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Review Article

Epigenetic modification in radiotherapy and immunotherapy for cancers

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Abstract

Radiotherapy (RT) is one of the primary treatment modalities in managing cancer patients. Recently, combined RT and immunotherapy (IT) (i.e., radio-IT [RIT]) have been aggressively investigated in managing cancer patients. However, several issues in conducting RIT are challenging, such as incorporating advanced irradiation techniques, predictive/prognostic biomarkers, and other treatment modalities. Several clinical efforts and novel biomarkers have been introduced and developed to solve these challenges. For example, stereotactic radiosurgery/stereotactic radiotherapy, stereotactic body radiotherapy/stereotactic ablative body radiotherapy, and FLASH-RT have been applied for delivering precise irradiation to lung and liver tumors in conjunction with IT. Besides, several novel IT agents and incorporations of other therapies, such as targeted and thermal therapies, have been further investigated. The present study reviewed the emerging challenges of RIT in modern oncology. We also evaluated clinical practice, bench research, and multimodality treatments. In addition to several clinically applicable biomarkers, we emphasize the roles of advanced irradiation techniques and epigenetic modification as predictive/prognostic biomarkers and potential therapeutic targets. For example, 6(m)A-based epigenetic agents demonstrate the potential to enhance the treatment effects of RIT. However, further prospective randomized trials should be conducted to confirm their roles.

Keywords: *Epigenetic modification, Immunotherapy, Outcome prediction, Radiotherapy, Toxicity*

Introduction

Radiotherapy in oncology

Radiotherapy (RT) is effective in managing cancer patients [1,2]. In radiobiology, RT attacks cells, mainly damaging the DNA [3]. Cancer cells generally demonstrate an impaired ability to repair their postirradiation DNA damage compared with normal cells [4]. As a result, irradiated cancer cells present more significant apoptosis and postmitotic death than normal cells. Post-irradiation damaged or dead cancer cells frequently released broken double-strand DNA (dsDNA) fragments into the peri-tumor microenvironment or peripheral blood circulation. Biologically, these released dsDNA fragments enrich cancer-specific mutations. If these mutations are significant enough in quality and amount, the anticancer host immune reaction may be apparent via the presentation of antigen-presenting cells (APC). The postirradiation abscopal effect partly supports this hypothesis in several clinical observations [5]. Hence, RT is recognized as a crucial treatment modality in synergizing the treatment effect of modern immunotherapy (IT) [6].

Immunotherapy in oncology

IT has been used to manage malignant melanoma patients for decades [7]. However, interferon-based IT is limited in clinical oncology mainly due to its constraints of treatment toxicities. Recently, after the introduction of PD-1/PD-L1 and CTLA-4 immune checkpoint blockages [8], IT has gained a considerable advance in managing cancer patients [9]. As mentioned above, combined RT and IT demonstrate a synergistic anticancer effect. Initially,

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this combination was mainly applied to cancer patients with recurrent and metastatic diseases. Recently, IT has extended its clinical application to several new indications. For example, IT is tested in the context of a neoadjuvant setting in patients with advanced [10] or resectable [11] head-and-neck cancers, intending to replace the role of systemic chemotherapy.

Combined radiotherapy and immunotherapy for managing cancer patients

Combined RT and IT (i.e., radio-IT [RIT]) is a hot trend in modern oncology [6]. As mentioned above, one promising reason for applying RIT is to activate the potential abscopal effect of RT to enhance the treatment effects of IT [12]. Clinically, this combination is useful in managing several types of cancer patients, such as head and neck [13], lung [12], liver [14], glioblastoma [15,16], melanoma [17,18], lymphoma [19], breast [20,21], uterine cervix [22,23], ovarian [24], urinary bladder [25,26], prostate [27], renal cell carcinoma [28], esophagus [29], and pancreas [30].

