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REVIEW – CANCER RESEARCH

Radiotherapy resistance: identifying universal biomarkers for various human cancers

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Abstract

Radiotherapy (RT) is considered as a standard in the treatment of most solid cancers, including glioblastoma, lung, breast, rectal, prostate, colorectal, cervical, esophageal, and head and neck cancers. The main challenge in RT is tumor cell radioresistance associated with a high risk of locoregional relapse and distant metastasis. Despite significant progress in understanding mechanisms of radioresistance, its prediction and overcoming remain unresolved. This review presents the state-of-the-art for the potential universal biomarkers correlated to the radioresistance and poor outcome in different cancers. We describe radioresistance biomarkers functionally attributed to DNA repair, signal transduction, hypoxia, and angiogenesis. We also focus on high throughput genetic and proteomic studies, which revealed a set of molecular biomarkers related to radioresistance. In conclusion, we discuss biomarkers which are overlapped in most several cancers.

Keywords Radiotherapy · Radioresistance · Biomarker · Cancer

Introduction

Radiation therapy (RT) is the most effective method of cytotoxic treatment based on ionizing radiation (Baskar and Itahana 2017). RT plays a key role in the treatment of many cancers, and approximately 50% of cancer patients are estimated to receive RT (Harrington et al. 2011). Indications for the appointment of RT include (a) radical treatment, (b) adjuvant therapy after surgery to eliminate residual disease, and (c) palliative care (Harrington et al. 2011). As an independent treatment strategy, RT can be used at earlier stages of the disease if surgical intervention is impossible (Das et al. 2010; Swanton et al. 2021). The primary purpose of radical RT is to achieve complete eradication of tumor cells by delivering sufficient doses of radiation. The levels of radical doses depend on the histological type of tumor, mitotic activity, and the degree of cell differentiation.

Tumor-specific radioresistance is a critical factor for RT failure and the development of locoregional relapse and distant metastases (Huang and Zhou 2020). The frequency of relapses after RT or chemoradiation therapy (CRT) varies between different cancers. It is 5.2% in head and neck cancer (Lindegaard et al. 2020), 16–20% in prostate cancer (Grün et al. 2020), 55% in cervical cancer (Ning et al. 2018), 8.63% and 4.31% (local recurrence and regional recurrence after RT) in breast cancer, and 6.5% in rectal cancer (Yu et al. 2008; Couch and Hemingway 2016; Huang et al. 2017).

The search for effective clinical, morphological, and molecular criteria for predicting the success of the treatment at the initial and follow-up steps is one of the key tasks in oncology. Despite the main and common molecular mechanisms of radioresistance being clear, the establishment of effective biomarkers is still a significant challenge. The antigen of squamous cell carcinoma (SCC-Ag) was recently established for determining a residual disease after treatment and the effectiveness of prescribed therapy, but it is not related to radioresistance (Yagi et al. 1987; Petrelli et al. 1988; Yoshimura et al. 1990). The development of novel radioresistance biomarkers universal for all cancers seems relevant and demanded.

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Radiation induces different alterations related to DNA damage and repair, cell cycle regulation, reactive oxygen species (ROS), hypoxia, tumor microenvironment (TME), angiogenesis, and epigenetic regulation (Willers et al. 2013; Tang et al. 2018). Plenty of existing studies investigates the radiation effects in vitro and in vivo. An increasing number of studies have also been trying to establish prognostic and predictive biomarkers of radioresistance in cancer patients.

In the present review, we analyze the available data on the potential biomarkers of radioresistance in different cancers defined as an unfavorable outcome in most cases. In particular, we focus on clinical studies demonstrating molecular factors associated with radioresistance. We also review genomic, transcriptomic, and proteomic studies that revealed the sets of molecular factors prognostic for cancer after RT. In conclusion, we discuss the complications in the search for a single biomarker and explain which attempts should be made in the future to overcome cancer radioresistance.

DNA damage and repair

In general, the success or failure of RT is determined by five R radiobiology: repair of DNA damage, cell redistribution in the cell cycle, repopulation, reoxygenation of hypoxic tumor areas, and radiosensitivity (Pajonk et al. 2010; Goedegebuure et al. 2019). A common feature of ionizing radiation is the induction of DNA damage directly leading to cancer cell death. Critical mechanisms of DNA damage include cleavage at the sugar-phosphate linkage region of a DNA polynucleotide chain (single-strand break, SSB), breaks on both DNA chains in adjacent or nearly adjacent sugar-phosphate-binding sites (double-strand break, DSB), intramolecular and intermolecular linkage between DNA or DNA-protein, degradation of organic bases, loss of a purine or pyrimidine base, and breaking of hydrogen bonds resulting in permanent deformation of DNA structure (Liu et al. 2020b). Among them, DSBs are the most lethal lesions which trigger a series of cellular DNA damage responses (DDRs), including the activation of DNA damage sensing and early transduction pathways, cell cycle arrest, and DNA repair (Huang and Zhou 2020). DSBs can be repaired either by homologous recombination (HR) or via nonhomologous end joining (NHEJ). HR is a crucial pathway for the accurate repair of DSBs and maintaining genomic stability (Shrivastav et al. 2008).

Several factors responsible for DNA repair are associated with radioresistance in several clinical studies (Table 1). Pretreatment protein expression of XRCC2, involved in NHEJ-based repair of DSBs, negatively correlates with 3-year overall survival (OS) after RT in patients with locally advanced rectal cancer (Qin et al. 2015). Among patients who achieved a pathological response, 66.7% of cases were negative for XRCC2 expression, and 33.3% were positive for XRCC2 expression (Qin et al. 2015). In NSCLC patients, XRCC2 SNPs were associated with RT response and OS (Yin et al. 2011; Yang and Liu 2020). The protein expression of BRCC3 and YB-1, which are involved in DNA repair, was upregulated in pretreatment biopsies of patients with nasopharyngeal carcinoma (NPC) who had worse OS and a higher risk of recurrence (Tay et al. 2009; Tu et al. 2015). Increased protein expression of Ku80 (XRCC5), a key mediator of DSB repair, correlates with locoregional recurrence in post-RT specimens of patients with HPV-negative head and neck squamous cell carcinoma (HNSCC) (Moeller et al. 2011).

In NPC patients treated with conventional RT, the radioresistance-associated biomarkers belonging to the heterotrimeric replication protein A (RPA) complex were demonstrated. The expression of DNA repair marker RPA3 in post-treatment specimens was higher in radioresistant NPC patients who experienced local recurrence. Analysis of TCGA data indicated that high pretreatment RPA3 expression also correlates with poor OS and a high recurrence rate in patients with HNSCC after RT (Qu et al. 2017).

