BRIEF REPORT

Infrequent chemoradiation-induced acute esophagitis in the Asian population: A meta-analysis of published clinical trials for unresectable stage III non-small cell lung cancer

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Abstract

Severe (grade 3 or higher) esophagitis is one of the major toxicities for chemoradiation in the treatment of stage III non-small cell lung cancer (NSCLC). The difference among ethnic groups has never been investigated in detail. Prospective trials with concurrent platinum-containing chemoradiation in unresectable disease were investigated, and a total of 116 treatment arms with 7520 patients were identified. Univariate analysis demonstrated that treatment arms conducted in Asia had significantly lower incidence of severe esophagitis (170/2534, 6.7%, odds ratio 0.289) than in other nations (1025/4986, 20.6%). In the multivariable model, Asian/non-Asian ethnicity, multi-/single-agent, and split are jointly significant predictors after adjusting for all possible factors. This study suggests that severe esophagitis occurs less frequently in the Asian population compared to the non-Asian population.

Introduction

Lung cancer is one of the leading causes of cancer mortality worldwide, and non-small cell lung cancer (NSCLC) accounts for the vast majority of cases.¹

Technically unresectable NSCLC disease without evidence of distant metastasis to other organs is now managed by combined modality treatment.² Landmark studies demonstrated that combined chemotherapy and radiation therapy improved long-term survival over radiation alone.³ Subsequent research has also shown that concurrent administration of chemotherapy and radiation prolonged survival over the sequential approach.⁴ Chemotherapy in this setting recommended by clinical guidelines is cisplatin- and carboplatin-containing regimens.²

In exchange for improved survival, the multi-modality approach is associated with an increased incidence and severity in toxicities. The common and dose-limiting

adverse events include esophagitis and pneumonitis. Severe acute esophagitis (grade 3 or higher) is one of the most common adverse events.^{2–4} An interruption to radiation treatment is generally not preferred, and it could be linked to accelerated cell growth.² A recent meta-analysis with individual patient data reported that V60, the volume of esophagus receiving 60 Gray of radiation, was the best predictor of developing severe esophagitis.⁵

However, ethnicity has never been incorporated into previous analysis. We noticed that several trials recently conducted in Japan consistently reported less than 10% of grade 3 or higher esophagitis.^{6–8} We, therefore, reviewed all of the prospective studies of concurrent chemoradiation for unresectable stage III NSCLC in the literature. We found that studies conducted in Asian countries had a decreased incidence of grade 3 or higher esophagitis compared to those in other nations.

Methods

Prospective trials with concurrent, platinum-based chemoradiotherapy for unresectable stage III NSCLC were identified for this meta-analysis. For randomized trials with different combined modalities, only the concurrent chemoradiation arms were eligible. Trials/treatment-arms must have been published in an English language journal, and included concurrent chemotherapy with cisplatin or carboplatin. They also must have reported frequency of acute grade 3 or higher esophagitis according to criteria from the World Health Organization (WHO)/Radiation Therapy Oncology Group (RTOG)/National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE).⁹

PubMed online database was used to screen the trials/arms. Articles containing “concurrent,” “chemotherapy,” “radiation,” and “non-small cell lung cancer” within the title or abstract were identified for initial screening. Searching the references of the identified PubMed articles located additional articles. We also searched PubMed for qualifying studies that were authored by the top experts in the field.

Treatment arms with sequential chemoradiation, radiation alone, non-platinum chemotherapy regimen, neoadjuvant chemoradiation with intent of surgery, and Phase I and dose escalation studies were excluded. Treatment arms with chemotherapy prior to (induction) and after (consolidation) concurrent chemoradiation were eligible.

Clinical variables available in all of the studies/arms were chosen for correlation studies. Treatment arms were divided into one of two groups by each variable. Two-sided univariate and multivariate multi-level mixed-effects logistic regression models were used with a significant *P*-value <0.05.

Results

Of the 792 candidate articles found by the initial PubMed search, 105 treatment arms were identified as eligible for the analysis. A total of 116 treatment arms and 7520 patients, including 11 arms found by additional search underwent further analysis.

Available variables for analysis were chemotherapy regimens (cisplatin vs. carboplatin, single vs. multi-agent, induction vs. no induction chemotherapy), radiation therapy (once-daily (QD) vs. twice-daily (BID), total dose >60Gy vs. ≤60Gy, split (scheduled interruption) + vs. -), year of enrolment (1998 onward vs. pre-1998), and study location (corresponding author’s location in Asian vs. non-Asian countries).

