A Meta-Analysis for Using Radiomics to Predict Complete Pathological Response in Esophageal Cancer Patients Receiving Neoadjuvant Chemoradiation

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Abstract. *Background: Preservation of organ function is important in cancer treatment. The 'watch-and-wait' strategy is an important approach in management of esophageal cancer. However, clinical imaging cannot accurately evaluate the presence or absence of residual tumor after neoadjuvant chemoradiation. As a result, using radiomics to predict complete pathological response in esophageal cancer has gained in popularity in recent years. Given that the characteristics of patients and sites vary considerably, a meta-analysis is needed to investigate the predictive power of radiomics in esophageal cancer. Patients and Methods: PRISMA guidelines were used to conduct this study. PubMed, Cochrane, and Embase were searched for literature review. The quality of the selected studies was evaluated by the radiomics quality score. I^2 score and Cochran's Q test were used to evaluate heterogeneity between studies. A funnel plot was used for evaluation of publication bias. Results: A total of seven articles were collected for this meta-analysis. The pooled area under the receiver operating characteristics curve of the seven selected articles for predicting pathological complete response in eosphageal cancer patient was quite high, achieving a pooled value of 0.813 (95% confidence intervaI=0.761-0.866). The radiomics quality score ranged from −2 to 16 (maximum score: 36 points). Three out of the seven studies used machine learning algorithms, while the others used traditional biostatistics methods. One of the seven studies used morphology class features, while four studies used first-order features, and five used second-order features. Conclusion: Using radiomics to predict complete pathological response after neoadjuvant chemoradiotherapy in esophageal cancer is feasible. In the future, prospective, multicenter studies should be carried out for predicting pathological complete response in patients with esophageal cancer.*

Esophageal cancer is a common gastrointestinal malignancy that causes more than 500,000 cancer deaths per year (1). The 5-year survival rate of patients with esophageal cancer is less than 25% (1). Developing a better treatment strategy for esophageal cancer is important.

The current treatment strategy for locally advanced esophageal cancer is neoadjuvant chemoradiotherapy followed by surgery. If complete metabolic response follows neoadjuvant treatment, then an active surveillance strategy can be considered (2). However, with the commonly used metabolic imaging methods, such as positron-emitted tomography/computed tomography, it is difficult to differentiate between inflammation and residual malignancy after concurrent chemoradiotherapy. In addition, residual malignancy is not always detected by PET/CT scan (3, 4). Other imaging methods, such as magnetic resonance imaging scan, and computed tomography alone, also have the same problem (3, 4). For this reason, attention has turned to using radiomics to predict complete pathological response in order to help patients and physicians to choose the best treatment approach when the watch-and-wait strategy is being considered.

Radiomics is a quickly growing field in which clinical images are transformed into quantitative features. These radiomics features can be further used to predict clinical outcomes. In esophageal cancer, radiomics has been widely used, as a previous review has reported (5). However, radiomics features were found to be associated with the imaging equipment used, technical setting, and processing kernel (6). As a result, there is an unmet need to conduct a meta-analysis to investigate the pooled predictive power of

