Emerging roles of non-coding RNAs in the response of rectal cancer to radiotherapy (Review)

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Received November 17, 2020; Accepted January 11, 2021

DOI: 10.3892/ijo.2021.5175

Abstract. Radiotherapy (RT) followed by radical surgery is an effective standard treatment strategy for various types of cancer, including rectal cancer. The response to RT varies among patients, and the radiosensitivity of cancer cells determines the clinical outcome of patients. However, the application of RT to patients with radioresistant tumors may result in radiation-induced toxicity without clinical benefits. Currently, there are no effective methods to predict the response to RT. The limitations of the methods currently used to evaluate tumor radiosensitivity, which are mainly based on clinical and radiological features, are low sensitivity and specificity. Non-coding RNAs (ncRNAs) have emerged as a class of biomarkers for predicting radiosensitivity. In particular, the expression pattern of ncRNAs can predict the response to RT in patients with rectal cancer. Thus, ncRNAs may be used as potential biomarkers and therapeutic targets to improve the diagnosis and treatment outcome of patients with rectal cancer. In the present review, the current knowledge on the limitations of RT for rectal cancer and the association between ncRNA expression and sensitivity of rectal cancer to RT are presented. Additionally, the potential of ncRNAs as predictive biomarkers and therapeutic targets to mitigate resistance of rectal cancer to RT is discussed.

Contents

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Key words: radiotherapy, rectal cancer, non-coding RNA, predictive biomarker, radioresistance

1. Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by radical surgery has been the standard treatment modality for patients with locally advanced rectal cancer (LARC); this treatment modality has improved the local control rate and alleviated the radiation-induced toxicity in patients with rectal cancer (1). However, the major challenges for enhancing the efficacy of radiotherapy (RT) are the development of radioresistance in the tumor and the radiation-induced complications and toxicities. Therefore, the efficacy of RT in rectal cancer may be improved with the identification of radioresistance markers and predictive biomarkers of radiosensitivity, as well as the elucidation of the mechanisms underlying radioresistance and radiation-induced toxicity and complications.

Radiosensitivity and radiation-induced toxicity are predicted based on the clinical factors and irradiation doses; however, these parameters have low predictive accuracy (2-4). Therefore, there is a need to identify biomarkers that can predict the response to RT in patients with LARC to optimize the radiation doses, minimize the radiation-induced complications and select the optimal treatment strategy. Previous studies have demonstrated that the expression patterns of non-coding RNAs (ncRNAs) can predict the response to RT in patients with rectal cancer (5-7). ncRNAs can be classified as short ncRNAs and long ncRNAs (lncRNAs). Short ncRNAs are further classified into several classes, including piwi-associated RNAs, short-interfering RNAs and microRNAs (miRNAs/miRs). miRNAs are short (18-25 nucleotides in length) highly conserved RNAs that regulate gene expression at the post-transcriptional level through the degradation and/or translational repression of their mRNA targets (8). Currently, various miRNAs are reported to

function as master regulators of several biological processes, including cell proliferation, apoptosis and cancer development and progression (9). Several miRNAs are present in the extracellular microenvironment (10,11). Some miRNAs are stable in biological fluids (12,13). The stability of circulating miRNAs can be attributed to their ability to form complexes with proteins in fluids, which prevents RNase-mediated miRNA degradation (14). Therefore, miRNAs are considered promising biomarkers and clinical therapeutic targets for rectal cancer.

lncRNAs contain >200 nucleotides with limited or no protein-coding capacity (15). Although experimental studies have identified only a small number of lncRNAs, previous studies have suggested that lncRNAs mediate several biological processes through the regulation of gene expression and alternative splicing (16,17). Additionally, a subset of lncRNAs is reported to be involved in maintaining pluripotency of stem cells (18). Further studies have indicated that dysregulated expression levels of lncRNAs are involved in tumorigenesis and promoting resistance to therapeutics (19-22). The present review summarizes the current findings on the ability of ncRNAs to predict the response of rectal cancer to RT and emphasizes their potential as therapeutic targets to enhance the radiosensitivity of rectal cancer.

Studies on the ability of ncRNAs to predict the response of rectal cancer to RT were searched in the following databases: Medline through Pubmed (https://pubmed.ncbi.nlm.nih.gov/) and Cochrane database (https://www.cochranelibrary.com/) of systemic reviews and reference lists from the retrieved papers (January 2008-October 2020). The search terms and groups of words used were: 'Rectal cancer', 'neoadjuvant radiotherapy', 'miRNAs in rectal cancers', 'lncRNAs' or 'non-coding RNA in rectal cancer'. The type of articles included in the present review were systemic reviews, meta-analyses, randomised controlled trials and clinical trials. Published conference extracts or non-peer reviewed manuscripts were excluded. A total of 229 related articles were identified and 23 studies were included in the final review (Fig. 1). Due to the small number of studies yielded by the search criteria, and the heterogeneity of outcomes, a narrative review has been performed.

2. Incidence of rectal cancer

Globally, colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer-associated mortality (23). Rectal cancer accounts for ~30% of all CRC cases (24). Among the rectal cancer cases, ~40% cases are LARC, which is associated with poor clinical outcomes (25). In the United States of America (USA), 147,950 new cases of CRC were estimated to be diagnosed in 2020, including 104,610 cases of colon cancer and 43,340 cases of rectal cancer, with high mortality expected among CRC cases (24).