The majority of treatment arms had multi-agent regimens without induction chemotherapy, and QD radiation without split. Forty and 76 arms were reported from Asian and non-Asian countries, respectively. Among the Asian arms, 24 were reported in Japan, and others were reported in China, Korea,

Singapore, Thailand, and India. The non-Asian group included studies in the US, Canada, Europe, Turkey, Egypt, and Australia. Because of its publication based analysis, we were unable to obtain individual data to correlate with esophagitis for other clinical backgrounds including age, gender, ethnicity, stage IIIA versus IIIB, performance status, response to treatment, and survival time. However, we assume that a vast majority of patients enrolled in Asian countries had Asian ancestry.

Univariate analysis demonstrated that Asian/non-Asian ethnicity, multi-/single-agent therapy, BID/QD, dose, and split are all individually predictive of grade 3 or higher esophagitis (Table 1). Of note, treatment arms conducted in Asia had significantly lower incidence (170/2534 patients, 6.7%, odds ratio 0.289) than in other nations (1025/4986, 20.6%). In the multivariable model, Asian/non-Asian ethnicity, multi-/single-agent, and split are jointly significant predictors after adjusting for all possible factors (Table 2). Additional multivariable models for each covariate were fit with Asian/non-Asian and an interaction term. None of the interaction terms were statistically significant and Asian/non-Asian ethnicity remained statistically significant in every model (Table 3). This leads us to believe that the relationship between grade 3 or higher esophagitis and Asian/non-Asian ethnicity does not vary significantly by the various levels of the other covariates, and remains a significant predictor of grade 3 or higher esophagitis after adjusting for each covariate individually.

Discussion

Patients with unresectable stage III NSCLC are now treated with concurrent platinum-containing chemoradiotherapy.^{1,2} Recent studies with this approach yielded 15–20% five-year overall survival, and, therefore, the disease is considered potentially curable. Grade 3 or higher esophagitis is one of the most common toxicities that could interrupt treatment prematurely. Understanding and prediction of severe toxicities might provide better management for this disease setting.

Recent studies indicate that several factors related to radiation dose and field are associated with a high incidence of esophagitis. Palma *et al.* conducted a comprehensive meta-analysis with individual patient data.⁵ They found that esophageal volume radiating 60 Gray and more was the best predictor of severe esophagitis. However, they have not included ethnicity for candidate variables. The study included 1082 patients worldwide and only 65 patients from Asian institutions. The total number of Asian patients in this study was not reported.

The study the West Japan Lung Cancer Group (WJLCG) reported by Furuse *et al.* was one of the landmark trials for unresectable stage III NSCLC.⁷ Inconsistent with other studies, such as RTOG9410,¹⁰ the Japanese study using

Table 1 Univariate analysis at predictive factors for grade 3 or higher esophagitis

	Total <i>n</i>	G3-5 Esophagitis	Univariate		
			Odds ratio	95% CI	<i>P</i> -value
Asian	2534	170 (6.7%)	0.289	(0.200, 0.417)	<0.0001
Non-Asian	4986	1025 (20.6%)	1.000	–	–
Carboplatin	3133	524 (16.7%)	1.284	(0.861, 1.915)	0.2200
Cisplatin	4387	671 (15.3%)	1.000	–	–
Multi agent	6791	1127 (16.6%)	2.008	(1.055, 3.823)	0.0337
Single agent	729	68 (9.3%)	1.000	–	–
Induction	1320	265 (20.1%)	1.635	(0.977, 2.735)	0.0610
No induction	6200	930 (15.%)	1.000	–	–
BID	1543	366 (23.7%)	1.645	(1.021, 2.650)	0.0407
QD	5977	829 (13.9%)	1.000	–	–
>60G	4137	768 (18.6%)	1.615	(1.088, 2.397)	0.0173
≤ 60G	3383	427 (12.6%)	1.000	–	–
RT split +	564	22 (3.9%)	0.230	(0.095, 0.556)	0.0011
No split	6956	1173 (16.9%)	1.000	–	–
Before 1998	3225	571 (17.7%)	1.133	(0.759, 1.691)	0.5416
1998 and later	4295	624 (14.5%)	1.000	–	–

Frequency counts and percent are presented, as well as odds ratios, 95% confidence intervals for the odds ratios, and associated *P*-values. BID, twice-daily; QD, once daily.

mitomycin C, vindesine, and cisplatin (MVP) demonstrated that concurrent chemoradiation was superior to a sequential approach in overall survival. This study, however, reported only 3% grade 3 or higher esophagitis in contrast to 22% in the once-daily radiation arm of RTOG9410. The successor trials of WJLCG in Japan using an MVP regimen also showed only 6% of grade 3 or higher esophagitis.^{8,11} This meta-analysis showed that grade 3 or higher esophagitis was significantly less frequent in the studies/treatment arms conducted in Asian countries than in other nations, and multivariate

analysis demonstrated that Asian/non-Asian ethnicity remained significant after adjusting for all possible factors. We believe that the definition of grade 3 or higher esophagitis (i.e. inability for oral intake and necessity for parenteral administration) is not ambiguous, and, therefore, do not think under-reporting significantly affected the result.