Many metastatic cancer patients are also benefits from RIT, including brain [31] and liver metastases [32]. However, for lung cancer patients, PD-1/PD-L1-based IT with or without RT may increase the risk of treatment-related pneumonitis [33]. Besides, current RIT still has several challenges that are required to be further investigated, such as the introduction of advanced irradiation techniques, investigation of predictive/prognostic biomarkers, and incorporation of other treatment modalities [34].

Epigenetics in oncology

Epigenetic modifications regulate gene function without altering its DNA sequence [35]. Several types of epigenetic modifications have been identified, such as DNA methylation [36], histone modification [37], and noncoding RNA regulations (e.g., micro-RNA [miRNA or miR] [38], long-noncoding RNA (lncRNA), and circular RNA [circRNA]) [39]. Biologically, epigenetic modification is a crucial investigating field in oncology [40], involving progression [41] and metastatic processes [42], carcinogenesis [43,44], angiogenesis [45], migration/invasion [46], and immune suppression and modulation [47,48]. Clinically, application in serving as diagnostic/predictive/prognostic biomarkers is a promising research topic in cancer epigenetics. For example, the lncRNA-miRNA network is recognized as potential cancer biomarkers [49,50]. More notably, epigenetic-based agents have been actively investigated as one potential anti-cancer treatment modality [51], particularly for managing treatment-resistant/recurrent patients [52].

One good point for investigating epigenetic-based biomarkers in oncology is that advanced epigenetic-exploring techniques are actively developing for pan-cancer noninvasive screening [53], liquid biopsy [54], and high-performance detection [55]. Hence, the present study aimed to review clinical challenges and available biomarkers of combined RT and IT in managing cancers. Emerging challenges of epigenetic application in potential biomarkers and therapeutic targets for RIT are also reviewed.

Clinical challenges and emerging issues for treatment advance, outcome prediction, and toxicities prevention of radio-immunotherapy

Clinical challenges in treatment advance, outcome prediction, and toxicities prevention of radio-immunotherapy

Several factors affect RIT's treatment response and patient prognosis in managing cancer patients, including patient, cancer, and treatment factors [Table 1]. For example, for rectal cancer patients with a bulky unresectable liver metastasis that showed enriched PD-L1 expression, stereotactic body radiotherapy (SBRT) may be a better irradiation technique than conventional RT in conjunction with IT. However, several issues are still challenging in clinical practice, especially when the incorporation of other treatment modalities is under consideration, such as chemotherapy, targeted therapy, and thermal ablation.

Clinical challenges in treatment advance of radio-immunotherapy, including advanced radiotherapy techniques and novel immunotherapy agent combinations

IT and RT showed a zigzag association in their synergic effects on treatment benefits. That is, RT demonstrates the role of immune sensitizer for IT [94], and IT also functions as a radiation sensitizer for local RT [95,96]. As a result, few studies suggested that IT followed by RT may be feasible in some specific clinical conditions. However, treatment sequencing about RIT is generally recommended as RT followed by IT. The biological reason is that RT enhances cancer-specific dsDNA exposure to APC and then synergizes the treatment effects of IT [97]. Clinical data mainly supported this type of treatment sequence.

Many studies have shown that patients who received RT combined with IT significantly benefit in overall survival when compared with those who received IT or RT alone [98]. Generally, a higher dose per fraction of RT may enhance cancer cell killing, improve clinical outcomes [99], and trigger the immune effect. For example, the combination of hypofractionated RT (>5 Gy per fraction) with IT has been reported to prolong patient survival [100]. Besides, a phase II clinical trial indicated that pembrolizumab given within 7 days after SBRT, which consisted of 3 fractions of 8 Gy, improves progression-free and overall survival in patients with metastatic NSCLC [101]. However, a prior report indicated that irradiation doses exceeding 12–18 Gy may trigger the exonuclease Trex 1, which diminishes radiation-induced immunogenicity by breaking down cytosolic DNA [102].

