



# Precision radiotherapy for non-small cell lung cancer

Wen-Chi Yang<sup>1,2</sup>, Feng-Ming Hsu<sup>1,2\*†</sup> and Pan-Chyr Yang<sup>2,3\*†</sup>

## Abstract

Precision medicine is becoming the standard of care in anti-cancer treatment. The personalized precision management of cancer patients highly relies on the improvement of new technology in next generation sequencing and high-throughput big data processing for biological and radiographic information. Systemic precision cancer therapy has been developed for years. However, the role of precision medicine in radiotherapy has not yet been fully implemented. Emerging evidence has shown that precision radiotherapy for cancer patients is possible with recent advances in new radiotherapy technologies, panomics, radiomics and dosiomics. This review focused on the role of precision radiotherapy in non-small cell lung cancer and demonstrated the current landscape.

**Keywords:** Precision radiotherapy, Non-small cell lung cancer, Dosiomics, Panomics, Radiomics

## Introduction

Precision medicine is an emerging new era of future healthcare [1]. It has become feasible because of advances in next generation sequencing (NGS) and panomics technologies as well as the integration of large-scale biologic databases and artificial intelligence to identify biomarkers, stratify patients and precisely guide clinical practices. It has significantly improved the treatment outcome of human diseases especially in cancer therapy.

Non-small cell lung cancer (NSCLC) is one of the examples of precision medicine being most successfully applied [2]. The standard guidelines for precision management in NSCLC recommend stratifying patients by histology (adenocarcinoma versus squamous cell carcinoma or large cell carcinoma), followed by gene testing

of druggable driver mutations (EGFR, ALK, ROS1, BRAF, NTRK, etc.) for target therapy. If patients were negative for druggable mutations, PDL-1 immunohistochemistry and/or tumor mutation burden will be tested to assess the suitability of immune checkpoint inhibitor therapy. The implementation of precision therapy has significantly improved the treatment outcome of NSCLC [3].

Radiotherapy is an effective anti-cancer treatment for nearly half of all cancer patients [4]. In NSCLC, radiotherapy may serve as a definitive treatment to early stage inoperable tumor [5] and local advanced disease [6, 7]. With the improvement in the survival of NSCLC cancer patients, the use of radiotherapy has become more common. Radiotherapy was also the greatest increase in Medicare expenditures between 2003 and 2009 in the U.S. [8]. It was used not only in definitive treatment but also in palliative therapy. For example, better local control can be achieved with thoracic re-irradiation for NSCLC [9]. Stereotactic radiosurgery (SRS) has been becoming the standard management to treat NSCLC patients with limited brain metastases [10]. The idea of

\* Correspondence: [hsufengming@ntuh.gov.tw](mailto:hsufengming@ntuh.gov.tw); [pcyang@ntu.edu.tw](mailto:pcyang@ntu.edu.tw)

<sup>†</sup>Feng-Ming Hsu and Pan-Chyr Yang contributed equally to this work.

<sup>1</sup>Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Rd, Taipei, Taiwan

<sup>2</sup>Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan

Full list of author information is available at the end of the article



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customized systemic precision management of NSCLC has been extended to combine local radiotherapy with the current standard options of chemotherapy, targeted therapy or immunotherapy. In the radical-palliative setting, stereotactic ablative radiotherapy (SABR) to oligo-metastatic NSCLC lesions was proved to be effective with promising outcome. Iyengar P. et al. conducted a phase two trial to compare maintenance chemotherapy alone versus SABR followed by maintenance chemotherapy for patients with limited (up to 5 metastatic sites) metastatic NSCLC. The results showed SABR arm tripled the progression-free survival [11, 12].

The term precision radiotherapy aims to stratify and precisely treat each individual cancer patient, using state-of-the-art new radiotherapy technology and biomarkers to improve treatment outcome and reduce adverse effects. The advances of radiotherapy technology make precision radiotherapy applicable. Technological advances provided better treatment modalities, although did not necessarily individualize the treatment plan for each patient. Emerging investigations and reviews have raised the attention of true personalized radiotherapy [13, 14] for different cancer types. In this article, we summarize the current landscape of precision radiotherapy for NSCLC (Fig. 1), focusing on recent advances in radiotherapy technology, radiomics and dosiomics, as well as biomarkers derived from panomics that may improve treatment outcome and reduce potential adverse effects (Table 1).