Age and environmental and lifestyle factors contribute to the development of CRC; hence, several studies have demonstrated that dietary habits, sedentary lifestyles and the increased prevalence of obesity have increased the risk of developing CRC among younger populations (<40 years old) compared with older populations (>40 years old) (26,27). Previous studies have suggested that occupational exposure to toxins may increase the risks of developing CRC (28-30). Long-term exposure to industrial fumes and wood or metal dust and the consumption of deep-fried and barbecued foods in young adulthood have been markedly associated with rectal cancer (31). Compared with individuals residing in urban areas and involved in non-farming occupations, individuals residing in rural areas where pesticides are not used and involved in farming occupations were associated with a lower risk of developing rectal cancer (32,33). Consistently, the history of exposure to industrial toxins, unhealthy dietary habits and sedentary lifestyle have been positively associated with an increased incidence of rectal cancer in young patients (26,34).

3. Current treatment paradigms for rectal cancer

Recent advances in cancer therapeutics have increased the therapeutic efficacy in patients with rectal cancer. Surgery is the only curative therapy for patients with rectal cancer, especially for those with rectal adenocarcinoma (35,36). The development of combined modality treatment strategies, such as the combination of RT, chemotherapy and total mesorectal excision (TME), has improved the clinical outcomes and decreased the local failure rates in patients with LARC (37). The development of improved staging and surgical techniques, and the utilization of targeted combinatorial therapies have resulted in a significant increase in loco regional control and slightly improved overall survival in trials (37-39).

Recent advances in the field of anatomy and physiology have contributed to the development of advanced surgical procedures. Heald *et al* (40) developed a breakthrough procedure called TME, which is now the standard surgical procedure for patients with LARC. TME involves the complete surgical resection of discontinuous tumor remaining in the mesorectum, which may cause local treatment failure, with the preservation of the pelvic nerves using sharp instruments under direct vision (41). Subsequently, MacFarlane *et al* (42) demonstrated that the local recurrence rates in patients with rectal cancer decreased from 30-40% without TME to <5% with TME. Another study reported that the local recurrence rates of 1,411 patients with rectal cancer decreased from 32-35% with conventional surgeries to 4-9% with TME (43). These results confirmed that TME is an optimal surgical procedure for patients with rectal cancer, in which it markedly improves the clinical outcome and decreases the local recurrence.

Although TME can markedly decrease the local recurrence rate in patients with early-stage rectal cancer (42), the local regional recurrence rate in patients with stage III rectal cancer is high (~30%), with a high frequency of lymph node metastasis in lower rectal cancer (44,45). However, extensive tumor resection is not prescribed due to the severe side effects associated with lateral dissection, including impaired urinary system, loss of sexual ability and decreased 5-year survival rate (46). Therefore, additional treatment strategies have been developed to decrease the tumor volume before surgery. nCRT followed by TME has been developed and recommended by the National Comprehensive Cancer Network (NCCN) guidelines (47) as the standard therapy for stage II/III RC treatment. It can be used to shrink the volume of primary or metastatic tumors, resulting in decreasing the tumor stages with reduced loco-regional recurrence and distant metastasis

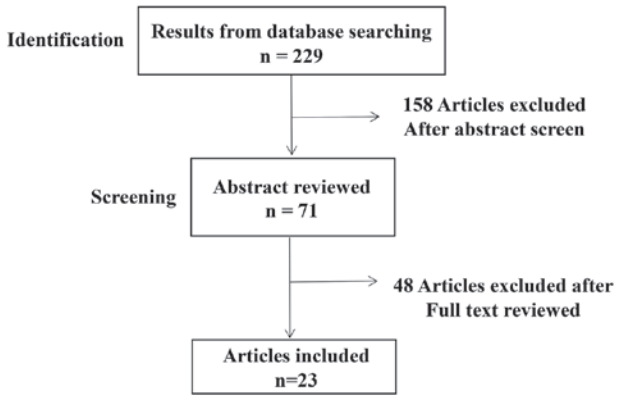

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the included and excluded articles of relevant studies. Based on database searching, a total of 229 studies were identified and 158 articles were excluded after abstract screening. Among the remaining 71 articles, 23 articles were finally selected after full text review.

rate (48). Most patients receiving nCRT before an operation are in better physical condition and have a better tolerance compared with those receiving CRT after operation (38). In case of patients with unresectable local advance RC, chemo-radiotherapy has become the only standard therapy until the patients are available for surgery (39). Except for patients with contraindications, recommended radiotherapy schedules for LARC include two radiation treatment paradigms: Short-course (SC)- and long-course (LC)-RT. SC-RT is given as 5 daily fractions of 5 Gy (5 Gy x 5 fractions) over 1 week or 25 Gy total followed by immediate surgical resection within 1 week (49). LC-RT has been shown as treatment of 45-50.4 Gy in 25-28 fractions with concurrent chemotherapy followed by delayed TME from 4 to 8 weeks after CRT (50). Both SC-RT and LC-CRT are effective therapies and multiple trials have demonstrated the equal efficacy and safety of SC-RT and LC-RT therapy, with no significant differences in long-term outcome with regards to local recurrence rate, survival and late toxicity between SC-RT and LC-CRT (51-53). However, the choice of the optimal approach remains controversial. In the USA, LC-RT has been used as the standard of care for treatment of patients with LARC, while preoperative SC-RT has been more used by radiation oncologists in Western Europe (54,55). Radiation oncologists in the USA have emphasized that LC-RT improves the complete response rate of patients, with lower surgical morbidity, less incidence of positive radial resection margins and increased tumor down-staging due to a longer delay between irradiation and surgical resection (56). SC-RT has just been prescribed for patients not receiving chemotherapy or having a geographic barrier to receiving LC-CRT (54). Conversely, supporters of SC-RT have suggested that patients treated with SC-RT received more benefits of lower cost and less acute radiation toxicity without different long-term outcomes compared with LC-RT (57). Although the positive outcomes of nCRT have been widely demonstrated and used in Western Europe and the USA, nCRT is still not a standard treatment in Japan (58,59). The application of nCRT to Japanese patients with LARC has met several obstacles. Normally, Japanese people are thinner and with less visceral fat than individuals in Western countries and the USA, therefore making surgery a favorable choice (60). Another reason is the lack of radiation oncologists, RT technologists and medical physicists in Japan, resulting in the rate of new patients with cancer who receive RT being less than half of that in Western countries (61,62). Evidence on the efficacy of preoperative RT in Japan is extremely limited (61,62).