The impact of copy number alterations in DDR genes on clinical outcome based on biochemical recurrence (defined as a rise in PSA level) was examined in patients with prostate cancer (PC) receiving radical RT (Berlin et al. 2014). Evaluation of pre-RT biopsies by a comparative genomic hybridization revealed CNAs predominantly in DDR-sensing genes: *NBN* (15.1%), *ATR* (8.6%), *PRKDC* (7.9%), and *ATM* (5.8%). In addition, *NBN* gain was an independent prognostic factor for 5-year biochemical recurrence (Berlin et al. 2014).

The molecular mechanisms of DDR are well known, and many in vitro studies have established them as first-line processes to protect tumors from irradiation inducing radioresistance. Above mentioned evidence indicates that increased pre-and post-treatment expression of DDR-associated factors correlates to poor prognosis; however, this correlation is not specific to cancer type. Only XRCC2 expression was predictive for radioresistance in several cancers (Fig. 1, Table 1). As far as DNA repair is complex, clinical investigation of other DDR-associated factors can help search for sensitive and effective biomarkers or signatures for tumor response to RT.

Tyrosine kinases and cell cycle control

Tyrosine kinases (TKs) are enzymes that regulate cell survival and cell proliferation in response to stress (Bhattacharya et al. 2018). TKs are primarily classified into receptor tyrosine kinases (RTKs) (e.g., EGFR, PDGFR, HER-2, FGFR, and IGF-1R) and non-receptor tyrosine kinases (NRTK): SRC, ABL, FAK, AKT, and Janus kinase (Paul and Mukhopadhyay 2004). They play a crucial role

Table 1 Common radioresistance biomarkers in various cancers

Marker	Method of detection	Cancer type (*N*)	Treatment	Prognostic significance	References
DNA damage and repair					
XRCC2	IHC	RC (*N* = 67)	RT	Poor 3-year OS	Qin et al. (2015)
	Genotyping	NSCLC (*N* = 261)	RT	Poor 100-months OS	Yin et al. (2011)
	Genotyping	NSCLC (*N* = 486)	3D-CRT	Lower RT efficacy	Yang and Liu 2020)
Tyrosine kinases					
IGF-1R	IHC	RC (*N* = 87)	RT	Poor response	Wu et al. (2014)
	RT-PCR	RC (*N* = 87)	RT	Poor response	
	IHC	PC (*N* = 136)	RT	Post-RT recurrence	Aleksic et al. (2017)
	IHC	BC (*N* = 25)	RT	Early breast tumor relapse	Turner et al. (1997)
pAKT	IHC	BC (*N* = 1004)	RT	Lower incidence of ipsilateral breast tumour recurrence	Sjöström et al. (2020)
	IHC	RC (*N* = 25)	CRT	Poor RT response	Koyama et al. (2018)
	IHC	RC (*N* = 70)	CRT	Better RT response	Davies et al. (2011)
	IHC	HNSCC (*N* = 120)	RT	poor OS/PFS	Freudlsperger et al. (2015)
	IHC	SCC (*N* = 119)	RT	poor OS/PFS	Kim et al. (2006)
Metabolic factors					
HIF-1α	IHC	SCC (*N* = 43)	CRT	Lower chance of complete response	Zhu et al. (2016)
		SCC (*N* = 179)	Concurrent CRT	Poor 5-year DFS and OS	Kim et al. (2013)
	IHC	HNSCC (*N* = 941)	CRT	Worse prognosis in oropharyngeal cancer and laryngeal cancer and better in oral cancer	Swartz et al. (2021)
	IHC	NPC (*N* = 129)	RT	Poor OS and DMFS	Chen et al. (2014)
	IHC	NPC (*N* = 90)	CRT	Poor OS	Hui et al. (2002)
	Meta-analysis	ESCC (*N* = 1261)	CRT	Poor response to CRT	Sun et al. (2013)
NRF2	IHC	ESCC (*N* = 164)	Concurrent CRT	Poor response to therapy and poor 8-year PFS and OS	Wang et al. (2020)
	IHC	NPC (*N* = 97)	RT	Reduced 8-year OS	Huang et al. (2020)
	mRNA profiling	RC (*N* = 127)	RT	Incomplete response to neoadjuvant RT	O'Cathail et al. (2021)
COX-2	IHC	SCC (*N* = 75)	CRT	Decreased 5-year OS and DFS	Kim et al. (2002)
	IHC	SCC (*N* = 167)	RT	Decreased 5-year OS and DFS	Chen et al. (2005)
		RC (*N* = 2095)	CRT	Poor RT response, local recurrence	Berbecka et al. (2021)
	IHC	ESCC (*N* = 76)	RT	Worse RT response	Zhang et al. (2017b)
Angiogenic regulators					
VEGF	ELISA	NSCLC (*N* = 1602)	RT	Poor response and 10-year OS	Fu et al. (2014)
	IHC	PC (*N* = 201)	RT	Higher risk of 12-year biochemical failure	Vergis et al. (2008)
	IHC	RC (*N* = 10)	RT	Lower rate of pCR	Zlobec et al. (2008)
	ELISA	BC (*N* = 268)	RT	Lower 5-year RFS	Manders et al. (2003)
	IHC	SCC (*N* = 100)	RT	Reduced OS and metastatic-free survival	Loncaster et al. (2000)
	IHC	SCC (*N* = 20)	RT	Post-RT relapse	Yoshida et al. (2018)
	cDNA microarray	HNSCC (*N* = 86)	RT	Poor response to RT	Akervall et al. (2014)

Table 1 (continued)

Marker	Method of detection	Cancer type (*N*)	Treatment	Prognostic significance	References
OPN	ELISA	NSCLC (*N* = 55)	RT/CRT	Poor OS	Ostheimer et al. (2014)
	ELISA	NSCLC (*N* = 106)	CRT	Poor 6-year survival	Dehing-Oberije et al. (2011)
	IHC	PC (*N* = 201)	RT	Higher risk of 12-year biochemical failure	Vergis et al. (2008)
	ELISA	HNSCC (*N* = 320)	RT	Poor RT response	Overgaard et al. (2005)
	IHC	HNSCC (*N* = 50)	RT	Increase in local recurrence	Etiz et al. (2013)
	ELISA	NPC (*N* = 44)	RT	Poor RT response	Hui et al. (2008)
	IHC	SCC (*N* = 111)	RT	Worse RT response and lower 5-year PFS rate	Huang et al. (2015)
	IHC	ESCC (*N* = 80)	RT	Poor pCR, worse OS and DFS	Chiu et al. (2018)
IL-6	IHC	ESCC (*N* = 173)	CRT	Development of locoregional failure or distant metastasis	Chen et al. (2013)
	ELISA	NPC (*N* = 314)	RT	Worse 2-year survival	Chow et al. (2003)
	TCGA data	HNC (*N* = 785)	RT	Worse radiotherapeutic outcome	You et al. (2019)
	ELISA	NSCLC (*N* = 322)	RT/CRT	Poor OS	Dehing-Oberije et al. (2011)