The sequence of RT and IT has also been demonstrated to influence the effectiveness of treatment [57]. In a phase III clinical trial (PACIFIC trial), stage III non-small cell lung cancer patients who received concurrent chemoradiotherapy were randomized into two groups: one receiving durvalumab and the other receiving placebo. Their results showed that durvalumab treatment led to substantially extended progression-free survival compared to the placebo group [103]. Recently, they reported cumulative 4-and 5-year clinical

Table 1: Factors affect the treatment response and patient prognosis of combined radiotherapy and immunotherapy in cancers

Factors	Description	Reference
Patient factor		
Performance status (e.g., ECOG)	ECOG performance score (i.e., 2 vs. 0–1) is an independent prognostic factor for OS and PFS	[56]
Cancer factor		
Lung cancer	RIT is effective in managing SCLC and NSCLC patients, even in those with brain or liver metastases	[9,12,32,57-68]
Esophagus cancer	RIT is synergized in managing esophagus cancer patients; further trials are required	[29]
Breast cancer	RIT is effective in managing triple-negative breast cancer, even for metastatic patients	[20,21]
Head-and-neck cancers	RIT is helpful and challenging in patients with primary, recurrent, and metastatic HNCs	[69-73]
GYN cancers	RIT is effective in managing patients with cervical and ovarian cancers	[22-24]
GU cancers	RIT is helpful in patients with prostate, urinary bladder, and renal cell carcinoma	[25,27,28]
RT techniques		
SABR/SBRT	Lung SABR/SBRT shows better outcomes than conventional RT	[74-77]
SRS/SRT	Combined SRS/SRT and IT is helpful in lung cancer with liver or brain metastases, which improves neurological outcomes	[31,32,62]
Charged-particle irradiation	Charged-particle irradiation may enhance the RIT treatment effect with limited toxicities	[78]
FLASH-RT	Combined FLASH-RT and IT in managing cancer patients are under investigation	[79]
BNCT	Combined BNCT and IT may be a benefit in tumor control *in vivo*	[80]
Combined therapy**		
Chemotherapy	Several chemotherapy agents enhance RIT effects	[81-84]
Targeted therapy	Several targeted therapy enhances RIT effects, such as MEK inhibitors	[81,82,85]
Thermal ablation	Combined thermal ablation may further enhance the treatment effects of IT	[86]
m(6) A epigenetic modifier	Applying m (6) A epigenetic modifier, such as FTO* inhibitors, can reprogram RNA epitranscriptome and enhance the IT effect	[87,88]
Novel IT agents***		
Nanoparticle-based IT	Nanoparticle-based IT may enhance RIT treatment effects	[89-91]
NKTR-214 IT	Combined NKTR-214 immunotherapy and RT to stimulate systemic CD8(+) T-cell responses may cure multi-focal cancers [92]	[92]
Dendritic cell-based IT	The role of DC-based IT in conjunction with RT and chemotherapy is still not well defined [93]. Further randomized trials are required	[93]

*FTO, an m(6) A demethylase, utilizes the FTO-mediated epigenetic regulation to evade immune surveillance, **Multimodality therapy is the keystone in managing cancer patients, particularly those with advanced diseases. Combined treatments may enhance tumor response with the cost of increasing toxicities, ***Several novel IT agents are potential for clinical use in conjunction with RT, such as tumor vaccine, cytokine-based therapy, and adoptive T-cell therapy [6]. ECOG: Eastern Cooperative Oncology Group, OS: Overall survival, PFS: Progression-free survival, RIT: Radio-immunotherapy, IT: Immunotherapy, SCLC: Small cell lung cancer, NSCLC: Non-small cell lung cancer, HNCs: Head-and-neck cancers, SABR: Stereotactic ablative body radiotherapy, SBRT: Stereotactic body radiotherapy, SRS: Stereotactic radiosurgery, SRT: Stereotactic (hypofractionated) radiotherapy, RT: Radiotherapy, BNCT: Boron neutron capture therapy, GU: Genitourinary cancer, GYN: Gynecology cancer

outcome data, indicating that adding IT after concurrent chemoradiotherapy increases both progression-free and overall survival [103-106].