CRT before TME is currently used as the standard therapy for patients with stage II/III rectal cancer. This strategy is used to shrink the volume of primary or metastatic tumors, which downgrades the tumor stage and decreases the loco-regional recurrence and distant metastasis rates (48). Patients who undergo CRT before surgery exhibit better physical health and therapy tolerance than those who receive CRT after surgery (38). In patients with unresectable LARC, CRT is the only standard therapy until the patients are eligible for surgery (63,64).

Additionally, other treatment strategies have been developed for special cases of rectal cancer. The 'watch and wait' strategy has been used for patients with rectal cancer who achieved a complete clinical response after nCRT without surgery; the advantages of this approach include the reduction in the local recurrence rate, which was similar to that of surgical resection, and the preservation of organ (65). The toxicities associated with RT and the ineligibility of some patients to undergo RT due to their tumor location have led to the development of neoadjuvant chemotherapy without radiation as an alternative therapeutic strategy for patients with rectal cancer (66). However, this treatment paradigm remains under consideration and is not yet recommended for use according to the NCCN guidelines (47), which recommend total neoadjuvant therapy, involving the combination of both chemotherapy and CRT before surgery, for patients with rectal cancer. This therapeutic strategy downgrades the tumor stage and improves the overall survival rate (67,68). Moreover, patients who receive total neoadjuvant therapy are eligible for the 'watch and wait' therapeutic strategy (69). Thus, this approach provides a viable treatment strategy for patients with rectal cancer as per the NCCN guidelines.

4. Limitations of RT for rectal cancer

The advantages of the therapeutic combination of preoperative RT and surgery for patients with LARC have been well documented in the last few decades. Preoperative RT markedly improves the outcome of patients with rectal cancer (70). However, the radiation-induced adverse effects and the development of radioresistance in the tumors have been the major limitations for the clinical application of this strategy (71). Radiation-induced toxicities are classified as acute and late toxicity based on the time of symptom onset (72). The symptoms of acute toxicities appear during or right after treatment (73). By contrast, the symptoms of late toxicity appear after prolonged treatment ranging from several months to years (73). The symptoms of acute toxicities include skin erythema, fatigue, nausea, diarrhea and neurological pain, as well as wound healing complications for patients undergoing surgical resection (74,75). Gastrointestinal dysfunction, urinary dysfunction, permanent neurological toxicities and increased risk of secondary cancers are the major complications associated with late toxicities (76).

In a TME trial, the combination of SC-RT and TME markedly decreased the recurrence rates of LARC from 30-50% to <15% (78) and improved the 10-year survival rate in patients with advanced rectal cancer compared with surgery alone (78). However, SC-RT markedly increased the acute toxicity-associated symptoms, such as lumbosacral plexopathy, stiff pain in the back and legs during RT, or chronic neurological pain 75). Additionally, a series of long-term follow-up randomized studies of Stockholm trials (79), Swedish rectal cancer trial (80) and Dutch TME trial (81) indicated that the frequency of late toxicity-associated symptoms, such as gastrointestinal dysfunctions with impaired bowel movements and fecal incontinence, was higher and more severe in patients who underwent RT compared with that in patients who underwent surgery alone (80,82). In particular, bowel dysfunction was observed in ~62% of patients who underwent RT, but in only 38% of patients who underwent TME alone in the Dutch TME trial (81). Daily activities were significantly decreased and sexual activity was impaired in patients who underwent preoperative SC-RT (83). Although the aforementioned Dutch TME study (81) suggested the negative effects of RT on the quality of life and sexual function, patients who underwent RT exhibited downgraded tumor stages compared with those who underwent only surgery. Moreover, a follow-up study based on the Uppsala trial revealed that the risk of secondary cancer in patients who underwent RT was two times higher than that in patients who did not undergo RT (84). RT-associated secondary pelvic cancers mostly appeared adjacent to other organs, such as the colon, prostate, bladder and ureter, in patients who underwent RT (77).

In addition to radiation-induced toxicities, resistance to preoperative RT is a major clinical obstacle for treating LARC. The biological complexities and heterogeneities of tumors, and the presence of cancer stem cells or accumulated mutations in the tumors (85,86) render the tumors radioresistant. Radioresistance is associated with tumor recurrence, metastasis and poor prognosis, which affect the therapeutic outcomes (87,88). Although a pathological complete response is obtained in numerous cases, several cases are resistant to RT, which is the main cause of rectal cancer-associated death (89,90). The pathological response to preoperative RT varies markedly among patients with LARC. Approximately 8-20% of patients with LARC respond to preoperative RT (91,92). However, >40% of patients have a partial response and ~20% of patients are resistant to preoperative RT (93). These different responses to preoperative RT are directly associated with local recurrence, distant metastasis and overall survival of patients with rectal cancer.

