



Teaching cancer imaging in the era of precision medicine: Looking at the big picture

Christopher N Chin^a, Ty Subhawong^b, James Grosso^b, Jeremy R. Wortman^c,
Lacey J. McIntosh^d, Ryan Tai^d, Marta Braschi-Amirfarzan^c, Patricia Castillo^b,
Francesco Alessandrino^{b,*}

^a Department of Surgery, Leonard M. Miller School of Medicine, Miami, FL, USA

^b Department of Radiology, Leonard M. Miller School of Medicine, Miami, FL, USA

^c Department of Radiology, Lahey Health Medical Center, Beth Israel Lahey Health, Tufts University school of Medicine, Boston, MA, USA

^d Department of Radiology, University of Massachusetts Chan Medical School, Memorial Health Care, Worcester, MA, USA

ARTICLE INFO

Keywords:

Oncologic imaging
Tumor response criteria
Checkpoint inhibitors
Molecular targeted therapies
Adverse events, clinical trials

ABSTRACT

The role of imaging in cancer diagnosis and treatment has evolved at the same rapid pace as cancer management. Over the last twenty years, with the advancement of technology, oncology has become a multidisciplinary field that allows for researchers and clinicians not only to create individualized treatment options for cancer patients, but also to evaluate patients' response to therapy with increasing precision. Familiarity with these concepts is a requisite for current and future radiologists, as cancer imaging studies represent a significant and growing component of any radiology practice, from tertiary cancer centers to community hospitals.

In this review we provide the framework to teach cancer imaging in the era of genomic oncology. After reading this article, readers should be able to illustrate the basics cancer genomics, modern cancer genomics, to summarize the types of systemic oncologic therapies available, their patterns of response and their adverse events, to discuss the role of imaging in oncologic clinical trials and the role of tumor response criteria and to display the future directions of oncologic imaging.

1. Introduction

The significant advancements in cancer genomics over the past twenty years have completely revolutionized the field of oncology [1–3]. High-throughput gene sequencing methods, which allowed whole cancer genome sequencing, ultimately facilitated the development of modern therapies which target various molecular pathways involved in cancer survival and proliferation. As such, a vast array of systemic oncologic therapies was made available in the past twenty years, each associated with different pattern of response and adverse events. Given the growing amount of cancer imaging studies performed in any radiology department, from large academic centers to private practices, current and future radiologists are expected to be familiar with the basic concepts of cancer genomics and the different types of targeted therapies available for cancer treatment.

Just as the direction of cancer therapy has changed, oncology has

grown to become a multidisciplinary field, with care coordinated among medical and surgical oncologists, radiation oncologists, radiologists, pathologists, and other medical providers. Radiologists at every level have become more and more involved in the management of cancer patients. Working closely with various oncology providers in multidisciplinary teams, radiologists should be fluent in the jargon of treatment options for oncologic patients [4].

Furthermore, imaging has become paramount in screening for, diagnosing, and staging cancer, as well as monitoring treatment response to different cancer therapies. Following the development of the imaging-based tumor response criteria, such as the World Health Organization (WHO) criteria in 1979 and the Response Evaluation Criteria in Solid Tumors (RECIST) in 2000, radiologists have been able to standardize assessments of response to systemic cancer treatments in clinical trials, underpinning evaluation of drug efficacy and significantly reducing time and costs for drug development with the use of imaging-

* Correspondence to: Division of Abdominal Imaging, Department of Radiology, Leonard M. Miller School of Medicine, 1611 NW 12th Ave, West Wing 279, Miami, FL 33136, USA.

E-mail address: falessandrino@med.miami.edu (F. Alessandrino).

<https://doi.org/10.1016/j.ejro.2022.100414>

based assessments [5,6]. As such, imaging-based survival endpoints represent the most efficient way to monitor response to therapies in cancer clinical trials [7]. Thus, radiologists are at the forefront of the late phases of drug development when analysis of therapeutic efficacy hinges on accurate and reproducible quantitative tumor measurements [8].

Since cancer imaging plays a central role in many radiology practices, it is crucial for radiology trainees to be familiar with three conceptual domains of modern cancer imaging: cancer genomics, oncologic therapies, and tumor response criteria in clinical trials.

In this review, we explore the framework for teaching cancer imaging in the era of genomic oncology, providing examples for each component: first, we will review the basics of modern cancer genomics; then we will summarize the different types of systemic oncologic therapies; finally, we discuss the role of imaging in oncologic clinical trials and the implementation of specific tumor response criteria. This manuscript serves as an overview of these important concepts in cancer imaging that can be used as a teaching tool for training future radiologists.

2. The cancer genome

Cancer is a disease of the genes [9]. Because certain gene mutations disrupt normal cell growth and death, uncontrolled proliferation of cells results in malignant transformation [10]. Fortunately, not all gene mutations and dysregulations lead to cancerous growths [11]. In fact, only a minority of alterations in the genome will actually lead to cancer. Therefore, the identification of the specific gene mutations that drive oncogenesis is a key factor in both understanding and treating this disease. To effectively understand cancer biology, it is crucial to identify the sites of common gene mutations in different cancer types and the different molecular pathways involved in cancer survival and proliferation.

Since the early 2000s when the human genome was analyzed via Sanger DNA sequencing, gene sequencing has been a prominent tool for understanding how genes regulate cell function [12,13]. While innovative at the time, this process was slow and costly [14]. The advent of high throughput sequencing significantly reduced costs and increase effectiveness of DNA analyses, allowing whole genome analysis of multiple cancer types, which in turn unveiled the genomic framework of human cancer [9, 15, 16].

When mutations disrupt pathways regulating cell growth, development, or death, uninhibited growth, lack of cell cycle arrest or apoptosis ensues, marking malignant transformation. Such oncogenic mutations are known as “driver mutations” and are responsible for the cancer phenotype, either through constitutive activation of proliferative signaling, or inactivation of tumor suppression [17]. However, these functional mutations comprise only a small fraction of myriad mutations found in a tumor; the vast majority are “passenger mutations” that have no direct neoplastic effect. However, they may serve as important markers of neoplastic clonality, even before morphological features of dysplasia become apparent [18].

A recently published compendium drawn from somatic mutations in more than 28,000 tumors (representing 66 cancer types) identified 568 cancer driver genes [19]. Importantly, while the most frequently mutated genes (at frequencies above 10%) have almost certainly already been discovered, their involvement across cancer types is probably even wider than previously suspected, with only about 10 driver genes considered “cancer-wide” drivers (e.g. *KRAS*, *TP53*, *PTEN*, *PI3K*, *RB1*, etc.) [19].

From this foundation of knowledge, different molecular pathways of driver mutations were identified. Each molecular pathway is associated with some aspect of cell growth, development, or death. When fully functional, they lead to the appropriate replication, development, and destruction of cells. However, when mutations arise in these pathways, some aspect of the cell regulation is lost, and this can lead to cancer development. Specifically, the mutations in the oncogenes lead to

uninhibited growth, lack of cell cycle arrest, or lack of apoptosis.

While discussion of all major pathways remains beyond the scope of this review, one well-known and clinically important pathway is the rat sarcoma virus (RAS) pathway (Fig. 1). It involves binding of epidermal growth factor (EGF) to its receptor (EGFR), which leads to a complex cascade of signaling genes including two separate pathways. Both these pathways, RAS-RAF-mitogen-activated protein kinase and the PI3 kinase (PI3K)-AKT-mechanistic target of rapamycin (mTOR) ultimately lead to cell proliferation, cell survival, and protein translation [20]. In fact, among human cancers, the PI3K-AKT pathway is the most frequently activated [21]. Some of the cancers most prominently associated with alterations in this pathway are melanoma, colorectal cancer, human epidermal growth factor receptor 2 (HER2) breast cancer, pancreatic cancer, isocitrate dehydrogenase (IDH-1) wild type glioma, lung adenocarcinoma, thyroid carcinoma. To combat the EGF-EGFR interaction, researchers have developed chemotherapeutic agents that prevent the binding of the ligand to the receptor, suppressing signal transduction.

When translating this information into the clinical setting, it would be appropriate to target the most common gene mutations leading to cancer. For cancers like non-small cell lung cancer (NSCLC), Kirsten-RAS (KRAS) mutations have been found to be a significant prognostic indicator of poor outcome [22]. In a study comparing the outcomes of patients with a KRAS mutation and those without, patients with the KRAS mutation had a 5-year survival rate of 11.5% compared to 64.1% in patients who did not have the mutation [23]. Additionally, KRAS can be used as a selection marker for specific oncologic treatments. In a study of 427 patients with metastatic colorectal cancer, patients identified with the KRAS mutation (43%) were found to have 0% response rate to the panitumumab treatment, compared to 17% response rate in wild type KRAS colorectal cancers [24].

Furthermore, specific mutations in these pathways have been associated with different imaging features and patterns of metastases in multiple cancers (Fig. 2) [25].

3. Oncologic therapies

In order to facilitate comprehension of the multitude of systemic oncologic therapies available, it is helpful to classify them in cytotoxic chemotherapies, molecular targeted therapies, hormonal therapies, and immunotherapies. Radiologists involved in cancer patients' care need to be familiar with their mechanism of action, patterns of response, and toxicity [26].

