



# Evolution of Radiological Treatment Response Assessments for Cancer Immunotherapy: From iRECIST to Radiomics and Artificial Intelligence

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Immunotherapy has revolutionized and opened a new paradigm for cancer treatment. In the era of immunotherapy and molecular targeted therapy, precision medicine has gained emphasis, and an early response assessment is a key element of this approach. Treatment response assessment for immunotherapy is challenging for radiologists because of the rapid development of immunotherapeutic agents, from immune checkpoint inhibitors to chimeric antigen receptor-T cells, with which many radiologists may not be familiar, and the atypical responses to therapy, such as pseudoprogression and hyperprogression. Therefore, new response assessment methods such as immune response assessment, functional/molecular imaging biomarkers, and artificial intelligence (including radiomics and machine learning approaches) have been developed and investigated. Radiologists should be aware of recent trends in immunotherapy development and new response assessment methods.

**Keywords:** Immunotherapy; RECIST; iRECIST; Radiomics; Artificial intelligence

## INTRODUCTION

In the last decade, immunotherapy has revolutionized cancer treatment and represents a new paradigm for cancer treatment interventions. Unlike molecular targeted therapies for cancer, which are based on specific genetic or molecular abnormalities, immunotherapy is based on the activation or restoration of immune function to eliminate tumor cells [1,2]. In this era of immunotherapy and molecular targeted therapy, precision medicine has gained

attention among oncologists. In addition to personalized medicine, these interventions aim to provide tailored treatments in accordance with the genetic or immune characteristics of the patient or disease. There are two key elements of precision medicine: 1) molecular and biomarker analysis, such as companion diagnostics or next-generation sequencing (NGS) and 2) early treatment response assessments, mostly performed using medical imaging [3,4].

Accurate treatment response assessment for an immunotherapy regimen is sometimes challenging for radiologists for various reasons, including the continued rapid development of immunotherapeutic agents. Although immune checkpoint inhibitors (ICIs) are currently the mainstay of immunotherapy, new types of immunotherapeutics such as antibody-drug conjugates (ADCs), bispecific antibodies (BsAbs), and cell therapies have emerged in recent years. Treatment response pattern determination using medical imaging can differ depending on the type of immunotherapeutic agent administered. Hence, radiologists must be aware of recent trends in immunotherapy [3,4]. Another challenge in making an accurate response

**Received:** March 20, 2022 **Revised:** August 11, 2022

**Accepted:** August 12, 2022

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assessment is the emergence of atypical response patterns, such as pseudoprogression or hyperprogression, following immunotherapy. Therefore, radiologists should also be familiar with the incidence, criteria, and imaging features associated with these atypical response patterns [5-7]. Current immune response assessment criteria, such as the Immune Response Evaluation Criteria in Solid Tumors (iRECIST) or Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC), may also have limitations in terms of providing accurate response assessment following immunotherapy [5]. Hence, significant efforts have been made to apply radiomics or artificial intelligence (AI) techniques to these evaluations. However, these novel imaging techniques and analyses must be validated for their advantages and pitfalls [4].

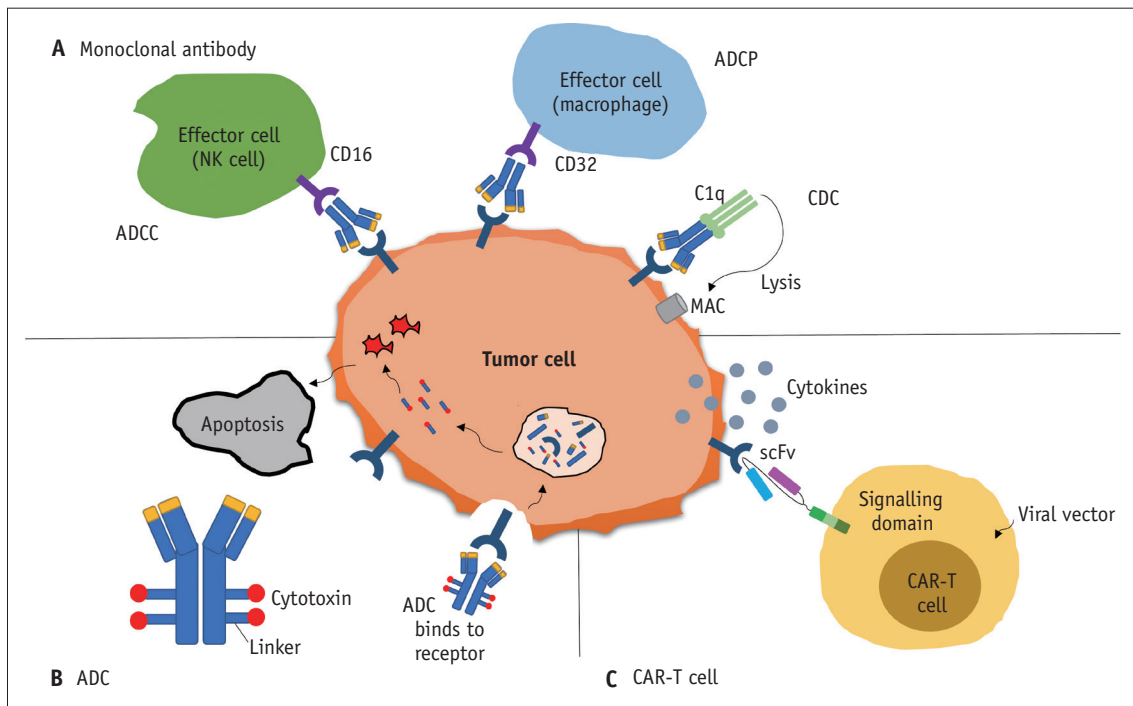
Herein, we review the principal issues that radiologists should be aware of in relation to the evolution of cancer immunotherapies, the crucial role of imaging in precision medicine, issues related to current immune response assessment criteria, and the status of novel radiomics, including AI imaging analysis techniques.

## Evolution of Cancer Immunotherapy

Immunotherapeutic agents have been developing rapidly, from ICIs to chimeric antigen receptor (CAR)-T cell therapies (Fig. 1). Accordingly, new response assessment methodologies using imaging, including immune response assessment, functional/molecular imaging biomarkers, and radiomics have also been developed (Fig. 2).