RT is an expensive and time-consuming procedure that is associated with a high risk of perioperative morbidity. Thus, the prediction of the response to RT has direct implications on the clinical decisions regarding treatment strategy. Patients who are sensitive to CRT must undergo a manual 'wait and see' procedure or transanal local excision treatment therapy (94,95). Conversely, patients with poor response to CRT require an alternative therapeutic strategy. The accurate prediction of the pathological and clinical response of patients with rectal cancer to RT may allow clinicians to select the optimal therapeutic strategy for each case and improve the clinical outcome of RT.

5. ncRNAs as predictive biomarkers for RT response in patients with rectal cancer

The response in patients with rectal cancer to preoperative CRT is a critical predictor of local recurrence and patient survival. However, there are no methods to predict the response to RT. Previous studies have reported that ncRNAs, which are key regulators of multiple biological signaling pathways, are involved in tumorigenesis and in the regulation of tumor sensitivity to RT (5,96,97). Aberrant ncRNA expression induces radioresistance by modulating the signaling pathways associated with cell cycle regulation, DNA repair, cell proliferation/apoptosis, hypoxia or self-renewal, and differentiation of cancer stem cells (98). Since ncRNAs are not digested by RNases, they are stable in fluids, such as blood, saliva and urine (99). Therefore, ncRNAs can be potential predictors of RT response in patients with cancer. However, there are limited studies that have examined the potential of ncRNA profiles as predictors of RT response in patients with rectal cancer. The following section will summarize the published studies on the ability of various ncRNAs in predicting the RT response of patients with rectal cancer (Table I).

lncRNAs. Some studies have examined the expression profile of lncRNAs in patients with rectal cancer who have undergone preoperative RT. Li *et al* (100) examined six patients with LARC who had undergone preoperative CRT and demonstrated that the lncRNA-miRNA-mRNA regulatory network was associated with the nCRT response. This analysis revealed that 282 lncRNAs were differentially expressed between the two groups (100). Previous studies have reported that lncRNAs may regulate gene expression through direct interaction with the target gene or interaction with miRNAs (101,102). Therefore, lncRNAs and their targets that were differentially expressed between the two groups were identified by constructing the lncRNA-miRNA-mRNA regulatory network with lncRNAs as key players, and the interaction pairs of lncRNA-miRNA and miRNA-mRNA were extracted (100). Specific lncRNAs (PRDM11, RPB10 and CWC15) were positively associated with the response to nCRT (100).

A comprehensive analysis of lncRNA profile was also performed using lncRNA-specific microarrays (103). Among the 8,127 lncRNAs represented in the microarrays, 11 were differentially expressed (two-fold change in expression) between responders and non-responders (103). Of these 11 lncRNAs, five (LINC00261, lncKIF3A-1, LINC00324, lncKLF7-1 and LINC00511) were upregulated and six (lncWAPAL-1, lncFGF10-3, lncMAB21L2-1, lncGALC-6, lncZNF-366-6 and lncHDAC2-2) were downregulated in the responders (103). Additionally, these differentially expressed lncRNAs were associated with the molecular mechanism underlying tumor progression and resistance to therapeutics (104-106).

Although the comprehensive analysis identified differentially expressed lncRNAs in patients with rectal cancer, the aforementioned studies had several limitations, such as the small size of the study cohort and the lack of functional analyses of lncRNA signatures. Therefore, these differentially expressed lncRNAs must be validated and further analyzed *in vitro* and *in vivo* to determine their ability to predict the response to CRT in patients with LARC.

Table I. Association between specific ncRNAs and response to therapy in studies of patients with rectal cancer.

A, lncRNA

First author, year	Specimen	Patients in T set, n	Patients in V set, n	Treatment dose (RT/CRT)	pCR rate, %	ncRNA platform	Differentially expressed ncRNAs, n	Identified ncRNAs and outcome	(Refs.)
Li *et al*, 2019	Frozen tumor tissues	6	No	Not specified	Not specified	lncRNA array	282	3 lncRNAs: PRDM11, RPB10 and CWC15. Aberrant expression between responders and non-responders	(100)
Ferrando *et al*, 2020	Frozen tumor tissues	30	No	50.4 Gy in 28 fractions with capecitabine	40	lncRNA microarray	11	2 upregulated lncRNAs (LINC00324 and lncKLF7-1) and 1 downregulated lncRNA (lncMAB21L2-1) in responders. Extremely high overall sensitivity and specificity: 91 and 94%, respectively	(103)

B, Individual miRNAs

First author, year	Specimen	Patients in T set, n	Patients in V set, n	Treatment dose (RT/CRT)	pCR rate, %	ncRNA platform	Differentially expressed ncRNAs, n	Identified ncRNAs and outcome	(Refs.)
Drebber *et al*, 2011	FFPE tissues	40	No	50.4 Gy with 5-FU	36.6	RT-qPCR	3	Low expression levels of intratumoral miR-145 post-treatment associated with worse response to neoadjuvant CRT	(107)
Lopes-Ramos *et al*, 2014	Tumor biopsies	27	16	50.4-54 Gy with 5-FU	T set: 25.9 V set: 43.8	miRNA sequencing	4	Upregulated miR-21 expression was associated with complete responders. Predictive sensitivity and specificity were 78 and 86%, respectively	(110)
Caramés *et al*, 2015	FFPE tissues	92	No	Radiation dose unspecified with 5-FU/capecitabine	13.2	RT-qPCR		High miR-21 expression associated with complete pathological response and good outcome. Positive and negative predictive values were 92 and 42.8%, respectively	(111)
Svoboda *et al*, 2008	Tumor biopsies	BR:35 AR:31	No	45-50.4 Gy with capecitabine	58.1	RT-qPCR	8	Upregulation of miR125b and miR137 expression in post-treatment patients was associated with worse outcome	(112)

Table I. Continued.

