



The predictive value of microRNAs for pathological response after neoadjuvant treatment in esophageal squamous cell carcinoma: a systematic review

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Abstract: Neoadjuvant treatment followed by esophagectomy has been the standard strategy for resectable locally advanced esophageal squamous cell carcinoma (ESCC). Pathological response after neoadjuvant treatment is of vital importance in the determination of long-term survival. Due to the involvement of microRNAs (miRNAs) in ESCC, some studies have proposed miRNA models to predict the pathological response. We aimed to summarize current studies on the predictive value of the miRNA models. We searched the relevant studies on PubMed, Web of Science and Cochrane Library up to February 14, 2020, using the following search term: (esophageal OR esophagus OR oesophageal OR oesophagus) AND (miR OR miRNA OR microRNA) AND (neoadjuvant OR preoperative OR induction). The initial search retrieved 206 studies. We briefly summarized the involvement of miRNAs in the origin, development and chemo- and radioresistance in ESCC. Then, 9 studies were enrolled in the systematic review. A great heterogeneity was observed across these studies. Of the 6 studies with diagnostic tests, the area under curve varied a lot. Although much evidence demonstrated the correlation between miRNAs and pathological response after in ESCC, the current studies has not established any promising models. A well-designed prospective study is essential to investigate the potential predictive models for pathological response after neoadjuvant treatment in ESCC.

Keywords: Esophageal squamous cell carcinoma (ESCC); microRNAs (miRNA); pathological response; predictive

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Introduction

Esophageal cancer is one of the most common malignancies worldwide, which led to approximately 500,000 deaths in 2018 (1). Its two main histological subtypes, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), have significant differences in epidemiology, etiology, and treatment response (2). In East Asia and Africa, ESCC is the predominant subtype (3).

Patients with ESCC have poor overall survival, which is partly due to advanced stages at initial diagnosis (4), and

the limited approaches for metastatic diseases (5,6). In recent years, neoadjuvant treatment, including neoadjuvant chemotherapy (nCT) or neoadjuvant chemoradiotherapy (nCRT), followed by esophagectomy, has been the standard strategy for resectable locally advanced esophageal cancer due to the survival benefit (7-9). Moreover, the pathological response after nCT or nCRT has been demonstrated to be independently associated with overall survival (10,11). Therefore, predicting pathological response is important. To date, researchers have proposed models based on

medical images (12), inflammatory markers (13), and nutrient indices (14); however, no promising models have been established.

MicroRNAs (miRNAs), short nucleotide as 28–25 base pairs, are considered potential candidates for predicting pathological response. They post-transcriptionally regulate gene expression, including that of oncogenes and onco-suppressor genes, by complementary binding to 3'-untranslated regions of the target messenger RNA. Previously published studies have reported that miRNAs are involved in the origin and development, and the chemo- and radio-resistance of ESCC (15–20). In recent years, some studies have further explored whether miRNAs could effectively predict tumor response after nCT or nCRT in ESCC. However, variable miRNAs, together with different pathological response classifications, lead to complex outcomes that require further consideration.

In the present study, we briefly reviewed the involvement of miRNAs in the development and treatment resistance of ESCC. This systematic review aimed to analyze the predictive value of miRNAs in the pathological response of ESCC after nCT or nCRT. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-3000>) (21).

Methods

Search strategy

A literature search of PubMed, Web of Science, and Cochrane Library was conducted using the following search terms: (esophageal OR esophagus OR oesophageal OR oesophagus) AND (miR OR miRNA OR microRNA) AND (neoadjuvant OR preoperative OR induction). The search was restricted to English-language literature published from inception to February 14, 2020.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) patients histologically diagnosed with esophageal cancer; (II) patients receiving nCT or nCRT followed by esophagectomy; and (III) studies on the association between miRNAs and pathological response to neoadjuvant treatment. The exclusion criteria were as follows: (I) published studies that were not original articles; (II) studies not on ESCC or miRNAs; and (III) studies not on pathological response. The reference lists of the original articles and literature

reviews were also examined.

Data extraction

Data including first author, year of publication, sample size, neoadjuvant treatment, testing materials, pathological response classification, miRNA model, and statistical methods were extracted.

All procedures were independently double-checked by two investigators (D Lin and X Chen). Discrepancies were resolved through group discussions with all the authors.