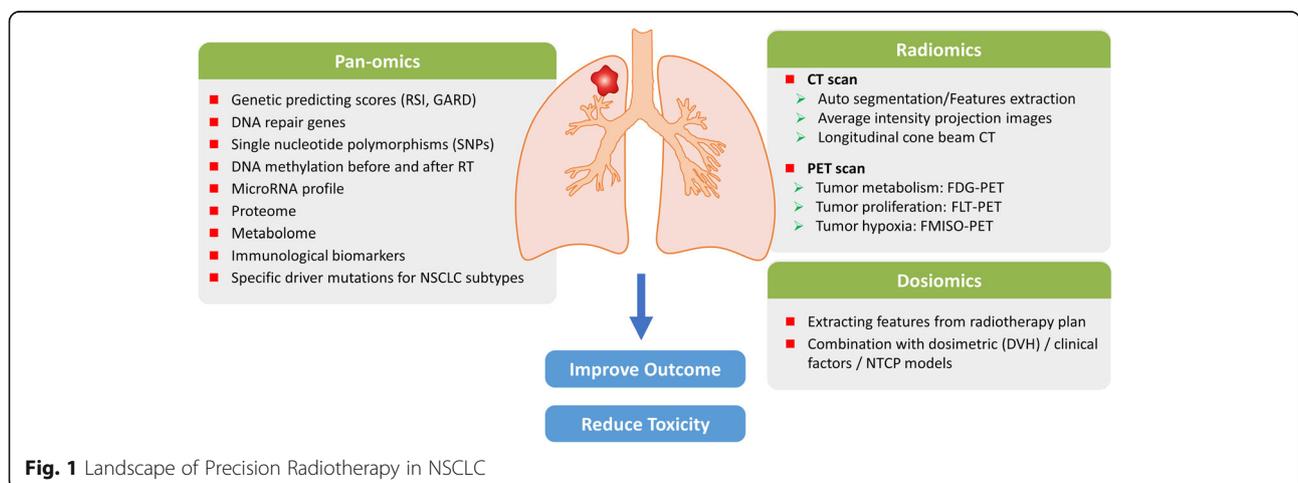
**Technological advancements for precision radiotherapy**

Precision radiotherapy was used for decades to describe the improvement of technology in medical ionizing irradiation. The development of radiotherapy techniques can be characterized into several aspects. First, the radiation machine improved from a low-voltage X-ray generator to a high voltage X-ray linear accelerator. Second,

in addition to conventional fractionated treatment, the idea of high-dose-single-shot stereotactic radiosurgery has also been developed to achieve better tumor control [5]. Through the development of planning systems and hardware, such as multi-leaf collimators, intensity modulated radiotherapy (IMRT) can be administered with adaption to the tumor location and surrounding normal tissues, which may improve tumor control and reduce toxicity [15]. For particle treatment, commercialized cyclotrons and synchrotrons make proton treatment more popular in real world practice. The development of Monte Carlo dose simulation has helped to overcome the treatment uncertainty in proton therapy [16]. Heavy particles are also under investigation and may be beneficial in some challenging cases [17]. Another improvement in radiotherapy is image registration modality for delivery precision. In-room cone beam CT on a linear accelerator improved the treatment accuracy. Some immobilization devices associated with adaptive software for breath control and gating system, also improve the treatment accuracy for moving targets, especially lung tumors. A recent recommendation was proposed by the European Organization for Research and Treatment of Cancer (EORTC) group, which provided a suggestion to provide high precision radiotherapy especially for lung cancer patients [18].

**Radiomics**

Radiomics is an emerging field in cancer treatment. For NSCLC, chest images are necessary for diagnosis and follow up, which makes NSCLC a good candidate for radiomics investigations [19]. In general, quantitative data from images for tumors were mined automatically to correlate with tumor behavior, treatment response, and clinical prognosis. The predictive power of radiomics provides a great opportunity for a non-invasive approach for precision radiotherapy. Without invasive