3.1. Cytotoxic chemotherapies

Cytotoxic chemotherapy involves the direct alteration of DNA and other cell components [27]. Primarily, the cells most affected from agents that affect cell division will be those with the highest rates of cell division [28]. Specifically, cells with the highest rates of *de novo* DNA synthesis are ideal targets for many of the cytotoxic chemotherapeutic agents. These agents take advantage of the ability of cancer cells to divide more rapidly than non-cancerous cells and target cellular DNA [29]. A primary example of cytotoxic chemotherapeutic agents are the platinum analogs. One such platinum analog, Cisplatin, is used in leukemia, lymphoma, breast, testicular, ovarian, and primary bone cancers [30]. It acts by binding to DNA strands forming both intrastrand and interstrand crosslinks with DNA. This cross linking makes the DNA inoperative, thus leading to cell death [31]. Although some patients will show an objective response to effective cytotoxic therapy with a decrease in tumor burden on imaging studies, many patients develop some type of resistance to the platinum analogs [32] [30, 33, 34]. It is hypothesized that epigenetic factors such as high levels of DNA repair mechanisms or interference with apoptosis can influence the efficacy of these agents [35].

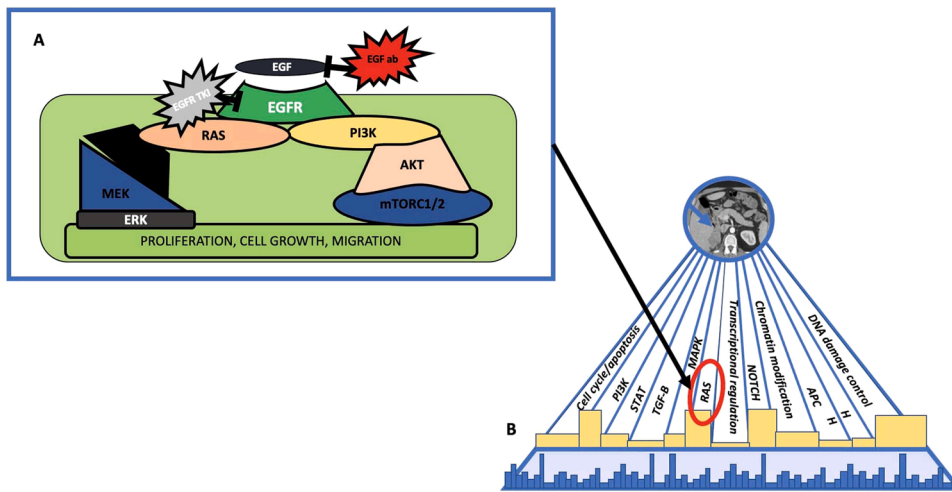


Fig. 1. RAS pathway (A) and cancer genome landscape overview (B). (A) The RAS pathway is activated by EGF and EGF antibody binding to its receptor, EGFR. This binding leads to a signaling cascade which includes PI3K-RAS-mTORC and RAS-RAF-MEK ultimately leading to cell growth, proliferation, and migration. EGFR tyrosine kinase inhibitors (TKI) (gray burst), such as erlotinib, used for treatment of non-small cell lung cancer, and EGF antibodies, such as cetuximab (red burst), used for treatment of colorectal cancer, block the signaling cascade, ultimately halting cancer cell proliferation. (B) Cancer genome landscape overview. Multiple passenger mutations (blue array) and driver mutations (yellow rectangles) form the base of the triangle and will ultimately lead to cancer proliferation (short blue arrow) through multiple molecular pathways, including RAS pathway (red circle). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

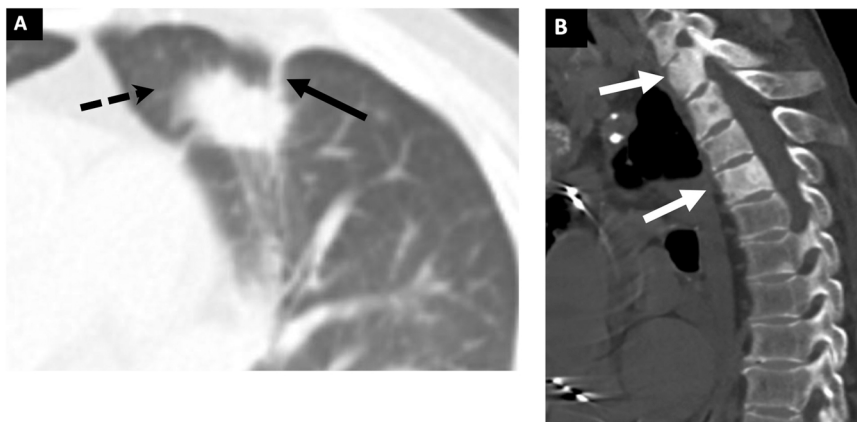


Fig. 2. 72-year-old man with EGFR-mutated non-small cell lung cancer (NSCLC) who developed lung and bone metastases. Axial CT of the chest in lung window (A) shows a mass with spiculated morphology (dashed arrow) and associated pleural retraction (arrow). (B) Sagittal reconstructed image of the thoracic spine shows multiple sclerotic lesions (arrows), representing metastases from NSCLC. EGFR mutated NSCLC is associated with air bronchograms, pleural retraction, small lesion size, and absence of fibrosis, compared to EGFR-wild type NSCLC. In addition, this NSCLC subtype is associated with increased bone and lung metastases compared to ALK-mutated NSCLC.

3.1.1. Adverse events

Due to the effect on cellular DNA, it is understandable that there is inherent risk to normal noncancerous cells. Generally, one of the most common side effects of the cytotoxic agents is suppression of newly formed cells within the bone marrow, or myelosuppression [36]. Specific adverse events for the platinum analogs are dose-dependent peripheral neuropathies, acute kidney injury, ototoxicity and cardiovascular toxicity [30, 37, 38–40].

3.2. Molecular targeted therapies

Molecular targeted therapy is directed at specific mechanisms of the cell signaling pathway that halt cancer growth [41]. Their action is based on their ability to hone in on distinct cell markers such as cell surface antigens, signal/gene transduction pathways, and growth factor receptors. Blockage of these targets leads to downstream inhibition and regulation of cell processes like cellular growth, DNA replication, and angiogenesis [42]. Because of this selective action, these agents have the potential to have less effect on non-cancerous cells [43]. The percentage of US patients with cancer estimated to benefit from genome-targeted therapy in 2006 was 0.70%, but by 2018 it had increased to 4.90% [44].

Nearly all the current molecular targeted chemotherapeutic agents have been designed to act on the cellular processes of cell growth, cell development, or maintenance of the genome [10]. However, as the name implies, each of these agents acts on a specific part of these vital

cell processes. Receptor tyrosine kinases (RTKs) are key regulators of cell growth and differentiation, cell cycle control, and cell survival. They involve binding of a ligand to a ligand receptor leading to cascade of events downstream from the initial binding site to perform some goal of cell metabolism [20,45]. A mutation in a receptor in a RTK will ultimately cause unregulated cell growth. Therefore, researchers have pushed to develop agents, RTK inhibitors, with specificity to act on these receptors and prevent unregulated cell growth. A prime example of a target that researchers have been able to direct antineoplastic agents against is the RAS pathway. One notable receptor in this pathway is EGFR, involved in many cancer types, including NSCLC and colorectal cancer [46–48]. A notable example of a targeted molecular therapy targeting EGFR is erlotinib, a 1st generation reversible EGFR inhibitor [49]. Its action prevents phosphorylation of the EGFR which leads to cessation of cell proliferation and growth, ultimately leading to tumor regression [50].

3.2.1. Adverse events

Receptor tyrosine kinase inhibitors show a wide range of adverse events including rash, gastrointestinal upset or pneumonitis. Erlotinib, specifically, has been associated with radiologic evidence of various adverse events, including gastrointestinal toxicity, which is observed in up to 15% of patients, most commonly presenting as fluid filled colon [51–53].

3.3. Hormonal therapies

Hormones are chemical messengers that act on targets that are distant from the source of messenger release. Some endogenous hormones, including testosterone and estrogen, help the body regulate cell growth and proliferation. As such, they can potentially play a role in oncogenesis when expressed in excess. In these cases, hormones can be used as mechanistic targets of hormone therapy in which the primary goals are a decrease in hormone production or hormone receptors antagonization [54].

Estrogen is essential for breast tissue growth and, therefore, has the potential to facilitate breast cancer growth in both premenopausal and postmenopausal women [55]. Because of this, inhibition of estrogen production is a possible mechanism by which breast cancer growth can be halted. Two primary means of preventing estrogen production are the aromatase inhibitors (AI) and the luteinizing hormone releasing hormone (LHRH) agonists. AI act on the endogenous enzyme present in breast tissue, aromatase, which catalyzes the conversion of androgens to estrogen, thereby preventing excess estrogen production [56]. Because of this mechanism of action, AIs have been shown to have the most efficacy in estrogen receptor (+) breast cancers [55]. Similarly, LHRH prevent estrogen production but through a different manner. These agents act by competitively binding to LHRH receptors in the anterior pituitary stimulating the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Initially, both LH and FSH cause an increase in testosterone production. However, over time the LHRH receptor in the pituitary becomes desensitized and causes a down-regulation in testosterone production, subsequently leading to a decrease in estrogen production [57].

3.3.1. Adverse events

Because of its effect on bone metabolism, decreases in estrogen lead to decreases in bone mineral density [58]. For this reason, a significant adverse effect of AIs and LHRH agonists is increased bone loss, which can be assessed by several techniques, including dual energy x-ray absorptiometry (DEXA) and quantitative CT [54, 59, 60]. Additionally, these agents are also associated with other symptoms of decreased estrogen such as vaginal dryness, hot flashes, sleep difficulties, and adverse mood changes [61].

3.4. Immunotherapies

Various immunotherapies are currently available for cancer treatment: immune checkpoint inhibitors, namely CTLA-4 inhibitors, programmed death (PD)-1 and PD-L1 inhibitors; Cancer vaccines; exogenous cytokines and interferons, including recombinant IL-2; and cellular immunotherapies, including chimeric antigen receptor T-cells therapies.