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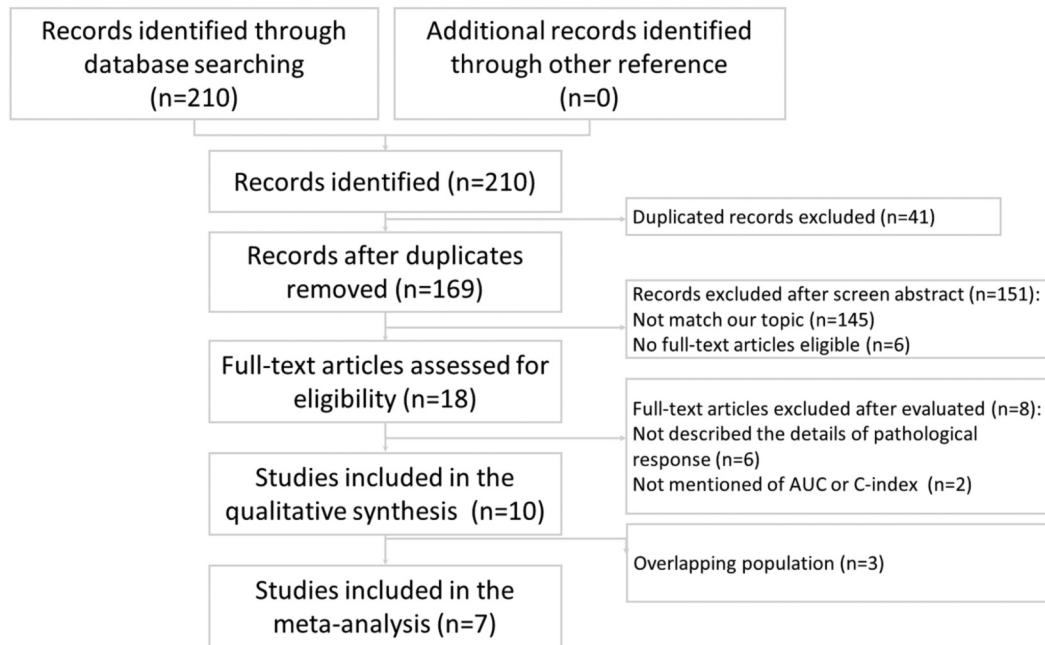
Figure 1. *The article collection flowchart.*

the current model. The results can be used as a benchmark for future large-scale radiomics studies for predicting complete pathological response in esophageal cancer.

Patients and Methods

PRISMA guidelines were used to conduct this study (7).

Eligibility criteria. Articles were included according to the rules provided below: i) Patients with esophageal cancer received neoadjuvant chemoradiation. ii) Radiomics was used to predict complete pathological response *versus* other responses and to report the area under the receiver operating characteristics curve (AUC). The radiomics features were defined in (8) as the Image Biomarker Standardization Initiative. iii) Full text article. iv) Article in English. v) Published up to 2021.

We excluded articles according to the rules provided below: i) Abstract only or short communication (9). ii) Deep learning only was used to generate features.

Literature search. The Authors searched PubMed, Cochrane, and Embase using key words: (esophageal cancer) AND (radiomics OR texture OR histogram) AND (response OR remission).

Data extraction. We extracted the primary endpoint, which was set as the highest AUC in the validation set (testing set). When there was no external validation set, the result from the internal validation set was chosen. When there was no internal validation, the result from the training set (development set) was chosen. When the result reported the C-index, it was used as the AUC. The collected model had to contain radiomics-related features but was also allowed to contain other features, such as clinical or pathological features.

We also extracted other information, including the region of interest, patient number, image type, radiomics feature type, and algorithm used in the outcome prediction.

Statistical analysis. The random-effects model was used to calculate the pooled AUC and to form the forest plot. The calculation of pooled AUC requires the standard error of the AUC; therefore, when the value was not reported in the literature, we used the formula proposed by Hanley and McNeil to calculate it (10). We also evaluated the study heterogeneity by I^2 score and Cochran's Q test. I^2 scores of less than 50% mean that there was low to moderate heterogeneity between the studies; otherwise, there is high heterogeneity between them. *p*-Values of less than 0.05 indicate statistical significance. The confidence interval calculation of the AUC was calculated using Excel (Microsoft, Redmond, Washington, MA, USA); all other statistics were accomplished using MedCalc (version 19.6.1; MedCalc, Acacialaan, Ostend, Belgium).

Risk of bias. Bias between the selected studies in meta-analysis was measured using a funnel plot. Since the number of collected articles was smaller than 10, we were unable to use Egger's test according to the recommendation provided by the Cochrane handbook (11).

Quality assessment. Study quality was evaluated by the radiomics quality score (RQS) (12). The quality of the selected literature was evaluated by both Authors. The inter-rater intra-class correlation was calculated based on the total RQS in order to evaluate inter-rater reliability (13).