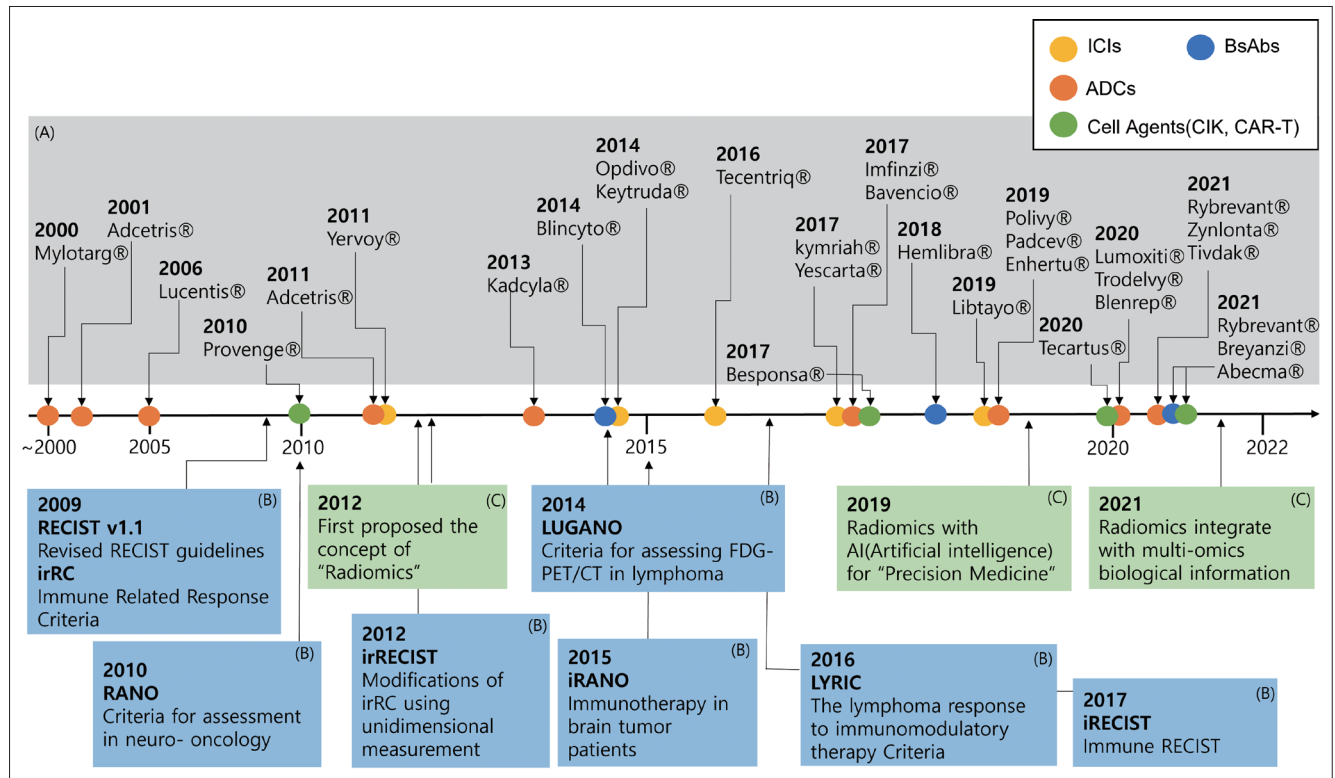
### ICIs

ICIs represent a class of drugs that block immune checkpoint proteins expressed on the surface of immune cells such as T cells and certain types of tumor cells [8]. The role of checkpoint proteins is to prevent an overactive immune response that could potentially damage or even destroy normal host cells. They do this by initiating an “off” signal to immune cells, such as T cells, if they interact with host cells, thus preventing an immune response. However, these proteins can also initiate this blocking function when T cells recognize and bind to tumor cells. Thus, ICIs work as cancer therapeutics by preventing checkpoint proteins



**Fig. 1. Mechanism of action of various cancer immunotherapies.**

**A.** Monoclonal antibodies kill target tumor cells based on three crucial mechanisms which include ADCC, ADCP, and CDC. **B.** ADCs kill cancer cells through the binding of the monoclonal antibody part to specific targets on the tumor surface, the internalization of ADC into the cell, and cancer killing by cytotoxins. **C.** CAR-T cells are genetically engineered patient’s T cells to express a CAR comprising a that can identify specific tumor antigens. After binding to the tumor cells, the CAR-T cells are activated, release cytokines, and directly kill tumor cells. ADC = antibody-drug conjugate, ADCC = antibody dependent cellular cytotoxicity, ADCP = antibody-dependent cellular phagocytosis, CAR = chimeric antigen receptor, CD = cluster of differentiation, CDC = complement dependent cytotoxicity, MAC = membrane attack complex, NK = natural killer, scFv = single chain fragment variable



**Fig. 2. Evolution of cancer immunotherapy and imaging response assessment methods.**

**A.** Representative cancer immunotherapeutic agents, including ICIs, ADCs, BsAbs, and cell therapy such as CIK cells or CAR-T cells. **B.** Evolution of immune response assessment criteria for cancer immunotherapy. **C.** Major advances in radiomics. ADC = antibody-drug conjugate, BsAb = bispecific antibody, CAR = chimeric antigen receptor, CIK = cytokine-induced killer, ICI = immune checkpoint inhibitor, iRANO = Immunotherapy Response Assessment in Neuro-Oncology, iRECIST = Immune-Response Evaluation Criteria in Solid Tumors, irRECIST = Immune-related Response Evaluation Criteria In Solid Tumors, LYRIC = Lymphoma Response to Immunomodulatory Therapy Criteria, RANO = Response Assessment in Neuro-Oncology, RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1

from inducing an “off” signal. To date, three main types of ICIs, including programmed cell death protein 1 (PD-1), its ligand (PD-L1), and cytotoxic T lymphocyte-associated antigen 4, have been developed for clinical use in treating various cancers [5], as summarized in Table 1 [9]. ICIs have been used to treat lung cancer, melanoma, brain metastases, head and neck squamous cell carcinoma, renal cell carcinoma, bladder cancer, endometrial cancer, cervical cancer, and ovarian cancer [10-12].