BC breast cancer, *CRT* chemoradiotherapy, *DFS* disease-free survival, *ELISA* enzyme-linked immunosorbent assay, *ESCC* esophageal squamous cell carcinoma, *HNSCC* head and neck squamous cell carcinoma, *IHC* immunohistochemistry, *NPC* nasopharyngeal cancer, *NSCLC* non-small-cell lung carcinoma, *OS* overall survival, *pCR* pathological complete response, *PC* prostate cancer, *RC* rectal cancer, *RT* radiotherapy, *SCC* squamous cervical carcinoma

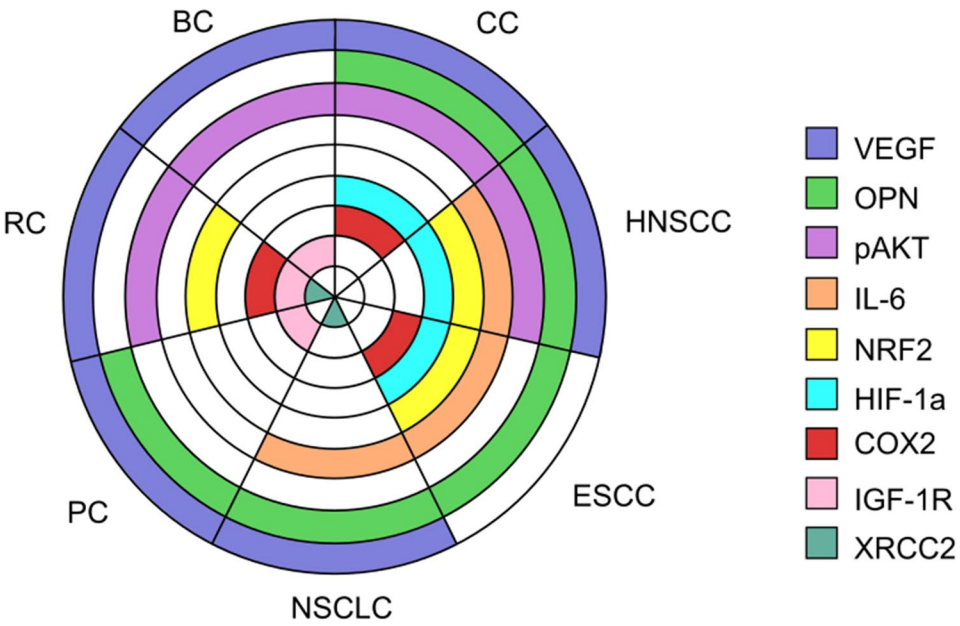

Fig. 1 Overlapping radioresistance biomarkers between different human cancers. Nine common biomarkers are shown in the seven most representative cancer types treated with RT. *BC* breast cancer, *CC* cervical cancer, *ESCC* esophageal squamous cell carcinoma, *HNSCC* head and neck squamous cell carcinoma, *NSCLC* non-small cell lung carcinoma, *PC* prostate cancer, *RC* rectal cancer

in radiation-activated DNA repair and cell survival (Bhattacharya et al. 2018) (Table 1).

HER-2 overexpression is related to distant metastasis of rectal cancer after neoadjuvant RT, especially in patients with poor response to treatment (Yao et al. 2014). Rectal, breast, and prostate cancer patients with low pretreatment protein and negative mRNA expression of IGF-1R display improved sensitivity to RT and decreased post-RT recurrence rate (Turner et al. 1997; Wu et al. 2014; Aleksic et al. 2017). High protein expression of Pim-1 and gene expression of FAK/PTK2 in post-treatment samples is associated with poor prognosis and worse

DFS in patients with HNSCC treated with RT (Peltola et al. 2009; Skinner et al. 2016). A high level of phosphorylated AKT (pAKT), regulating DDR, in samples obtained after RT correlates with poor OS/PFS in patients with squamous cell cervical carcinoma, glioblastoma, and advanced HNSCC (Kim et al. 2006; Suzuki et al. 2007; Freudlsperger et al. 2015). Oppositely, a high pretreatment level of pAKT is associated with a lower incidence of recurrence and better RT response in breast and rectal cancers (Davies et al. 2011; Sjöström et al. 2020).

The outcome of irradiation depends on the regulation of the cell cycle (Otani et al. 2016). Cells in the G2/M phase are more vulnerable to irradiation than cells in G1 or S phases, where rapid DNA repair can successfully result in radioresistance (Pawlik and Keyomarsi 2004). Tumors with high expression of checkpoint serine/threonine kinase 1 (Chk1), a key cell cycle mediator involved in DNA repair, display radioresistant phenotype. DNA damage induces the activation of Chk1, facilitating the DDR and initiation of the cell cycle checkpoints (Patil et al. 2013). High expression of Chk1 in pretreatment samples is significantly associated with shorter progression-free survival (PFS) and shorter time to local recurrence in patients with gastric cancer and breast cancer treated with CRT and RT, respectively (Alsubhi et al. 2016; Bargiela-Iparraguirre et al. 2016). High protein expression of P16INK4A, a cyclin-dependent kinase (CDK) inhibitor belonging to tumor suppressors, in pre-RT samples is prognostic for the improved 5-year OS and DFS rates in patients with cervical cancer receiving adjuvant RT or concurrent CRT (Fu et al. 2018). CDKs are essential for cell cycle progression through the G1-S phases and initiation of DNA repair. CDK inhibition combined with RT is proposed to diminish the radioresistance development (Johnson and Shapiro 2010). In cervical cancer, high expression of KLF4 (cell cycle regulator in G1–S phases) after treatment is found in radiation-resistant patients and associated with increased rates of local recurrence and distant metastases (Liu et al. 2017a; Hou et al. 2017; Yang et al. 2020; Köster et al. 2020).