B, Individual miRNAs

First author, year	Specimen	Patients in T set, n	Patients in V set, n	Treatment dose (RT/CRT)	pCR rate, %	ncRNA platform	Differentially expressed ncRNAs, n	Identified ncRNAs and outcome	(Refs.)
D'Angelo *et al*, 2016	Tumor biopsies and serum samples	38 34	No	45 Gy with 5-FU/capecitabine with or without oxaliplatin	47.4	miRNA microarray	11	High miR-125b expression in both tumor tissues and serum was associated with a poor response in patients with rectal cancer	(113)
Yu *et al*, 2016	Tumor biopsies and serum samples	20 87	20 42	50.4-54 Gy	50 38	miRNA microarray	16	High miR-345 expression was significantly associated with a poor response to neoadjuvant CRT and poor locoregional control in patients with rectal cancer	(114)
Caramés *et al*, 2016	FFPE tissues	78	No	Radiation dose unspecified with 5-FU	12.2	RT-qPCR		Overexpression of miR-31 significantly predicted a poor pathological response and worse overall survival	(115)
D'Angelo *et al*, 2018	Tumor biopsies	38		Not specified	21	miRNA microarray		High miR-194 expression was closely associated with radiation-sensitive patients	(119)

C, miRNA signatures

First author, year	Specimen	Patients in T set, n	Patients in V set, n	Treatment dose (RT/CRT)	pCR rate, %	ncRNA platform	Differentially expressed ncRNAs, n	Identified ncRNAs and outcome	(Refs.)
Della Vittoria Scarpati *et al*, 2012	Frozen tumor biopsies	35	No	45 Gy with capecitabine-oxaliplatin	21.6	miRNA microarray	53	11 miRNAs were upregulated (miR-1183, miR-622, miR-483-5p, miR-125a-3p, miR-1224-5p, miR-1471miR-188-5p, miR-671-5p, miR-1909*, miR-630 and miR-765) and 2 miRNAs were downregulated (miR-1274b and miR-720) in complete responders. Predictive sensitivity and specificity were significant	(122)

Table I. Continued.

C, miRNA signatures

First author, year	Specimen	Patients in T set, n	Patients in V set, n	Treatment dose (RT/CRT)	pCR rate, %	ncRNA platform	Differentially expressed ncRNAs, n	Identified ncRNAs and outcome	(Refs.)
Hotchi *et al*, 2013	Tumor biopsies	22	21	40 Gy in 22 fractions with S-1, a novel oral fluoropyrimidine	T set: 31.8 V set: 42.8	miRNA microarray		The response to CRT was evaluated using three parameters: i) in responders by histopathological examination (2 upregulated miRNAs, miR-223 and miR-142-3p); ii) in responders by RECIST (1 upregulated miRNA, miR-223, and 8 downregulated miRNAs, miR-20b, miR-92a, let-7a*, miR-20a, miR-17*, miR-106a, miR-17 and miR-20a); iii) in responders by downstaging (3 upregulated miRNAs, miR-223, miR-630 and miR-126*)	(123)
Azizian *et al*, 2016	Tumor biopsies	45	147	50.4 Gy in 28 fractions with capecitabine/ oxaliplatin	Not specified	miRNA microarray	19	High expression of four-miRNA signature (miR-515-5p, miR-573, miR-579 and miR-802) was associated with a poor outcome	(127)
Campayo *et al*, 2018	Tumor biopsies	12	96	45-50 Gy with 5-FU	V set: 25	miRNA microarray	377	Low expression of three-miRNA signature (miR-21, miR-99b and miR-375) was positively associated with complete responders. Predictive sensitivity and specificity were 60 and 82.9%, respectively	(129)
Machackova *et al*, 2020	Tumor biopsies	40	87	Radiation dose unspecified with 5-FU	V set: 17	Small RNA sequencing	69	High expression of five-miRNA signature (miR-324-3p, miR-15b-5p, miR-146a-5p, miR-193a-5p and miR-487a-3p) was positively associated with non-responders. miR-487a-3p was considered as the best candidate among 5 selected miRNAs	(130)

Table I. Continued.

C, miRNA signatures

First author, year	Specimen	Patients in T set, n	Patients in V set, n	Treatment dose (RT/CRT)	pCR rate, %	ncRNA platform	Differentially expressed ncRNAs, n	Identified ncRNAs and outcome	(Refs.)
Li *et al*, 2018	Peripheral blood samples	BR: 38 AR: 31	BR: 24 AR: 24	(2 Gy/day) from 3-6 months	Not specified	qPCR array	22	The three-miRNA signature with higher levels of miR-374-5p and lower levels of miR-342-5p and miR-519d-3p in plasma was associated with a worse prognosis	(131)

ncRNA, non-coding RNA; lncRNA, long ncRNA; miR/miRNA, microRNA; T set, training set; V set, validation set; FFPE, formalin-fixed paraffin-embedded; BR, before radiation; AR, after radiation; RT, radiotherapy; CRT, chemoradiotherapy; pCR, pathological complete response; 5-FU, 5-fluorouracil; RT-qPCR, reverse transcription-quantitative PCR.