**Fig. 1** Landscape of Precision Radiotherapy in NSCLC

**Table 1** Biomarkers predicting outcome and toxicity in radiotherapy for NSCLC

Types of Biomarkers	Outcome predictors	Toxicity predictors
Panomics		
Genomics	Genomic predicting scores: Radiosensitivity Index (RSI), Genomic-adjusted radiation dose (GARD) Lung adenocarcinoma associated gene: KRAS Squamous cell carcinoma associated genes: KEAP1, NFE2L2	DNA repair genes: ATM Other mutated genes: PTEN, RB1, TP53 ...
SNPs	DNA repair gene sites: XRCC1, BRCA1, and ERCC1	DNA repair gene sites: ATM, RAD51, XRCC family, LIG4, MTHFR Inflammatory gene sites: TGFβ1 Immune modulated gene sites: CBLB
Epigenetics	DNA methylation profile, IGFBP-3 Micro RNA: p53 regulation, RAD51 regulation (MiR-34a)	–
Proteome /Metabolome	–	Serum inflammatory biomarkers: TGFβ, IL-1, KL-6, IL-6, IL-8, PDGF, TGFα, TNFα, CXCL10 (IP-10), CCL2 (MCP-1), Eotaxin, and TIMP-1 Novel proteins identified by mass spectroscopy: C4BPA, VTN, α2M, CO4A, CO5
Immunological markers	Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil count, lymphocyte count	Neutrophil-to-lymphocyte ratio (NLR)
Radiomics		
CT scan	Post SABR local recurrence prediction: enlarging opacity at 12 months after SABR, bulging margin, loss of linear margin and air bronchogram loss Post SABR recurrence free survival: tumor size, pleural retraction, vessel attachment For adaptive RT during chemoradiation: LARTIA trial	Combination of radiomic signatures predict radiation pneumonitis
PET	FDG-PET: Max SUV, metabolic volume, total lesion glycolysis FLT-PET: sensitive than FDG-PET to predict tumor response F-MISO-PET: identify radioresistant area for adaptive treatment	FLT-PET: predict hematological toxicity (bone marrow)
Dosimetrics		Dosimetric information + dosimetric information (DVH) + clinical factors better predict radiation pneumonitis

Abbreviations: NSCLC Non-small cell lung cancer. CT Computed tomography. PET Positron emission tomography. SABR Stereotactic ablative radiotherapy. DVH Dose volume histogram

procedures, tissue, blood or fluid samples, tumor characteristics can be represented from images themselves. Improvements in data processing tools and deep learning techniques help interpret data more efficiently and make clinical use possible. The major imaging methods used in NSCLC radiomics are CT and PET scans. The ideas between these two images are different. The tumor structure, shape, and compaction on a CT scan can be associated with tumor biological behavior and clinical outcome. In contrast, PET scan is a functional imaging tool, and the use of different tracers can directly show distinct biological features of disease.

#### Computed tomography (CT)

CT is the most common tool in radiomics studies for lung cancer. In the radiotherapy field, the main utilization of CT radiomics includes auto-segmentation and feature extractions [20–22]. For radiotherapy treatment of lung cancer, one of the most challenging issues is consistent contouring for an organ at risk (OAR) and accurate delineation for the gross tumor volume (GTV). The Thoracic Auto-Segmentation Challenge organized

at the 2017 Annual Meeting of American Association of Physicists in Medicine (AAPM) reported the outcome of thoracic auto-segmentation with different approaches. In general, lung and heart can be segmented consistently in most algorithms, while deep learning can better delineate the esophagus. This tool improves the treatment quality and precision [23]. As a moving target, the blurred border of lung tumors makes accuracy in contouring difficult. Besides, the collapsed lung field, pleural traction, and regional bronchus and vessels were not easy to differentiate from true GTV. A semi-automated method with three-dimensional lung CT was developed [24]. The GrowCut algorithm, an interactive region segmentation strategy, was reported to be able to reduce inter-physician differences in lung tumor contouring.

More popular issues are the feature extraction and prognostic or predictive values from different radiomic features. Features, which include lesion shape, intensity, texture and wavelet, together with location, can be extracted [21]. Longitudinal pattern changes were used to associate the response to radiotherapy. Definitive stereotactic ablative radiotherapy (SABR) is a treatment

of choice for early stage lung cancer. For medically inoperable NSCLC patients with impaired lung function (for example, FEV1 < 40% predicted), SABR provided excellent outcome and became the standard of care [5]. Without other intervention procedures, SABR might be the least confounded treatment modality to investigate radiomics in radiotherapy treatment outcome. There are several applications of radiomics in NSCLC patients receiving SABR, and these include the assessment of early recurrence post SABR, the correlation between pretreatment radiomic features and clinical outcome, and the prediction of radiation induced lung toxicity.

A retrospective series analyzed the radiomic features associated with a higher risk of local and distant recurrence. CT density changes are common after SABR. In a systemic review, high risk features related to local recurrence were identified including enlarging opacity at different time points after SABR, bulging margin, loss of linear margin and air bronchogram loss [25]. These features were validated [26, 27] in other series. Enlargement of opacity 12 months after SABR was considered most predictive compared with other parameters. Opacity change in the primary lesion within 1 year may be related to post-irradiation change and subacute radiation pneumonitis. Considering that the lung is a moving organ, it was reported that average intensity projection images (AIP) are better than free breathing CT in a lung radiomics study [28] for predicting the treatment outcome. The main clinical implication is to help physicians make decisions for the diagnosis of local recurrence. In a retrospective study, physician assessment and a radiomic prediction tool for local recurrence diagnosis were compared. A high false negative rate was noticed in the physician assessment group [29]. With radiomic prediction assistance, local recurrence after SABR can be identified earlier than physician's assessment.