Table I. *The details of articles in the quantitative meta-analysis.*

Author (Ref)	Country, year	Cancer	ROI	Imaging	Training set	External validation	Highest AUC±SE
Beukinga *et al.* (14)	NL, 2017	EC	GTV	PET	97	No	0.74±0.05
Beukinga *et al.* (15)*	NL, 2018	EC	GTV	PET	73	No	0.81±0.05
Beukinga *et al.* (16)*	NL, 2020	EC	GTV	PET	96	No	0.70±0.06[a]
Hu *et al.* (17)	CHN, 2020	EC	GTV periGTV	CT	161	70	0.88±0.05
Hu *et al.* (18)*	CHN, 2020	EC	GTV	CT	161	70	0.725±0.01
Rossum *et al.* (19)	USA, 2016	EC EGJC	GTV	PET	217	No	0.77±0.03[b]
Hirata *et al.* (20)	JPN, 2020	EC	GTV	MRI	58	No	0.86±0.08
Yang *et al.* (21)	CHN, 2019	EC	GTV	CT	44	11	0.79±0.16
Rishi *et al.* (22)	USA, 2020	EC EGJC	GTV	PET CT	68	No	0.87±0.01
Yip *et al.* (23)	USA, 2016	EC	GTV	PET	45 (30)	No	0.65±0.10[c]

AUC: Area under the receiver operating characteristics curve; CHN: China; CT: computed tomography; EC: esophageal cancer; EGJC: esophageal-gastric junction cancer; GTV: gross tumor volume; JPN: Japan; MRI: magnetic resonance imaging; NL: Netherlands; periGTV: peritumoral area; PET: positron-emission tomography; USA: United States of America. *Excluded from the quantitative meta-analysis. [a]Subgroup AUC was also reported but AUC for the whole group, which was higher, was used here. [b]C-index was reported. [c]Total of 45 patients; area under the curve is reported here for eight with complete response *versus* 22 partial response.
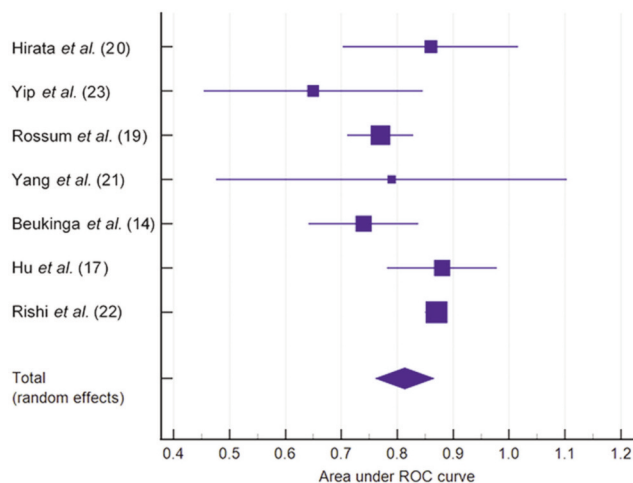

Figure 2. *Forest plot for the area under the receiver operating characteristics (ROC) curve for predicting pathological complete response in patients with esophageal cancer.*
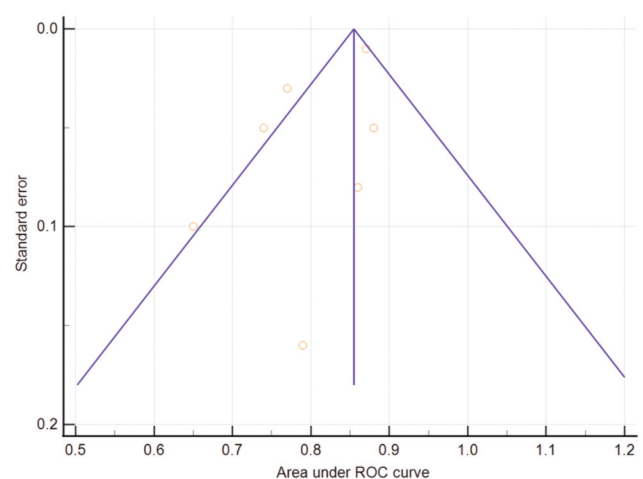

Figure 3. *Funnel plot.*

Results

A total of 210 articles were gathered. The article selection flowchart is provided in Figure 1. After the selection process, 10 articles remained for qualitative meta-analysis. Three articles were conducted by Beukinga *et al.* (14-16), therefore we only chose one of these for further analysis. Two articles were conducted by Hu *et al.* (17, 18), therefore we selected only one of them for the subsequent analysis. As a result,

seven articles were chosen for quantitative meta-analysis. The details of the collected literature are listed in Table I. All articles extracted radiomics features from the gross tumor volume. In addition, one article also extracted radiomics features from the peri-tumoral area.