In another study involving metastatic non-small cell lung cancer, a Phase II trial (PEMBRO-RT; NCT02492568) investigated the efficacy of immunotherapy (pembrolizumab) following RT. The initial dose of pembrolizumab was administered after the final dose of RT (24 Gy in 3 fractions). They observed positive outcomes in the PD-L1–negative subgroup, showing notable improvements in both progression-free and overall survival [101]. Conversely, another trial (NCT02444741) investigated the concurrent treatment of IT (pembrolizumab) and RT (either 50 Gy in 4 fractions or 45 Gy in 15 fractions). However, no significant differences were found in terms of objective response rates or progression-free survival [107]. While a pooled analysis of these two randomized trials showed adding IT to RT significantly increased responses and outcomes in patients with metastatic non-small cell lung cancer [57], clinical outcomes may be largely influenced by age, tumor stage, cancer type, and the specific IT drug used.

Besides, preclinical studies showed the optimal sequence may vary depending on the specific immunomodulatory agent used. For instance, RT may demonstrate the highest synergy with anti-PD-L1 when administered simultaneously [108]. In contrast, administering a transforming growth factor-beta (TGF-β) inhibitor before RT might enhance the survival rate *in vivo* [109]. In a preclinical study comparing the sequencing of anti-CTLA-4 and anti-OX40 in relation to RT, the most favorable outcomes were observed when anti-CTLA-4 was administered before RT. However, the highest percentage of survival was noted in the group receiving anti-OX40 1 day after RT [110]. Currently, the sequencing of IT and RT remains a subject of debate, with uncertainty regarding its effects across different cancer types. More clinical data are needed.

When combined with IT, lymphocyte-sparing irradiation should be critically considered [111], particularly in vulnerable elderly cancer patients. Lymphocyte-sparing RT limits irradiation dose to lymphocyte-enriched tissue/organs, such as large blood vessels, noninvolved lymph nodes, spleen, and bone marrow. Clinically, a high accumulated dose of RT to the above tissue/organs induces transient or persistent

lymphocytopenia, including depletion of CD8(+) T-cells, which may vastly reduce the treatment effect of IT. As a result, for medical-fit patients, it is wise to limit irradiation dose to lymphoid-enriched organs at risk (OARs) according to the principle of "as low as reasonably achievable [112]," particularly in patients treated with combined pelvic irradiation and IT [113,114]. In this regard, advanced RT techniques, such as intensity-modulated radiotherapy [115] and volumetric-modulated arc therapy [116], are clinically helpful.

In contrast, for patients with bulky tumors, applying advanced RT techniques to deliver high tumor dose with maximum tolerated dose to nonlymphoid-enriched adjacent OARs for achieving the ultimate tumor control may be considered [117,118]. Advanced RT techniques are useful in RIT, such as stereotactic radiosurgery (SRS)/stereotactic radiotherapy [31] and SBRT/stereotactic ablative body radiotherapy [74-77,119] [Table 1]. The main reason is that advanced irradiation techniques largely improved therapeutic gains – increasing tumor control and decreasing treatment toxicities simultaneously. Furthermore, combined SRS and IT have been observed to enhance tumor control and improve neurological outcomes in lung cancer patients with brain metastases [31].

Some modern RT techniques demonstrated better clinical outcomes than conventional RT in the context of the RIT setting [17], such as charged particle irradiation [78], proton therapy [120], and FLASH-RT [79,121]. However, these RT techniques should be further tested in randomized clinical trials to demarcate their actual effective sizes.

Several novel IT agents are potential for clinical use in conjunction with RT, such as tumor vaccine, cytokine-based therapy, adoptive T-cell therapy, and nanoparticle-based IT [6]. Concurrently investigating potential predictive biomarkers is the trend in managing cancer patients treated with RIT [122]. For example, combined NKTR-214 IT and RT to stimulate systemic CD8(+) T-cell responses are tested for curing multi-focal cancers [92]. In this regard, the amount and function quality of activated CD8(+) T-cells may play crucial roles in predicting treatment response [123].