Radiomic features extracted from pre-treatment CT scans can be used to associate with clinical outcomes such as progression-free survival and overall survival [30–34]. Radiomic features from images were sorted into clusters and correlated with survival outcome. Li Q et al. [30] established a prognostic model incorporating clinical and genomic features. In addition to tumor size, an extracted feature from histogram analysis, measured the energy of Hounsfield unit (HU) values within the lesion, and this was considered a prognostic factor for recurrence and was incorporated into their prognostic model. Timmerman et al. [35, 36] used features extracted from cone-beam CT (CBCT) during radiotherapy treatment to validate the previously reported radiomic features for NSCLC outcome prediction [37]. Their works demonstrated that some CT and CBCT radiomic features are interchangeable. Longitudinal CBCT information can be potentially useful clinically in outcome prediction.

Radiomics predictions were not merely applied in the SABR cohort. A study focused on stage III NSCLC patients treated with concurrent chemoradiation proposed that a specific radiomic signature can be used in prediction tumor shrinkage [31]. Specific feature pattern differences between tumor shrinkage or not during chemoradiation can help in treatment decisions for radiotherapy plan adaptation. This study group proposed an ongoing prospective trial (LARTIA Trial, NCT03583723) based on these predictive features, but the results are not available yet.

Similarly, radiation induced lung toxicity can be predicted with similar methods [38–41]. Post SABR CT images were analyzed and certain radiomic features were found to have a dose response relationship [41], suggesting that radiomic features can provide a quantitative measurement of radiation induced lung toxicity after SABR. Traditionally radiation pneumonitis can be predicted with clinical factors including age, combination of systemic treatment, or dosimetric factor, the lung dose exactly. It was shown that incorporating radiomic factors into a prognostic model can better predict radiation pneumonitis [39]. If these radiomic signatures associated with recurrence patterns or toxicity can be validated externally, they might be a good imaging biomarker for radiation treatment.

#### **Positron emission tomography (PET)**

FDG-PET scan is a common diagnostic tool and is considered standard procedure used in NSCLC staging workup. PET-CT can provide two dimensional information, which includes feature information, which is the same as that of a CT scan, and the biological information, such as maximum standardized uptake value (SUV), metabolic tumor volume (MTV) and total lesion glycolysis (TLG). PET has been utilized in radiotherapy contouring and planning for more than a decade [42]. The idea to target the metabolic tumor volume rather than gross tumor volume is proposed to enhance the therapeutic ratio. Unsupervised machine learning of radiomic features combining functional and texture parameters from FDG-PET scans showed predictive value for treatment response in early stage NSCLC patients post SABR [43]. A high level of pre-treatment SUVmax generally predicted worse local control [44] and possibly worse survival [45]. FDG-PET was also applied in locally advanced lung cancer. Since FDG-PET aims to target the metabolic function of tumors, the question was raised if interim FDG-PET scans can help to better adapt treatment. A prospective single arm study revealed that FDG-PET during chemoradiotherapy is predictive of one-year survival [46]. Individual studies also showed prognostic values of FDG-PET, and PET directed MTV has a better response assessment to radiotherapy than

that of the traditionally CT based tumor volume [47]. However, a systemic review failed to show the benefit of interim FDG-PET [48]. The lack of univocal PET parameters among studies might be the major issue. A pilot trial revealed the potential local control benefit of dose escalation based on during-treatment FDG-PET with a fixed risk of radiation induced lung toxicity (RILT) [49]. RILT, or radiation pneumonitis, is common in thoracic irradiation, and is usually correlated with poor quality of life, impaired lung function, and may be lethal. RILT has been widely studied not only in lung cancer patients but also in esophageal cancer, lymphoma, and breast cancer patients. Ongoing study RTOG 1106, is a PET-directed phase II randomized trial intended to validate this finding. The application of PET scan may be broadened if more solid evidence is available.

FLT-PET, with the tracer fluorothymidine, targets tumor proliferation and is also used in lung cancer and radiotherapy. FLT uptake reduction was observed during and after radiotherapy for lung tumor [50], and was considered more sensitive than FDG-PET scans in comparative studies [51, 52]. With the adjunctive use of FLT-PET, postirradiation changes can be distinguished from tumor recurrence more clearly [53]. Interestingly, correlation with the changes in FLT-PET uptake with a clinical outcome showed that stable FLT uptake was paradoxically associated with longer overall survival and progression-free survival. The results suggested that suppression of tumor cell proliferation might lead to the protection of tumor cell damage from irradiation [51]. Reduction in the bone marrow was also observed during radiotherapy treatment [54, 55], which may be a predictive marker for hematological toxicity.

