Original Article
Antihistamines H1 use on survival outcomes in esophageal squamous cell carcinoma patients undergoing concurrent chemoradiotherapy

Chia-Lun Chang[1,2], Kuan-Chou Lin[3,4], Wan-Ming Chen[5,6], Ben-Chang Shia[5,6], Szu-Yuan Wu[5,6,7,8,9,10,11,12,13]

[1]Department of Hemato-Oncology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; [2]Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [3]Division of Oral and Maxillofacial Surgery, Department of Dentistry, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; [4]School of Dentistry, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan; [5]Graduate Institute of Business Administration, College of Management, Fu Jen Catholic University, Taipei, Taiwan; [6]Artificial Intelligence Development Center, Fu Jen Catholic University, Taipei, Taiwan; [7]Department of Food Nutrition and Health Biotechnology, College of Medical and Health Science, Asia University, Taichung, Taiwan; [8]Division of Radiation Oncology, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [9]Big Data Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [10]Department of Healthcare Administration, College of Medical and Health Science, Asia University, Taichung, Taiwan; [11]Cancer Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [12]Centers for Regional Anesthesia and Pain Medicine, Taipei Municipal Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; [13]Department of Management, College of Management, Fo Guang University, Yilan, Taiwan

Abstract: Esophageal squamous cell carcinoma (ESCC) is a leading cause of cancer-related mortality in Taiwan, with poor survival rates despite standard treatment with concurrent chemoradiotherapy (CCRT). Antihistamines H1 (AH1) may have anticancer effects by reducing allergic reactions, activating mitogen-activated protein kinases, and regulating the immune system. However, the impact of AH1 use during CCRT on survival outcomes in patients with ESCC remains uncertain. A propensity score-matched cohort study was conducted using data from the Taiwan Cancer Registry Database and National Health Insurance Research Database. The primary outcome measures were overall survival and ESCC-specific survival. We analyzed the effects of AH1 use during CCRT on these outcomes using multivariable Cox proportional hazards regression models. The current study involved 981 individuals diagnosed with ESCC who underwent standard CCRT. Out of these, 309 were placed in the non-AH1 group and 672 in the AH1 group. AH1 use during CCRT was found to be associated with improved overall survival (adjusted hazard ratio [HR], 0.52; 95% CI, 0.44-0.60; $P<0.0001$) and ESCC-specific survival (adjusted HR, 0.47; 95% CI, 0.39-0.56; $P<0.0001$) compared with nonuse. A dose-response relationship was also observed, with higher cumulative defined daily doses of AH1 associated with lower mortality. The optimal daily intensity dose for AH1 use was found to be 0.84 defined daily doses with the lowest mortality. Our study demonstrates that AH1 use during CCRT for ESCC is associated with improved overall survival and ESCC-specific survival.

Keywords: Esophageal squamous cell carcinoma, antihistamines H1, concurrent chemoradiotherapy, survival, dose-response relationship

Introduction

Esophageal cancer is a leading cause of cancer-related mortality in Taiwan, with over 95% of cases being diagnosed as esophageal squamous cell carcinoma (ESCC) [1-3]. This differs from Western countries, where esophageal adenocarcinoma is more prevalent [4, 5]. In Taiwan, the standard treatment for esophageal cancer is concurrent chemoradiotherapy (CCRT), administered in accordance with National Comprehensive Cancer Network (NCCN) guidelines and regimens recommended by the INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial [6, 7]. Despite this, the 5-year overall survival rate for ESCC patients

receiving CCRT in Taiwan remains below 20% [8]. This poor survival rate highlights the need for additional treatment options that can enhance the anticancer effects of CCRT [1]. Therefore, identifying safe and well-tolerated agents that can improve outcomes for these patients is of paramount importance.

