whole-body MR imaging [146]	Radiology. 2008 Aug;248(2):632–42	129
6	Prognostic Value of Metabolic Tumor Volume and Total Lesion Glycolysis on Preoperative ^{18}F-FDG PET/CT in Patients with Pancreatic Cancer [101]	J Nucl Med. 2014 Jun;55(6):898–904	125
7	^{18}F-FDG PET/CT of thymic epithelial tumors: usefulness for distinguishing and staging tumor subgroups [58]	J Nucl Med. 2006 Oct;47(10):1628–34	121
8	Clinical role of ^{18}F-FDG PET-CT in suspected and potentially operable cholangiocarcinoma: a prospective study compared with conventional imaging [44]	Am J Gastroenterol. 2008 May;103(5):1145–51	118
9	Volume-based parameter of 18)F-FDG PET/CT in malignant pleural mesothelioma: prediction of therapeutic response and prognostic implications [84]	Ann Surg Oncol. 2010 Oct;17(10):2787–94	118
10	Diagnosis and staging of primary ovarian cancer: correlation between PET/CT, Doppler US, and CT or MRI [47]	Gynecol Oncol. 2010 Mar;116(3):389–94	108

in osteosarcoma [65]. After that, other clinical studies also dealt with a value of FDG PET/CT after neoadjuvant chemotherapy as a response predictor in osteosarcoma were published in 2012 and 2013, respectively [66, 67].

Since the reporting system for FDG PET/CT, such as Positron Emission tomography Response Criteria In Solid Tumors (PERCIST) and Deauville score, has been introduced and start to be accepted internationally, many studies of PET/CT response using PERCIST or Deauville score were published [68–70]. In 2013, interim PET/CT-based study using Deauville score, SUV, and MTV was published, which showed that PET/CT result has a significant negative predictive value for disease progression and a high potential for predicting outcomes in diffuse large B cell lymphoma [68]. In 2015, large-scaled multicenter study was published, which reported that post-treatment Deauville score on PET-CT scan can predict the risk of treatment failure in extranodal natural killer/T-cell lymphoma, nasal type [69]. In 2019, the pooled study comparing the morphologic criteria and metabolic criteria for the assessment of tumor responses demonstrated the significant discordance between RECIST and PERCIST [71].

Recurrence Evaluation

Early clinical studies for detecting recurrent tumors by FDG PET/CT were published in 2007, which showed that FDG PET/CT is a sensitive post-therapy surveillance modality for the detection of recurrent cervical cancer and recurrent ovarian cancer, respectively [72, 73]. In 2008, the studies dealt with the post-therapy surveillance for gynecologic malignancy reported that PET/CT was not only highly effective in discriminating true recurrence in patients with suspected recurrence, but it was also highly sensitive in detecting recurrence in asymptomatic patients [74, 75]. In 2009, FDG PET/CT study dealt with post-therapy surveillance of high-risk renal cell carcinoma was published, which showed that the performance of FDG PET/CT was as good as conventional methods [76].

Prognosis Prediction

The first prognosis prediction study by FDG PET/CT was published in 2007, which showed that complete metabolic response by FDG PET/CT was significantly associated with better clinical outcome in esophageal cancer [63]. In the same 2007, another Korean clinical study dealing with prognostic value of PET/CT was published, which reported that high SUV_{max} suggests poor survival outcome in large-cell neuroendocrine carcinomas, and small-cell lung cancer [77]. In 2008, clinical FDG PET/CT study with gefitinib-treated non-small cell lung cancer patients was published, which reported that low SUVs at baseline scan can predict favorable response and survival [78]. In

2009, another FDG PET/CT study with non-small cell lung cancer patients also showed a prognostic value of baseline PET/CT, in which SUV of the primary tumor was independent prognostic factor for disease free survival [79]. In the same 2009, the study dealing with a prognostic value of FDG PET/CT was published. This study has a value of first FDG PET/CT study reporting the value of MTV as an independent prognostic factor in pharyngeal cancer [80]. Another important FDG PET and PET/CT study was published in 2009. This study showed that baseline FDG uptake was an independent predictor of tumor recurrence in HCC patient who underwent liver transplantation [81].