Among the immune checkpoint inhibitors, pembrolizumab is a monoclonal antibody with action against the PD-1 protein, which has demonstrated improved overall survival in various cancers such as NSCLC and melanoma [62,63]. Its antitumor activity is based on the inhibition of the PD-1, a receptor expressed on regulatory and effector T cells whose role is to suppress the activation of T cells, when activated by its circulating ligands [64,65]. When PD-1 receptors are blocked, T cells initiate an inflammatory response against any susceptible tissue, including cancer cells and healthy tissues, leading to shrinkage of the tumor as well as a spectrum of potential autoimmune-like adverse events, termed immune-related adverse events (irAEs) [66,67].

Immune checkpoint inhibitors, including pembrolizumab, are associated with four unique patterns of treatment response, originally described in patients with advanced melanoma treated with ipilimumab: 1) no new lesions and decrease in size of baseline lesion within twelve weeks; 2) stable disease with no significant change in baseline lesions followed by slow steady decline in tumor burden; 3) initial increase in tumor burden followed by decrease in tumor burden; 4)

apparent “new” lesions followed by a decrease in tumor burden more than twelve weeks after treatment start (Fig. 3) [68,69]. The latter two are termed pseudoprogression [70]. Initial increases and apparent “new” lesions represent either true tumor growth in the period before the immune system is able to combat tumor or immune infiltration of existing or micrometastatic disease.

3.4.1. Adverse events

Immune checkpoint inhibitors are associated with a unique set of toxicities that are related to the body’s autoimmune response, and include pneumonitis, dermatitis, colitis, myositis, to mention a few (Fig. 4) [68]. Multiple studies are investigating the imaging appearances of these irAEs [71,72]. As a representative example, a study on 137 patients with NSCLC treated with the PD-1 inhibitor nivolumab demonstrated that 13% of patients developed radiographically evident abdominal irAEs, which included colitis, hepatitis, pancreatitis, nephritis, and enteritis, with a median time of onset of approximately two months [71,72].

4. Cancer imaging in clinical trials and tumor response criteria

Imaging plays a dominant role in clinical trial design, frequently forming the basis for primary endpoints, and familiarity with the role of imaging in the various phases of a drug trial provides the necessary framework to introduce the concepts of tumor response criteria [7].

Clinical trials are a primary means by which researchers are able to evaluate the efficacy of novel chemotherapeutic agents [73]. Commonly divided into five phases, clinical trials can assess tolerability and pharmacokinetics of the new drug, dosing, efficacy, and toxicity. While in the pre-clinical stage, or phase 0, researchers are primarily invested in assessing the safety profile in animal models and approximating safe doses for human therapy. In phase I, the agents are introduced into a small number of human volunteers, with or without disease, with the goal of assessing dose-limiting toxicity. In phase II, a larger group of people with the disease of interest are given the new drug with aims at assessing pharmacokinetics, pharmacodynamics, safety, and survival. In phase III, using randomized control trials, researchers are able evaluate correlations between response and therapy, eliminate the possibly of confounders, and determine systematic differences between groups [74, 75]. Following a phase III trial, the US Food and Drug Administration (FDA) can require a fourth phase, phase IV, to assess less common adverse events after a drug is released on the open market. More recently, new ways to assess drug efficacy have been developed, termed master protocols, which includes various types of trials, such as umbrella trials or basket protocols, and allow evaluation of multiple treatments in different diseases, to facilitate recruitment of patients with rare diseases and to expedite oncology drug development (Fig. 5) [8,76].

To obtain FDA regulatory approval, a drug must show evidence of clinical benefit, the gold standard being overall survival (OS). Crucially, objective response rate (ORR) and progression-free survival (PFS) have been deemed by the FDA as adequate markers of clinical benefit sufficient to inform drug approval decisions, greatly expediting drug development [77,78]. Comparisons of these parameters (frequently defined over an interval such as 6-month PFS) can then be carried out among the arms of the trial to establish drug efficacy.

During the various phases of the trials, researchers are constantly monitoring treatment response, assessing when to continue therapy, and evaluating when therapy should be halted. Currently, a significant portion of evaluation clinical response during these trials is done via imaging. In this manner, changes in tumor size or characteristics on imaging serve as surrogate endpoint, or indicator to measure the true outcome, total regression, of an oncologic therapy [79]. In each phase of a clinical trial, researchers are gauging response imaging endpoints. Often this includes evaluating change in tumor size, checking for new lesions or changes in perfusion or vascularity of lesions. To standardize this process, response evaluation criteria in solid tumors (RECIST) were

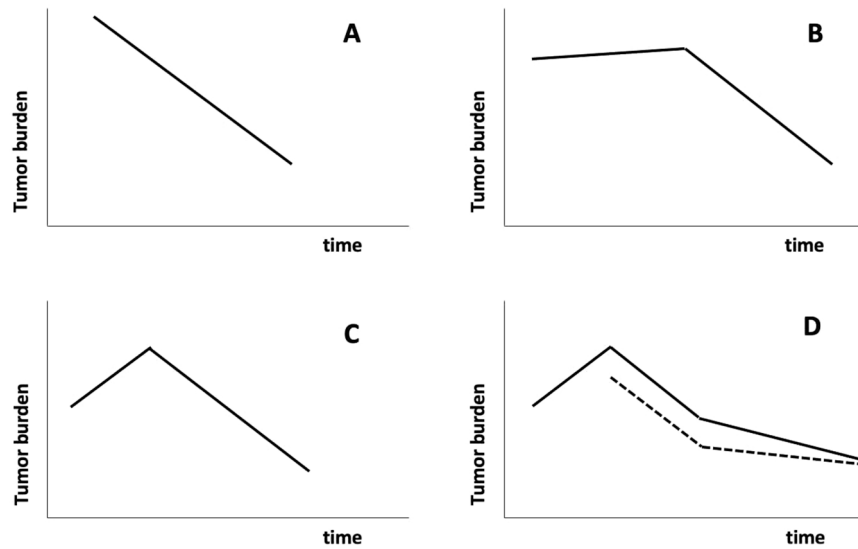


Fig. 3. Patterns of response to immune checkpoint inhibitors, as initially described in patients with melanoma treated with ipilimumab. Images ABCD show four patterns of response, with change in tumor burden during treatment: (A) Steady decrease in tumor burden; (B) Stable disease followed by slow, steady decrease in tumor burden; (C) Response after initial increase in tumor burden; (D) Reduction in tumor burden after appearance of new lesions (dashed line).

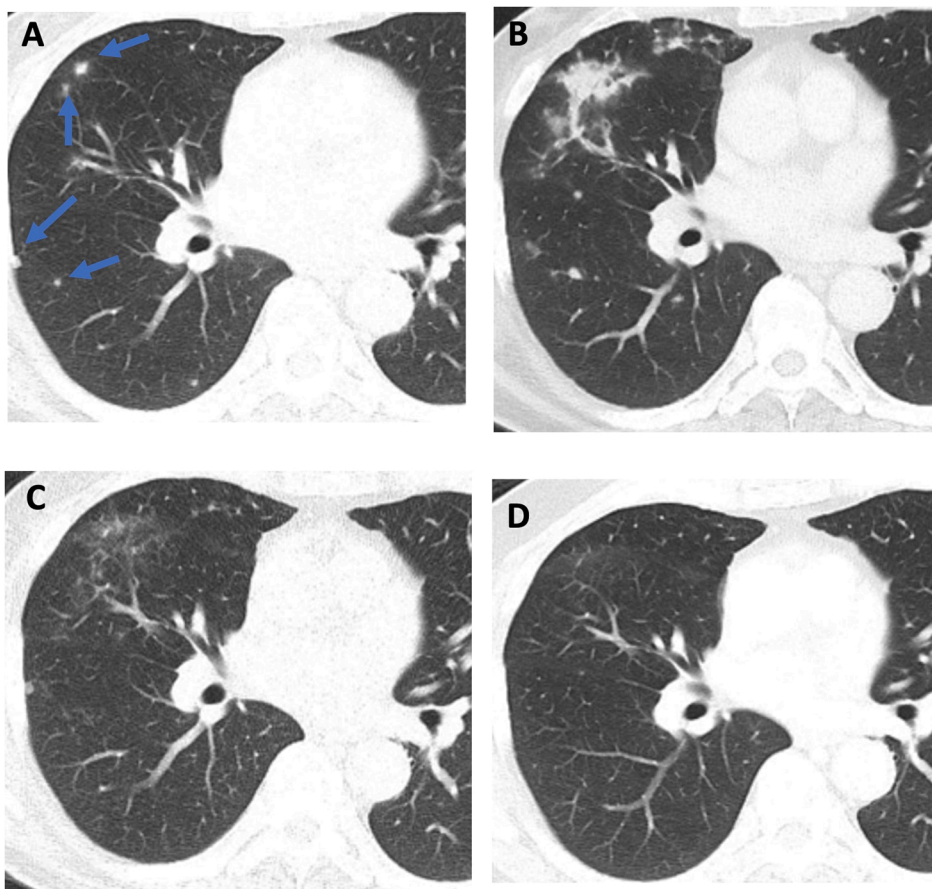


Fig. 4. Pulmonary toxicity in a 50-year-old man with metastatic melanoma on immune checkpoint inhibition. Axial CT chest performed before starting nivolumab and ipilimumab (two immune checkpoint inhibitors) shows small right middle and right lower lobe metastatic lung nodules (A) (arrows). CT performed three months after treatment with immune checkpoint inhibitors started shows consolidative opacity in the right middle lobe (B). Patient had shortness of breath and immune related pneumonitis was suspected. Prednisone taper was started and ipilimumab was stopped. Follow up CTs show residual ground glass changes in the middle lobe (C) and resolution of the lung nodules (D).

developed in 2000 and then revised in 2009 to become RECIST 1.1 [5, 80].