### Antibody Derivatives

Monoclonal antibodies (mAbs) are the mainstay of immunotherapeutics and can specifically bind to target antigens on tumor cells or tumor-associated proteins [13]. The main mechanisms by which mAbs can target and eliminate tumor cells include immune-mediated cell killing, direct blockade of receptors required for essential cell metabolism, and specific effects on the tumor vessels and microenvironment, such as the tumor stroma [14]. With recent advances in antibody engineering technologies,

several new antibodies or antibody derivatives have been developed to enhance the efficacy of these treatments. In general, there are four types of antibody derivatives currently used: 1) ADCs, 2) BsAbs, 3) antibody fragments, and 4) fusion proteins, including immunocytokines [13], as detailed in Table 2 [13,15,16]. Antibody derivatives are increasingly being used for treating various types of cancer.

### Cell Therapy

With recent advances in cell engineering technologies, cell-based immunotherapies have seen a rapid rise as cancer immunotherapy options. The fundamental principle of this treatment is to bring effective immune cells to the tumors. The process of adoptive immune cell therapy includes the isolation of blood from patients or donors, ex vivo expansion of immune cells using stimulatory processes or specific engineering applications, and infusion of these cell products into the patient [17]. Several types of immune effector cells can be used to recognize and ultimately eliminate cancer cells; they are as follows: 1)

cytokine-induced killer (CIK) cells, 2) natural killer cells, 3) dendritic cell vaccines, 4) tumor-infiltrating lymphocytes, 5) engineered T cells, including T cell receptors or CARs. Of these, CIK and CAR-T cell agents have been approved and are used in current clinical practice (Table 3) [18].

## Imaging Biomarkers for Immunotherapy

### Imaging Biomarkers as a Predictive Biomarker

The concept of precision medicine has gained attention in cancer immunotherapy, as it is important to select a

**Table 1. US-FDA Approved Immune Checkpoint Inhibitors**

Drug	Format	Target	Indication
Ipilimumab (Yervoy®)	mAb	CTLA-4	Melanoma, renal cell carcinoma, colorectal cancer, non-small cell lung cancer, hepatocellular carcinoma (used with nivolumab)
Nivolumab (Opdivo®)	mAb	PD-1	Melanoma, non-small cell lung cancer, small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck squamous cell carcinoma, hepatocarcinoma, colorectal cancer, esophageal cancer
Pembrolizumab (Keytruda®)	mAb	PD-1	Melanoma, non-small cell lung cancer, non-squamous cell lung cancer (with high PD-L1 expression), renal cell carcinoma, classic Hodgkin's lymphoma, head and neck squamous cell carcinoma gastric or gastroesophageal junction adenocarcinoma, urothelial carcinoma, cervical cancer, large B-cell lymphoma, merkel cell carcinoma
Atezolizumab (Tecentriq®)	mAb	PD-L1	Urothelial carcinoma, non-small cell lung cancer, breast cancer, non-squamous non-small cell lung cancer, small-cell lung cancer
Durvalumab (Imfinzi®)	mAb	PD-L1	Urothelial carcinoma, non-small cell lung cancer
Avelumab (Bavencio®)	mAb	PD-L1	Merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma
Cemiplimab-rwlc (Libtayo®)	mAb	PD-1	Cutaneous squamous cell carcinoma

CTLA-4 = cytotoxic T lymphocyte antigen-4, FDA = Food and Drug Administration, mAb = monoclonal antibody, PD-L1 = programmed death-ligand-1, PD-1 = programmed cell death protein-1, US = United States

**Table 2. US-FDA Approved Antibody Derivatives for Cancer Immune Therapy**

Drug	Format	Target	Indications
Gemtuzumab ozogamicin (Mylotarg™)	Antibody-drug conjugate	CD33	Acute myeloid leukemia
Brentuximab vedotin (Adcetris®)	Antibody-drug conjugate	CD30	Hodgkin lymphoma, aystemic anaplastic large cell lymphoma
Trastuzumab emtansine (Kadcyla®)	Antibody-drug conjugate	HER2	HER2-positive breast cancer
Inotuzumab ozogamicin (Besponsa®)	Antibody-drug conjugate	CD22	Relapsed or refractory B-cell precursor acute lymphoblastic leukemia
Moxetumomab pasudotox (Lumoxiti®)	Antibody-drug conjugate	CD22	Hairy cell leukemia
Polatuzumab vedotin-piiq (Polivy®)	Antibody-drug conjugate	CD79	Diffuse large B-cell lymphoma
Enfortumab vedotin (Padcev®)	Antibody-drug conjugate	Nectin-4	Advanced urothelial cancer
Trastuzumab deruxtecan (Enhertu®)	Antibody-drug conjugate	HER2	HER2-positive breast cancer
Sacituzumab govitecan (Trodelvy®)	Antibody-drug conjugate	Trop-2	Triple negative breast cancer
Belantamab mafodotin-blmf (Blenrep®)	Antibody-drug conjugate	BCMA	Relapsed or refractory multiple myeloma
Loncastuximab tesirine-lpyl (Zynlonta®)	Antibody-drug conjugate	CD19	Diffuse large B-cell lymphoma
Tisotumab vedotin-tftv (Tivdak®)	Antibody-drug conjugate	Tissue factor	Advanced cervical cancer
Blinatumomab (Blincyto®)	Bispecific antibodies	CD3 and CD19	B-cell precursor acute lymphoblastic leukemia
Amivantamab-vmjw (Rybreant®)	Bispecific antibodies	CD3 and EpCAM	Non-small cell lung cancer
Emicizumab-kxwh (Hemlibra®)	Bispecific antibodies	FIXa/FX	Hemophilia A

BCMA = B-cell maturation antigen, CD = cluster of differentiation, EpCAM = epithelial cell adhesion molecule, FDA = Food and Drug Administration, FIXa/FX = coagulation factor Ixa/coagulation factor X, HER2 = human epidermal growth factor receptor 2, US = United States

group of patients who would benefit from certain types of immunotherapeutic agents. For example, if the PD-L1 level and total mutation burden are high in a patient's tumor, the patient can be treated with a PD-1 inhibitor [4,19]. Therefore, it is important to establish predictive biomarkers of precision medicine. Imaging-based biomarkers might be more promising than traditional biomarkers (e.g., blood or joint fluid, biopsy) in that they can better reflect tumor burden and identify tumor heterogeneity invasively [20]. In molecular targeted therapy, imaging biomarkers are an important tool for evaluating effectiveness, and molecular and functional imaging can be an attractive option for in-depth analysis of the therapeutic effect of precision treatment in patients with cancer [1]. Early response assessments via imaging analyses are also regarded as a potential predictive biomarker [4,19]. Liu et al. [21] tentatively identified the effect of image-based biomarkers using pre-processed CT images to predict PD-L1 expression in patients with advanced non-small cell lung cancer retrospectively. As such, from the viewpoint of precision medicine, the need for reliable predictive imaging markers to evaluate early response to ICIs is also increasing [22].