Thus, IGF-1R, belonging to RTKs, and pAKT, a non-receptor tyrosine kinase, possess predictive RT value in several cancers (Fig. 1, Table 1). However, it is questionable whether TKs can be effective biomarkers as they regulate multiple signaling pathways. Nevertheless, due to the involvement of RTKs and cell cycle control proteins in DNA repair, combining RT with TK inhibitors can be a promising approach to increase RT efficacy. Recent studies showed that RTKs and CDK inhibitors display remarkable anti-tumor efficacy in lung, colorectal, hepatocellular, renal, and breast cancers, as well as leukemia and melanoma (Pottier et al. 2020; Zhang et al. 2021).

Hypoxia and metabolism

Hypoxia is a common feature of solid tumors resulting from the imbalance between oxygen availability and consumption (Wang et al. 2019b). Hypoxia generates an intratumoral oxygen gradient that contributes to tumor plasticity and heterogeneity and activates the DDR pathways (Jing et al. 2019). Thus, hypoxic cancer cells acquire a more aggressive and metastatic phenotype and become resistant to any cytotoxic treatment, including RT and CRT (Zhu et al. 2016). On the contrary, molecular oxygen may react with radiation-induced DNA radicals to generate DNA damage. Therefore, well-oxygenated cancer cells are more sensitive to irradiation than hypoxic ones (Willers et al. 2013).

Hypoxia-inducible factor-1α (HIF-1α) is an important transcription factor, which is increased in hypoxic conditions. RT promotes HIF-1 activation by vascular damage or reactive oxygen species (ROS) (Huang and Zhou 2020). In cervical cancer, HIF-1α expression after CRT is absent in cases with complete response (CR) and is found in 63% of patients with partial response (Zhu et al. 2016). High HIF-1α expression before CRT is considered a predictive biomarker for poor response to preoperative CRT in squamous cervical, oropharyngeal, esophageal, and laryngeal cancers, but for better prognosis in oral squamous carcinoma (Sun et al. 2013; Zhu et al. 2016; Swartz et al. 2021). Increased level of HIF-1α in pre-CRT/RT samples is a poor prognostic biomarker for OS and metastasis-free survival in patients with cervical cancer and NPC (Hui et al. 2002; Kim et al. 2013; Chen et al. 2014).

ROS, such as superoxide anion (O_2-), hydroxyl radicals (OH−), and hydrogen peroxide (H_2O_2), are generated by water radiolysis in extracellular environments and are toxic to cancer cells and adjacent normal tissues (Zou et al. 2017). ROS can induce genetic instability (Perillo et al. 2020) (Figure 2). The high expression of ROS modulator 1 (ROMO1) after RT is associated with worse PFS and OS and shorter locoregional recurrence in NSCLC patients treated with definitive RT (Kong et al. 2019). Expression of coenzyme A synthase (COASY) measured after RT is associated with radioresistance in rectal cancer patients. Patients with no response to CRT have significantly higher COASY expression than other patients (Ferrandon et al. 2020). Low expression of pH2AX, a damage-associated protein, and MAP17, a ROS-related protein, is associated with better OS (Rivero et al. 2018). In pretreatment biopsy samples, protein expression of oxidative stress-associated factor RKIP is significantly downregulated, while the level of NRF2 and NQO1 is upregulated in radioresistant NPC. A low level of RKIP and a high level of NRF2 and NQO1 correlate to reduced OS (Huang et al. 2020). In patients with locally advanced esophageal squamous-cell carcinoma (ESCC) and rectal cancer, high NRF2 expression indicates a poor response to RT/CRT