Individual miRNAs. A study examining the ability of miRNAs to predict the nCRT response in patients with rectal cancer reported that miR-145 expression in the tumor tissues after therapy was upregulated compared with that in the tumor tissues before therapy. Therefore, the downregulated expression of intratumoral miRNA-145 post-treatment was positively associated with a poor response to neoadjuvant therapy in patients with rectal cancer (107). miR-21 is one of the most promising predictors of response to RT in different types of cancer, such as nasopharyngeal carcinoma and non-small-cell lung cancer (108,109). Several clinical trials have examined the roles of miR-21 in patients with rectal cancer undergoing CRT. Sequencing analysis of 27 rectal tumor biopsies before CRT revealed that miR-21 was a predictive biomarker in complete responders and that the sensitivity and specificity of miR-21 to predict therapeutic response in responders were 78 and 86%, respectively (110). Caramés *et al* (111) examined 92 patients with LARC undergoing CRT to investigate the roles of miR-21 in clinical and molecular characteristics of the tumor, pathological response and clinical outcome. The aforementioned study indicated that the preoperative expression levels of miR-21 could distinguish the responders from the non-responders with 92% positive predictive value and 42.8% negative predictive value (111).

In addition to miR-21, there are other miRNAs that can predict the response to therapy in patients with rectal cancer undergoing CRT. Svoboda *et al* (112) observed 35 patients with LARC undergoing CRT and identified that several miRNAs (miR-10a, miR-21, miR-145, miR-212, miR-339 and miR-361) were differentially expressed after RT. Among these, miR-125 and miR-137 were markedly upregulated after the initiation of therapy in most samples (112). The upregulated expression levels of both miR-125 and miR-137 have been associated with a poor response to neoadjuvant therapy (112). Additionally, serum miR-125 levels in the non-responders are significantly upregulated compared with those in the responders, and are associated with an excellent discriminating power (112,113). Additionally, the upregulated expression levels of miR-345 in both tissues and serum have been significantly associated with a poor response to neoadjuvant CRT (114).

Caramés *et al* (115) also examined 78 patients diagnosed with LARC who were undergoing nCRT and demonstrated that miR-31 may be used as a novel predictive marker for both pathological response and clinical outcome of the patients. miR-31, which was markedly upregulated in 32.4% of cases, was positively associated with a lack of pathological response and worse overall survival (115). By contrast, downregulated miR-31 expression was positively associated with improved responses to neoadjuvant therapy (115). Previous studies reported that miR-194, which is frequently downregulated in colorectal cancer (116,117), is a potential tumor suppressor (117,118). Therefore, D'Angelo *et al* (119) investigated the potential of miR-194 to predict the response to CRT using biopsy samples collected from 38 patients diagnosed with LARC. Patients with radiosensitive LARC were associated with upregulated miR-194 expression (119). These findings suggest that miR-194 may serve as a radiosensitive marker in patients with rectal cancer. Additionally, the results of the aforementioned studies support the hypothesis that CRT may modulate the miRNA expression profiles in both tissue

and serum samples. Thus, the expression levels of miRNAs have the potential to predict tumor response to treatment and may be used as potential prognostic biomarkers.

miRNA signature. A group of miRNAs can be a reliable biomarker that can accurately predict tumor response to RT. Most studies have included pathological staging analysis before and after preoperative CRT as the tumor stage is associated with prognosis and performed large-scale analysis of the expression levels of several miRNAs (120,121). Previous miRNA expression profile analysis has revealed the differential expression patterns of miRNA signatures between responders and non-responders after preoperative CRT (122,123). Della Vittoria Scarpati *et al* (122) examined the changes in the expression levels of selected miRNAs in rectal cancer biopsies from 38 patients diagnosed with T3-4/N+ rectal cancer who were treated with capecitabine-oxaliplatin and underwent RT followed by surgery. Microarray was performed to analyze the expression of 373 miRNAs in frozen biopsies obtained before treatment (122). In total, 13 differentially expressed miRNAs were identified between good responders and non-responders (122). Of these 13 miRNAs, 11 (miR-1183, miR-483-5p, miR-622, miR-125a-3p, miR-1224-5p, miR-188-5p, miR-1471, miR-671-5p, miR-1909*, miR-630 and miR-765) were significantly upregulated in good responders, while 2 (miR-1274b and miR-720) were downregulated (122). The specificity and sensitivity of differentially expressed miRNAs indicated that they could predict complete response cases, especially two miRNAs (miR-622 and miR-630) that are involved in DNA repair mechanisms (122).

To identify the expression pattern of miRNAs to predict the response of rectal cancer to CRT, Hotchi *et al* (123) analyzed 43 patients with rectal cancer before preoperative CRT using miRNA microarray. The response to CRT was evaluated based on the following three parameters: Histopathological examination of surgically resected specimens, response evaluation criteria in solid tumors (RECIST) and downstaging (123). Histopathological examination of surgically resected specimens revealed that the expression levels of two miRNAs (miR-223 and miR-142-3p) in the responders were significantly higher than those in the non-responders (123). Based on the RECIST parameter, nine miRNAs were identified as predictive biomarkers of RT response (123). Compared with that in the non-responders, the expression of one miRNA (miR-223) was upregulated, while that of eight miRNAs (miR-20b, miR-92a, let-7a*, miR-20a, miR-17*, miR-106a, miR-17 and miR-20a) was downregulated in the responders (123). The downstaging evaluation revealed that the expression levels of three miRNAs (miR-223, miR-630 and miR-126*) were associated with response to RT (123). These results indicated that the upregulated expression levels of these miRNA signatures had the potential to predict the response of patients with rectal cancer to CRT with high sensitivity and specificity (123).