F-MISO-PET, focused on tissue hypoxia, can help to identify hypoxic areas in tumors for the adaptation of treatment. The uptake of F-MISO was not completely correlated with FDG, suggesting the discordance between tumor glycolysis and hypoxia [56]. During conventional fractionated radiotherapy for NSCLC, a comparison study showed a rapid decrease in FLT uptake, a modest decrease in FDG, and stable uptake of F-MISO [57]. Those results suggested that F-MISO reflected the hypoxia and potentially radioresistant area, not the tumor response during treatment. Adaptive radiotherapy with an escalating dose to the hypoxic area was proposed [58, 59]. Prospective trial based on F-MISO PET is ongoing (RTEP5 trial, [NCT01576796](#)).

#### **Dosimetrics**

Dosimetrics is a novel idea of radiotherapy emerged in these 2 years. It is an extension from radiomics. The 3D information from the dose distribution in the radiotherapy plan can also be considered as an image for data extraction. In addition to the traditional dose volume

histogram (DVH) and logistic normal tissue complication probability (NTCP) model, dosimetrics provides a new approach for modeling treatment related toxicity. This approach was proposed in the prostate cancer HYPRO trial to predict gastrointestinal (GI) and genitourinary (GU) toxicities [60], and the results showed that including dosimetric factors can improve prediction performance. Dosimetrics has also been applied in thoracic malignancy to predict radiation pneumonitis [61]. Traditionally, dosimetric factors in lung from a DVH analysis were the most commonly used in predicting RILT. The mean lung dose (MLD) and the percentage of lung volume received more than 20 Gy (V20) are the two common parameters. NTCP is a mathematical model to predict toxicity via transforming heterogeneous dose distribution to an equivalent uniform dose. These two approaches were compared with dosimetrics factors in the NSCLC radiotherapy cohort. The results demonstrated that the dosimetrics outperformed the MLD, V20, and NTCP models in predicting radiation pneumonitis [61]. More investigations are warranted to elucidate the application of dosimetrics in NSCLC, its predictive value or its further application in adaptive radiotherapy.

#### **Panomics biomarkers to improve treatment outcome and reduce toxicities**

##### **Genetics**

Like response to drug varied among every single person with the same disease diagnosis, response and toxicity to radiotherapy also differed according to inherent genetic features. Since the biological basis of radiotherapy is to cause DNA double-strand breaks, genes correlated with DNA repair were reported to enhance radiation effects [62, 63] in *in vitro* and *in vivo* models. With the generalization of genetic testing tools, several genetic testing models to predict radiotherapy responses have been proposed. The standard approach was to identify the different genetic features between radiosensitive and radioresistant samples, either from cell lines, animal models, or patients. Furthermore, to validate the prognostic models in other cohorts.

The most widely studied was the radiosensitivity index (RSI) proposed by Javier F. Torres-Roca and his colleagues [64]. From cancer cell lines, inherent radiosensitivity was tested by measuring the survival fraction at 2 Gy (SF2). Ten genes were selected to derive the prediction model for the tumor radiotherapy response. This genetic prediction model was validated in breast, esophageal, rectal, head and neck, glioblastoma, pancreas, and prostate malignancies and in brain metastases cohorts [65–72]. Despite the good association achieved in retrospective series, no prospective investigations based on RSI are currently available. This study group further combined the RSI and the linear quadratic model

to obtain the genomic-adjusted radiation dose (GARD) [73]. GARD was tested in patients from the Total Cancer Care (TCC) protocol, a prospective, observational database. GARD was shown to independently predict clinical outcome in breast, lung, pancreatic, and glioblastoma cancer patients. For the NSCLC cohort, GARD significantly predicted local control with adjusted surgery, stage, histology, and lymphovascular invasion. Currently there are no clinical trials designed based on GARD.

Implications of genetic testing for radiotherapy were studied recently. The major concern is whether germline mutations will increase radiation toxicity or not. The American Society for Radiation Oncology (ASTRO) recently held a workshop to address this issue [74]. As previously known, bi-allelic pathological mutations at certain DNA repair genes, such as those found in ataxia telangiectasia [75], was considered contraindicated to radiotherapy. However, according to the currently available data, no single copy genetic alteration related to the radiation response will definitely increase radiation related toxicity.

The information for the relationship between somatic mutations in tumors and the radiation response was not sufficient to generate a consensus.