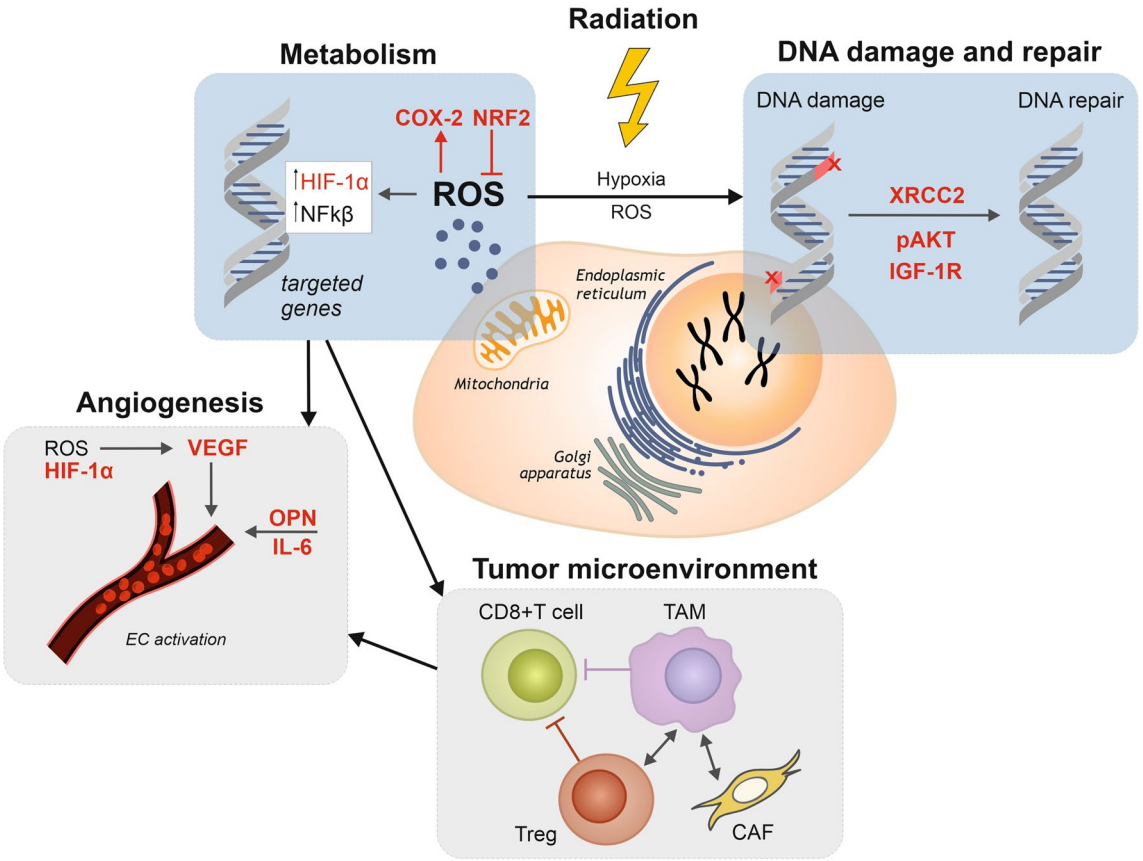

Fig. 2 Overlapping radioresistance biomarkers among the key processes related to radioresistance. Irradiation results in ROS generation and DNA damage. In response to irradiation, DNA repair is activated, accompanied by increased tyrosine kinase activity via multiple signal transduction pathways. The effects of ionizing radiation depend on the oxygenation/hypoxia metabolic balance in the tumor. Oxygenation induces ROS generation, which triggers DNA damage, but can activate the expression of pro-angiogenic genes. In contrast, hypoxia interferes with the effect of RT and can also stimulate the upregulation of angiogenic factors and immunosuppressive immune responses. The suppression of anti-tumor immune response is followed by the RT-induced metabolic and transcriptional changes in the pro-tumor phenotypes of tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), and Tregs. TAMs and Tregs additionally promote angiogenesis. Boxes in blue reflect intracellular processes, boxes in grey demonstrate extracellular components, which trigger radioresistance in tumor cells. Common radioresistance biomarkers are given in the corresponding boxes and highlighted in red

and unfavorable survival (Wang et al. 2020; O'Cathail et al. 2021).

Analysis of TCGA data revealed that HNSCC patients with high ACLY (ATP citrate lyase) expression experience poor OS (Göttgens et al. 2019). Expression of IGF-1 and GLUT1 in post-treatment samples correlates with poor OS in patients with cervical cancer who underwent RT/CRT (Moreno-Acosta et al. 2017). In breast cancer, expression of p-S6K1, a critical downstream effector of the mTOR pathway, before treatment correlates with decreased locoregional recurrence-free survival (Choi et al. 2020b).

Expression of COX-2, regulating oxidative phosphorylation, is a poor prognostic factor for patients with cervical cancer. Five-year OS and DFS are decreased in COX-2-positive patients (Kim et al. 2002; Chen et al. 2005). CC patients with the double expression of iNOS- and COX-2 after RT have the poorest survival rates (Chen et al. 2005). COX-2 expression negatively correlates with complete response to RT and local recurrence in rectal cancer and ESCC (Zhang et al. 2017b; Berbecka et al. 2021).

Thus, tumor metabolic status determines radiotherapeutic sensitivity through tumor oxygenation and ROS production. Since ROS is non-specifically induced by radiation, it is challenging to use ROS level as a predictive biomarker. Oppositely, hypoxia-associated factors, such as HIF-1α and COX-2, and NRF2, a transcriptional activator of antioxidant genes, could be used to predict failed RT response in several human cancers (Figure 1, Table 1).

Tumor microenvironment

Radiation affects not only cancer cells but also the tumor microenvironment (TME) (Barker et al. 2015) (Fig. 2). The TME comprises diverse cell types, including cancer-associated fibroblasts (CAFs), endothelial cells, tumor-associated macrophages (TAMs), and other immune cells (Balkwill et al. 2012; Fridman et al. 2017). Complex crosstalk between cancer cells and components of TME facilitates tumor growth, angiogenesis, invasion, and metastasis (Stakheyeva et al. 2017; Larionova et al. 2019).

CAFs, a significant component of tumor stroma, promote cancer cell recovery and tumor relapse after radiotherapy (Wang et al. 2017). CAFs are responsible for the synthesis of extracellular matrix (ECM) proteins, including matrix metallopeptidases (MMPs), and secretion of cytokines and growth factors that regulate tumor proliferation, invasion, and metastasis (Wang et al. 2019b; Ansems and Span 2020). CAFs can recruit macrophages and potentiate their biological functions by modifying the ECM. The interaction of CAFs and TAMs establishes immunosuppressive conditions in TME (Ansems and Span 2020). Radiation-treated fibroblasts display increased expression of factors involved in cell cycle arrest, DNA repair, ROS scavenging, ECM remodeling, and Wnt and IGF signaling pathways (Rødningen et al. 2005; Wang et al. 2019b). Different factors expressed by CAFs after RT mediate subsequent fibrosis, EMT/invasion, and treatment resistance. Fibrosis, in turn, supplies proliferation and invasion signals to cancer cells, leading to radioresistance and tumor progression (Ansems and Span 2020).

CAF-secreted factors are associated with the prognosis of different human cancers (Ham et al. 2021). High gene expression of stromal CXCL12 and FAP, essential for the fibrotic process, correlates with poor OS in rectal cancer with preoperative CRT (Saigusa et al. 2010, 2011). High protein expression of TGF-β in CAFs is associated with poor OS in ESCC patients treated with CRT (Zhang et al. 2017a). High post-treatment expression of PLOD3 (procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3), involved in fibrotic processes and tissue remodeling, is associated with poor 5-year survival in lung cancer patients treated with RT (Baek et al. 2019).

TAMs are a crucial component of innate immunity in TME, promoting tumor growth, angiogenesis, metastasis, and tumor regrowth after chemo- and radiotherapy (Larionova et al. 2019, 2020). Numerous tumor models demonstrate that irradiation induces monocyte/macrophage infiltration via CXCL12, CCL2, and CSF1-dependent mechanisms, and accumulation of M2-like TAMs promotes tumor vasculogenesis and immunosuppression that limits RT efficacy (Xu et al. 2013; Genard et al. 2017; Wu et al. 2017). Increased CD68+ macrophage infiltration is associated with poor OS and DFS in OSCC patients who received radiation (Ai et al. 2021). High expression of pro-tumor M2 macrophage markers indicates poor survival and metastasis (Larionova et al. 2020). Cervical cancer and HNSCC patients with increased M2 marker CD163 show unfavorable disease outcomes after RT/CRT (Balermpas et al. 2014; Lippens et al. 2020). High expression of HIF-2α in TAMs correlates to low DFS rates and increased risk of local recurrence (Kawanaka et al. 2008).