Antihistamines H1 (AH1) may have effects against cancer by reducing allergic reactions, activating mitogen-activated protein kinases, inhibiting the combination of autophagosomes and lysosomes, promoting anti-inflammation, and regulating the immune system [9-20]. Studies have shown that concurrent use of AH1 targeting histamine receptor H1 (HRH1) improves survival outcomes in patients with melanoma or lung cancer [9]. Similar trends have also been observed in patients with breast or colon cancer, but the data did not reach statistical significance due to a small sample size [9]. Additionally, AH1 has been found to enhance T cell activation, which can influence the response to immunotherapy [9]. Follow-up experiments in mice have revealed that the binding of histamine to HRH1 receptors on the surface of tumor-associated macrophages suppresses T cell function, leading to tumor resistance to immunotherapy [9]. A large Swedish national observational cohort study found that AH1 use is associated with improved survival for various types of cancer such as gastric, colorectal, anal, pancreatic, lung, breast, prostate, kidney, and bladder cancer, melanoma, and Hodgkin lymphoma [21]. However, there have been no reports on the impact of AH1 use on survival during CCRT for ESCC patients.

Currently, there is a lack of research specifically examining the efficacy of AH1 use during CCRT in patients with ESCC. As a result, the potential impact of AH1 use on the survival of patients with ESCC receiving standard CCRT remains uncertain. To investigate this issue, we conducted a head-to-head propensity score matching (PSM) cohort study using a real-world database. The aim of this study was to estimate the effects of AH1 use during the CCRT period on overall survival and ESCC-specific survival in patients with ESCC receiving standard CCRT. Additionally, we evaluated the impact of cumulative doses, and daily intensities of AH1 use on the survival of ESCC patients receiving standard CCRT.

Patients and methods

Study cohort

This cohort study utilized patient data obtained from the Taiwan Cancer Registry Database (TCRD) linked with the National Health Insurance Research Database (NHIRD) to gather information on individuals diagnosed with ESCC between January 1, 2012 and December 31, 2018. The study began at the index date, which is the date standard CCRT treatment for ESCC began, and the follow-up period extended until December 31, 2020. The TCRD, maintained by the Collaboration Center of Health Information Application, contains detailed information on cancer patients including clinical stage, treatment methods, chemotherapy regimens, pathology, radiation treatment and protocols [1]. The study's protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Inclusion and exclusion criteria

To be eligible for the study, patients had to meet certain criteria. They had to be 18 years or older, have a diagnosis of ESCC, be in clinical stage I-IVA without distant metastasis as per the American Joint Committee on Cancer (AJCC) 8th edition, and have an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients who had a previous history of cancer, distant metastasis, missing sex data, age under 18, unclear staging, unknown cigarette smoking or alcohol use, or non-squamous cell carcinoma histology were excluded. Furthermore, patients who had undergone esophagostomy followed by CCRT were also excluded to ensure that the results related to the survival effects of AH1 use for ESCC after standard CCRT were not influenced.

The standard CCRT in our study for ESCC is a combination of platinum-based chemotherapy, such as cisplatin or carboplatin, and intensity-modulated radiation therapy with a total dose of 5040 cGy in 28 fractions [7]. The Charlson comorbidity index (CCI) [22-24] was used to evaluate the presence of comorbidities within 6 months prior to the index date and were recorded and classified using codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or

International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) from the first inpatient visit or after more than two outpatient visits.

AH1 use after ESCC receiving CCRT

AH1 prescription was determined using a previously reported protocol [12], and included any AH1 taken for asthma, allergic rhinitis, medication allergies, environmental allergies, or viral infection symptoms. AH1 is covered by Taiwan's National Health Insurance. We gathered information on the type of drug, dosage, method of administration, prescription date, and total number of pills dispensed by the pharmacy. As patients may have taken AH1 at different times during the study period and may have had varying drug use patterns, we treated AH use as a time-varying factor in our Cox model. The cumulative dose was calculated by multiplying the number of pills dispensed by the prescribed dose and then dividing by the number of days for which the medication was prescribed. In this paper, AH dosage is presented in defined daily doses (DDDs), as defined by the World Health Organization, which is the average maintenance dose per day for a drug used for its main indication in adults.

In this study, patients who received definitive chemoradiotherapy for ESCC and took a minimum of 28 cumulative defined daily doses (cDDDs) of AH1 were classified as AH1 users, while those who did not take any AH1 during the follow-up period were considered non-users. The use of AH1 was allowed in the case group before the index date, but not in the control group. After the completion of chemoradiotherapy, the AH1 user group was permitted to continue using AH1, and we analyzed the association between cDDD and the hazard ratio of mortality. To evaluate the dose-response effects of AH1 use on oncologic outcomes in ESCC patients receiving chemoradiotherapy, we also divided the patients into subgroups based on different cDDD of AH1 use. The case and control groups underwent the same protocol of CCRT. All analyses were adjusted for covariates, as listed in **Table 1**.