As immunotherapy has become an important strategy for cancer treatment, new areas of research are being conducted to discover imaging biomarkers in addition to molecular biomarkers. Several clinical trials using specialized imaging markers or radiolabels that can provide prognostic insight into immune checkpoint protein responses are currently available [23].

### Imaging Biomarkers for Response and Toxicity Evaluation

Response patterns and toxicity patterns differ for each type of immunotherapy (e.g., ICIs, antibody derivatives, or cell therapy) and each therapeutic agent. Imaging should be used for response assessment and toxicity evaluation in patients receiving immunotherapy. ICIs can cause atypical responses that are not conventionally observed with traditional cytotoxic chemotherapeutic agents or targeted therapies. These atypical responses can be categorized into four types: pseudoprogression, hyperprogression, durable response, and dissociated response (Table 4) [24]. Representative examples of pseudoprogression and hyperprogression are shown in Figures 3 and 4, respectively. Of these categories, pseudoprogression is a significant issue

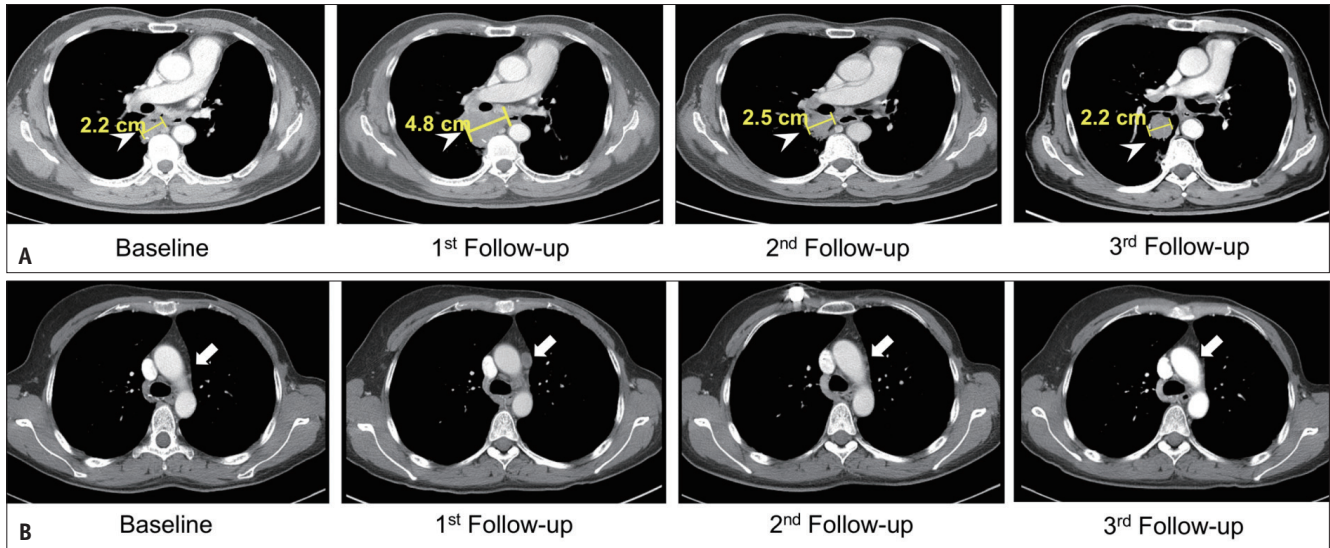
**Table 3. US-FDA Approved Cell Agents**

Drug	Format	Target	Indications
Sipuleucel-T (Provenge®)	Autologous CIK	Prostate-specific antigen	Metastatic, asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer
Tisagenlecleucel (Kymriah®)	CAR-T	CD19	B-cell precursor acute lymphoblastic leukemia
Axicabtagene ciloleucel (Yescarta®)	CAR-T	CD19	Large B-cell lymphoma
Brexucabtagene autoleucel (Tecartus®)	CAR-T	CD19	Relapsed or refractory mantle cell lymphoma
Lisocabtagene maraleucel (Breyanzi®)	CAR-T	CD19	Lymphoma
Idecabtagene vicleucel (Abecma®)	CAR-T	BCMA	Multiple myeloma

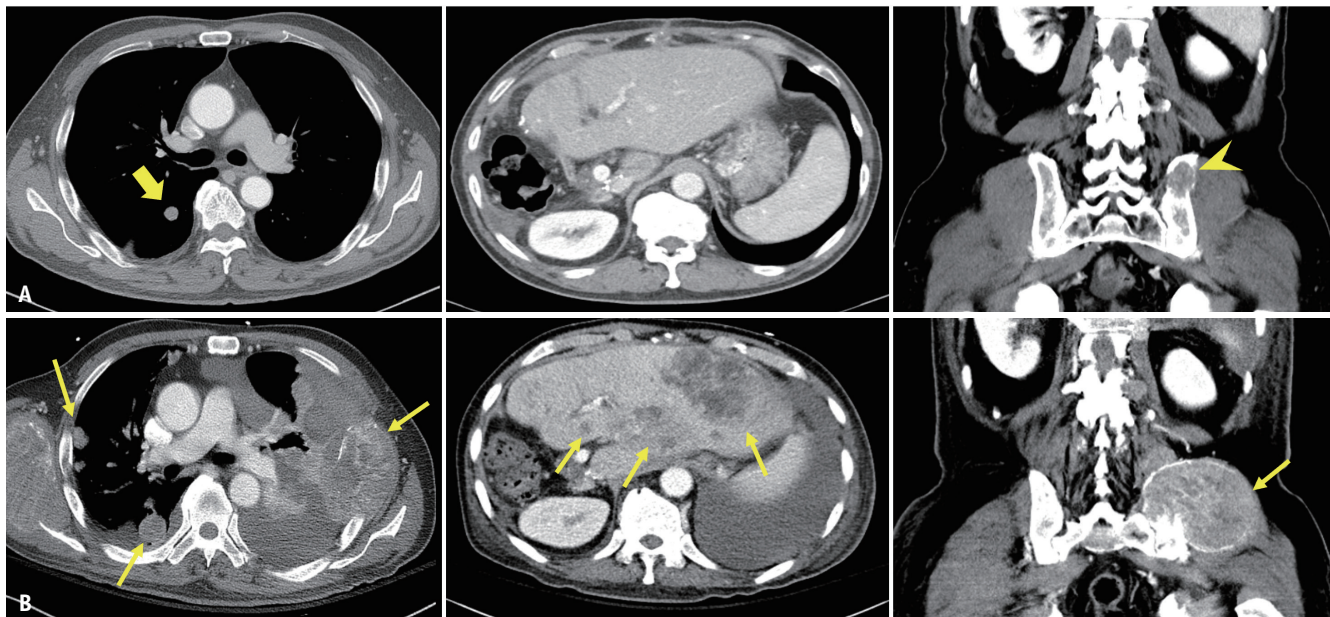
BCMA = B-cell maturation antigen, CAR-T = chimeric antigen receptor-T cell, CD = cluster of differentiation, CIK = cytokine-induced killer