CD8+ cytotoxic T lymphocytes (CTLs) are the essential immune cells for killing cancer cells presenting MHC I molecules (Farhood et al. 2019). In NSCLC, increased CD8+ T-cell counts, CD4/Treg ratio, and higher CD103+ cell infiltration after RT/CRT are observed in responsive patients (complete and partial response vs. stable disease) and associated with better OS and DFS (Komdeur et al. 2017; Liu et al. 2019; Boulle et al. 2020). The cervical cancer-specific survival is significantly higher in patients with increased CD8 post-treatment scores, high CD8/CD4 and CD163/CD68 ratios, or PD-L1 expression in more than 5% of immune cells (Lippens et al. 2020). Contradictory results are obtained for the PD-L1 expression in NSCLC. Programmed cell death-1 (PD-1) is a co-stimulatory receptor of the CD28 family that plays a crucial role in tumor cell tolerance (Keir et al. 2006). PD-1/PD-L1 interaction inhibits T-lymphocyte proliferation, survival, and effector functions, induces apoptosis of antigen-presenting T cells, promotes differentiation of CD4+ T cells into FoxP3+ regulatory cells, and provides resistance of tumor cells to a cytotoxic response (Iwai et al. 2002; Wang et al. 2008). In patients with NSCLC who received RT/CRT, lower baseline soluble PD-L1 level correlates to the most prolonged OS and objective response to treatment (Zhao et al. 2017; Sui et al. 2021). Oppositely, high post-treatment PD-L1 expression in lung cancer tissue predicts a greater radiosensitivity and better outcome (Fiedler et al. 2018).

Other immune molecules belonging to different function classes were found to be associated with prognosis and to predict the response to RT. NF-κB is a transcriptional factor that regulates multiple aspects of innate and adaptive immune functions and serves as a pivotal mediator of the inflammatory response (Liu et al. 2017b). The expression of NF-κB positively correlates with increased rates of distant metastases, locoregional failure, and overall (local and distant) relapse in cervical cancer patients (Garg et al. 2010). Increased pretreatment expression of CCR6, an inflammatory CC chemokine receptor, is observed in the non-pCR patients with rectal cancer who received CRT (Chang et al. 2018). Negative expression of ICAM-3, an adhesion molecule for leukocytes, was found in normal tissue compared to tumor tissue, and in 65% of radiosensitive cervical cancer cases. In comparison, ICAM-3 was detected in 83% of radioresistant tumors and associated with poor 5-year PFS

(Chung et al. 2005). High pretreatment protein expression of CD59, a membrane-bound complement regulatory protein, indicates poor OS and DFS in ESCC patients who received RT (Zhou et al. 2018). The possible mechanism of CD59-mediated radioresistance can be related to induced DDR in cancer cells (Zhou et al. 2018). The level of secreted protein CD166, belonging to the immunoglobulin superfamily, was detected in the serum of NPC patients before treatment. The concentration of CD166 is higher in the radioresistant cases possessing local recurrent disease after RT (Lin et al. 2017). The expression of annexin A1 (ANXA1), a glucocorticoid-induced anti-inflammatory protein, after treatment, oppositely, is significantly decreased in radioresistant NPC compared to radiosensitive tumors (Liao et al. 2018).

RT induces tissue damage and triggers activation of stromal components that can synergistically function along with therapy to kill cancer cells or support tumors. The balance shift to the tumor-supportive activity can be crucial for radioresistance development. However, there are still not enough data to address whether diverse factors produced by key players of TME—CAFs, TAMs, and T-lymphocytes—modulate RT response (Fig. 2). Further studies should focus on the detailed investigation of changes in the expression of growth factors, cytokines, soluble mediators, and surface receptors during RT and their role in radioresistance.

Pro-angiogenic factors

Effects of ionizing radiation strongly depend on the oxygenation of the tumor. As mentioned above, the well-vascularized and perfused tumors are more sensitive to RT due to the enhanced generation of ROS. Vice versa, hypoxic tumors with a lack of blood vessels prevent treatment efficiency (Overgaard 2007; Goedegebuure et al. 2019). Irradiation with different doses leads to varying effects on the vascular system. High dose irradiation (above 10 Gy) induces acute vascular damage caused by endothelial cell apoptosis (Park et al. 2012). It can lead to hypoxia and in the switch to the pro-angiogenic pathways. Fractionated low dose radiotherapy (per 2 Gy daily) positively affects the tumor vasculature and tissue perfusion due to decreased oxygen consumption (Park et al. 2012; Goedegebuure et al. 2019).

The critical factor regulating tumor angiogenesis is VEGF (Larionova et al. 2021) (Fig. 2). Angiogenesis is also associated with metalloproteinases (MMP-2, MMP-9, and MMP-14), tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2), thymidine phosphorylase (TP), urokinase plasminogen activator (uPA), osteopontin (OPN), and other molecules (Shih et al. 2002; DuBois and Demetri 2007; Larionova et al. 2021). Most of them are also crucial regulators of cancer invasion and metastasis.

Here, we collected the studies demonstrating that pro-angiogenic factors may serve as markers for radioresistance. Pretreatment VEGF serum level and tumor expression negatively correlate with the RT efficacy and recurrence-free, metastasis-free, and overall survival in NSCLC, cervical, and breast cancer patients (Manders et al. 2003; Fu et al. 2014). The contradictory results were shown in ESCC, where high pretreatment VEGF expression significantly correlates with a complete response to CRT (Yoon et al. 2011).

High plasma levels of hypoxic and angiogenic biomarkers OPN, VEGF, CEA, IL-6, CYFRA 21-1, and CA IX before CRT/RT are independent predictors for poor OS in patients with NSCLC (Dehing-Oberije et al. 2011; Ostheimer et al. 2014, 2018; Fu et al. 2014). Elevated pre-RT serum IL-6 level is associated with worse 2-year survival in NPC patients (Chow et al. 2003). In ESCC, IL-6 tumor overexpression correlates to poor CRT response, locoregional failure, and distant metastasis (Chen et al. 2013). In patients with inoperable or metastasized NSCLC who received RT/CRT, a low level of urokinase plasminogen activator PAI-1 before treatment is associated with significantly reduced OS and PFS. Combined low level of PAI-1 and high level of OPN demonstrate an additive prognostic impact on unfavorable NSCLC prognosis with increased risk of death (Ostheimer et al. 2018). In prostate cancer patients, increased pretreatment protein expression of HIF-1α, VEGF, and OPN is significantly associated with a higher risk of biochemical failure after RT (Vergis et al. 2008). Elevated pretreatment plasma and tumor OPN levels indicate poor RT response and higher locoregional and disease-specific mortality in HNSCC, NPC, ESCC, and cervical cancer (Overgaard et al. 2005; Hui et al. 2008; Snitcovsky et al. 2009; Etiz et al. 2013; Chiu et al. 2018).