Large number of clinical FDG PET/CT studies by Koreans demonstrated a usefulness of FDG PET/CT for predicting prognosis and identifying subgroups of patients at higher risk in various tumors including small-cell lung cancer [82, 83], malignant pleural mesothelioma [84], non-small cell lung cancer [85–91], head and neck cancer [92–95], cervical cancer [96], breast cancer [97, 98], diffuse large B-cell lymphoma [99, 100], pancreatic cancer [101, 102], advanced gastric cancer [103], hepatocellular carcinoma [104–106], and biliary tract cancer [107]. Most of these studies using the volumetric PET parameters such as MTV and TLG showed the potential to provide prognostic information.

Oncological PET/MR

Prior to the implement of PET/MR system in Korea, oncological studies with fusion of PET images and MR images obtained separately were published [67, 108, 109].

In 2014, the first oncological study using PET/MR scanner was published, which showed that PET/MR has acceptable accuracy for T staging and higher accuracy for N staging compared than conventional imaging tools in esophageal cancer [110]. In the same 2014, first oncological study using integrated PET/MR scanner were published. In that preliminary study, whole-body PET/MRI showed a feasibility as a single modality for staging in a clinical setting [111]. In the same 2014, the integrated PET/MR study, which was firstly published in international journal, showed that simultaneous PET/MR scan could provide an accurate diagnosis in case of small breast cancer that are less than 1 cm in size [112]. In 2016, the PET/MR study was published, which showed that PET/MR imaging can yield significantly higher diagnostic performance in the detection of liver metastases in colorectal cancer [113]. 1n 2017, important prospective study with PET/MR was published, which showed that FDG PET/MR has a similar diagnostic performance to PET/CT plus contrast-enhanced multidetector CT in the preoperative staging of pancreatic cancer [114].

Others

In 2013, to create high-level evidence of efficacy for nuclear medicine study and promote cooperative research among members, Korean society of nuclear medicine (KSNM) initiate Clinical Trial Network (CTN). As a result, many valuable multicenter studies have been published and are still in progress. In 2016, the first CTN study with FDG PET/CT was published, which showed that FDG uptake in tumor was an independent prognostic factor for survival in hepatocellular carcinoma (HCC) patients treated with TACE or CCRT [115]. In the same 2016, another CTN study regarding the prognostic value of FDG uptake on pretreatment PET/CT in patient with early HCC was published [116]. In 2017, CTN study with thyroid cancer patients was published, which showed that PET/CT was more sensitive than neck CT for preoperative LN staging [117]. In the same 2017, another CTN study showed FDG uptake on pretreatment PET/CT had an incremental prognostic value for overall survival in advanced HCC [106].

Metabolic radiomics based on FDG PET/CT have been investigated by Korean researchers. Although there are not many studies yet, interesting radiomic studies based on FDG PET/CT were published recently [118–121]. In 2017, FDG PET/CT study showed that metabolic radiomics patterns of tumor are associated with Ki67 expression, pathologic complete response after neoadjuvant chemotherapy, and risk of recurrence in advanced breast cancer [118].

Only a few radiogenomics studies based on FDG PET/CT by Korean were published. In 2018, the radiogenomic study was published, which showed that a gene network that accounts for immune cell microenvironment was associated with FDG uptake in HNSCC [122]. In the same 2018, another radiogenomic study was published, which reported that they developed a transcriptome-based tumor metabolism estimation model using RNA sequencing and FDG image data [123]. In 2019, metabolic radiogenomic study based on FDG PET/CT was published, which showed that PET radiomic feature has a significant correlation with genetic characteristics of lung cancer [124]. In the same 2019, radiogenomics studies were published, which showed the association between PET image features and genetic features in head and neck cancer [125] and intrahepatic cholangiocarcinoma [126].