Statistical analysis

It is well known that the part of Statistical Analysis is essential in original articles. However, this is a systematic review with no meta-analysis due to the heterogeneity across the enrolled studies. So, we think that the part of statistical analysis can be waived in our review article. We look forward to further communication at any time.

Results

Study characteristics

The initial search retrieved 206 studies. According to the inclusion and exclusion criteria, 197 studies were eliminated and 9 were finally selected for the review. The literature retrieval process is shown in *Figure 1*.

All 9 studies were published in the past decade (22–30). As summarized in *Table 1*, the 4 studies from Japan used nCT, while the other 5 studies, from China, Germany, and Canada, used nCRT. All chemotherapy regimens were platinum-based. The radiotherapy doses ranged from 30 to 60 Gy. Significant diversity was also observed in the testing materials, pathological response classifications, and the miRNA models. These findings indicated great heterogeneity among the studies, which eliminated the need for a quantitative analysis. The pathological response criteria are presented in *Table S1*.

Involvement of miRNAs in the origin and development of ESCC

In 2008, Guo *et al.* first reported the global microRNA expression profile of ESCC (31). They identified 46 miRNAs that were differentially expressed in malignant and adjacent normal tissue, of which 7 could distinguish between the

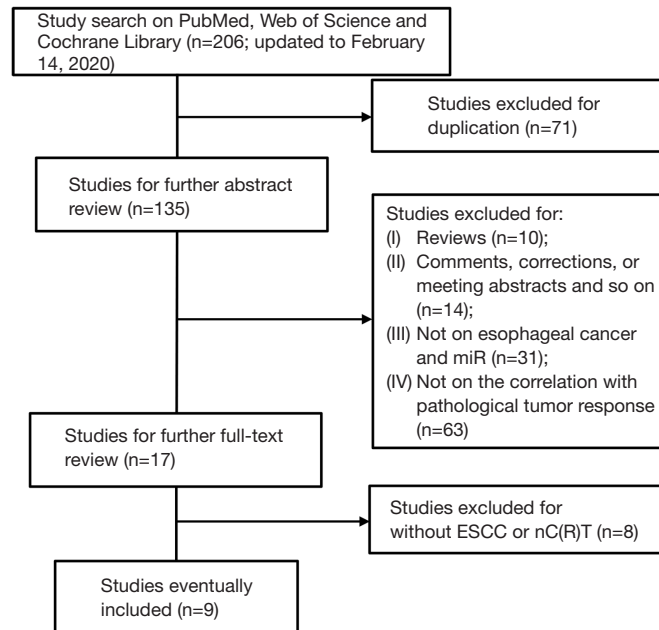


Figure 1 Flow diagram of study search and selection.

malignant and normal tissues. Moreover, they determined that miR-103/107 could be an independent prognostic marker. Kano *et al.* reported that the downregulation of miR-145, miR-133a, and miR-133b could lead to the activation of FSCN1, which promotes cell growth and invasion (32). Hamano *et al.* reported that miR-200c expression knockdown is associated with the increased expression of PPP2R1B, which might inhibit tumor invasiveness. Liu *et al.* revealed that ADAM9 is a key target of miR-126, and that the ectopic expression of miR-126 or silencing of ADAM9 reduces the proliferation and migration abilities of ESCC cells (22). Harada *et al.* stated that the complicated dysregulation of miRNAs could be responsible for the origin and development of ESCC (19).

Involvement of miRNAs in treatment sensitivity or resistance of ESCC

Chen *et al.* revealed that the combined downregulation of miR-133a and miR-133b enhances chemosensitivity to paclitaxel-based chemotherapy (33), and miR-141 was revealed to confer resistance to cisplatin in ESCC (34). Zang *et al.* revealed that miR-199a-3p regulates radio-resistance by targeting the AK4 gene (35). Moreover, miR-96 promotes chemo- and radio-resistance in ESCC through

the downregulation of RECK (36). Accumulating evidence has confirmed the associations between miRNAs and chemo- or radio-resistance, or chemo- or radio-sensitivity in ESCC. Vrana *et al.* stated that the role of miRNAs was interactive and complicated (20).