The four specific response categories of RECIST 1.1 include the disappearance of all lesions and reduction of pathological lymph nodes to < 10 mm, or complete response (CR); the reduction of at least 30% in the sum of diameters of all target lesions, or partial response (PR)

(assuming non-target lesions do not show unequivocal progression); an increase by 20% in the sum the diameters of all target lesions, or progressive disease (PD); if the change in size of lesions fails to qualify as PD or PR, the timepoint response is stable disease (SD) [77,80]. Unequivocal progression in non-target lesions or the appearance of new lesions constitute PD, regardless of the target-lesion response. Importantly,

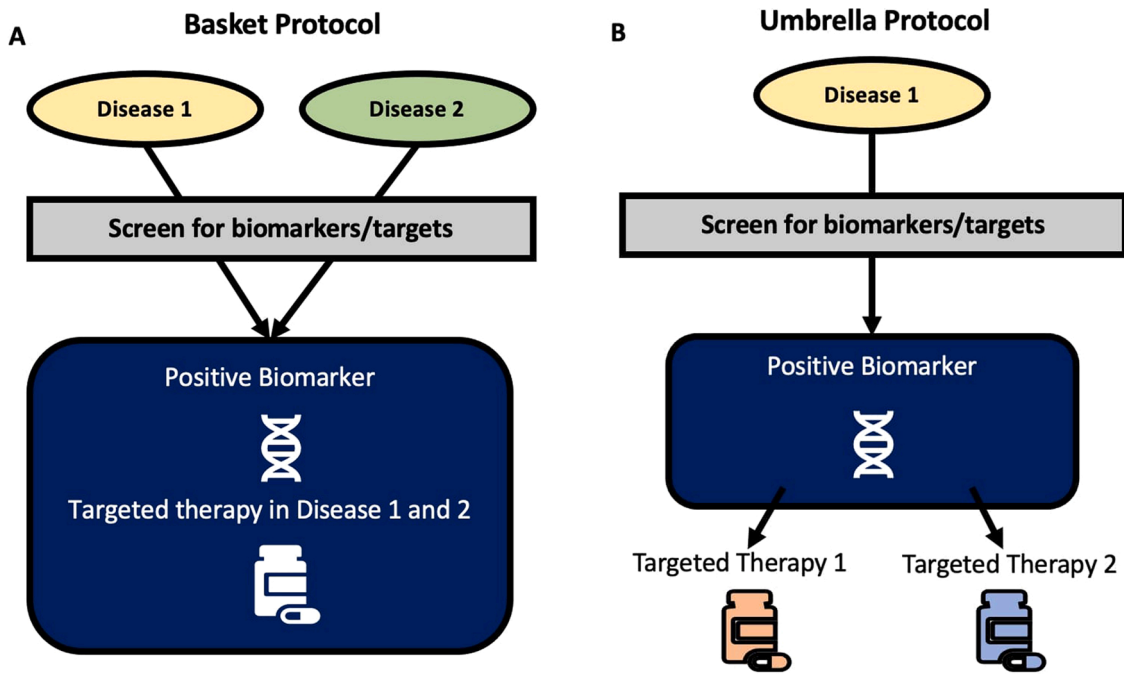


Fig. 5. Clinical trial design. Basket (A) and umbrella (B) protocols, two types of Master Protocols which allow for the evaluation of multiple treatments in different diseases (A) and evaluation of different treatments for the same disease (B). Master protocols facilitate recruitment of patients with rare genetic subtypes of a disease and allow a faster evaluation of treatment compared to randomized controlled clinical trials.

bone lesions are generally not considered measurable, unless there is a soft tissue component. RECIST 1.1 objective responses, used in calculating the ORR, encompass both CR and PR categories, while non-responders include SD and PD.

Because these criteria involve changes in size or new lesions, imaging is paramount in determining endpoints for new clinical drug trials. However, different oncologic drugs demonstrate varied imaging

responses to treatment. This poses a challenge for oncologic agents which manifest changes in enhancement or tumor viability rather than size decrease as treatment response, including various molecular targeted therapies, and responses may not be captured using RECIST 1.1. For cytotoxic chemotherapy, in which patterns of response are generally marked by a decrease in tumor burden, RECIST1.1 is well-suited to evaluate an effective clinical response. On the contrary, for molecular

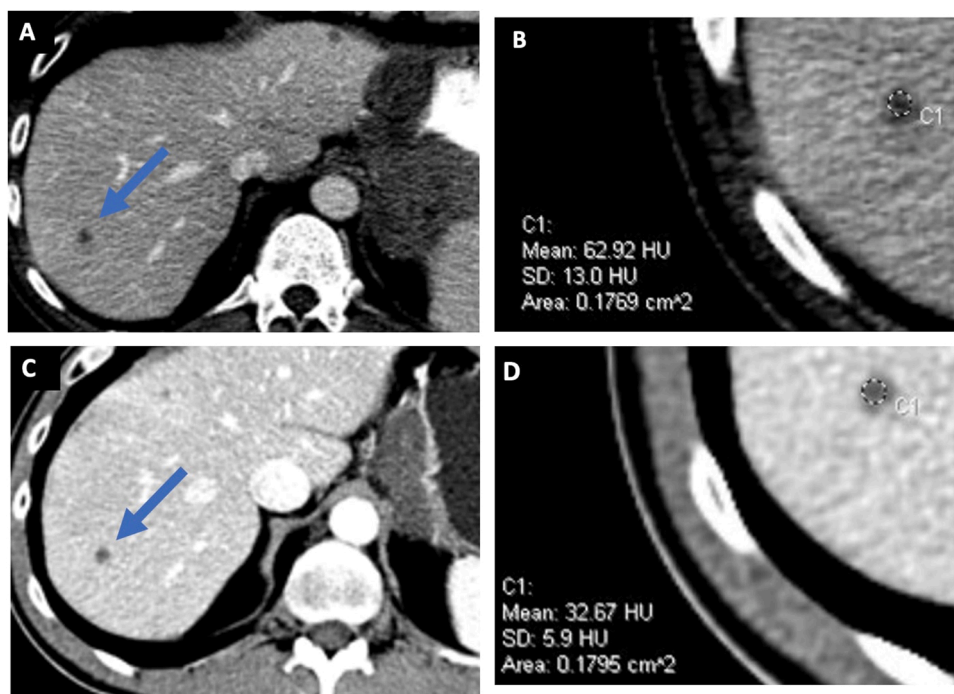


Fig. 6. Density changes in targeted therapy response. 75-year-old man with gastrointestinal stromal tumor metastatic to the liver. (A,B) Axial CT image performed before starting imatinib shows a hypodense liver lesion (arrow) with mean density of 63 Hounsfield Units. (C,D) Axial CT image performed three months after imatinib was started, shows similar size of the liver lesion but decreased attenuation of the lesion (arrow), with mean density of 33 Hounsfield Units.

targeted therapy and immune checkpoint therapy, pseudoprogression can occur, with the ostensible development of “new” lesions actually representing only increased conspicuity of pre-existing lesions; or apparent early increase in tumor size due to intratumoral hemorrhage or immune cell infiltration before tumor shrinkage ultimately occurs [81]. In these cases, RECIST1.1 might inaccurately categorize these therapies as ineffective leading to premature cessation of the trial before a full assessment of biologic treatment response is achieved [82,83].

To evaluate treatment response for chemotherapeutic agents in which changes in tumor size is less apparent, alternate tumor response criteria were developed, such as the Choi criteria in gastrointestinal stromal tumors [81]. While maintaining the four parameters of CR, PR, PD, and SD, the Choi criteria made modifications to the PR category such that it takes into account changes in tumor enhancement as a surrogate for viability, and which manifests on CT as a change in tumor attenuation (Fig. 6). The PD category also differs slightly in that the Choi criteria PD denotes new or increasing intratumoral lesions or mural nodules, whereas the RECIST 1.1 only considers maximum lesion diameter. Through these modifications, the Choi criteria facilitate more accurate assessments of tumor response (Fig. 7) [84].

For immunotherapies, a variety of additional response criteria were developed, including iRECIST. These identified specific response categories include immune complete response (iCR), immune partial response (iPR), immune unconfirmed progressive disease (iUPD), immune confirmed progressive disease (iCPD), and immune stable disease (iSD). These criteria take into account the concept of pseudoprogression that is often demonstrated in patients treated with immunotherapies. The most notable differences are in the iUPD and iCPD. These categories are based on the general principles of the RECIST 1.1 PD, however, iUPD characterizes lesions that are new or have increased in size since initial identification within a specific time window. If within this preset interval, new or increasing lesions are identified, these lesions are determined to be iUPD. If these new lesions persist or continue to grow beyond the set interval, they are then categorized as iCPD. If these lesions disappear or shrink before the window ends, then these lesions can be re-categorized into either iCR or iPR. Ultimately, the iRECIST criteria allow for accurate identification and evaluation of pseudoprogression seen in immunotherapy (Fig. 8) [85]. There are a multitude of other response criteria for various imaging modalities (e.g. PERCIST, Lugano, RANO, etc.) that are often disease or site specific. A detailed discussion of these criteria is beyond the scope of this article, but software is available that aids the radiologist in applying the criteria uniformly and conforming to the often complex set of guidelines laid out for each one.