With the advent of the artificial intelligence (AI) era, AI techniques such as machine learning and deep learning have been adopted into oncological PET/CT study. In 2019, radiomic studies were published, which showed that FDG PET-based radiomic features using machine learning algorithm approach has a predictive value in non-small cell lung cancer [120] and osteosarcoma [127], respectively. In 2020, FDG PET/CT studies using AI techniques were published. One study reported that they developed FDG PET-based deep

learning model that can predict tumor immune microenvironment in lung adenocarcinoma [128]. The other study showed that deep learning model using PET/MR images can predict the early response to neoadjuvant chemotherapy in advanced breast cancer [129].

In 2009, the first Korean clinical FDG PET/CT study of cancer screening in asymptomatic volunteers was published, which showed that the sensitivity, specificity, positive predictive value, and negative predictive value of PET for cancer screening were 68.8%, 97.2%, 23.4%, and 99.6%, respectively. The overall detection rate of PET/CT was 0.8% [130].

Oncological Non-FDG PET

There are several non-FDG PET radiopharmaceuticals in nuclear oncology such as C-11 methionine, C-11 acetate, F-18 NaF, F-18 fluorothymidine (FLT), F-18 FDOPA, F-18 fluorocholine, F-18 fluoromisonidazole (FMISO), Ga-68 DOTA-somatostatin receptor (SSR), Ga-68 prostate specific membrane antigen (PSMA), and F-18 fluoroestradiol (FES) clinically available in Korea (Table 2).

The first clinical non-FDG PET study for oncological indication by Korean authors was a study using C-11 methionine and was published in 2002 [131]. In this paper, C-11 methionine PET findings in various brain lesions, including glioma, were compared with FDG PET findings, showing superior performance in evaluation of malignancy grading and proliferation index, and so far, it has been cited 194 times. Since then, researchers have published more than 20 papers on C-11 methionine PET or PET/CT in patients with brain tumors, medullary thyroid cancer, or parathyroid adenoma.

The First study for C-11 acetate PET for oncological indication by Korean authors was published in 2008. This study is a prospective study comparing the diagnostic accuracy of C-11 acetate and FDG in hepatocellular carcinoma and has been cited 163 times [132]. Since then, about 10 papers have been published about hepatocellular carcinoma, glioma, bladder cancer, and renal cell carcinoma.

A F-18 NaF PET study was first published in 2010 [133]. In this paper, F-18 NaF PET findings of 18 patients with malignant or benign bone disease were described, and the sensitivity and specificity for discriminating bone metastases from non-metastatic lesions were calculated. Since then, more than 30 papers have been published, mainly to confirm bone metastasis of breast cancer and urological cancer, and to know findings of non-neoplastic diseases such as arteriosclerosis or joint disease.

Table 2 New health technology assessment and national healthcare insurance coverage status for oncological non-FDG PET in Korea

Radiopharmaceutical	Approval date	Target disease	Insurance coverage
C-11 Methionine	2013–02-28	Brain tumors, hyperparathyroidism, prostate cancer, lung cancer, kidney cancer*	Diagnosis/staging, detection of recurrence, treatment planning, response evaluation of brain tumors, Localization of parathyroid adenoma or hyperplasia in hyperparathyroidism, diagnosis of prostate cancer, diagnosis of lung cancer
C-11 Acetate	2010–12-03	FDG non-avid primary or recurrent hepatocellular carcinoma	Evaluation, diagnosis, monitoring of primary or recurrent hepatocellular carcinoma
F-18 NaF	2018–01-29	Metastatic bone lesion	Evaluation, diagnosis, monitoring of metastatic bone lesion
F-18 FLT	2012–07-18	Lung cancer	Early treatment response evaluation and prediction of prognosis of lung cancer
F-18 FDOPA	2014–06-10	Brain tumors, Neuroendocrine tumors	Diagnosis/staging, grading, detection of recurrence, treatment planning of brain tumors, diagnosis/staging, detection of recurrence, treatment planning of brain tumors, diagnosis/staging, detection of recurrence, treatment planning of neuroendocrine tumors
F-18 Fluorocholine	2018–01-29	Prostate cancer, hyperparathyroidism	Diagnosis/staging of prostate cancer, Localization of parathyroid adenoma or hyperplasia
F-18 FMISO	2015–04-08	Malignant tumors	Confirmation of intratumoral hypoxic lesions for planning, prediction of prognosis, evaluation of treatment response
Ga-68 DOTA-TOC	2014–12-08	Neuroendocrine tumors	Diagnosis/staging, detection of recurrence, treatment planning of primary or metastatic neuroendocrine tumor
F-18 FES	2020–12-16	Recurrent or metastatic breast cancer	Evaluation of estrogen receptor status