**Table 4. Patterns of Atypical Responses and Their Clinical Implications for Immunotherapy**

Patterns of Response	Definitions and Clinical Implications
Pseudoprogression	<ul style="list-style-type: none"> <li>- Early response of primary tumor size or the appearance of new lesions after immunotherapy</li> <li>- The decision to "treat beyond progression" is only applicable to carefully selected patients who experience clinical benefit and have not shown significant toxicity</li> </ul>
Hyperprogression	<ul style="list-style-type: none"> <li>- A phenomenon in which cancer grows faster than expected after immunotherapy</li> <li>- Transition to other effective therapies is required and early clinical and imaging evaluations must be performed</li> </ul>
Durable response	<ul style="list-style-type: none"> <li>- A standardized definition does not yet exist</li> <li>- It is also not yet defined whether treatment should be continued until disease progression or treatment should be stopped after a certain period of time</li> </ul>
Dissociated response	<ul style="list-style-type: none"> <li>- A phenomenon in which the sizes of some lesions increase and others decrease after immunotherapy</li> <li>- In the case of oligometastatic disease progression, combining immunotherapy with local treatment can be discussed through an oncology board review</li> </ul>



**Fig. 3. Examples of pseudoprogession due to size increase and decrease (A) and occurrence of a new lesion (B).**  
**A.** A patient with lung cancer patient treated using pembrolizumab shows a 2.2 cm mediastinal metastatic lymphadenopathy on baseline CT. The metastatic lymph node increased up to 4.8 cm, as observed on the first follow-up CT. However, the tumor decreased to 2.5 cm and 2.2 cm, as observed on the second and third follow-up CT (A4), respectively, indicative of pseudoprogession of metastatic lymphadenopathy. **B.** A patient with breast cancer patient treated using pembrolizumab plus chemotherapy showed a new mediastinal lymph node (arrow) on the first follow-up CT that was not observed on the baseline CT (arrow). The second and third follow-up CT revealed the resolution of the mediastinal lymph node (arrow), suggestive of pseudoprogession.



**Fig. 4. Examples of hyperprogession in a patient with hepatocellular carcinoma treated using atezolizumab.**  
**A.** Baseline chest CT demonstrates lung metastasis in the right lower lobe (arrow). No tumor recurrence was observed in the liver. Osteolytic bone metastasis in the left iliac bone (arrowhead). **B.** Numerous new metastatic lesions were observed throughout the lung, pleural cavity, muscles, bones, and liver (arrows) on the first follow-up CT taken 8 weeks after treatment initiation, indicating rapid and extensive disease progression.

for any treatment response assessment because it may cause early treatment cessation in patients who benefit from therapy. The mechanism underlying pseudoprogession is related to the infiltration of T cells into the tumor, which may lead to an increased tumor burden caused by this

immune cell invasion rather than a true progression of tumor cells during treatment. This phenomenon has been observed in several different cancers, including solid tumors, lymphomas, and brain tumors. A recent meta-analysis of solid tumors reported an overall pseudoprogession incidence of

6.0% in an ICI trial [6]. In another recent meta-analysis of patients with lymphoma, the incidence of pseudoprogression was reported as 10% [7]. Pseudoprogression can be assessed using new response criteria frameworks such as iRECIST, Immunotherapy Response Assessment in Neuro-Oncology (iRANO), or LYRIC. However, no method for assessing hyperprogression has been established yet. Several sets of assessment criteria have been proposed for hyperprogression, and a consensus will require future international efforts. The pseudoprogression phenomenon has also been observed in other types of immunotherapies, such as ADCs and CAR-T cell therapy [25,26]; however, its incidence may be extremely low, and further evidence needs to be accumulated.

ICI-related toxicities are generally immune-related adverse events (irAEs), either symptomatic or subclinical. Many irAEs, including pneumonitis, hepatitis, enterocolitis, thyroiditis, hypophysitis, pancreatitis, and sarcoid-like reactions, can be observed using medical imaging such as CT, MRI, and fluorodeoxyglucose (FDG) PET/CT scans [27] (Table 5). However, the incidence of irAEs was low, suggesting that ICIs have good toxicity profiles. For example, the incidence of pneumonitis has been reported to be approximately 5% [28]. These irAEs usually occur within the first 6 months of treatment at the first re-staging scan

but may occur up to 1 year after discontinuation of ICI therapy [29]. In this regard, it is important to understand the pattern of irAE occurrence induced by ICIs and the effective management [30].

In contrast, toxicities related to CAR-T cell therapy can be serious, as CAR-T cell therapy can cause cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), or hemophagocytic lymphohistiocytosis/macrophage activation syndrome (Table 5) [31,32]. The typical time for CRS is approximately 1–5 days after infusion, with an approximate incidence of 42%–100% and severe incidence in 0%–46% of patients. ICAN usually occurs within 1–3 weeks after infusion and in 0%–50% of severe cases [32,33]. Although CRS and ICANS are usually concomitant and correlated, they rarely occur independently. Since imaging plays a crucial role in evaluating CRS and ICANS after CAR-T cell treatment, radiologists need to understand these phenomena [31].