Overall literature assessment. The pooled AUC for the seven collected studies was 0.813 (95% confidence intervaI=0.761-0.866). The forest plot is provided in Figure 2. The I^2 score

Table II. *Radiomics Quality Score table.*

Criteria/study	Beukinga *et al.* (14)	Hu *et al.* (17)	Rossum *et al.* (19)	Hirata *et al.* (20)	Yang *et al.* (21)	Rishi *et al.* (22)	Yip *et al.* (23)
Image protocol quality	2	1	1	1	1	1	1
Multiple segmentations	1	1	1	0	0	2	0
Phantom study on all scanners	0	0	0	0	0	0	0
Imaging at multiple time points	0	0	0	1	1	0	0
Feature reduction or adjustment for multiple testing	3	3	3	−3	3	3	3
Multivariable analysis with non-radiomics features	1	1	1	0	0	0	0
Detect and discuss biological correlates	0	1	0	0	0	0	0
Cut-off analyses	0	1	0	1	0	0	1
Discrimination statistics	2	1	2	1	2	2	1
Calibration statistics	2	1	2	0	0	0	0
Prospective study registered in a trial database	0	0	0	0	0	0	0
Validation	2	3	2	−5	2	2	−5
Comparison to 'gold standard'	0	0	2	0	0	0	2
Potential clinical utility	2	2	2	2	2	2	2
Cost-effectiveness analysis	0	0	0	0	0	0	0
Open science and data	0	0	0	0	0	0	0
Total score (Maximum score: 36 points)	15	15	16	−2	11	12	5

was 70.28% (Cochran's Q test: p=0.0026), which means that high heterogeneity existed within our studies. The funnel plot appeared asymmetric (Figure 3). However, because we only included seven studies in our meta-analysis, we cannot determine whether publication bias exists or not by examining the funnel plot.

Quality of radiomics studies. The quality of each of the seven studies was assessed by RQS, as seen in Table II. The intra-class correlation between the two reviewers who independently evaluated the articles was 0.9317 (95% confidence interval=0.6027-0.9883). High intra-class correlation means that our quality assessment was reliable. Inconsistencies were discussed by the reviewers, and the finalized results (Table II) were reached by consensus. The RQS ranged from −2 to 16 in the selected studies. Given that the maximum was 36 points, the highest-rated study received only 40% of the points.

Review of type of radiomics feature and other features in selected studies. According to International Symposium on Biomedical Imaging (ISBI) standards, the radiomics features can be divided into morphology class, first-order class, and second-order class. The second-order class includes the gray-level (GL) co-occurrence matrix, GL run-length matrix, GL size-zone matrix, GL distance-zone matrix, neighborhood gray tone difference matrix, and neighboring GL dependence

Table III. *Features used in the model with the highest area under the curve of the selected studies.*

Author (Ref)	Radiomics feature type	Other features
Beukinga *et al.* (14)	GLRLM	Histology, clinical T stage
Hu *et al.* (17)	First-order class, GLCM, GLSZM	None
Rossum et al. (19)	Morphology class, first-order class	None
Hirata *et al.* (20)	First-order class	None
Yang *et al.* (21)	First-order class, GLRLM	None
Rishi *et al.* (22)	First-order class, GLRLM, GLSZM, GLDZM, fractal feature*	None
Yip *et al.* (23)	GLCM, GLRLM, GLSZM	None

*Fractal feature is not listed as a type of International Symposium on Biomedical Imaging feature (8). GLRLM: Gray-level run-length matrix; GLCM: Gray-level co-occurrence matrix; GLSZM: Gray-level size-zone matrix; GLDZM: Gray-level distance-zone matrix.