Correlation between miRNAs and pathological response

As mentioned above, the involvement of miRNAs in ESCC is an important precondition of potential predictive models. Recent studies have investigated whether single or panel miRNAs could effectively predict pathological response after nCT or nCRT in ESCC (25-30). As shown in *Table 2*, regarding the statistical methodology, 3 studies published from 2011–2013 that did not use diagnostic tests reported a correlation between miRNAs and pathological response. The other 6 studies, which were all published after 2013, used diagnostic tests, despite the absence of the STARD guidelines and external validation.

Studies that did not use diagnostic tests

In 2011, Hamano *et al.* reported that miR-200c was significantly correlated with pathological response ($P=0.007$) to nCT based on cisplatin, adriamycin and 5-FU (22).

Table 1 Summary of nine studies on the miRNAs and pathological response after neoadjuvant treatment in ESCC

Authors (year)	Ref	Sample size	Neoadjuvant treatment	Testing materials	Pathological response classification (response criteria)	miRNA models
Niwa <i>et al.</i> (2019)	(26)	92	nCT (multiple drugs based on platinum)	Pretreatment serum (microarray, qPCR)	Responders vs. non-responders (JES: Grade 2–3 vs. 0–1)	The panel of miR-23a-5p, 193b-5p and Ly; the panel of miR-193-5p and 873-3p; the panel of miR-23a-5p, 193-5p and 873-3p
Slotta-Huspenina <i>et al.</i> (2018)	(29)	84	nCRT (DDP/OXA, 5-Fu; 30–60 Gy)	Pretreatment biopsy, FFPE (microarray, qPCR)	Responders vs. non-responders (TRG Criteria: TGR 1a vs. 3)	miR-194; miR-665; the panel of miR-194 and 665
Chan <i>et al.</i> (2018)	(30)	67	nCRT (DDP, 5-Fu; 40 Gy)	Pretreatment serum (microarray, qPCR)	Good vs. poor responders (0 vs. $\geq 50\%$ viable tumor cells)	miR-193b
Komatsu <i>et al.</i> (2016)	(28)	37	nCT (DDP, 5-Fu)	Pretreatment plasma (microarray, qPCR)	Low vs. high response grade (JES: Grade 0–1a vs. 1b–3)	miR-23a
Komatsu <i>et al.</i> (2016)	(27)	37	nCT (DDP, 5-Fu)	Pretreatment plasma (microarray, qPCR)	Low vs. high response grade (JES: Grade 0–1a vs. 1b–3)	miR-21
Wen <i>et al.</i> (2016)	(25)	106	nCRT (DDP, NVB; 40 Gy)	Pretreatment biopsy (microarray, qPCR)	Responders vs. non-responders ($\leq 50\%$ vs. $> 50\%$ viable tumor cells)	the panel of miR-145-5p, 152, 193b-3p and 376a-3p
Odenthal <i>et al.</i> (2013)	(24)	88	nCRT (DDP, 5-Fu; 40 Gy)	Pretreatment biopsy (microarray, qPCR)	Major vs. minor response ($< 10\%$ vs. $\geq 10\%$ vital tumor cells)	NA (miR-192, 194 cluster)
Ko <i>et al.</i> (2012)	(23)	25	nCRT (DDP, CPT-11; 50.4 Gy)	Pretreatment biopsy, (microarray)	pCR vs. non-pCR	NA (miR-296)
Hamano <i>et al.</i> (2011)	(22)	98	nCT (DDP, ADM, 5-Fu)	FFPE, fresh-frozen (microarray qPCR)	Responders vs. non-responders (JES: Grade 3 vs. 0–2)	NA (miR-200c)

Ref, reference; Ly, lymphatic invasion; DDP, cisplatin; 5-Fu, fluorouracil; NVB, vinorelbine; CPT-11, irinotecan; ADM, adriamycin; JES, Japan Esophageal Society; TRG, tumor regression grade.

In a study of pathological complete response (pCR) and non-pCR patients, Ko *et al.* found that 71 miRNAs were significantly different, and 5 miRNAs had greater than 2-fold differences (23). This study included 5 cases with ESCC and 20 with EAC. Odenthal *et al.* reported that the expression of miR-192 ($P=0.005$) and miR-194 ($P=0.040$) were significantly different between ESCC patients who showed minor and major response (24). Further, these studies found that the expression levels of specific miRNAs changed significantly before and after nCT or nCRT. These dynamic changes offered a possibility of early evaluation during neoadjuvant treatment. These studies revealed a significant correlation between miRNAs and pathological response.