On the bench side, several signaling pathways have been reported to be bridged in RT and IT, such as the IFN-JAK-STAT axis [124] and well-known cGAS/STING signaling [125]. In this regard, epigenetic modification has been observed to play a role in conjunction with immune checkpoint inhibitors in several cancers, such as colorectal cancer [126] and melanoma [127].

Challenges of outcome prediction of radio-immunotherapy

Exploring clinically useful RIT biomarkers for outcome prediction is crucial and challenging in cancer patients [122,128]. Some outcome-predicting biomarkers have been reported, such as PD-L1 expression level, tumor mutation burden (TMB) [129-131], and imaging biomarkers [132,133] [Table 2]. Recently, combined biomarkers have been introduced clinically, such as the Integration of oncogene-based genomic profiling, tumor mutational burden, and PD-L1 expression [152,154]. In addition to the above biomarkers, one potential type of outcome-predicting biomarkers is epigenetic-based regulating factors. For example, the m6A RNA methylation has been observed to associate with the immune microenvironment, TMB, and PD-L1 level, predicting response to anti-PD-L1 IT [134]. Furthermore, the miRNA signature also demonstrates a value in predicting response to IT [122].

Remarkably, developing imaging biomarkers is particularly attractive for radiation oncologists [155]. The main reason is that the visible intra-tumor metabolic-hot part is crucial for guiding precise high-dose irradiation. Clinically, some metabolic-function-based Imaging biomarkers are introduced, such as (18) F-FET [132], (18) F-FDG [133], and preclinical [(64) Cu] NOTA-CD8a [153] positron emission tomography (PET). Note that evidence from [(64) Cu] NOTA-CD8a PET is based on preclinical *in vivo* experiments [153], revealing that identifying novel appropriate isotopes of PET for clinical application is challenging in terms of precisely targeting, clinical availableness, and cost-effectiveness.

Challenge of toxicity prevention for radio-immunotherapy

RT and IT have their treatment toxicities in managing cancer patients, respectively. Clinically, some treatment toxicities may be enhanced by applying RIT. For example, radiation-associated cardiovascular disease (RACVD) is a well-recognized late sequela in irradiated cancer survivors. In this regard, IT may also result in cardiovascular dysfunctions [156]. Hence, when IT is delivered in conjunction with RT, the risk of RACVD may be enhanced [157]. Besides, other RT-associated side effects may be enhanced with IT, such as lung fibrosis [158], particularly in patients treated with lung, breast, and esophagus RT. These toxicity enhancements may impair clinical outcomes and patients' life quality.

As mentioned previously, some agents may help to prevent the occurrence of RACVD, such as statins (HMG-CoA reductase inhibitors) [159] and candesartan (an angiotensin II receptor antagonist) [160]. However, more clinical data are required to confirm whether these agents still benefit from preventing cardiovascular toxicities in the context of RIT.

Emerging challenge: Further multimodality combinations, including epigenetic agents, should be tested in randomized clinical trial settings

RIT gains clinical success in managing several types of cancer patients. However, post-RIT survived cancer cells may obtain acquired radioresistance and develop other strategies to evade immune surveillance [161]. To avoid such a condition, applying multimodality management, such as chemotherapy, targeted therapy [81,82], local intervention (e.g., thermal ablation [86]), or epigenetic modifier [87], may be considered in medically suitable patients who burden advanced cancer diseases. For example, cancer cells may modulate the TGF-β activation [162] or utilize the FTO-mediated epigenetic regulation to evade immune surveillance [87]. In the latter condition, applying agents to inhibit the activity of FTO, a m (6) A demethylase, can reprogram RNA epitranscriptome and synergize the treatment effect of IT [87].