In cervical cancer patients treated with CRT, high pretreatment protein expression of MMP-2 and TIMP-2 in tumor stroma and MMP-9 in tumor nest and stroma are significantly associated with poorer 12-year survival (Azevedo Martins et al. 2020). Increased pretreatment expression of pro-angiogenic chitinase-like protein YKL-40 is significantly associated with resistance to RT in glioblastoma patients (Pelloski et al. 2005).

Anti-angiogenic drugs (e.g., anti-VEGF agent bevacizumab) are widely used in first- and second-line therapy to improve cancer treatment efficacy (Larionova et al. 2021). Anti-angiogenic treatment is also proposed to increase RT efficiency (Goedegebuure et al. 2019). The accumulating data demonstrate that at least three pro-angiogenic factors, VEGF, IL-6, and OPN, are strongly related to RT failure in numerous solid tumors, making them promising universal biomarkers (Figs. 1 and 2, Table 1).

Cancer stem cells

Cancer stem cell (CSC) repopulation is considered an adaptive response to the cytotoxic effects of radiation (Willers

et al. 2013). CSCs exhibit self-renewal, differentiation, and proliferation capacities similar to normal hematopoietic stem cells (Aponte and Caicedo 2017; Peitzsch et al. 2017). Self-renewal and metastatic potential of CSCs, which are crucial mechanisms of tumorigenesis, are regulated by multiple cytokines and growth factors produced by TME. Hypoxia protects CSCs from radiation, preventing the detrimental effect of ROS by upregulation of ROS scavengers (Peitzsch et al. 2014; Najafi et al. 2019). Key activities of CSCs are regulated by Wnt/β-catenin, Notch, Sonic Hedgehog, PTEN, TGF-ß, and other signaling pathways (Olivares-Urbano et al. 2020). Activation of Notch signaling by irradiation results in entering breast CSCs into the cell cycle and acquiring EMT and self-renewal properties (Venkatesh et al. 2018). In cervical cancer, posttreatment high expression of delta-like ligand 4 (DLL4), a transmembrane Notch ligand, is found in radiation-resistant patients (Liu et al. 2017a; Venkatesh et al. 2018; Wang et al. 2019c).

The findings of the CSC role in radioresistance are scarce, and further studies are warranted. Moreover, CSCs are highly heterogeneous and represented by different cell populations with specific phenotypical and functional features. Nevertheless, the question remains open whether the radioresistance degree varies between CSC subsets.

Epigenetic mechanisms

DNA methylation

Epigenetic mechanisms control diverse processes in tumors and have a crucial role in developing radiation resistance (Fardi et al. 2018). Radiotherapy changes the epigenetic landscape of cancer cells towards radioresistance and disease progression. DNA methylation, histone post-translational modifications, and chromatin remodeling are implicated in the control of gene expression related to DNA repair, cell survival and proliferation, evasion of apoptosis, and EMT regulation, thus protecting cancer cells from the cytotoxic effect of radiation (Cabrera-Licona et al. 2021).

DNA methyltransferases (DNMTs) regulate the chromosome stability and genome integrity, while overexpression of DNMTs in various tumors results in hypermethylation and oncogenic activation (Zhang and Xu 2017). High gene expression of *DNMT3B* predicts shorter OS in patients with NPC and HNSCC (Wu et al. 2020). In pretreatment samples, the nuclear protein expression of RUNX3, a downstream target of the TGF-β signaling pathway, is associated with complete or partial response to RT in ESCC patients. The hypermethylation and transcriptional repression of *RUNX3* are found in 96.7% of irradiated ESCCs patients and are associated with low survival (Sakakura et al. 2007). Promoter methylation of tumor suppressor genes *RASSF1/RASSF2A* and the consequent activation of Ras/PI3K/Akt signaling are significantly related to poorer DFS in OSCC patients who underwent RT after surgery (Huang et al. 2009). The panel of eight hypermethylated genes, controlling cell proliferation and adhesion and associated with metastasis development, was found for determining complete response after RT in oropharyngeal cancer patients (Kurokawa et al. 2020). Pretreatment methylation of *ROBO1, ULK4P3, MYOD1, LBX1, CACNA1A, IRX4, DPYSL3*, and *ELAVL2* genes distinguishes patients with a long time of DFS and OS and patients with tumor recurrence or progression after RT (Kurokawa et al. 2020).

Histone modification

Histones, central chromatin components, acquire diverse post-translational modifications, including acetylation/deacetylation, methylation, and phosphorylation, to form the epigenetic patterns underlying transcriptional processes (Cabrera-Licona et al. 2021).

The expression of histone deacetylases HDAC4 and HDAC6 negatively correlates with OS in patients with glioblastoma treated with RT (Marampon et al. 2017). H3K4me3 demethylase KDM5B, playing an essential role in repairing DSB, correlates with poor response to radiation in patients with lung cancer (Bayo et al. 2018). Hypoxia-induced KDM3A overexpression results in radioresistance in vitro and can indicate RT failure in ESCC patients (Macedo-Silva et al. 2020). Impaired gene expression of NuRD complex (the nucleosome remodeling and deacetylase) subunits (*CHD4, CHD3, HDAC1, HDAC2, MTA2, MBD3, RBBP4, and RBBP7*), involved in chromatin remodeling and histone deacetylase activity, is identified in patients with rectal cancer treated with CRT (Wang et al. 2019a). Post-treatment expression of *CHD3* and *CHD4* is higher in non-responding rectal cancer patients than in responders. *CHD4* overexpression is also an independent prognostic factor for metastasis-free survival (Wang et al. 2019a).

A recent study indicated that HDAC activity significantly varies between different cancers (Sharda et al. 2020). Therefore, identifying histone code in each cancer type is essential to predict response to RT. Moreover, discovering epigenetic targets is needed to counteract RT in refractory cancers.

MicroRNAs and lncRNAs

Non-coding RNAs, including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), have been identified as key molecules in radiotherapy failure in many cancer types (Podralska et al. 2020). Recent studies emphasized extracellular miRNAs as potential liquid biomarkers of radioresistance (Nowicka et al. 2019).

The current data indicates the involvement of both serum and intratumor miRNAs in RT response and tumor

progression in patients with lung, rectal, cervical, head and neck, and esophageal cancers. Post-treatment expression levels of miR-96, miR-130a, miR-25, miR-196a, and miR-191* are increased in the serum of patients with RT-treated NSCLC compared to healthy controls and associated with recurrence and low survival rate (Suh et al. 2015; Lv et al. 2020; Zheng et al. 2021). MiR-622 is upregulated in rectal cancer patients without tumor regression before CRT (Ma et al. 2015). In cervical cancer, the expression of oncogenic miR-21 after CRT is higher in resistant patients (Liu et al. 2020c). ESCC patients with high pretreatment miR-205 expression have a poorer OS (Pan et al. 2017). The serum level of miR-504 is upregulated during RT and higher in radioresistant NPC patients (Zhao et al. 2015).