The ability of miRNA signatures to predict the response to treatment has piqued the interest of the scientific community. Most studies involve a small number of samples with no validation group (123-125). The investigations involving small cohorts are associated with a high risk of false-positive cases, which has hindered or delayed the clinical application of diagnostic and prognostic biomarkers (126). To overcome these limitations, Azizian *et al* (127) performed microarray analysis of a training set comprising 45 preoperative biopsies from patients with rectal cancer to identify potential miRNAs that can predict tumor regression grade and other clinical parameters. The selected miRNAs were then validated using reverse transcription-quantitative PCR (RT-qPCR) with an independent set of 147 patients with rectal cancer (127). The upregulated expression levels of four miRNAs (miR-515-5p, miR-573, miR-579 and miR-802) were significantly associated with overall survival and cancer-specific survival in patients with rectal cancer (123,128). The miRNA signature comprising the four aforementioned miRNAs may predict the treatment response before RT in patients with rectal cancer.

Campayo *et al* (129) analyzed the miRNA expression levels in a training group comprising 12 selected patients (six responders and six non-responders) and a validation set comprising 96 pretreatment biopsies from patients with rectal cancer. Among the 377 miRNAs, eight (let-7b, let-7e, miR-21, miR-99b, miR-183, miR-328, miR-375 and miR-483-5p) could predict the response to CRT (129). Of these eight miRNAs, three (miR-21, miR-99b and miR-375) could predict the response to CRT in the cohort comprising 96 patients (129). The downregulated expression levels of miR-21, miR-99b and miR-375 could distinguish the responders from the non-responders (129). Recently, a large-scale miRNA analysis of 40 tumor biopsy samples using small RNA sequencing revealed that five miRNAs (miR-324-3p, miR-15b-5p, miR-146a-5p, miR-193a-5p and miR-487a-3p) were differentially expressed between responders and non-responders (130); among the selected miRNAs, miR-487a-3p expression in the non-responders was significantly upregulated compared with that in the responders and had the highest potential to predict CRT response (130).

miRNA signature in the plasma may also potentially predict tumor response to CRT. Li *et al* (131) screened the miRNA profile of plasma samples derived from 26 patients with rectal cancer before and after RT. The selected miRNAs in the testing and training groups were validated using RT-qPCR (131). A group of three miRNAs comprising miR-374a-5p, miR-342-5p and miR-519d-3p emerged as potential predictive markers for distinguishing the responders from the non-responders before RT (131). In particular, the downregulated expression levels of miR-342-5p and miR-519d-3p in the plasma were associated with a worse prognosis and a short 5-year survival in patients with rectal cancer (131). These results demonstrate the clinical importance of both tissue and blood miRNA signatures in predicting the clinical outcomes of rectal cancer and emphasize the necessity for validation studies in a clinical setting.

From the aforementioned studies, it is clear that miRNAs are becoming involved in the response to RT. They are not only shown as a predictor of RT to select responding or non-responding patients, but also used to predict the survival and post-radiation toxicity. Although emerging evidence has indicated promising roles of miRNAs as valuable clinical tools for personalized care of rectal cancer in the future, any potential biomarker requires multiple and large cohorts to validate its reproducibility. Therefore, statistically rigorous independent validation studies in different cohorts and different types of cancer are critical to confirm the prognostic or predictive value of these emerging findings.

Table II. ncRNAs as potential therapeutic targets in rectal cancer.

A, miRNAs

First author, year	ncRNAs	Target	Effect	(Refs.)
Lopes-Ramos *et al,* 2014	miR-21-5p	SATB1	Modulating the malignant behavior and multidrug resistance	(110)
Ha Thi *et al,* 2019	miR-130a	SOX4	Reducing the irradiation-induced cell invasion and damaged DNA repair	(144)
Ruhl *et al,* 2018	miR-451	EMSY, CAB39	Inhibiting cell proliferation and DNA damage repair	(146)
Luo *et al,* 2018	miR-519b-3p	ARID4B	Inhibiting cell proliferation, migration and invasion	(147)

B, lncRNAs

First author, year	ncRNAs	Target	Effect	(Refs.)
Yang *et al,* 2017	lincRNA-ROR	miR-145	Inducing radiation-mediated cell death	(149)
Zou *et al,* 2018	lncRNA OIP5-AS1	miR-363-3p	Inducing radiation-mediated cell death	(150)
Wang *et al,* 2014	lincRNA-p21	Wnt/β-catenin pathway	Inducing radiation-mediated apoptosis	(151)

ncRNA, non-coding RNA; lncRNA, long ncRNA; miR/miRNA, microRNA.