Combined chemotherapy or targeted therapy's role in enhancing IT's treatment effect is also interesting in clinical

Table 2: Potential biomarkers in predicting treatment response and patient prognosis of combined radiotherapy and immunotherapy in cancers

Potential biomarkers	Description	Reference
	Epigenetic-based potential biomarkers	
m6A RNA methylation	The m6A RNA methylation associates with the immune microenvironment, TMB, and PD-L1 level, predicting response to anti-PD-L1 IT Besides, developing m6A RNA epigenetic agents is a potential direction to the synergy treatment effect of IT	[87,88,134]
miRNA signature	Several miRNAs and their associated gene expression/signature are potential for predicting/prognostic biomarkers in RIT	[49,50,122,135-137]
miR-16-5p	Serum exosomal miR-16-5p regulates PD-L1 expression, serving as a biomarker for PD-L1-based IT	[135]
miR-195/miR-497	miR-195/miR-497 regulates PD-L1 (i.e., CD274) expression in triple-negative breast cancer	[136,138]
IMS	A high immune microenvironment score shows a better response to PD1/PDL1-based IT	[139]
5mC score	A high 5mC score predicts low sensitivity to IT, neoadjuvant chemotherapy, and RT	[140]
lncRNA	Several immune-related lncRNAs predict prognosis and treatment response	[49,50,141-143]
circRNA	Has_circ_0006692 promoted NSCLC progression via the mir-205-5p/CDK10 axis and might serve as a prognostic biomarker and therapeutic target	[39]
	Nonepigenetic-based potential biomarkers	
TCR	Post-RT-released cancer dsDNAs activate the cGas-STING pathway and host T-cells. The function of activated T-cells plays an essential role in RIT	[144]
CD8(+) T-cells	CD8(+) T-cell signature plays a role in the outcome prediction of IT	[123]
PNI	PNI and NLR may predict treatment response in IT	[56]
NLR	Elevated NLR was a poor predictor for OS in advanced and brain-metastatic NSCLC	[9,56,145]
TMB	High TMB predicts better IT outcomes in several cancers, such as gastric cancer and NSCLC	[129-131]
MSI-H	IT is effective in MSI-H cancer patients	[146]
MMR-P	IT alone is ineffective in patients with MMR-P mCRC, even in conjunction with RT	[146,147]
PD-L1 expression	PD-L1 expression is clinically applied for prescribing PD-L1-based IT	[131,148,149]
TME score	TME score predicts prognosis and treatment response to IT in breast cancer patients	[150]
Serum tumor markers	Dynamic changes of serum tumor markers, such as CEA, CA-125, and SCC-Ag, may be prognostic in IT	[151]
KMT2C/TP53 co-mutation	KMT2C/TP53 co-mutation in conjunction with PD-L1 expression and TMB may be effective biomarkers in IT	[152]
Imaging biomarkers	PET-based imaging biomarkers, such as (18) F-FET, (18) F-FDG, and preclinical [(64) Cu] NOTA-CD8a PET*, help monitor the treatment response of IT and RT	[132,133,153]

*The evidence from [(64) Cu] NOTA-CD8a PET is based on preclinical *in vivo* experiments [153], revealing that identifying novel appropriate isotopes of PET for clinical application is challenging in terms of precisely targeting, clinical availableness, and cost-effectiveness. TCR: T-cell receptors, PNI: Prognostic nutrition index, NLR: Neutrophil-to-lymphocyte ratio, TMB: Tumor mutational burden, MSI-H: Microsatellite instability-high, PD-L1: Programmed death ligand-1, IR: Ionizing radiation, IT: Immunotherapy, IMS: Immune microenvironment score, ceRNA: Competitive endogenous RNA, NSCLC: Non-small cell lung cancer, lncRNA: Long noncoding RNA, MMR-P: Mismatch repair-proficient, mCRC: Metastatic colorectal cancer, TME: Tumor microenvironment, PET: Positron emission tomography, miR: MicroRNA, also termed miRNA, OS: Overall survival, RT: Radiotherapy

oncology [81,82]. For example, combined short-course RT and IT are evaluated in conjunction with chemotherapy in the context of total neoadjuvant therapy for patients with local-regionally advanced rectal cancer [163]. If medical fit, one potential treatment direction is combining chemoradiotherapy and IT in patients with locoregionally advanced diseases [83]. However, the above new combinations of multimodality therapies planned to combine with RIT should be further tested in randomized clinical trials to define their effective sizes in tumor control and the potential harms of treatment toxicity.