Furthermore, we evaluated the daily intensity of AH1 use by dividing the average dose of AH1 by the total days of the prescription. We determined the association between hazard ratios of all-cause mortality, ESCC-specific mortality, and the daily intensity of AH1 (DDDs) to identify the ideal daily intensity of AH1 use for reducing mortality in ESCC patients receiving definitive CCRT.

Propensity score matching

To consider any potential confounding factors when comparing the survival outcomes between the AH1 user and non-user groups, all patients were matched using PSM based on variables including age, sex, AJCC clinical stage, income level, urbanization, cigarette smoking habits, alcohol consumption habits, and CCI scores (as listed in **Table 1**). The AH1 user and non-user groups were matched in a 1:1 ratio using the greedy matching method with a caliper of 0.2 [25]. Continuous variables are presented as means ± standard deviations where appropriate.

Outcome measures

The primary focus of the study was to compare the all-cause mortality rate among ESCC patients who did and did not use AH1 during standard definitive chemoradiotherapy. The secondary outcome was to compare the rate of ESCC-specific mortality.

Statistical analysis

We studied the correlation between AH1 use during standard definitive CCRT and survival outcomes in patients with ESCC. To account for differences in baseline characteristics between AH1 and non-AH1 users, we used time-varying Cox regression models, taking into account factors such as age, sex, AJCC clinical stage, income level, urbanization, cigarette smoking habits, alcohol consumption habits, and CCI scores. We employed a time-dependent Cox hazard model to compare mortality rates between those who did and did not receive AH1, while controlling for these confounding factors. Data on AH1 prescriptions were collected every 3 months to determine a user's status, and was considered as a time-dependent variable. Person-times of users before their first prescription and during the 3-month period without AH1 prescription were classified as unexposed follow-up times to avoid bias. Additionally, we estimated the risk of mortality by individual AH1. Mortality rates

Table 1. Comparison of characteristics between patients with and without AH1 use following standard definitive CCRT for ESCC

	Before PSM					After PSM				
	AH1 nonusers		AH1 users			AH1 nonusers		AH1 users		
	N=309		N=672		P-value	N=309		N=309		P-value
	N	%	N	%		N	%	N	%	
Age (mean ± SD), years-old	57.10 ± 11.57		61.48 ± 13.26		<0.0001	57.10 ± 11.57		57.35 ± 12.15		0.7967
Age, median (IQR, Q1, Q3)	55.00 (49.00, 64.00)		60.00 (51.00, 72.00)		<0.0001	55.00 (49.00, 64.00)		57.00 (48.00, 65.00)		0.6047
Age group, years					<0.0001	0.9590				0.7854
≤50	93	30.10%	153	22.77%		93	30.10%	98	31.72%	
51-60	111	35.92%	198	29.46%		111	35.92%	105	33.98%	
61-70	61	19.74%	137	20.39%		61	19.74%	62	20.06%	
≥70	44	14.24%	184	27.38%		44	14.24%	44	14.24%	
Sex					0.0094					0.3266
Female	23	7.44%	88	13.10%		23	7.44%	17	5.50%	
Male	286	92.56%	584	86.90%		286	92.56%	292	94.50%	
Income levels					0.3600					0.8107
Low income	5	1.62%	10	1.49%		5	1.62%	6	1.94%	
Financially dependent	60	19.42%	170	25.30%		124	40.13%	111	35.92%	
≤20,000	124	40.13%	257	38.24%		79	25.57%	85	27.51%	
20,001-30,000	79	25.57%	166	24.70%		34	11.00%	38	12.30%	
30,001-45,000	34	11.00%	54	8.04%		7	2.27%	4	1.29%	
>45,000	7	2.27%	15	2.23%		60	19.42%	65	21.04%	
Urbanization					0.3293					0.3911
Rural	96	31.07%	230	34.23%		96	31.07%	106	34.30%	
Urban	213	68.93%	442	65.77%		213	68.93%	203	65.70%	
AJCC clinical stage					0.0237					0.9548
I	12	3.88%	54	8.04%		12	3.88%	14	4.53%	
II	25	8.09%	69	10.27%		25	8.09%	29	9.39%	
IIIA	90	29.13%	168	25.00%		90	29.13%	84	27.18%	
IIIB	134	43.37%	252	37.50%		134	43.37%	135	43.69%	
IVA	48	15.53%	129	19.20%		48	15.53%	47	15.21%	
Current Cigarette Smoking	41	13.27%	200	29.76%	<0.0001	41	13.27%	42	13.59%	0.9061
Current Alcohol consumption	57	18.45%	148	22.02%	0.2005	57	18.45%	55	17.80%	0.8346