### Imaging Criteria for Response Assessment in Clinical Trials

Treatment response assessments are key determinants of clinical trial success or failure. Imaging biomarkers with regulatory approval can be used as the primary endpoints in

**Table 5. Imaging Findings for Immunotherapy-Related Toxicities**

Toxicity	Imaging Findings
Interstitial pneumonitis	Four major patterns: organizing pneumonitis (most common), non-specific interstitial pneumonia (second most common), hypersensitivity pneumonitis, and acute interstitial pneumonia
Hepatitis	Hepatomegaly, heterogenous parenchymal enhancement, periportal edema, periportal lymphadenopathy, subserosal edema of gallbladder wall, and ascites
Enterocolitis	Bowel wall thickening, mucosal enhancement, air-fluid levels, perivisceral stranding, and mesenteric hyperemia
Thyroiditis	Heterogenous echogenicity on ultrasonography Marked hypervascularity on a Doppler study Intense and diffuse FDG uptake on an FDG-PET/CT scan
Hypophysitis	Symmetric enlargement of the pituitary glands with diffuse enhancement FDG uptake in the pituitary gland on FDG-PET/CT
Pancreatitis	Pancreas parenchymal enlargement, focal or segmental hypo-enhancement, peripancreatic fat stranding, and peripancreatic fluid collection
Sarcoid-like reaction	Bilateral symmetric hilar and mediastinal lymphadenopathy Pulmonary peri-lymphatic nodules with a predominance in the upper lobes
Cytokine release syndrome	Pulmonary edema, pleural effusion, atelectasis, consolidation
ICANS	Cerebral edema (abnormal white matter T2 hyperintensity), leptomeningeal enhancement, cerebral cortical infarct, multifocal microhemorrhages, subarachnoid hemorrhage, and mass effect (midline shift)
HLH/MAS	Hepatosplenomegaly, periportal edema, gallbladder wall thickening, hepatic steatosis, ascites, bilateral lung infiltrates, and pleural effusion

FDG = fluorodeoxyglucose, HLH/MAS = hemophagocytic lymphohistiocytosis/macrophage activation syndrome, ICANS = immune effector cell-associated neurotoxicity syndrome

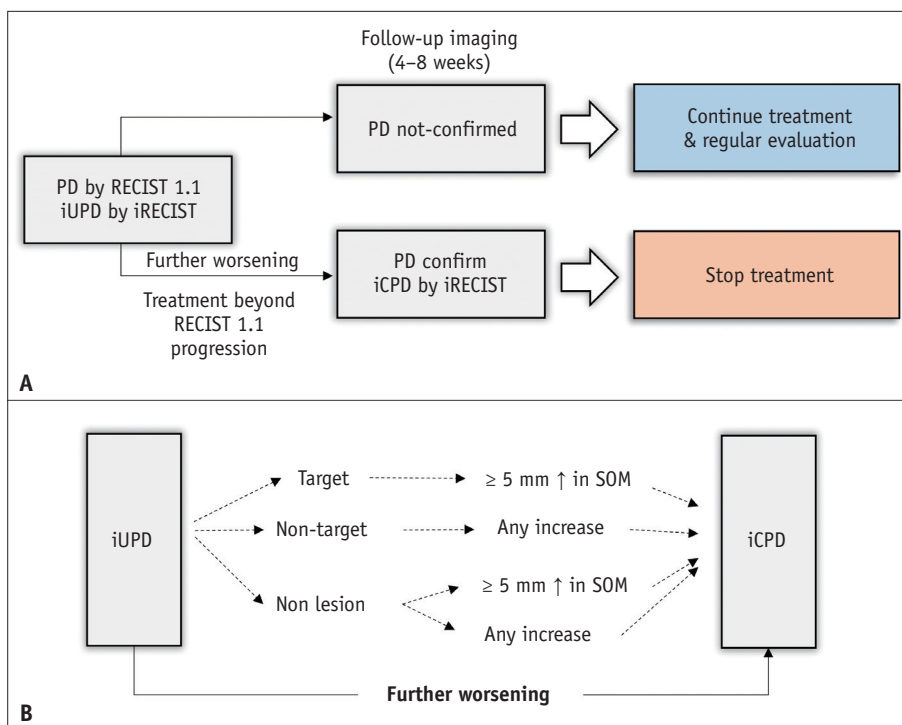
these assessments. The findings from response assessment criteria, such as the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, Lugano classification, and Response Assessment in Neuro-Oncology (RANO), have been used as primary endpoints in most oncologic clinical trials over the last few decades (Fig. 2). As cancer drugs evolve from being targeted to immunotherapeutic agents, response assessment criteria have also evolved. Notably, immune response criteria have been proposed for solid cancers (iRECIST), lymphomas (LYRIC), and brain tumors (iRANO) [6].

Traditionally, the RECIST based on tumor extent changes has been used for treatment response assessments [34]. The iRECIST was released in 2017 to better assess treatment responses, particularly for ICIs.

As mentioned above, tumor responses to ICI therapies can arise as atypical response patterns, termed pseudoprogression, which may not be captured by RECIST 1.1 [8,35]. In this regard, some investigators believe that RECIST 1.1 did not consider unusual response patterns, such as pseudoprogression after ICI treatment, and that this was evaluated as progressive disease (PD), which could lead to treatment discontinuation [5,36]. After considering

the response patterns associated with immunotherapy and attempting to supplement the limitations of the existing criteria, a new set of immune response assessment guidelines (termed iRECIST) was developed by the RECIST Working Group in 2017.