5. Future directions

Standard imaging response criteria may not correlate with therapeutic effect for targeted therapies and immunotherapies. As such,

quantitative imaging methods for measurement or prediction of tumor response to therapies in clinical trials are currently under development, promoted by various national and international organizations, including the National Cancer Institute through the Quantitative Imaging Network (QIN) or the European Society of Radiology through the European Imaging Biomarkers Alliance (EIBALL) [86,87]. Furthermore, tumor specific metabolic imaging methods are actively underdevelopment, such as the CD-38 targeted immuno-PET, in which Daratumumab, a monoclonal antibody that targets CD38, an antigen expressed on nearly all myeloma cell is labeled with the positron-emitting radionuclide zirconium 89 (89Zr) for immunologic PET imaging of multiple myeloma [88].

Finally, radiogenomics, a high-throughput method to combine imaging features with genomic and other patient’s data to characterize tumors and predict outcomes, is experiencing a significant expansion due to technological improvements and the implementation of deep learning methods (Fig. 9). Techniques such as texture analysis have been developed to extract information that may not be apparent to the naked eye to analyze tumor phenotype and environment, creating new biomarkers. Potentially, radiogenomics may allow genetic analysis for prediction of tumor prognosis and guide therapeutic strategies in the routine clinical setting [89,90].

6. Integrating practice into teaching

As cancer imagers on a multidisciplinary team, it is critical for radiologists to go beyond simply reporting findings on images and to consider these findings in the context of individualized treatment plans to achieve an accurate interpretation. Radiologists must be aware of existing and new treatments on the horizon and consider atypical response patterns and the impact on patient care. Radiologists should also be familiar with terminology surrounding response criteria, know how and when to use certain terms such as partial response and progression, and understand the limitations of imaging in certain cases where follow-up may be required for an accurate assessment.

Teaching this particular aspect of radiology is challenging due to the ever-changing landscape of precision cancer treatments and the highly individualized treatment plans being used at present. It can be difficult to figure out exactly where this type of education fits into the curriculum as it spans multiple modalities and anatomic areas. As cancer imaging is integrated into all departmental divisions; it may not be feasible or practical to offer rotations specifically in cancer imaging. Therefore, teaching of cancer imaging requires the investment and participation of all divisional faculty.

Beyond traditional teaching at the workstation, trainees can be engaged through interactive didactic lectures, self-directed learning, and blended learning such as the flipped classroom. Audience response systems can make didactic lectures more engaging, can assess for

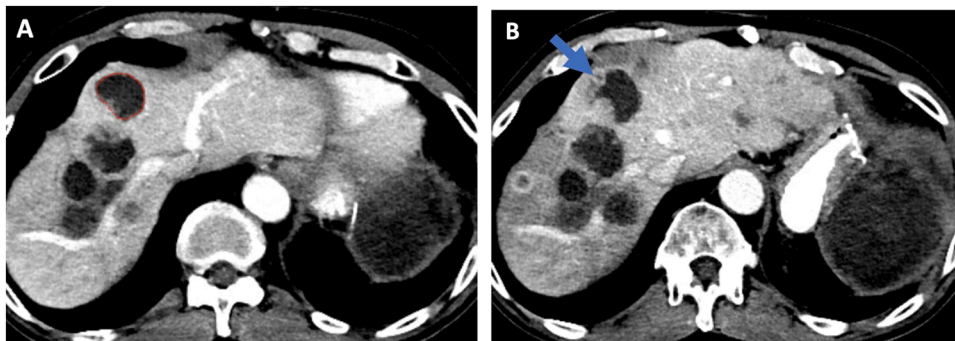


Fig. 7. Choi criteria for assessing response to targeted therapy in metastatic GIST. 69-year-old man with gastrointestinal stromal tumor with metastatic disease to the liver being treated with sunitinib, a vascular endothelial growth factor inhibitor. (A) Axial CT image acquired during treatment with sunitinib shows multiple lesions in the liver, including a hypodense nonenhancing lesion in segment 4A (red circle). (B) Axial CT image acquired at next follow-up shows multiple enhancing mural nodules in the hypodense segment 4A lesion (arrow) reflecting disease progression. Per RECIST 1.1, this would be inaccurately categorized as stable disease as the lesions did not change in size, while per Choi criteria this would be correctly characterized as progressive

disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

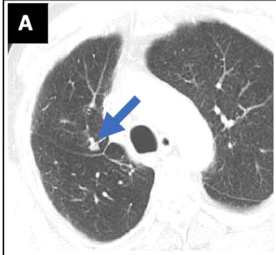
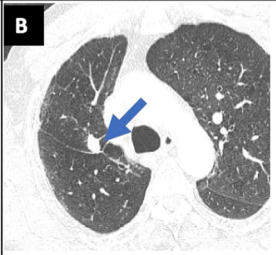

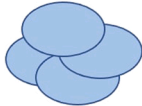
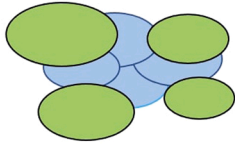

	BASELINE	FOLLOW-UP 1	FOLLOW-UP 2
	A 	B 	C 
TUMOR BURDEN	1.0 cm	1.9 cm	0.5 cm
% SIZE CHANGE FROM NADIR	0	217%	-50%
ASSESSMENT	BASELINE	UNCONFIRMED PROGRESSIVE DISEASE	PARTIAL RESPONSE (new nadir)
TUMOR	 Pre-treatment tumor (blue circles)	 Immune infiltration (green circles) into tumor mass	 Treated tumor

Fig. 8. Treatment response evaluation using iRECIST criteria in a 76-year-old man with non-small cell lung cancer. CT of the chest (A) obtained before treatment with pembrolizumab was started shows a right lung nodule (arrow). Follow up CT of the chest (B) obtained 2 months after initiation of pembrolizumab shows increased size of the lesion (arrow), which decreased in size at follow-up CT obtained after 8 weeks (C), indicating pseudoprogression. iRECIST requires confirmation of progressive disease in 4–8 weeks to avoid misinterpreting pseudoprogression as true progression of disease, as mentioned in the accompanying chart.

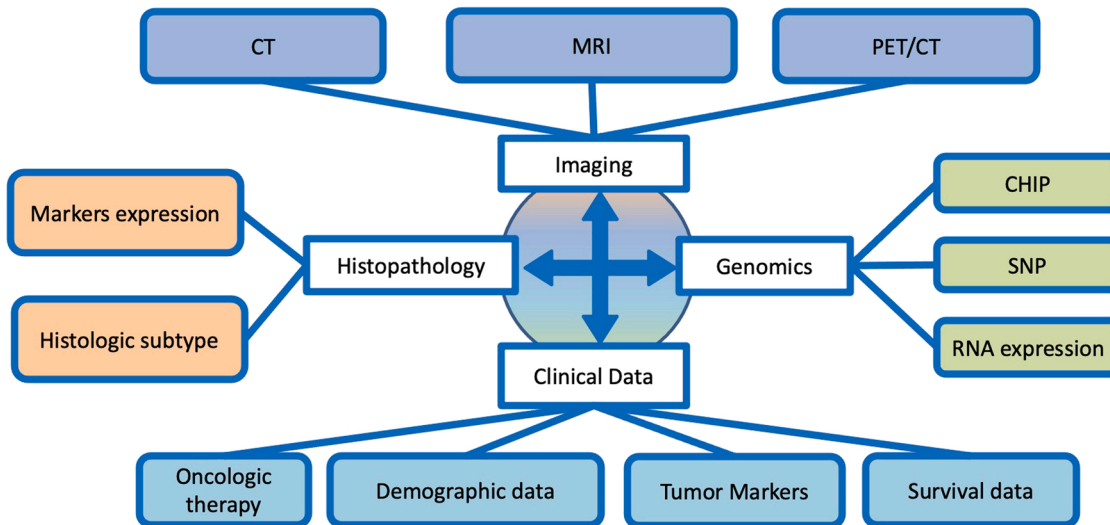


Fig. 9. Radiogenomics: integration of imaging features, histopathologic data, genomics, and clinical data. CHIP: chromatin immunoprecipitation; SNP: Single nucleotide polymorphisms.

knowledge gaps, and can provide instant feedback to trainees [91]. Self-directed learning includes using educational applications such as question banks, watching online videos, and reading relevant textbooks and articles. Blended learning incorporates elements of both self-learning and traditional classroom learning. For example, prior to lecture, the trainees are asked to review a complicated oncology case relevant to the didactic topic; during lecture, the trainees discuss the case, which can lead to increased comprehension of the lecture material. Blended learning can lead to higher rates of participation, increased

retention of information, as well as a more positive learning environment [92].

Trainees should also be encouraged or required to participate in multidisciplinary tumor boards commensurate with their degree of training. Through tumor boards, trainees can learn about the relevance of certain imaging findings and how these findings can impact treatment decisions through discussions with colleagues from medical, surgical, and radiation oncology. Additionally, through discussions at tumor boards, trainees can better understand decisions regarding image-

guided biopsies, for example, on deciding which suspicious mass to biopsy or what trajectory to choose for a suspected musculoskeletal sarcoma biopsy.

As with other subsections in radiology, a defined curriculum should be created that clearly explains concepts and materials to be covered, as well as objectives that address the three fundamental components of radiology learning: perception, interpretation, and diagnosis [93]. The curriculum should incorporate readings and resources appropriate for each level of training, from first-year radiology resident to fellow.

Regular evaluation of performance should occur regarding retention and integration of concepts into clinical practice through assessment of read-outs, reports, follow-up recommendations, and communications with clinicians. Real time and tangible feedback, as well as remediation goals should be provided. As teachers, it is our study to “foster doubt, to facilitate discovery, and to nourish change” [93].