*C-11 methionine was limitedly allowed for diagnosis of kidney cancer during 2016/8/1 ~ 2019/7/31

The first original article by a Korean researcher on F-18 FLT PET was published in 2005 [134]. This study evaluated the feasibility of using F-18 FLT PET for the diagnosis, grading of brain tumors and cellular Ki-67 expression, and was cited 122 times. Since then, more than 20 papers have been published, and the paper with the highest number of citations was the one that evaluated the treatment response of gefitinib in pulmonary adenocarcinoma patients using F-18 FLT PET, which was published in 2008, and has been cited 129 times [135].

F-18 FDOPA was a field where research by Korean researchers was sluggish. In 2016, an animal experiment with PET radiopharmaceuticals of various amino acids including F-18 FDOPA was published [136], and a review article [137] and a meta-analysis study [138] have been published. But the original article about clinical use of F-18 FDOPA PET has not been published yet.

The first Korean researcher's original clinical paper on F-18 fluorocholine was using PET/MR, and it was a study to evaluate the usefulness of various PET parameters in diagnosing prostate cancer [139]. Since then, four more original clinical papers have been published.

The first PET study using Ga-68 labeled SSR by Korean researchers was published in Germany in 2011 [140], and seven more papers have been published. Among them, meta-analysis papers comparing diagnostic results with other radiopharmaceuticals in pheochromocytoma and paraganglioma published in 2019 showed the highest citations with 41 times [141].

A preclinical study of Korean authors using F-18 FMISO to evaluate tumor hypoxia in response to radiation therapy published in 2016 [142]. But a clinical study using this radiopharmaceutical has not been published yet.

A meta-analysis about Ga-68 PSMA PET on the management of patients with prostate cancer published in 2018 showed a high number of citations of 118 [143]. Since then, some in-vitro studies and review articles have been published, but there is no original clinical article in this field.

F-18 FES studies were conducted through thoroughly prepared clinical trials unlike other radiopharmaceuticals. The first published study using F-18 FES PET in a phase 2 clinical study to evaluate the therapeutic efficacy and safety of neoadjuvant letrozole and lapatinib in 2016 [144]. The first and subsequent three papers were all carried out by the same institution, and the results of the phase III clinical study published in 2019 were published in "Lancet Oncology," a leading international academic journal in the field of oncology [145]. This study proved that F-18 FES PET is a safe test that can evaluate estrogen receptor status in multiple sites and predict the responsiveness of hormone therapy.

Conclusions

Since the foundation of the Korean Society of Nuclear Medicine in 1961, clinical nuclear oncology has been continuously developed and has been a major part of clinical nuclear medicine in Korea. Especially, oncological PET/CT has been established as a major tool in clinical nuclear oncology in Korea. It is expected that clinical nuclear oncology will continuously make progress in Korea.

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Declarations

Conflict of Interest Seung Hwan Moon, Young Seok Cho, and Joon Young Choi declare no conflict of interest.

Ethical Statement This study procedure followed the medical research protocols and ethics guidelines defined by the World Medical Association's Declaration of Helsinki throughout the study.

Informed Consent Informed consent was not necessary, because the study design was a review based on previous studies.

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