#### **Single nucleotide polymorphisms**

Single nucleotide polymorphisms (SNPs) were also applied to predict radiotherapy response in cancer. Polymorphisms at genes related to DNA repair were most reported. These include XRCC1, BRCA1, and ERCC1 [76–78]. A polymorphism within the promoter of the TGF $\beta$ 1 gene is also reported to be associated with radiation sensitivity [77]. SNPs were more widely used in predicting RILT. SNPs at DNA repair or synthesis genes including ATM, RAD51, XRCC family, LIG4, and MTHFR were published in many single institutional studies to predict RILT [79–83]. Other SNPs at inflammatory genes, such as TGF $\beta$ 1 [84–86], or immune modulated genes, such as CBLB [87], a regulator of T-cell response, were also associated with a higher grade of radiation pneumonitis. The problem for SNPs is the reproducibility and generalization across different patient populations [88]. Yuan X et al. reported that a single nucleotide polymorphism at rs1982073:T869C of the TGF $\beta$ 1 gene is predictive of a higher grade of RP [86] in Caucasian population. Niu X et al. then showed ethnic differences in TGF $\beta$ 1 gene polymorphisms [84]. The rs1982073:T869C did not predict radiation pneumonitis in the Chinese population. Another SNP in the TGF $\beta$ 1 gene, the AG/GG genotype of n rs11466345 was associated with a higher risk of RP in Chinese NSCLC patients after thoracic radiotherapy.

#### **Epigenetics**

Radiation induced DNA methylation changes were found with dose dependent relationship and tissue specificity [89–91]. The most successful clinical application is the methylation status of the O<sup>6</sup>-methylguanine-DNA-methyltransferase (MGMT) promoter, which predicts radiation response and prognosis in glioblastoma [92]. Epigenetic control also plays an important role in radiation response in NSCLC. Differential methylation profiles were detected in radiosensitive and resistant NSCLC cell lines. Artificially changed methylation profiles by gene knockdown or knockin also modified the in vitro radiation response [93]. The unmethylated IGFBP-3 promoter was found to be associated with poor response to radiation in NSCLC cell lines and poor outcome for patients who received adjuvant chemoradiotherapy [94]. In addition to DNA methylation, non-coding RNA was also identified to have an impact on the tissue response to ionizing irradiation. A global decrease in microRNA (miRNA) levels is a common observation in human cancers, indicating that miRNAs may have function in tumor suppression [95]. The most important pathway was to modify p53 tumor suppression network [95–97]. Another subset of miRNAs involved in DNA repair function, is also important in modulating the radiation response. For example, miR-34a, an important tumor-suppressing microRNA, was tested in vivo to sensitize lung tumor to radiation through RAD51 regulation [98]. Collectively, current evidence suggests that gene polymorphisms or epigenetic profiles may serve as biomarkers to predict radiation induced lung toxicity. The information might not be strong enough to guide radiotherapy decisions.

#### **Proteome and metabolome**

The systemic effect of radiotherapy at the proteome and metabolome profile is another way to predict treatment related toxicity. Serum inflammatory biomarkers as TGF $\beta$ , IL-1, KL-6, IL-6, IL-8, PDGF, TGF $\alpha$ , and TNF $\alpha$  are the most addressed [99]. Some early response changes in the levels of CXCL10 (IP-10), CCL2 (MCP-1), eotaxin, and TIMP-1 were also reported to correlate with RILT [100]. However, no single molecule outperforms others in predicting RILT well. A combination approach is more favored. IL-8 and TGF $\beta$ 1 combined with mean lung dose was reported to have good predictive values for RILT [85]. In addition to inflammatory markers, mass spectrometry (MS)-based proteomic techniques can be used to identify new biomarkers in the prediction of radiation induced lung fibrosis [101]. Pre-RT C4BPA, VTN,  $\alpha$ 2M, CO4A and CO5 were some peptides identified with mass based strategies to correlate lung toxicity [102, 103]. Immunological markers were also proposed to predict outcome and toxicity. In

an NSCLC SABR cohort, pre-treatment high neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), high neutrophil count and the presence of lymphopenia were associated with poor overall survival. Besides, patients with a higher NLR and low serum albumin level had less symptomatic radiation related toxicities [104].

#### **Lung cancer specific driver genes**

Lung adenocarcinoma is a unique cancer notable for its driver gene dominant patterns. EGFR activating mutation, ALK translocation, KRAS mutation, and HER2 amplification and mutation are the most common driver gene alterations. EGFR mutation, the most important targetable gene mutation, was also investigated for its impact on radiotherapy response [105, 106]. In basic research, EGFR mutant lung cancer cell lines were reported to have better radiosensitivity in low dose fractionation [107]. EGFR is known to modulate nonhomologous end-joining DNA repair. Impaired EGFR potentially sensitized tumors to radiation [108, 109]. Considering the complexity of lung cancer treatments and interactions between treatment strategies, the influence of EGFR mutations on the radiation response has seldom been proven in clinical studies. Radiation response differences between EGFR mutant and wild type patients is an issue under debate and the clinical data showed inconsistent results. A chemoradiation cohort suggested that EGFR mutant patients have shorter progression free survival than patients with wild-type EGFR [110], while another retrospective study showed better in-field local control for EGFR mutant patients after chemoradiation [111]. The discrepancy between studies might reflect the distinct biological feature of EGFR mutant lung cancer. The failure patterns in clinical series [111–113] showed that EGFR mutant tumors tend to distant metastasize rather than local recurrence. Even if the tumor is more responsive, the overall outcome may not be determined by radiotherapy alone.