7. Conclusion

Familiarity with the three pillars of genomic-based cancer imaging is crucial for any radiologists: knowledge of cancer genomics, oncologic therapies, and the role of imaging in clinical trials should be the focus of any cancer imaging teaching curriculum, with the goal of facilitating dialogue between radiologists and oncologists, and ultimately improving patient care.

Funding

The authors did not receive funding for this work.

Conflict of interests

Lacey J. McIntosh, DO, MPH: Bioclinica/Clario, Consultant, central reader for clinical trials. Other authors have no conflicts of interest to disclose.

References

- [1] M. Arruebo, N. Vilaboa, B. Saez-Gutierrez, J. Lambea, A. Tres, M. Valladares, A. Gonzalez-Fernandez, Assessment of the evolution of cancer treatment therapies, *Cancers* (2011) 3279–3330.
- [2] Y. Chen, Y. Jia, W. Song, L. Zhang, Therapeutic potential of nitrogen mustard based hybrid molecules, *Front. Pharmacol.* 9 (2018) 1453.
- [3] L.A. Garraway, J. Verweij, K.V. Ballman, Precision oncology: an overview, *J. Clin. Oncol.* 31 (15) (2013) 1803–1805.
- [4] P. Selby, R. Popescu, M. Lawler, H. Butcher, A. Costa, The value and future developments of multidisciplinary team cancer care, *Am. Soc. Clin. Oncol. Educ. Book* 39 (2019) 332–340.
- [5] L.H. Schwartz, S. Litiere, E. de Vries, R. Ford, S. Gwyther, S. Mandrekar, L. Shankar, J. Bogaerts, A. Chen, J. Dancy, W. Hayes, F.S. Hodi, O.S. Hoekstra, E. P. Huang, N. Lin, Y. Liu, P. Therasse, J.D. Wolchok, L. Seymour, RECIST 1.1-Update and clarification: from the RECIST committee, *Eur. J. Cancer* 62 (2016) 132–137.
- [6] W.H. Organization, 1979. WHO handbook for reporting results of cancer treatment. Geneva (Switzerland); World Health Organization Offset Publication (No. 48) 1979.
- [7] P. Murphy, D.M. Koh, Imaging in clinical trials, *Cancer Imaging* (2010) S74–S82.
- [8] F. Alessandrino, D.A. Smith, A. Spierling, E. Kikano, B. Somarouthu, S.H. Tirumani, N.H. Ramaiya, Cancer clinical trials: what every radiologist wants to know but is afraid to ask, *AJR Am. J. Roentgenol.* 216 (4) (2021) 1099–1111.
- [9] B. Vogelstein, N. Papadopoulos, V.E. Velculescu, S. Zhou, L.A. Diaz Jr., K. W. Kinzler, Cancer genome landscapes, *Science* 339 (6127) (2013) 1546–1558.
- [10] F. Alessandrino, D.A. Smith, S.H. Tirumani, N.H. Ramaiya, Cancer genome landscape: a radiologist's guide to cancer genome medicine with imaging correlates, *Insights Imaging* 10 (1) (2019) 111.
- [11] H. Ledford, Big science: the cancer genome challenge, *Nature* 464 (7291) (2010) 972–974.
- [12] E.S. Lander, L.M. Linton, B. Birren, C. Nusbaum, M.C. Zody, J. Baldwin, K. Devon, K. Dewar, M. Doyle, W. FitzHugh, R. Funke, D. Gage, K. Harris, A. Heaford, J. Howland, L. Kann, J. Lehoczky, R. Levine, P. McEwan, K. McKernan, J. Meldrum, J.P. Mesirov, C. Miranda, W. Morris, J. Naylor, C. Raymond, M. Rosetti, R. Santos, A. Sheridan, C. Sougnez, Y. Stange-Thomann, N. Stojanovic, A. Subramanian, D. Wyman, J. Rogers, J. Sulston, R. Ainscough, S. Beck, D. Bentley, J. Burton, C. Clee, N. Carter, A. Coulson, R. Deadman, P. Deloukas, A. Dunham, I. Dunham, R. Durbin, L. French, D. Graffham, S. Gregory, T. Hubbard, S. Humphray, A. Hunt, M. Jones, C. Lloyd, A. McMurray, L. Matthews, S. Mercer, S. Milne, J.C. Mullikin, A. Mungall, R. Plumb, M. Ross, R. Showkeen, S. Sims, R.H. Waterston, R.
- [13] K. Wilson, L.W. Hillier, J.D. McPherson, M.A. Marra, E.R. Mardis, L.A. Fulton, A. T. Chinwalla, K.H. Pepin, W.R. Gish, S.L. Chissoe, M.C. Wendl, K.D. Delehaunty, T. L. Miner, A. Delehaunty, J.B. Kramer, L.L. Cook, R.S. Fulton, D.L. Johnson, P. J. Minx, S.W. Clifton, T. Hawkins, E. Branscomb, P. Predki, P. Richardson, S. Wenning, T. Slezak, N. Doggett, J.F. Cheng, A. Olsen, S. Lucas, C. Elkin, E. Uberbacher, M. Frazier, R.A. Gibbs, D.M. Muzny, S.E. Scherer, J.B. Bouck, E. J. Sodergren, K.C. Worley, C.M. Rives, J.H. Gorrell, M.L. Metzker, S.L. Naylor, R. S. Kucherlapati, D.L. Nelson, G.M. Weinstock, Y. Sakaki, A. Fujiyama, M. Hattori, T. Yada, A. Toyoda, T. Itoh, C. Kawagoe, H. Watanabe, Y. Totoki, T. Taylor, J. Weissenbach, R. Heilig, W. Saurin, F. Artiguenave, P. Brottier, T. Bruls, E. Pelletier, C. Robert, P. Wincker, D.R. Smith, L. Doucette-Stamm, M. Rubenfield, K. Weinstock, H.M. Lee, J. Dubois, A. Rosenthal, M. Platzer, G. Nyakatura, S. Taudien, A. Rump, H. Yang, J. Yu, J. Wang, G. Huang, J. Gu, L. Hood, L. Rowen, A. Madan, S. Qin, R.W. Davis, N.A. Federspiel, A.P. Abola, M.J. Proctor, R. M. Myers, J. Schmutz, M. Dickson, J. Grimwood, D.R. Cox, M.V. Olson, R. Kaul, C. Raymond, N. Shimizu, K. Kawasaki, S. Minoshima, G.A. Evans, M. Athanasiou, R. Schultz, B.A. Roe, F. Chen, H. Pan, J. Ramser, H. Lehrach, R. Reinhardt, W. R. McCombie, M. de la Bastide, N. Dedhia, H. Blocker, K. Hornischer, G. Nordsiek, R. Agarwala, L. Aravind, J.A. Bailey, A. Bateman, S. Batzoglou, E. Birney, P. Bork, D.G. Brown, C.B. Burge, L. Cerutti, H.C. Chen, D. Church, M. Clamp, R.R. Copley, T. Doerks, S.R. Eddy, E.E. Eichler, T.S. Furey, J. Galagan, J.G. Gilbert, C. Harmon, V.J. Pollar, C.P. Ponting, G. Schuler, J. Schultz, G. Slater, A.F. Smit, E. Stupka, J. Szustakowski, D. Thierry-Mieg, J. Thierry-Mieg, L. Wagner, J. Wallis, R. Wheeler, A. Williams, Y.I. Wolf, K.H. Wolfe, S.P. Yang, R.F. Yeh, F. Collins, M.S. Guyer, J. Peterson, A. Felsenfeld, K.A. Wetterstrand, A. Patrino, M.J. Morgan, P. de Jong, J.J. Catanese, K. Osoegawa, H. Shizuya, S. Choi, Y.J. Chen, J. Szustakowski, International human genome sequencing, initial sequencing and analysis of the human genome, *Nature* 409 (6822) (2001) 860–921.
- [14] B.M. Crossley, J. Bai, A. Glaser, R. Maes, E. Porter, M.L. Killian, T. Clement, K. Toohey-Kurth, Guidelines for sanger sequencing and molecular assay monitoring, *J. Vet. Diagn. Invest.* 32 (6) (2020) 767–775.
- [15] J.A. Reuter, D.V. Spacek, M.P. Snyder, High-throughput sequencing technologies, *Mol. Cell* 58 (4) (2015) 586–597.
- [16] T.C.G.A. Network, 2020. The Cancer Genome Atlas, 2020.
- [17] N. Cancer Genome Atlas Research, J.N. Weinstein, E.A. Collisson, G.B. Mills, K. R. Shaw, B.A. Ozenberger, K. Ellrott, I. Shmulevich, C. Sander, J.M. Stuart, , The cancer genome atlas pan-cancer analysis project, in: *Nat. Genet.* 45, 2013, pp. 1113–1120.
- [18] F. Mantovani, L. Collavin, G. Del Sal, Mutant p53 as a guardian of the cancer cell, *Cell Death Differ.* 26 (2) (2019) 199–212.
- [19] J.J. Salk, M.S. Horwitz, Passenger mutations as a marker of clonal cell lineages in emerging neoplasia, *Semin. Cancer Biol.* 20 (5) (2010) 294–303.
- [20] F. Martinez-Jimenez, F. Muinos, I. Sentis, J. Deu-Pons, I. Reyes-Salazar, C. Arnedo-Pac, L. Mularoni, O. Pich, J. Bonet, H. Kranas, A. Gonzalez-Perez, N. Lopez-Bigas, A compendium of mutational cancer driver genes, *Nat. Rev. Cancer* 20 (10) (2020) 555–572.
- [21] M.A. Lemmon, J. Schlessinger, Cell signaling by receptor tyrosine kinases, *Cell* 141 (7) (2010) 1117–1134.
- [22] G. Hoxhaj, B.D. Manning, The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism, *Nat. Rev. Cancer* 20 (2) (2020) 74–88.
- [23] S. Beganovic, Clinical significance of the KRAS mutation, *Bosn J. Basic Med. Sci. Suppl* 1 (2009) 17–20.
- [24] M. Harada, H. Dosaka-Akita, H. Miyamoto, N. Kuzumaki, Y. Kawakami, Prognostic significance of the expression of ras oncogene product in non-small cell lung cancer, *Cancer* 69 (1) (1992) 72–77.
- [25] R.G. Amado, M. Wolf, M. Peeters, E. Van Cutsem, S. Siena, D.J. Freeman, T. Juan, R. Sikorski, S. Suggs, R. Radinsky, S.D. Patterson, D.D. Chang, Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer, *J. Clin. Oncol.* 26 (10) (2008) 1626–1634.
- [26] F. Alessandrino, K. Williams, A.H. Nassar, R. Gujrathi, S.G. Silverman, G. Sonpavde, A.B. Shinagare, Muscle-invasive urothelial cancer: association of mutational status with metastatic pattern and survival, *Radiology* 295 (3) (2020) 572–580.
- [27] R. Thomas, S.A. Howard, S.L. Laferriere, M. Braschi-Amirfarzan, A review of the mechanisms and clinical implications of precision cancer therapy-related toxicity: a primer for the radiologist, *AJR Am. J. Roentgenol.* 215 (3) (2020) 770–780.
- [28] N. Dervisis, S. Klahn, Therapeutic Innovations: tyrosine kinase inhibitors in cancer, *Vet. Sci.* 3 (1) (2016).
- [29] T.J. Mitchison, The proliferation rate paradox in antimetabolic chemotherapy, *Mol. Biol. Cell* 23 (1) (2012) 1–6.
- [30] T.V. Bagnyukova, I.G. Serebriiskii, Y. Zhou, E.A. Hopper-Borge, E.A. Golemis, I. Astsaturov, Chemotherapy and signaling: how can targeted therapies supercharge cytotoxic agents? *Cancer Biol. Ther.* 10 (9) (2010) 839–853.
- [31] A. Brown, S. Kumar, P.B. Tchounwou, Cisplatin-based chemotherapy of human cancers, *J. Cancer Sci. Ther.* 11 (4) (2019).
- [32] Z.H. Siddik, Cisplatin: mode of cytotoxic action and molecular basis of resistance, *Oncogene* 22 (47) (2003) 7265–7279.
- [33] T.G. Oliver, K.L. Mercer, L.C. Sayles, J.R. Burke, D. Mendus, K.S. Lovejoy, M. H. Cheng, A. Subramanian, D. Mu, S. Powers, D. Crowley, R.T. Bronson, C. A. Whittaker, A. Bhatnagar, S.J. Lippard, T. Golub, J. Thomale, T. Jacks, E.A. Sweet-Cordero, Chronic cisplatin treatment promotes enhanced damage repair and tumor progression in a mouse model of lung cancer, *Genes Dev.* 24 (8) (2010) 837–852.