Antihistamines in ESCC CCRT

CCI Scores										
Mean (SD)		2.87 ± 3.09		2.47 ± 3.01	0.0551		2.87 ± 3.09		2.45 ± 2.92	0.0779
Median (IQR, Q1-Q3)		2.00 (0.00, 6.00)		1.00 (0.00, 4.50)	0.1409		2.00 (0.00, 6.00)		1.00 (0.00, 6.00)	0.1380
CCI Scores					0.5935					0.3703
0	125	40.45%	284	42.26%		125	40.45%	136	44.01%	
≥1	184	59.55%	388	57.74%		184	59.55%	173	55.99%	
CCI scores										
Congestive Heart Failure	10	3.2%	37	5.5%	0.1221	10	3.2%	13	4.2%	0.5238
Dementia	4	1.3%	17	2.5%	0.2144	4	1.3%	6	1.9%	0.5237
Chronic Pulmonary Disease	45	14.6%	149	22.2%	0.0054	45	14.6%	42	13.6%	0.7286
Rheumatic Disease	0	0.0%	1	0.2%	0.4975	0	0.0%	0	0.0%	0.9999
Liver Disease	72	23.3%	168	25.0%	0.5653	72	23.3%	82	26.5%	0.3524
Diabetes with complications	9	2.9%	28	4.2%	0.3382	9	2.9%	7	2.3%	0.6124
Hemiplegia and Paraplegia	0	0.0%	0	0.0%	0.9999	0	0.0%	0	0.0%	0.9999
Renal Disease	4	1.3%	38	5.7%	0.0017	4	1.3%	4	1.3%	0.9999
Acquired Immunodeficiency Syndrome	0	0.0%	0	0.0%	0.9999	0	0.0%	0	0.0%	0.9999
cDDD of AH1										
Non use	309	100.0%	0	0.0%		309	100.0%	0	0.0%	
0-one third	0	0.0%	223	33.2%		0	0.0%	109	35.3%	
One third-two third	0	0.0%	221	32.9%		0	0.0%	100	32.4%	
> two thirds	0	0.0%	228	33.9%		0	0.0%	100	32.4%	
Oncologic Outcomes										
All-Cause Death	266	86.08%	495	73.66%	<0.0001	266	86.08%	230	74.43%	0.0003
ESCC death	241	77.99%	373	55.51%	<0.0001	241	77.99%	180	58.25%	<0.0001

Abbreviations: ESCC, Esophageal squamous cell carcinoma; CCRT, Concurrent chemoradiotherapy; AJCC, American Joint Committee on Cancer; PSM, Propensity score matching; CCI, Charlson comorbidity index; cDDDs, cumulative defined daily doses; DDD, defined daily doses; SD, standard deviation; IQR, interquartile range; AH1, antihistamine H1.

were estimated using the Kaplan-Meier method, and differences between AH1 users and non-users were determined using the stratified log-rank test to compare mortality curves. Mortality rates were also estimated using the Kaplan-Meier method, and differences between AH1 users at different dosage of cDDD and non-users were determined using the stratified log-rank test. We also estimated the cDDD, DDD, and hazard ratio of ESCC-specific mortality in patients with and without AH1 use following standard definitive CCRT. All statistical analyses were conducted using SAS version 9.4.

Results

The current study involved 981 individuals diagnosed with ESCC who underwent standard CCRT. Out of these, 309 were placed in the non-AH1 group and 672 in the AH1 group. According to **Table 1**, the AH1 group had a higher proportion of older individuals, more females, more advanced stage IVA disease, more smokers, and more patients with chronic pulmonary and renal diseases, when compared to the non-AH1 group. After adjusting for potential confounding factors using propensity score matching, 618 patients were included in the final analysis, with equal numbers in each group. The median follow-up period was 2.92 years. The all-cause mortality rate was higher in the non-AH1 group (86.08%) compared to the AH1 group (74.43%) (P=0.0003). Similarly, the ESCC-specific mortality rate was also higher in the non-AH1 group (77.99%) compared to the AH1 group (58.25%) (P<0.0001) (**Table 1**).