6. ncRNAs are promising targets to enhance the radiosensitivity of rectal cancer

Previous preliminary studies have demonstrated that ncRNAs can be potential therapeutic targets for cancer (132,133). ncRNAs can function as oncogenes or tumor suppressors and are involved in cancer initiation, progression and resistance to therapeutics (134-136). Hence, various strategies have been developed to utilize ncRNAs as therapeutic targets in cancer. Recent targeting strategies consist of the application of ncRNA inhibitors, such as ncRNA mimics, ncRNA vectors, ncRNA sponges, antisense oligonucleotides, ncRNA-mask oligonucleotides or clustered regularly interspaced short palindromic repeat-Cas9 technology (137). The modulation of ncRNA expression levels may be also achieved by transferring ncRNAs using various delivery systems. Currently, different strategies have been used to deliver ncRNAs, such as viral-based vector systems (lentiviruses, retroviruses, adenoviruses or adeno-associated viruses) and non-viral delivery systems (physical and chemical approaches) (138,139). The advantages of non-viral systems include decreased toxicity, low immunogenicity and the ability to transfer large-sized passenger ncRNAs (139). The viral-based vector systems are associated with high transfection efficiency, long half-life and high biodegradability (140). Therefore, designing a precise delivery system to ensure the stability of synthetic ncRNAs in circulation, a high transfection efficiency and tumor-specific targeting is indispensable to translate ncRNA therapy to the clinic. The modulation of ncRNAs or ncRNA-regulated signaling pathways can be a potential therapeutic strategy to enhance the radiosensitivity of rectal cancer (Table II).

Lopes-Ramos *et al* (110) reported that miR-21-5p, which was upregulated in complete responders of RT, may be a promising therapeutic candidate for rectal cancer. Upregulated miR-21-5p expression in rectal cancer cells (compared with that in control cells) increased the sensitivity of cancer cells to CRT (110). Conversely, the inhibition of miR-21-5p decreased the sensitivity of rectal cancer cells to CRT (110). Mechanistically, miR-21-5p negatively regulated the mRNA expression levels of *SATB1*, which is reported to induce malignant behavior and confer multidrug resistance (110). Additionally, miR-21-5p expression was positively associated with a poor prognosis in several types of cancer, including rectal cancer (110,141). miR-205 and miR-95 enhance the sensitivity of tumors to RT by targeting specific mRNAs, such as *ZEB1*, *Ubc13* or *SGPP1* (142,143). Recently, Ha Thi *et al* (144) have identified miR-130a as a promising candidate to modulate the radioresistance of rectal cancer. Mechanistically, miR-130a suppressed the repair pathway of irradiation-induced DNA damage by directly targeting *SOX4*, which encodes a transcription factor (144). Additionally, upregulated miR-451a expression enhanced the radiosensitivity of rectal cancer by modulating the mRNA expression levels of *EMSY* and *CAB39*, which are involved in cell proliferation and DNA damage repair (145,146), and are positively correlated with the upregulation of the SHP2 and RAF signaling pathways (145). Therefore, pretreatment with SHP2 and RAF inhibitors may benefit patients with rectal cancer who have a limited response to CRT and exhibit low miR-451a expression. Additionally,

miR-519b-3p was reported to be a promising candidate to overcome the radioresistance of rectal cancer (147). miR-519b-3p expression was upregulated in good responders among patients with LARC and was inversely correlated with the mRNA expression levels of *ARID4B*, which is associated with tumor growth, migration and invasion (148).

Several lncRNAs can modulate radiosensitivity through multiple mechanisms in rectal cancer. The suppression of lincRNA-ROR sensitizes rectal cancer cells by inducing cell death after irradiation (149). lincRNA-ROR regulates radiosensitivity by promoting the expression levels of p53 and miR-145, and consequently modulating the expression levels of p21 and Myc (149). lncRNA OIP5-AS1 inhibits miR-363-3p expression and promotes DYRK1A expression (150). Ectopic expression of lncRNA OIP5-AS1 promotes radiation-induced cell death and enhances the radiosensitivity of rectal cancer by targeting DYRK1A (150). Additionally, lincRNA-p21 promotes the radiosensitivity of rectal cancer by targeting the Wnt/β-catenin signaling pathway (151), and lincRNA-p21 overexpression enhances radiation-induced apoptosis by inducing *Noxa* expression, a pro-apoptotic gene (151).

7. Conclusion

Previous studies have demonstrated that ncRNAs mediate tumor response against radiation. Several ncRNAs may enhance tumor radiosensitivity, while others confer resistance to radiation by modulating the irradiation-associated signaling pathways. Additionally, experimental studies have demonstrated that the modulation of ncRNA expression levels may markedly enhance the radiosensitivity of rectal cancer cells *in vitro* and *in vivo*. These findings suggest that ncRNAs may serve as potential therapeutic targets to improve the outcome of RT. Additionally, ncRNAs can be targeted in combination therapy for cancer.

The ncRNA-based therapies for cancer have yielded promising results in preclinical studies. However, the implementation of these techniques in a clinical setting is associated with several challenges. The expression levels of ncRNAs vary among different types of human cancer and even among the same tumor type in different studies. The tumor microenvironment serves an essential role in regulating tumor biological behavior and may hinder the quantification of ncRNA expression. Tumor progression during RT is a dynamic process that is accompanied by dynamic changes in ncRNA expression. To enhance the therapeutic efficacy of ncRNA-based RT, the delivery system of ncRNAs should be modified to increase their stability and specificity. Therefore, further technical and scientific development and clinical investigation are warranted to overcome these challenges.

Acknowledgements

Not applicable.

Funding

The present review was supported by the National Research Foundation of Korea grant funded by the Korean government (grant no. 2020R1F1A1061122).

Availability of data and materials

Not applicable.

Authors' contributions

HTHT and SH were involved in the conceptualization of the study, and confirmed the authenticity of the data. HTHT and HQD wrote the manuscript, and SH edited and revised it. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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