- [33] C. Bokemeyer, C.C. Berger, M.A. Kuczyk, H.J. Schmoll, Evaluation of long-term toxicity after chemotherapy for testicular cancer, *J. Clin. Oncol.* 14 (11) (1996) 2923–2932.
- [34] I. Tachibana, E. Bandali, A.C. Calaway, N. Krishnan, L. Cheng, N. Adra, H. Z. Kaimakliotis, Urothelial carcinoma in situ response to cisplatin-based neoadjuvant chemotherapy, or lack thereof: Impact on patient selection for organ preservation in muscle-invasive disease? *Urol. Oncol.* 38 (11) (2020) 850 e1–850 e7.
- [35] S.L. Colton, X.S. Xu, Y.A. Wang, G. Wang, The involvement of ataxia-telangiectasia mutated protein activation in nucleotide excision repair-facilitated cell survival with cisplatin treatment, *J. Biol. Chem.* 281 (37) (2006) 27117–27125.
- [36] A. Basu, P. Ghosh, A. Bhattacharjee, A.R. Patra, S. Bhattacharya, Prevention of myelosuppression and genotoxicity induced by cisplatin in murine bone marrow cells: effect of an organovanadium compound vanadium(III)-l-cysteine, *Mutagenesis* 30 (4) (2015) 509–517.
- [37] H. Starobova, I. Vetter, Pathophysiology of chemotherapy-induced peripheral neuropathy, *Front. Mol. Neurosci.* 10 (2017) 174.
- [38] M. Yu, J. Han, P. Cui, M. Dai, H. Li, J. Zhang, R. Xiu, Cisplatin up-regulates ICAM-1 expression in endothelial cell via a NF-kappaB dependent pathway, *Cancer Sci.* 99 (2) (2008) 391–397.
- [39] T. Sekijima, A. Tanabe, R. Maruoka, N. Fujishiro, S. Yu, S. Fujiwara, H. Yuguchi, Y. Yamashita, Y. Terai, M. Ohmichi, Impact of platinum-based chemotherapy on the progression of atherosclerosis, *Climacteric* 14 (1) (2011) 31–40.
- [40] M. Brydoy, J. Oldenburg, O. Klepp, R.M. Bremnes, E.A. Wist, T. Wentzel-Larsen, E. R. Hauge, O. Dahl, S.D. Fossa, Observational study of prevalence of long-term Raynaud-like phenomena and neurological side effects in testicular cancer survivors, *J. Natl. Cancer Inst.* 101 (24) (2009) 1682–1695.
- [41] Y.T. Lee, Y.J. Tan, C.E. Oon, Molecular targeted therapy: treating cancer with specificity, *Eur. J. Pharmacol.* 834 (2018) 188–196.
- [42] N. Saijo, Progress in cancer chemotherapy with special stress on molecular-targeted therapy, *Jpn J. Clin. Oncol.* 40 (9) (2010) 855–862.
- [43] T.A.C.S.m.a.e.c. team, 2021. How Targeted Therapies Are Used to Treat Cancer, 2021.
- [44] J. Marquart, E.Y. Chen, V. Prasad, Estimation of the percentage of US patients with cancer who benefit from genome-driven oncology, *JAMA Oncol.* 4 (8) (2018) 1093–1098.
- [45] T. Regad, Targeting RTK Signaling Pathways in Cancer, in: *Cancers*, 7, Basel, 2015, pp. 1758–1784.
- [46] Y. Wang, G.F. Hu, Q.Q. Zhang, N. Tang, J. Guo, L.Y. Liu, X. Han, X. Wang, Z. H. Wang, Efficacy and safety of gemcitabine plus erlotinib for locally advanced or metastatic pancreatic cancer: a systematic review and meta-analysis, *Drug Des. Dev. Ther.* 10 (2016) 1961–1972.
- [47] G. da Cunha Santos, F.A. Shepherd, M.S. Tsao, EGFR mutations and lung cancer, *Annu. Rev. Pathol.* 6 (2011) 49–69.
- [48] J. de Castro-Carpeno, C. Belda-Iniesta, E. Casado Saenz, E. Hernandez Agudo, J. Feliu Battle, M.G. Baron, Baron, EGFR and colon cancer: a clinical view, *Clin. Transl. Oncol.* 10 (1) (2008) 6–13.
- [49] G.J. Riely, W. Pao, D. Pham, A.R. Li, N. Rizvi, E.S. Venkatraman, M.F. Zakowski, M. G. Kris, M. Ladanyi, V.A. Miller, Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib, *Clin. Cancer Res.* 12 (3) (2006) 839–844.
- [50] M. Takeda, I. Okamoto, K. Nakagawa, Survival outcome assessed according to tumor response and shrinkage pattern in patients with EGFR mutation-positive non-small-cell lung cancer treated with gefitinib or erlotinib, *J. Thorac. Oncol.* 9 (2) (2014) 200–204.
- [51] Y. Kiyohara, N. Yamazaki, A. Kishi, Erlotinib-related skin toxicities: treatment strategies in patients with metastatic non-small cell lung cancer, *J. Am. Acad. Dermatol.* 69 (3) (2013) 463–472.
- [52] T. Suzumura, T. Kimura, S. Kudoh, K. Umekawa, M. Nagata, H. Tanaka, S. Saito, M. Yoshimura, Y. Kira, K. Hirata, Comparison of adverse events of erlotinib with those of gefitinib in patients with non-small cell lung cancer: a case-control study in a Japanese population, *Osaka City Med. J.* 58 (1) (2012) 25–34.
- [53] D. Pfau, E. Guler, D.A. Smith, F. Matsunaga, E.G. Kikano, S.H. Tirumani, A. Dowlati, N.H. Ramaiya, Imaging features of gastrointestinal toxicity in non-small cell lung cancer patients treated with erlotinib: a single institute 13-year experience, *Clin. Imaging* 68 (2020) 210–217.
- [54] A. Fairchild, S.H. Tirumani, M.H. Rosenthal, S.A. Howard, K.M. Krajewski, M. Nishino, A.B. Shinagare, J.P. Jagannathan, N.H. Ramaiya, Hormonal therapy in oncology: a primer for the radiologist, *AJR Am. J. Roentgenol.* 204 (6) (2015) W620–W630.
- [55] P. Ratre, K. Mishra, A. Dubey, A. Vyas, A. Jain, S. Thareja, Aromatase inhibitors for the treatment of breast cancer: a journey from the scratch, *Anticancer Agents Med. Chem.* 20 (17) (2020) 1994–2004.
- [56] Y. Osawa, T. Higashiyama, M. Fronckowiak, N. Yoshida, C. Yarborough, J. Aromatase, *Steroid Biochem.* 27 (4–6) (1987) 781–789.
- [57] M.K. Brawer, Challenges with luteinizing hormone-releasing hormone agonists: flare and surge, *Rev. Urol. Suppl* 7 (2004) S12–S18, 6.
- [58] J.A. Cauley, Estrogen and bone health in men and women, *Steroids* 99 (Pt A) (2015) 11–15.
- [59] S. Servitja, T. Martos, M. Rodriguez Sanz, N. Garcia-Giralt, D. Prieto-Alhambra, L. Garrigos, X. Noguees, I. Tusquets, Skeletal adverse effects with aromatase inhibitors in early breast cancer: evidence to date and clinical guidance, *Ther. Adv. Med. Oncol.* 7 (5) (2015) 291–296.
- [60] J.L. Peters, A. Fairney, P. Kyd, A. Patel, S. Rogers, J.J. Webster, J.A. Vale, R. O. Witherow, Bone loss associated with the use of LHRH agonists in prostate cancer, *Prostate Cancer Prostatic Dis.* 4 (3) (2001) 161–166.
- [61] N. Santoro, C.N. Epperson, S.B. Mathews, Menopausal Symptoms and Their Management, *Endocrinol. Metab. Clin. North Am.* 44 (3) (2015) 497–515.
- [62] G.X. Wang, V. Kurra, J.F. Gainer, R.J. Sullivan, K.T. Flaherty, S.I. Lee, F. J. Fintelmann, Immune checkpoint inhibitor cancer therapy: spectrum of imaging findings, *Radiographics* 37 (7) (2017) 2132–2144.
- [63] G.V. Flynn JP. Pembrolizumab, 2021. StatPearls Publishing 2021.
- [64] H. Dong, S.E. Strome, D.R. Salomao, H. Tamura, F. Hirano, D.B. Flies, P.C. Roche, J. Lu, G. Zhu, K. Tamada, V.A. Lennon, E. Celis, L. Chen, Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion, *Nat. Med.* 8 (8) (2002) 793–800.
- [65] B.T. Fife, K.E. Pauken, T.N. Eagar, T. Obu, J. Wu, Q. Tang, M. Azuma, M. F. Krummel, J.A. Bluestone, Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal, *Nat. Immunol.* 10 (11) (2009) 1185–1192.
- [66] A. Mekki, L. Dercle, P. Lichtenstein, A. Marabelle, J.M. Michot, O. Lambotte, J. Le Pavec, E. De Martin, C. Balleyguier, S. Champiat, S. Ammari, Detection of immune-related adverse events by medical imaging in patients treated with anti-programmed cell death 1, *Eur. J. Cancer* 96 (2018) 91–104.
- [67] L.M. Francisco, V.H. Salinas, K.E. Brown, V.K. Vanguri, G.J. Freeman, V. K. Kuchroo, A.H. Sharpe, PD-L1 regulates the development, maintenance, and function of induced regulatory T cells, *J. Exp. Med.* 206 (13) (2009) 3015–3029.
- [68] A.C. O'Neill, F. Alessandrino, S.H. Tirumani, N.H. Ramaiya, Hallmarks of cancer in the reading room: a guide for radiologists, *AJR Am. J. Roentgenol.* 211 (3) (2018) 470–484.
- [69] J.D. Wolchok, A. Hoos, S. O'Day, J.S. Weber, O. Hamid, C. Lebbe, M. Maio, M. Binder, O. Bohnsack, G. Nichol, R. Humphrey, F.S. Hodi, Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria, *Clin. Cancer Res.* 15 (23) (2009) 7412–20.
- [70] M. Braschi-Amirfarzan, S.H. Tirumani, F.S. Hodi, Jr, M. Nishino, Immune-Checkpoint inhibitors in the era of precision medicine: what radiologists should know, *Korean J. Radiol.* 18 (1) (2017) 42–53.
- [71] F. Alessandrino, S. Sahu, M. Nishino, A.E. Adeni, S.H. Tirumani, A.B. Shinagare, M. M. Awad, Frequency and imaging features of abdominal immune-related adverse events in metastatic lung cancer patients treated with PD-1 inhibitor, *Abdom. Radiol.* 44 (5) (2019) 1917–1927.
- [72] R. Thomas, B. Sebastian, T. George, N.F. Majeed, T. Akinola, S.L. Laferriere, M. Braschi-Amirfarzan, A review of the imaging manifestations of immune checkpoint inhibitor toxicities, *Clin. Imaging* 64 (2020) 70–79.
- [73] P.C. Minneci, K.J. Deans, Clinical trials, *Semin. Pediatr. Surg.* 27 (6) (2018) 332–337.
- [74] K. Stanley, Design of randomized controlled trials, *Circulation* 115 (9) (2007) 1164–1169.
- [75] C.A. Umscheid, D.J. Margolis, C.E. Grossman, Key concepts of clinical trials: a narrative review, *Postgrad. Med.* 123 (5) (2011) 194–204.
- [76] Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry, in: U.S.D.O. H.a.H.S.F.a.D.A.C.F.D.E.a.R.C.C.f.B.E.a.R.C. Oncology (Ed.) 2018.
- [77] K. Ruchalski, M. Braschi-Amirfarzan, M. Douek, V. Sai, A. Gutierrez, R. Dewan, J. Goldin, A primer on RECIST 1.1 for oncologic imaging in clinical drug trials, *radiol imaging, Cancer* 3 (3) (2021), e210008.
- [78] E.H. Hsiue, T.J. Moore, G.C. Alexander, Estimated costs of pivotal trials for U.S. Food and Drug Administration-approved cancer drugs, 2015–2017, *Clin. Trials* 17 (2) (2020) 119–125.
- [79] T.R. Fleming, J.H. Powers, Biomarkers and surrogate endpoints in clinical trials, *Stat. Med.* 31 (25) (2012) 2973–2984.
- [80] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancy, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij, New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), *Eur. J. Cancer* 45 (2) (2009) 228–247.
- [81] H. Choi, C. Charnsangavej, S.C. Faria, H.A. Macapinlac, M.A. Burgess, S.R. Patel, L. L. Chen, D.A. Podoloff, R.S. Benjamin, Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria, *J. Clin. Oncol.* 25 (13) (2007) 1753–1759.
- [82] V.L. Chiou, M. Burotto, Pseudoprogression and immune-related response in solid tumors, *J. Clin. Oncol.* 33 (31) (2015) 3541–3543.
- [83] S.H. Tirumani, J.P. Jagannathan, K.M. Krajewski, A.B. Shinagare, H. Jacene, N. H. Ramaiya, Imatinib and beyond in gastrointestinal stromal tumors: a radiologist's perspective, *AJR Am. J. Roentgenol.* 201 (4) (2013) 801–810.
- [84] Z. Weng, J. Ertle, S. Zheng, T. Lauenstein, S. Mueller, A. Bockisch, G. Gerken, D. Yang, J.F. Schlaak, Choi criteria are superior in evaluating tumor response in patients treated with transarterial radioembolization for hepatocellular carcinoma, *Oncol. Lett.* 6 (6) (2013) 1707–1712.
- [85] L. Seymour, J. Bogaerts, A. Perrone, R. Ford, L.H. Schwartz, S. Mandrekar, N. U. Lin, S. Litiere, J. Dancy, A. Chen, F.S. Hodi, P. Therasse, O.S. Hoekstra, L. K. Shankar, J.D. Wolchok, M. Ballinger, C. Caramella, E.G.E. de Vries, R.w. group, iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics, *Lancet Oncol.* 18 (3) (2017) e143–e152.
- [86] Quantitative Imaging Network. Cancer Imaging Program, National Cancer Institute. (https://imaging.cancer.gov/programs_resources/specialized_initiatives/qin/about/default.htm). Page Accessed 6 February 2022.
- [87] European Imaging Biomarkers Alliance - EIBALL. European Society of Radiology. (<https://www.myesr.org/research/european-imaging-biomarkers-alliance-eiball>). Page Accessed 6 February 2022.