More evidence shows the involvement of miRNA overexpression in high RT efficacy in lung cancer. The post-treatment plasma level of miR-18a-5p, hsa-miR-98-5p, hsa-miR-302e, hsa-miR-495-3p, and hsa-miR-613 is significantly higher in patients with unresectable stage III and IV NSCLC demonstrating complete or partial response than in cases with refractory tumors (Chen et al. 2016, 2018). The low miR-29c level correlates with shorter RFS of NSCLC patients treated with RT (Arechaga-Ocampo et al. 2017). The high expression of miR-148b before RT and baseline serum level of let-7 significantly correlate with better survival in patients with lung cancer (Wang et al. 2016; Xie et al. 2016). At the same time, the post-treatment level of let-7 is significantly lower in serum of RT-sensitive lung cancer patients with brain metastasis (Liu et al. 2018).

The same findings were found in other cancers. The low miR-203 expression in pretreatment biopsies correlates with local larynx cancer recurrence after RT (de Jong et al. 2015). The low miR-339-5p level is significantly associated with poor OS and DFS in ESCC patients treated with RT (Luo et al. 2019). The positive response to RT is associated with high expression of hsa-miR-1281 and hsa-miR-6732-3p in NPC, miR-339-5p in ESCC, and miR-125a in cervical carcinoma (Pedroza-Torres et al. 2018; Luo et al. 2019; Li et al. 2020).

Thus, no data demonstrate common epigenetic radioresistance biomarkers in different cancers. It can be explained by high epigenetic instability and variability of cancer cells, and insufficient findings. Further studies should indicate whether radioresistance of various cancers can be related to universal molecular mechanisms.

Gene and protein signatures

As multiple processes are associated with RT response, the panels of biomarkers with diverse functional activity can predict radioresistance and determine the cancer prognosis. Recent studies reporting the prognostic value of gene signatures for different cancers have attracted widespread interest (Cantini et al. 2017). Gene signatures are developed to predict therapy response and disease outcome based on the expression of a relatively small number of genes. The sensitivity and specificity of multiple gene models are significantly higher than single biomarkers. Additionally, gene signatures can be used for identifying molecular targets (Gönen 2009).

Several prognostic gene signatures were established in cervical cancer. The eight-gene signature (*CCDC136, ABCG2, CYP26A1, TNNI3, CXCL5, SYT13 FOXC2, ITGB3,* and *TMEM233*) predicts OS in cervical cancer patients following RT (Xie et al. 2019). Improved OS is associated with hypermethylation of the *CCDC136, ABCG2, CYP26A1*, and *TNNI3* genes, while poor OS correlates with hypomethylation of the *SYT13, FOXC2, CXCL5,* and *TMEM233* genes (Xie et al. 2019). The seven gene signature (*UBE2C, MMP3, DCUN1D5, SDCCAG8, IGF2BP2, CCL18,* and *FST*) predicts the risk of poor DFS in cervical cancer patients following RT with 64% sensitivity and 100% specificity (Rajkumar et al. 2009). A proteomic panel of ERCC1, CD133, HER2, BCL2, and CAIX predicts DFS and OS in cervical cancer patients treated with CRT (Choi et al. 2020a).

Numerous predictive models have been revealed for head and neck cancers. The gene panel of *VEGF, BCL-2, CLAUDIN-4, YAP-1,* and *c-MET* was developed to predict no response/partial response to RT in HNSCC. High *YAP-1* and *BCL-2* and low *CLAUDIN-4* expression before RT significantly predict poor recurrence-free survival. *YAP-1, BCL-2,* and *VEGF* overexpression correlates to poor cause-specific survival (Akervall et al. 2014). Another predictive panel includes nine genes: *CHAC2, CLEC9A, GNG10, JCHAIN, KLRB1, NOG, OLR1, PRELID2, SYT1, VWCE, ZNF443*. The high expression of *CHAC2, GNG10, JCHAIN, OLR1, KLRB1, PRELID2, SYT1,* and *ZNF443* in peripheral blood mononuclear cells is related to poor survival, while the upregulation of *CLEC9A, NOG, and VWCE*—with improved survival in HNSCC patients (Liu et al. 2020a). Combined expression of *IGF1R, LAMC2, ITGB1,* and *IL-6* genes predicts worse radiotherapeutic outcome in HNSCC (You et al. 2019). The analysis of the CHIT1, PDGFB, PNKD, RP2, SERPINC1, SLC4A, STIM1, and THPO proteins expression together with the VEGFA gene variant rs69947 in post-treatment samples predict HNSCC radiosensitivity (Drobin et al. 2020). Post-treatment serum levels of SPARC, SERPIND1, C4B, PPBP, PODXL, SRGN, PPIB, S100A4, and CTSF are significantly higher in the radioresistant patients with NPC. The ERAP1, GC, ITIH1, NRP1, MINPP1, F13A1, C1QB, ITIH2, IGFBP6, and FAM173A proteins are significantly downregulated in the radioresistant cases. The panel based on the SPARC, SERPIND1, C4B, PPIB, and FAM173A proteins predicts the RT response in NPC patients with the sensitivity of 94% and the specificity of 92.6% (Zhang et al. 2019).

Thus, different gene and protein panels have been developed to predict RT response and prognosis in cervical and HNSCC patients. Further studies are needed to determine whether these panels are valid in other cancers or propose some new ones that are universal for different malignancies. Nevertheless, gene and protein panels are generally expensive and time-consuming and thus are challenging to translate to clinical practice.

Conclusion

Based on the above findings, we summarize that no universal radioresistance biomarkers exist. Some biomarkers, mainly VEGF, OPN, and pAKT, are described as associated with RT efficacy simultaneously in breast, rectal, prostate, head and neck, lung, cervical, and esophageal cancers. The involvement of these proteins in radioresistance is confirmed by the studies showing that blood vessel normalization and TK inhibition enhance the clinical benefit of radiotherapy (Goedegebuure et al. 2019; Pottier et al. 2020; Zhang et al. 2021). Further research should be directed toward elucidating the involvement of these biomarkers in radioresistance in other cancers.

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Declarations

Conflict of Interest The authors declare no conflicts of interest.

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