Studies that used diagnostic tests

In 2016, Wen *et al.* identified 10 miRNAs with greater than 1.5-fold changes between pathological responders ($< 50\%$ residual tumor) and non-responders ($\geq 50\%$ residual tumor), and established a combination of 4 miRNAs (miR-145-5p, miR-152, miR-193-3p, and miR-376a-3p) as a predictive model (25). The model provided a satisfactory predictive value for pathological response in an external validation cohort [area under the curve (AUC): 0.8682, 95% confidence interval (CI): 0.7710–0.9653, $P<0.001$]. In this study, patients underwent homogeneous concurrent nCRT. But the underlying mechanism of these miRNAs was still unclear.

Table 2 Summary of six studies with diagnostic tests on the predictive value of miRNA for pathological response after neoadjuvant treatment in ESCC

Authors (year)	Ref	Sample size of external validation	Methods of diagnostic tests	Most valuable predictive models	Predictive power (at the optimal cutoff)	
					AUC (95% CI)	Predictive power
Niwa <i>et al.</i> (2019)	(26)	NA	Multiple logistic model; ROC analysis	the panel of miR-23a-5p, 193b-5p and Ly	0.73 (0.60–0.86)	No data
Slotta-Huspenina <i>et al.</i> (2018)	(29)	NA	ROC analysis	the panel of miR-194 and miR-665	0.824 (0.713–0.935)	No data
Chan <i>et al.</i> (2018)	(30)	NA	ROC analysis	miR-193b	0.8949 (0.7912–0.9987)	No data
Komatsu <i>et al.</i> (2016)	(28)	NA	ROC analysis	miR-23a	0.696 (no data)	Sen: 79.2%, Spe:64.3%
Komatsu <i>et al.</i> (2016)	(27)	NA	ROC analysis with Youden index	miR-21	0.6794 (no data)	Sen: 92.3%, Spe: 54.2%, Acc: 67.6%
Wen <i>et al.</i> (2016)	(25)	79	Support vector machine; quadratic discriminant analysis; ROC analysis	the panel of miR-145-5p, 152, 193b-3p and 376a-3p	0.8682 (0.7710–0.9653)	Sen: 83.3%, Spe: 88.1%, Acc: 87.3%

Ref, reference; ROC, receiver operative characteristic curve; AUC, area under the curve; 95% CI, 95% confidence interval; Ly, lymphatic invasion; JES, Japan Esophageal Society; TRG, tumor regression grade; Sen, sensitivity; Spe, specificity; Acc, accuracy.

In recent years, circulating miRNAs have attracted significant attention due to their non-invasiveness and convenience. In 2019, Niwa *et al.* conducted serum-based miRNA signature research, which was carried out in accordance with the STARD guidelines (26). They identified 62 miRNAs in responders (grades 2–3) and non-responders (grade 0–1) after nCT. MiR-193b-5p, miR-873-3p, and miR-23a-5p, as well as microscopic lymphatic invasion, were included in the models. Consequently, receiver-operative characteristic (ROC) analysis confirmed that the combination of miR-193b-5p, miR-873-3p, and lymphatic invasion achieved the highest predictive value (AUC: 0.73, 95% CI: 0.60–0.86; no sensitivity, specificity, or accuracy data). However, the models did not show any independent prognostic value for long-term survival.

Komatsu *et al.* proposed miR-21 (27) and miR-23a (28) from pretreatment plasma as useful biomarkers for pathological response. However, these 2 miRNAs were found to have only low predictive value (AUC: 0.6794, sensitivity: 92.3%, specificity: 54.2%, and accuracy: 67.6%; AUC: 0.696, sensitivity: 79.2%, and specificity: 64.2%, respectively).

Slotta-Huspenina *et al.* identified 12 miRNAs from 15 responders [tumor regression grade (TRG) 1a]

and 16 non-responders (TRG 3) after nCRT (29). ROC analysis confirmed the predictive value of miR-194*, miR-665, and their combination for pathological response (AUC: 0.811, 0.817, and 0.824, respectively) in the expanded 53 cases including 26 responders (TRG 1a) and 27 non-responders (TRG 3) after nCRT. Similarly, Chan *et al.* identified 3 miRNAs from 10 good responders (with no viable tumor cells) and 10 poor responders ($\geq 50\%$ viable tumor cells) after nCRT (30). The subsequent validation among 24 patients with good response (with no viable tumor cells) and 23 patients with poor response ($\geq 50\%$ viable tumor cells) revealed that miR-193b had a strong predictive power to discriminate between the patients (AUC: 0.8949, 95% CI: 0.7912–0.9987, $P < 0.0001$).