The use of AH1 after beginning standard CCRT was found to have a significant impact on all-cause mortality in patients with ESCC. An analysis of the data revealed that the adjusted hazard ratio (aHR) for all-cause mortality in the group of patients who used AH1 was 0.52 (with a 95% confidence interval [CI] of 0.44-0.60) when compared to the group of patients who did not use AH1 (**Table 2**). Furthermore, several other factors were also identified as independent poor prognostic factors for all-cause mortality, including age above 70, advanced AJCC stage (IIIA, IIIB, IVA), and a CCI score of 1 or higher. The aHR of all-cause mortality for these factors were 1.43, 2.53, 2.78, 3.57 and 1.53 respectively.

The use of AH1 following initiation of CCRT was found to have a significant and independent impact on ESCC-specific mortality among patients with ESCC receiving standard CCRT. An analysis of aHR revealed that the use of AH1 was associated with a 0.47 (95% CI: 0.39-0.56, P<0.0001) reduction in ESCC-specific mortality in comparison to non-users of AH1 (**Table 3**). Additionally, advanced age (greater than 70 years), stages IIIA, IIIB, IVA, and CCI score greater than or equal to 1 were identified as independent poor prognostic factors for ESCC-specific mortality. Specifically, the aHR for ESCC-specific mortality was 1.30 (95% CI: 1.01-1.69), 3.01 (95% CI: 1.68-5.41), 3.46 (95% CI: 1.99-6.01), 4.18 (95% CI: 2.39-7.32), and 1.50 (95% CI: 1.25-1.79) for individuals over 70 years of age, stages IIIA, IIIB, IVA, and CCI score greater than or equal to 1, respectively, in comparison to individuals between 18-50 years of age, stage I and CCI score of 0.

The present study investigated the correlation between the cDDD of AH1 use and the HRs of all-cause mortality and ESCC-specific mortality in patients receiving standard CCRT for ESCC (**Table 4**). The study population was divided into four groups based on cDDD of AH1 use: 0, 1-one third, one third-two third, and greater than two thirds cDDDs. Time-varying Cox multivariate analysis was performed to evaluate the HRs of all-cause mortality and ESCC-specific mortality. The results indicated that the HRs of all-cause mortality for 1-one third, one third-two third, and greater than two thirds cDDDs of AH1 use were 0.75 (0.62-0.92), 0.45 (0.37-0.55), and 0.38 (0.30-0.47) respectively, compared to the 0 cDDD group. The trend was statistically significant (P<0.0001) with a dose-response relationship for the reduction of all-cause mortality. In addition, the HRs of ESCC-specific mortality for 1-one third, one third-two third, and greater than two thirds cDDDs of AH1 use were 0.72 (0.58-0.89), 0.40 (0.32-0.50), and 0.31 (0.24-0.40) respectively, compared to the 0 cDDD group. The trend was also statistically significant (P<0.0001) with a dose-response relationship for the reduction of ESCC-specific mortality.

The 2-year overall survival rates for patients in the group receiving AH1 and those in the group not receiving AH1 were found to be significantly

Table 2. Cox proportional hazards regression model of all-cause mortality in PSM patients with and without AH1 use following standard definitive CCRT for esophageal squamous cell carcinoma