KRAS mutations are associated with poor survival in NSCLC without adequate target treatment [114]. They were also reported to correlate with radioresistance, yet the biological basis was not fully understood [114–117]. Downstream pathway molecules of RAS including PI3K and Akt were reported to contribute to radioresistance [116, 118]. Other mechanisms are still under investigation. A subset phenotype of KRAS mutant NSCLC characterized by osteopontin/EGFR-dependent MLCC mitosis-like condensed chromatin (MLCC). It was shown to protect against radiation-induced DNA double-strand breaks and to repress negative regulators, including CRMP1 and BIM in *in vitro* and in animal models [117]. Clinical data addressing this issue are limited. A proton-based liver SABR phase II study showed

that KRAS mutations were associated with worse local control. However, lung cancer patients in this study only accounted for less than 10% of the participants [119]. An early stage NSCLC SABR cohort showed that KRAS is a negative predictor of cancer specific survival [120].

Although less discussed, the response to radiation may be more important in squamous cell carcinoma (SqCC). Generally, SqCC is more sensitive to radiotherapy than adenocarcinoma. Aside from immunotherapy, systemic treatment strategies for SqCC are relatively limited without available target therapy. The lack of effective systemic treatment makes radiotherapy more important in squamous lung cancer management. Abazeed ME et al. [121] found that in lung squamous cell carcinoma cell lines, activation of NFE2L2 and KEAP1, key regulators of the oxidative stress response, is associated with radiation resistance though the transcription factor NRF2. NRF2 is responsible for cell protection including the function of scavenging reactive oxygen species (ROS), which was reported to confer radioresistance [122]. The authors proposed the radiation sensitizing effect of a selective PI3K inhibitor, which negatively regulated NFE2L2 and reduce NRF2 levels. Further clinical studies are warranted to prove this concept.

The radiogenomic approach is becoming more applicable as genetic testing techniques improve. We summarized all biomarkers addressed in this review and categorized the strength in predicting radiosensitivity into three categories as shown in Table 2. Biomarkers with clinical references and independent validation were considered strong predictors (category A) for radiation response or toxicity. Those who had several institutional studies with inconclusive results were characterized as moderate predictors (category B). Biomarkers from single retrospective series or data from cell lines / animal models were considered as weak predictors (category C). Collectively, simple biomarkers like CT radiographic patterns or FDG-PET SUV values were easily to be validated in clinical use. However, the benefit could be small. The CT radiographic information may not provide additional information for adaptive treatment. FDG-PET information was applied successfully in treatment adaptation for Hodgkin lymphoma [123] but failed to show definite clinical benefit in driving clinical judgements in head and neck cancer [124]. Current data generally focus on the predictive and prognostic effects. Guiding the adaptive radiotherapy according to genomic information is scarce and not solid enough to support practice changes in non-small cell lung cancer fields.

#### **Conclusion**

Emerging data suggesting that incorporating the information genomic, radiomics, and dosiomics techniques