As presented in Figure 5, the crucial difference between iRECIST and RECIST 1.1 is that PD on RECIST 1.1 is divided into unconfirmed PD (iUPD) and confirmed PD (iCPD) on iRECIST. Based on the iRECIST, even if PD is determined by RECIST 1.1, treatment beyond progression (TBP) can be continued with consideration of the patient's clinical condition (Fig. 5A). Follow-up images are required 4–8 weeks after the initial iUPD (refer to the initial PD rules per RECIST 1.1). If there are any findings suggestive of a further worsening of the disease, PD is confirmed (iCPD). Figure 5B shows various circumstances wherein further worsening can be observed. The new concepts underlying iRECIST, which best reflect the pseudoprogression phenomenon of ICI therapy, are now being used as an exploratory endpoint to evaluate treatment efficacy in most clinical trials [5]. Although iRECIST may increase the burden on image interpretation and data management, many clinical trials



**Fig. 5. New concepts of iRECIST.**

**A.** Initial PD in RECIST 1.1 is classified as iUPD in the iRECIST. Treatment beyond progression is continued when the patient is clinically stable. If there are any findings suggestive of a further worsening of the disease on subsequent follow-up imaging, PD is confirmed and classified as iCPD.  
**B.** Various situations of a further worsening include at least a 5-mm increase in the SOM of the target lesions, any increase in non-target lesions, and an increase in new lesions (either new lesion target or new lesion non-target). iCPD = immune confirmed PD, iRECIST = Immune Response Evaluation Criteria in Solid Tumor, iUPD = immune unconfirmed PD, PD = progressive disease, SOM = sum of the measurement



now use RECIST 1.1 and iRECIST simultaneously [5].

There has been some controversy as to whether iRECIST has a significant impact on RECIST 1.1 while evaluating ICI treatment efficacy. A recent meta-analysis has demonstrated that iRECIST had a minor impact on progression-free survival compared with RECIST 1.1, i.e., a pooled difference of 0.46 months (14 days). However, no significant differences were observed between these systems in terms of the objective response rate (23.6% and 24.7%, respectively,  $p = 0.72$ ) or disease control rate (45.3% and 48.7%, respectively,  $p = 0.56$ ) [5].

Another noteworthy issue is the possibility of futile treatment for most patients who do not experience pseudoprogression. In general, pseudoprogression has an incidence of less than 10% in solid tumors and lymphomas [37]. TBP may continue in patients with initial progression according to RECIST 1.1. Of these cases, there was concern that only a minor portion would benefit from TBP. Recently, Won et al. [8] reported however that TBP in patients with cancer patients showed an overall survival benefit compared with those in whom this intervention was not implemented (median overall survival 17.2 months vs. 7.5 months, respectively,  $p < 0.001$ ).

### Molecular Imaging Biomarkers for Immunotherapy

Response criteria based on anatomy, such as RECIST 1.1 and iRECIST, may have limitations with respect to an early treatment response assessment. Hence, sizeable efforts have been made to develop new functional or molecular imaging biomarkers. Currently, the most commonly used imaging modality for functional and molecular imaging biomarkers is FDG-PET [38]. In 2014, the United States Food and Drug Administration (FDA) authorized this imaging modality for treatment response assessments in patients with lymphoma using the Lugano criteria. The LYRIC was developed for immunotherapy response assessment in lymphoma (Fig. 2B). LYRIC is a modification of the Lugano criteria to address the atypical response patterns of immunological agents and apply the current lymphoma response criteria appropriately to immune-based therapies. This introduces a new response category called the indeterminate response (IR) while maintaining the concept of the existing immune response criteria. IR is a point in time to recognize that both delayed response and immune-mediated inflammation may occur during the initial treatment and may be challenging to distinguish from progression on imaging alone. In addition, this allows for the flexible continuation of follow-

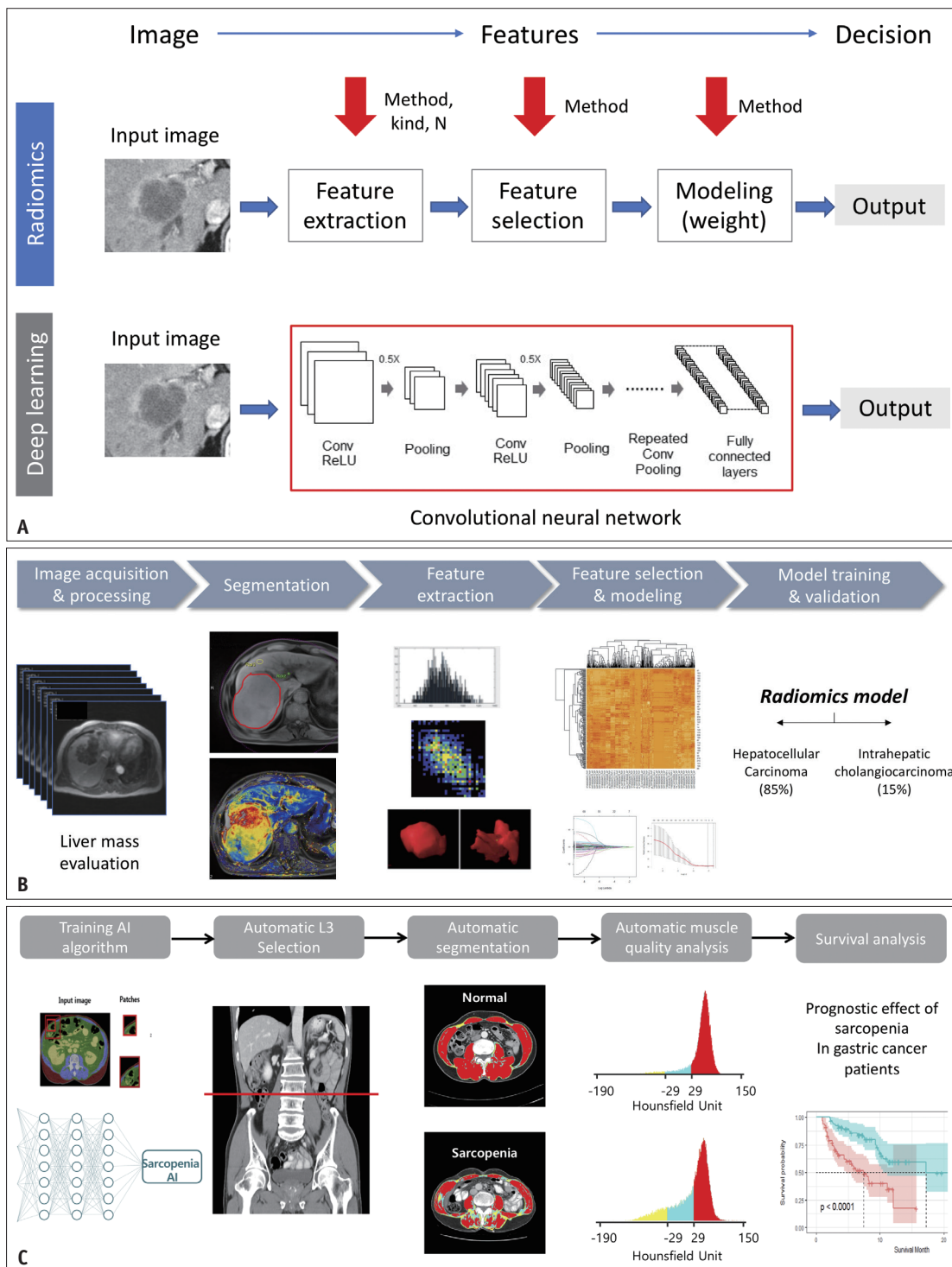
up treatment after IR and requires a mandatory follow-up evaluation within 12 weeks to confirm or refute true PD [39].