	All-Cause Death				
	Crude HR	(95% CI)	P-value	aHR*	(95% CI)	P-value
AH1 (ref. no AH1 use)						
AH1 use	0.53	(0.46, 0.62)	<0.0001	0.52	(0.44, 0.60)	<0.0001
Age group, years-old (ref. 18-50)						
51-60	1.06	(0.87, 1.28)	0.5584	1.03	(0.84, 1.25)	0.7803
61-70	1.08	(0.69, 1.17)	0.1834	1.09	(0.71, 1.14)	0.3832
>70	1.30	(1.07, 1.60)	0.0101	1.43	(1.13, 1.81)	0.0025
Sex (ref. Female)						
Male	1.32	(0.72, 2.43)	0.3720	1.01	(0.52, 1.93)	0.9892
Income levels (ref. Low income)						
Financially dependent	0.86	(0.27, 2.81)	0.8076	0.60	(0.17, 2.08)	0.4222
≤20,000	0.97	(0.3, 3.09)	0.9594	0.52	(0.16, 1.69)	0.2745
20,001-30,000	0.91	(0.28, 2.91)	0.8700	0.63	(0.19, 2.07)	0.4470
30,001-45,000	0.89	(0.27, 2.97)	0.8481	0.51	(0.15, 1.78)	0.2935
>45,000	0.86	(0.19, 3.83)	0.8373	0.49	(0.11, 2.27)	0.3601
Urbanization (ref. rural)						
Urban	1.14	(0.83, 1.56)	0.4089	1.15	(0.82, 1.6)	0.4264
AJCC clinical stage (ref. Stage I)						
II	1.42	(0.87, 2.3)	0.1571	1.43	(0.88, 2.31)	0.1486
IIIA	2.43	(1.57, 3.74)	<0.0001	2.53	(1.64, 3.90)	<0.0001
IIIB	2.69	(1.70, 4.24)	<0.0001	2.78	(1.76, 4.39)	<0.0001
IVA	3.48	(2.24, 5.4)	<0.0001	3.57	(2.30, 5.53)	<0.0001
Current Cigarette Smoking (ref. never smoking)	1.08	(0.9, 1.3)	0.4251	1.05	(0.87, 1.26)	0.6353
Current Alcohol consumption (ref. never alcohol consumption)	1.18	(0.78, 1.31)	0.2857	1.17	(0.66, 1.21)	0.2916
CCI scores (ref. CCI=0)						
CCI≥1	1.77	(1.52, 2.05)	<0.0001	1.53	(1.30, 1.80)	<0.0001

Abbreviations: ESCC, Esophageal squamous cell carcinoma; CCRT, Concurrent chemoradiotherapy; PSM, Propensity score matching; CI, Confidence interval; aHR, Adjusted hazard ratio; HR, hazard ratio; CCI, Charlson comorbidity index; cDDDs, cumulative defined daily doses; DDD, defined daily doses; ref., reference group; AH1, antihistamine H1. *All covariates presented in this table were adjusted.

different, with rates of 46.26% and 19.84%, respectively (P<0.0001; **Figure 1A**). Similarly, the 2-year ESCC-specific survival rates for patients in the group receiving AH1 and those in the group not receiving AH1 were found to be significantly different, with rates of 51.14% and 21.74%, respectively (P<0.0001; **Figure 1B**). These findings suggest that the use of AH1 after the initiation of CCRT for ESCC patients may be associated with an improvement in overall survival and ESCC-specific survival. The Kaplan-Meier Curves of overall survival and ESCC-specific survival in patients with different cumulative defined daily doses of AH1 following standard definitive CCRT also demonstrated a dose-response relationship (P<0.0001; **Figure 2**). It was further observed that the cDDD, and hazard ratio of ESCC-specific mortality were inversely proportional to the cDDD (Supplementary Figure 1). Addition-

ally, the optimal daily intensity of AH use was found to be 0.84 DDD, with the lowest HR of ESCC-specific mortality (Supplementary Figure 2).

Discussion

The utilization of AH1 in various types of cancer has been demonstrated to enhance survival outcomes via various mechanisms, including reduction of allergic reactions, activation of mitogen-activated protein kinases, inhibition of autophagosomes and lysosomes formation, promotion of anti-inflammatory responses and regulation of the immune system. These mechanisms have been supported by a plethora of preclinical and clinical studies providing a strong rationale for the use of AH1 in cancer treatment [9-20]. Despite their safety as traditional medications, further research is needed

Table 3. Cox proportional hazards regression model of esophageal squamous cell carcinoma-specific mortality in PSM patients with and without AH1 use following standard definitive CCRT