matrix (8). We reviewed the radiomics feature type used and other types of features of the selected articles, and the results are provided in Table III. The feature type provided in the table is the feature used in the model with the highest AUC. One of the seven studies used the morphology class feature

Table IV. *Algorithms used in the predictive model.*

Author (Ref)	Algorithm
Beukinga *et al*. (14)	Multivariate logistic regression with LASSO
Hu *et al*. (17)	Support vector machine with radial basis kernel
Rossum *et al*. (19)	Multivariable logistic regression with stepwise backward elimination
Hirata *et al*. (20)	Univariate analysis
Yang *et al*. (21)	Multivariate logistic regression with LASSO
Rishi *et al*. (22)	Kaplan-Meier method with log-rank test
Yip *et al*. (23)	Kaplan-Meier method with log rank test

LASSO: Least absolute shrinkage and selection operator.

(19), four studies used the first-order feature (17, 20-22), and five studies used the second-order feature (14, 17, 21-23).

Review of the algorithms used in predictive models. The details of the algorithms used in the selected studies are provided in Table IV. Of the selected studies, three used machine learning algorithms (LASSO and SVM) (14, 17, 21), while the others used traditional biostatistical methods (19, 20, 22, 23).

Discussion

To our knowledge, this study is the first meta-analysis of the use of radiomics to predict a complete pathological response after neoadjuvant chemoradiotherapy in esophageal cancer. The pooled AUC of the seven selected articles was found to be quite high, at 0.813 (95% CI=0.761-0.866), and the I^2 score was 70.28% (*p*=0.0026). High heterogeneity existed between the studies, which is reasonable given that radiomics features are influenced by imaging equipment, technical setting, and processing kernel (6). The funnel plot shows a symmetric pattern, indicating no publication bias between the selected studies.

Although the predictive power of radiomics was good, the overall quality of the selected studies was poor. The radiomics quality score ranged from −2 to 16 (maximum score: 36 points). Although RQS is widely used in evaluation of the quality of radiomics studies, some of its items are difficult to achieve. For example, it is difficult to conduct analysis of cost-effectiveness for radiomics in cancer. In a radiomics review about lung cancer, among the 14 collected studies, none had performed a cost-effectiveness analysis (24). In addition, carrying out phantom studies for all scanners for radiomics studies is not routine. In a review of renal cell carcinoma studies, none of the 57 studies had performed phantom studies for use of different scanners (25). None of the studies included in this meta-analysis of esophageal cancer performed a cost-effectiveness analysis or carried out phantom studies.

Five studies in our analysis used second-order radiomics features in the predictive model. Second-order radiomics features show the inter-voxel relationship, which can be used to evaluate intra-tumoral homogeneity (26). The intra-tumoral heterogeneity was shown to be correlated to tumor resistance in many cancer types, such as glioblastoma (27) and lung cancer (28).

A machine learning algorithm was used in three out of the seven studies. The machine learning approach has become highly popular in recent years. However, none of the selected studies used deep-learning techniques. This is not surprising as deep learning requires a large sample size to demonstrate its power (29). However, in a single-institution setting, it is difficult to achieve sample sizes of 500 or more patients. A prospective, multicenter radiomics study with deep-learning techniques is anticipated to be launched soon.

A limitation of this study is that no prospective radiomics study was found. Moreover, we only include seven studies in this meta-analysis, so evaluation of publication bias was not feasible. Radiomics features may be influenced by image equipment technical settings, reconstruction kernel, contrast infusion speed, tumor delineation ability, and radiomics software (6). A multi-institutional, prospective study should be conducted to further investigate the predictive power of a radiomics study.

Conclusion

Using radiomics to predict complete pathological response after neoadjuvant chemoradiotherapy in esophageal cancer is feasible.

Conflicts of Interest

None.

Authors' Contributions

Concept design: Kao Y.S.; Data collection: Kao Y.S. and Hsu Y.; Statistical analysis: Kao Y.S.; Manuscript writing: Kao Y.S. and Hsu Y. Final approval of manuscript: Kao Y.S. and Hsu Y.

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