- [88] G.A. Ulaner, N.B. Sobol, J.A. O'Donoghue, A.S. Kirov, C.C. Riedl, R. Min, E. Smith, L.M. Carter, S.K. Lyashchenko, J.S. Lewis, C.O. Landgren, CD38-targeted Immuno-PET of multiple myeloma: from Xenograft models to first-in-human imaging, *Radiology* 295 (3) (2020) 606–615.
- [89] L. Shui, H. Ren, X. Yang, J. Li, Z. Chen, C. Yi, H. Zhu, P. Shui, The era of radiogenomics in precision medicine: an emerging approach to support diagnosis, treatment decisions, and prognostication in oncology, *Front. Oncol.* 10 (2021), 570465.
- [90] Y. Qi, T. Zhao, M. Han, The application of radiomics in predicting gene mutations in cancer, *Eur. Radiol.* (2022), <https://doi.org/10.1007/s00330-021-08520-6>.
- [91] O.A. Awan, Analysis of common innovative teaching methods used by radiology educators, *Curr. Probl. Diagn. Radiol.* 51 (1) (2022) 1–5.
- [92] M. Sertic, L. Alshafai, L. Guimaraes, L. Probyn, N. Jaffer, Flipping the classroom: an alternative approach to radiology resident education, *Acad. Radiol.* 27 (6) (2020) 882–884.
- [93] T. Van Deven, K.M. Hibbert, R. Chhem, *The Practice of Radiology Education: Challenges and trends*, Springer, 2010.