Discussion

Pathological response is of importance for long-term survival after neoadjuvant treatment (10,11). Therefore, numerous efforts have been made to establish predictive models. In the past decade, miRNAs have been the focus of attention in cancer research. Vrana *et al.* analyzed the involvement of miRNAs in the origin and development of ESCC, and in the chemo- and radio-resistance of

ESCC (20). All of these formed one precondition for the hypothesis that miRNAs might be biomarkers for pathological response.

The aim of our review was to analyze studies on the predictive value of miRNAs for pathological response after nCT or nCRT in ESCC. After the selection and evaluation of articles, however, we observed great heterogeneity among the studies, and their methodologies and outcomes required further consideration.

Of the 6 studies that used diagnostic tests, 3 reported AUCs >0.80. Wen *et al.* proposed a predictive panel of miRNAs miR-145-5p, 152, 193b-3p, and 376a-3p in patients undergoing homogeneous nCRT (25). The effects of these miRNAs on tumor invasion varied. MiR-145-5p has been found to have an oncogenic function in esophageal cancer (37), while the overexpression of miR-152 sensitizes cisplatin-resistant ovarian cancer cells (38). Meanwhile, miR-193b-3p and 376a-3p have been shown to be tumor suppressors (39,40). In this study, however, Wen *et al.* did not investigate its prognostic value. In our opinion, complete or major pathological response is an indicator of long-term survival. Survival benefit, rather than pathological response, is the aim of any potential predictive model. An ideal model with the aims of predicting response and selecting patients should also have an independent association with survival benefit.

Apart from Wen *et al.*'s study, Slotta-Huspenina *et al.* (29) and Chan *et al.* (30) respectively reported models with high predictive values. However, in these latter 2 studies, we observed that the miRNA candidates were identified from 2 extreme pathological response classifications: TRG1a and TRG3 in Slotta-Huspenina *et al.*'s study, and no viable tumor cells versus $\geq 50\%$ viable tumor cells in Chan *et al.*'s study. The spectrum bias would overestimate the predictive power (41). Moreover, the models were validated among patients with extreme pathological response classifications. The models offer limited value for decision-making in the clinical setting. Therefore, future well-designed studies that adhere to the standard guidelines of diagnostic tests are essential (42).

All 9 studies used pretreatment specimens as the testing materials. The studies in the early period had found the dynamics of miRNAs before and after nCT or nCRT. The possibility of early evaluation during neoadjuvant treatment could be an important direction. Four studies used serum or plasma specimens as the testing materials. Circulating miRNAs could serve as sensitive and informative biomarkers

for certain diseases (43). However, inconsistencies between miRNAs in serum and miRNAs in tumor tissues have been reported (44). The use of miRNA panels, with or without clinicopathological factors, was also observed to have increased in recent years. The combination of miRNAs and other potential biomarkers, such as medical images, inflammatory markers, and nutrient indices, deserves further investigation.

Our systematic review has several limitations. First, the retrospective nature of the enrolled studies led to inherent selection bias. Second, only studies published in English were enrolled, leading to publication bias. Third, heterogeneity existed in treatment regimens, response classifications, and miRNA panels across the enrolled studies. Although previous studies have comprehensively analyzed the involvement of miRNAs in ESCC treatment resistance (20), the present review concentrated on the predictive value of miRNAs in pathological response after nCT or nCRT in ESCC. Despite the limited number of enrolled studies, our review uncovered some issues and proposed our opinions, and these would be helpful to further studies.

Conclusions

More and more evidence has demonstrated the correlation between miRNAs and pathological response after nCT and nCRT in ESCC. However, the current studies had not established any promising model. A well-designed prospective study is essential to investigate the potential models for pathological response after neoadjuvant treatment in ESCC.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-3000>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The data used in this study are from the database, so ethical approval and informed consent of the patient are not required.

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