**Table 2** Strength of biomarkers in predicting radiation sensitivity in NSCLC

Types of biomarkers	Outcome predictors	Reference	Strength Category
<b>Panomics</b>			
Genomics	Radiosensitivity Index (RSI)	[64–72]	A
	Genomic-adjusted radiation dose (GARD)	[73]	B
	Lung adenocarcinoma associated gene: KRAS	[114–117]	B
	Squamous cell carcinoma associated genes: KEAP1, NFE2L2	[121]	C
	DNA repair genes: ATM and other mutated genes: PTEN, RB1, TP53 ...	[74, 75]	C
SNPs	DNA repair gene sites: XRCC1, BRCA1, and ERCC1 in predicting radiation response	[76–78]	C
	SNPs in predicting radiation related toxicity	[79–83]	B
	DNA repair gene sites: ATM, RAD51, XRCC family, LIG4, MTHFR	[84–86, 88]	B
	Inflammatory gene sites: TGFβ1 Immune modulated gene sites: CBLB	[87]	C
Epigenetics	unmethylated IGFBP-3 predicting radiation response	[94]	C
	miRNAs level in predicting radiation response	[95–97]	C
Proteome /Metabolome	Serum inflammatory biomarkers in predicting radiation induced toxicity IL-1, KL-6, IL-6, PDGF, TGFα, TGFβ, IL-8 CXCL10 (IP-10), CCL2 (MCP-1), eotaxin, and TIMP-1	[85, 99] [100]	B B
	Mass spectrometry (MS)-based proteomic markers in predicting lung fibrosis C4BPA, VTN, α2M, CO4A, CO5	[101–103]	B
	Serum markers in predicting SABR outcome neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), high neutrophil count	[104]	C
<b>Radiomics</b>			
CT scan	Post SABR local recurrence prediction: Enlarging opacity at 12 months after SABR Bulging margin; loss of linear margin, air bronchogram loss	[25–27]	A
	Combined radiomic features in predicting post SABR recurrence and irradiation	[30–37]	B
	Combined radiomic features in predicting radiation pneumonitis	[38–41]	B
PET	FDG-PET: Max SUV, metabolic volume, total lesion glycolysis in predicting treatment response	[43–47]	A
	FLT-PET change in predicting tumor response	[50–53]	B
	F-MISO PET in predicting radioresistant area for dose escalation	[56–59]	B
Dosimetrics	Combined 3D dosimetric information in prediction GI, GU and lung toxicity	[60, 61]	B

Abbreviations: NSCLC Non-small cell lung cancer. CT Computed tomography. PET Positron emission tomography. SUV Standard uptake volume. SABR Stereotactic ablative radiotherapy. SNP Single nucleotide polymorphisms

into clinical practice can improve treatment quality and make personalized radiotherapy in NSCLC possible. Basic studies addressing genomic issues are plenty, and this study topic has been studied for more than two decades; however, the application remains in outcome and toxicity predictions. The data based on genomic information have not yet extended its use to guide personalized radiotherapy. In contrast, radiomics and dosimetrics are rapidly growing fields in the past 10 years. Adaptive radiotherapy according to radiomics information is more common and some clinical trials are ongoing (**Supplementary Table 1**). The reproducibility might be the major cause of this discrepancy. Genomic guided treatment might be at higher cost and time consuming than radiomics guided treatment. Nevertheless, breast cancer is considered a successful example. A 21-gene recurrence

score assay has been established as a standard approach in adjuvant treatment for early breast cancer [125]. With a better integration of clinical, genomic, radiomics and even dosimetrics factors, it may be expected that precision radiotherapy will be feasible for the treatment of NSCLC in the near future.

### Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12929-020-00676-5>.

**Additional file 1: Supplementary Table 1.** Ongoing or recent completed clinical trials with precision radiotherapy strategies in non-small cell lung cancer

### Abbreviations

NGS: Next generation sequence; NSCLC: Non-small cell lung cancer; SABR: Stereotactic ablative radiotherapy; IMRT: Intensity modulated

radiotherapy; EORTC: European organization for research and treatment of cancer; CT: Computed tomography; OAR: Organ at risk; GTV: Gross tumor volume; AAPM: American association of physicists in medicine; AIP: Average intensity projection images; CBCT: Cone-beam CT; PET: Positron emission tomography; SUV: Standardized uptake value; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis; DVH: Dose volume histogram; NTCP: Normal tissue complication probability; MLD: Mean lung dose; V20: Percentage of volume received more than 20 Gy; SF2: Survival fraction at 2 Gy; GARD: Genomic-adjusted radiation dose; SNPs: Single nucleotide polymorphisms; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio

#### Availability of supporting data

No additional supporting data in this article.

#### Authors' contributions

Dr. Wen-Chi Yang wrote the article and recorded as the first authors. Dr. Feng-Ming Hsu and Prof. Pan-Chyr Yang contributed equally and were both listed as corresponding authors. The author (s) read and approved the final manuscript.

#### Funding

The study was supported by Academia Sinica [AS-SUMMIT-108] and Ministry of Science and Technology [MOST 107-0210-01-19-01, MOST 108-3114-Y-001-002, MOST107-2320-B-002-016-MY3].

#### Ethics approval and consent to participate

This review article is not involved in personal information and ethical approval is not required.

#### Consent for publication

Not applicable.

#### Competing interests

All the authors declared there is no conflict of interest or ethical concern in this article.

#### Author details

<sup>1</sup>Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Rd, Taipei, Taiwan. <sup>2</sup>Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan. <sup>3</sup>Department of Internal Medicine, National Taiwan University Hospital, No.1 Sec 1, Jen-Ai Rd, Taipei 100, Taiwan.

Received: 24 April 2020 Accepted: 17 July 2020

Published online: 22 July 2020

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