Emerging challenge: The role of epigenetic modification in radiotherapy and immunotherapy in terms of potential biomarkers and therapeutic targets

As mentioned above, in addition to clinically applicable biomarkers, such as PD-L1 expression and TMB [129-131], several studies investigated novel predictive/prognostic biomarkers for RIT. Of these, endogenous noncoding RNAs, e.g., miRNA and lncRNA, that function in modulating gene expression grasp interests in both outcome-predicting biomarkers and potential treatment targets [164].

Emerging challenge of bench studies for outcome prediction in radio-immunotherapy, focusing on epigenetic biomarkers

Detecting miRNA levels in plasma or serum is actively investigated in outcome prediction and disease follow-up. Several miRNAs have been reported to show potential roles in predicting outcomes in cancer patients treated with RIT [49,50], such as miR-16-5p [135] and miR-195/miR-497 [136] [Table 2]. In epigenetics, one biological effect of circular RNAs (circRNAs) is to act as miRNA sponges that attenuate the function of pair-matched miRNAs [165]. As a result, circRNAs have been reported as one candidate of epigenetic biomarkers in RIT, e.g., Has_circ_0006692 [39]. Besides, other epigenetic-based biomarkers are potential for clinical application in RIT, such as 5 mC score [140] and lncRNA [49,50]. Note that the competitive endogenous RNA (ceRNA) network analysis should be considered to investigate the role of miRNA or lncRNA [141]. Besides, as mentioned previously [166], applying epigenetic biomarkers in clinical practice have some limitations and challenges. For example, different test timing may show different results that affect interpretations. Hence, at least two test time

points should be implemented and denoted as pretreatment references, i.e., before initiating RT and IT, respectively.

Emerging challenge of bench studies for epigenetically therapeutic targets in radio-immunotherapy

Epigenetic regulation plays an active role in RT. For example, epigenetic dysregulation has been recognized to involve cancer radioresistance [167]. Remarkably, epigenetic regulators may reprogram the epigenome and restore radiosensitivity [168]. Similarly, applying epigenetic agents, such as HDAC inhibitors [169], to IT also gains ongoing interest [170]. Several epigenetically biological targets are investigated in RIT, such as PD-L1 [171], YTH domain containing 2 [172], and m6A RNA modification.

Of these, m6A RNA modification has been reported to be involved in cancer treatment resistance [88], and applying m6A RNA epigenetic agents may reverse the resistance and restore treatment effect [87]. Besides, DNA methylation of some target genes has been reported to correlate with immune infiltration and survival [173], serving as potential candidates for treatment targets. However, DNA-methylation-based epigenetic therapy has a challenge for clinical application. That is, targeted methylation/de-methylation is difficult to be achieved [174]. Unfortunately, this type of epigenetic modification is essential to leading DNA-methylation-based epigenetic therapy being clinically helpful and applicable. Remarkably, targeting noncoding RNAs, such as miRNA and lncRNA, are the preferred epigenetic modulation in cancer epigenetic-based therapy [175]; however, the role in the context of RIT should be further demarcated.

Conclusion

Combined RT and IT are one active treatment direction in managing cancer patients. Further efforts from clinical trials are ongoing to define the best combination, such as incorporating advanced RT techniques, novel IT agents, and other treatment modalities. Besides, bench and clinical studies are emergently required to improve the prediction of treatment response and clinical outcomes. Integrating other treatment modalities in conjunction with RIT, such as chemotherapy, targeted therapy, and other local therapies (e.g.,, thermal ablation), is warranted and ongoing. On ClinicalTrials.gov [176], more than 800 clinical trials are registered for investigating challenging issues of RIT in several cancer diseases. These data show a still hot trend of combined RIT in oncology. Results from these prospective trials are expected. Further investigations to explore effective epigenetics-based biomarkers and potential treatment targets are encouraged.

Data availability statement

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

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Conflicts of interest

There are no conflicts of interest.

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