One of the possible explanations for a different esophagitis rate by ethnicity is a difference in host genetic background. Recently, the MD Anderson group demonstrated that CT/TT genotypes of TGFβ1 rs1800469:C-509T were associated with

Table 2 Multivariate analysis at predictive factors for grade 3 or higher esophagitis

	Total <i>n</i>	G3-5 Esophagitis	Multivariate		
			Odds ratio	95% CI	<i>P</i> -value
Asian	2534	170 (6.7%)	0.315	(0.212, 0.470)	<0.0001
Non-Asian	4986	1025 (20.6%)	1.000	–	–
Carboplatin	3133	524 (16.7%)	0.811	(0.575, 1.144)	0.2332
Cisplatin	4387	671 (15.3%)	1.000	–	–
Multi agent	6791	1127 (16.6%)	1.906	(1.078, 3.370)	0.0264
Single agent	729	68 (9.3%)	1.000	–	–
Induction	1320	265 (20.1%)	1.255	(0.804, 1.959)	0.3169
No induction	6200	930 (15.%)	1.000	–	–
BID	1543	366 (23.7%)	1.138	(0.745, 1.740)	0.5497
QD	5977	829 (13.9%)	1.000	–	–
>60G	4137	768 (18.6%)	0.973	(0.685, 1.383)	0.8796
≤ 60G	3383	427 (12.6%)	1.000	–	–
RT split +	564	22 (3.9%)	0.353	(0.161, 0.773)	0.0093
No split	6956	1173 (16.9%)	1.000	–	–
Before 1998	3225	571 (17.7%)	1.089	(0.750, 1.582)	0.6552
1998 and later	4295	624 (14.5%)	1.000	–	–

The multivariable model contained all covariates. No model selection procedures were utilized. BID, twice-daily; CI, confidence interval; QD, once daily.

Table 3 Multivariable models for grade 3 or higher esophagitis

Model	Variable	Referent	Odds ratio	95% CI	P-value
1	Asian	Non-Asian	0.267	(0.167, 0.426)	<0.0001
	Carboplatin	Cisplatin	0.965	(0.473, 1.965)	0.9207
	Interaction				0.7817
2	Asian	Non-Asian	0.294	(0.148, 0.585)	0.0005
	Multi agent	Single agent	2.081	(1.192, 3.631)	0.0099
	Interaction				0.3380
3	Asian	Non-Asian	0.288	(0.195, 0.425)	<0.0001
	Induction	No induction	1.649	(0.411, 6.612)	0.4802
	Interaction				0.5836
4	Asian	Non-Asian	0.319	(0.215, 0.473)	<0.0001
	BID	QD	0.730	(0.227, 2.354)	0.5988
	Interaction				0.3666
5	Asian	Non-Asian	0.266	(0.158, 0.447)	<0.0001
	>60G	≤ 60G	1.415	(0.747, 2.680)	0.2874
	Interaction				0.4687
6	Asian	Non-Asian	0.305	(0.210, 0.441)	<0.0001
	RT split +	No split	0.424	(0.158, 1.143)	0.0899
	Interaction				0.4934
7	Asian	Non-Asian	0.361	(0.226, 0.577)	<0.0001
	Before 1998	1998 and later	0.608	(0.317, 1.165)	0.1334
	Interaction				0.1189

The models were adjusted for each covariate, Asian/non-Asian, and the interaction between each covariate and Asian/non-Asian. BID, twice-daily; CI, confidence interval; QD, once daily.

grade 3 radiation-induced esophagitis.¹² Allele frequency in different ethnic groups, however, has never been reported. Ethnic difference in polymorphic genotypes associated with grade 3 or higher esophagitis might be of great interest for future studies.

There are some limitations in this study. We assume that studies conducted in Asia enrolled mostly Asian population, and those in other nations included mostly non-Asian patients. This is most likely the case. We found that only 14 trials have reported the number of Asian patients, and that only one trial reported that Asians were more than 10% of total population. However, it would be intriguing to directly compare esophagitis across ethnic groups in prospective studies. Under-reporting toxicity in certain ethnic groups because of cultural reasons may exist and play a role in patient-reported toxicities, such as esophagitis. This study was also based on published studies in English literature, which might cause a degree of publication bias. Most importantly, we were unable to obtain individual patient information that might have provided a valuable outcome. This includes the technique used for radiation planning (i.e. 2D vs. 3D), and radiated esophageal volume.

Nevertheless, this study suggests that grade 3 or higher esophagitis during concurrent chemoradiation is infrequent in the Asian population. Future studies are needed to confirm this finding and must clarify mechanisms that can attribute to the ethnic difference in radiation toxicity.

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Disclosure

No authors report any conflict of interest.

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