In May 2021, the United States FDA approved piflufolostat F-18 (Pylarify), a targeted PET imaging agent, as an imaging biomarker to detect prostate-specific membrane antigen (PSMA)-positive lesions in men with suspected metastases or recurrences in prostate cancer based on prostate-specific antigen levels. Various clinical trials for patients with high-risk prostate cancer have demonstrated the correct anatomical disease location, showed high specificity, and confirmed meaningful clinical information for subsequent management [40]. PSMA PET/CT-based response criteria have been suggested for response assessments of the efficacy of immunotherapeutics, such as sipuleucel-T, dostarlimab, and pembrolizumab, against metastatic prostate cancer [41]. In addition, PSMA-targeting immunotherapeutic agents, such as PSMA-targeted CAR T cells or PSMA-targeted bispecific T cell-directed therapy, have been actively developed with encouraging preclinical data and early phase clinical trial data [42]. PSMA PET/CT is expected to be a new option for treatment response assessment beyond diagnosis in patients with advanced/metastatic prostate cancer who need PSMA-targeted treatment.

### Future Imaging Biomarkers: From Radiomics to AI Techniques

Advances in computer image engineering techniques have enabled us to perform quantitative and automated image analysis beyond traditional image analysis by experts. Of these, radiomics and AI are the most actively applied techniques. In the field of cancer imaging, radiomics is commonly used to extract tumor phenotypic features from medical images using data characterization algorithms and retrieve clinically meaningful information [43]. Particularly, radiomics has gained emphasis as a tool for precision medicine, with the hypothesis that imaging phenotypes can reflect tumor biological behavior and thus can provide useful diagnostic and prognostic information. AI, such as deep learning, is the most actively investigated technique in medical imaging. Unlike radiomics, which uses extracted features according to predefined rules, deep learning techniques use neural network algorithms that learn the best features to achieve a given task independently (Fig. 6A).

Radiomics is a multidisciplinary approach involving radiologists, imaging and data scientists, and clinicians,



**Fig. 6. Application of radiomics and AI in the field of cancer imaging.**

**A.** Radiomics and deep learning processes. Radiomics uses extracted features according to predefined rules in the segmented cancer region. In contrast, deep learning uses neural network algorithms which learn the best features on their own. **B.** Example of radiomics for cancer diagnosis. The large mass in the right liver shows indistinct imaging features. The radiologist established a differential diagnosis of hepatocellular carcinoma and cholangiocarcinoma. The radiomics technique extracts image features such as shape, histogram, texture, and high-order features and performs comprehensive classification modeling with random forest and support vector machine, leading to the probability of hepatocellular carcinoma and cholangiocarcinoma. **C.** Example of AI for sarcopenia evaluation in patients with cancer. In patients with gastric cancer who underwent gastrectomy, the deep learning algorithm automatically selects CT slices at the L3 vertebral body level, segments muscle and intramuscular fat areas, and performs survival analysis to predict the overall survival according to the severity of sarcopenia. AI = artificial intelligence, Conv = convolution layer, ReLU = rectified linear unit

following processes that include tumor segmentation, image pre-processing, feature extraction/selection, and model training and validation [44]. Thus, it has the potential to express quantitative values for imaging characteristics that are challenging to do with the human eye (Fig. 6B) [45]. AI has been applied in medical imaging for automated disease diagnosis or classification, segmentation, prognostication, and response assessment. The most important characteristic of AI might be process automation, which can increase the efficiency of image analysis and save human resources (Fig. 6C). Over the past 10 years, studies on radiomics combined with AI have increased rapidly, and it has become possible to process massive amounts of image data more effectively [46].

In the field of oncology, many studies have reported the clinical value of radiomics and AI for predicting clinical outcomes, such as treatment response, tumor histology, and overall survival [47]. Regarding the use of immunotherapeutic agents, there have been reports that radiomics can overcome the issues by accurately assessing pseudoprogression. A prior study by Barabino et al. [48] demonstrated that delta-radiomics, which extracts features from sequential CT scans, can distinguish pseudoprogression from true progression. Basler et al. [36] also reported that PET/CT-based radiomics, lesion volume, and blood markers are promising predictive biomarkers for early differentiation of pseudoprogression from true progression.

Radiomics has thus been shown to be a promising tool for realizing precision medicine in the era of immunotherapy by providing a comprehensive characterization of tumor biology via conventional medical imaging [43,49]. However, any model that combines radiomics and high-level computing technology still requires external validation and evaluation within the various clinical pathways being applied as a decision-making tool by clinicians [50]. The existing gap between knowledge and clinical needs causes a lack of clinical utility in studies. Of note, feature extraction and selection based on algorithms are largely dependent on the settings used for the radiomics or AI processes, which limits human understanding. Therefore, it may be necessary to develop human-explainable AI or radiomics. In addition, standardization of radiomics processes, such as pre-processing and modeling, is needed and should be based on international consensus guidelines and/or accumulated evidence [43,51].

## Conclusion

Immunotherapy is a new paradigm in anti-cancer treatment. The emergence of new immunotherapies and advances in precision medicine have highlighted the important roles of imaging and early and accurate treatment response assessments. This has, in turn, prompted the evolution of imaging analysis methodologies from immune response assessment criteria, such as iRECIST, to radiomics and AI technologies. Radiologists, as key members of multidisciplinary cancer treatment teams, need to keep abreast of these recent trends.

## Availability of Data and Material

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

## Author Contributions

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### Funding Statement

This work was supported in part by grants from the National Research Foundation of Korea (NRF-2021R1A2B5B03001891).

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