	All-Cause Death				
	Crude HR (95% CI)	P-value	aHR* (95% CI)	P-value
AH1 (ref. no AH1 use)					
AH1 use	0.46 (0.39, 0.55)	<0.0001	0.47 (0.39, 0.56)	<0.0001
Age group, years-old (ref. 18-50)					
51-60	0.99 (0.8, 1.22)	0.9260	0.97 (0.78, 1.2)	0.7432
61-70	0.84 (0.66, 1.07)	0.1545	0.92 (0.71, 1.19)	0.5186
>70	1.08 (0.86, 1.35)	0.5214	1.30 (1.01, 1.69)	0.0476
Sex (ref. Female)					
Male	1.15 (0.91, 1.65)	0.1843	1.08 (0.76, 1.63)	0.3096
Income levels (ref. Low income)					
Financially dependent	0.70 (0.37, 1.32)	0.2664	0.76 (0.39, 1.47)	0.4157
≤20,000	0.78 (0.41, 1.46)	0.4290	0.83 (0.44, 1.57)	0.5666
20,001-30,000	0.73 (0.38, 1.38)	0.3276	0.79 (0.41, 1.51)	0.4751
30,001-45,000	0.64 (0.32, 1.26)	0.1985	0.67 (0.33, 1.32)	0.2440
>45,000	0.48 (0.2, 1.12)	0.0907	0.51 (0.21, 1.2)	0.1229
Urbanization (ref. rural)					
Urban	1.00 (0.84, 1.18)	0.9890	0.99 (0.83, 1.17)	0.8787
AJCC clinical stage (ref. Stage I)					
II	2.73 (1.52, 4.91)	0.0008	1.77 (0.97, 3.23)	0.0638
IIIA	3.79 (2.16, 6.67)	<0.0001	3.01 (1.68, 5.41)	0.0002
IIIB	4.98 (2.91, 8.54)	<0.0001	3.46 (1.99, 6.01)	<0.0001
IVA	5.83 (3.38, 10.06)	<0.0001	4.18 (2.39, 7.32)	<0.0001
Current Cigarette Smoking (ref. never smoking)	1.13 (0.94, 1.36)	0.1941	0.95 (0.77, 1.17)	0.6335
Current Alcohol consumption (ref. never alcohol consumption)	1.03 (0.83, 1.27)	0.7889	1.02 (0.80, 1.22)	0.9135
CCI scores (ref. CCI=0)					
CCI≥1	1.73 (1.47, 2.04)	<0.0001	1.50 (1.25, 1.79)	<0.0001

Abbreviations: ESCC, Esophageal squamous cell carcinoma; CCRT, Concurrent chemoradiotherapy; PSM, Propensity score matching; CI, Confidence interval; aHR, Adjusted hazard ratio; HR, hazard ratio; CCI, Charlson comorbidity index; cDDDs, cumulative defined daily doses; DDD, defined daily doses; ref., reference group; AH1, antihistamine H1. *All covariates presented in **Table 2** were adjusted.

Table 4. cDDD of AH1 use and HRs of all-cause mortality and ESCC-specific mortality

	Crude HR	95% CI	P-value	aHR*	95% CI	P-value	P for trend
	All-Cause Mortality						
cDDD of AH1 (ref. no AH1 use)							<0.0001
1-one third	0.73	(0.60, 0.88)	0.0011	0.75	(0.62, 0.92)	0.0044	
One third-two third	0.49	(0.40, 0.60)	<0.0001	0.45	(0.37, 0.55)	<0.0001	
> two thirds	0.42	(0.35, 0.52)	<0.0001	0.38	(0.30, 0.47)	<0.0001	
	ESCC-Specific Mortality						
cDDD of AH1 (ref. no AH1 use)							<0.0001
1-one third	0.69	(0.56, 0.85)	0.0004	0.72	(0.58, 0.89)	0.0019	
One third-two third	0.42	(0.34, 0.52)	<0.0001	0.40	(0.32, 0.50)	<0.0001	
> two thirds	0.33	(0.26, 0.42)	<0.0001	0.31	(0.24, 0.40)	<0.0001	

Abbreviations: ESCC, Esophageal squamous cell carcinoma; CCI, Confidence interval; aHR, Adjusted hazard ratio; HR, hazard ratio; CCI, Charlson comorbidity index; cDDDs, cumulative defined daily doses; ref., reference group; AH1, antihistamine H1. *All covariates presented in **Table 2** were adjusted.

to determine if AHs can increase overall survival and ESCC-specific survival in ESCC patients.

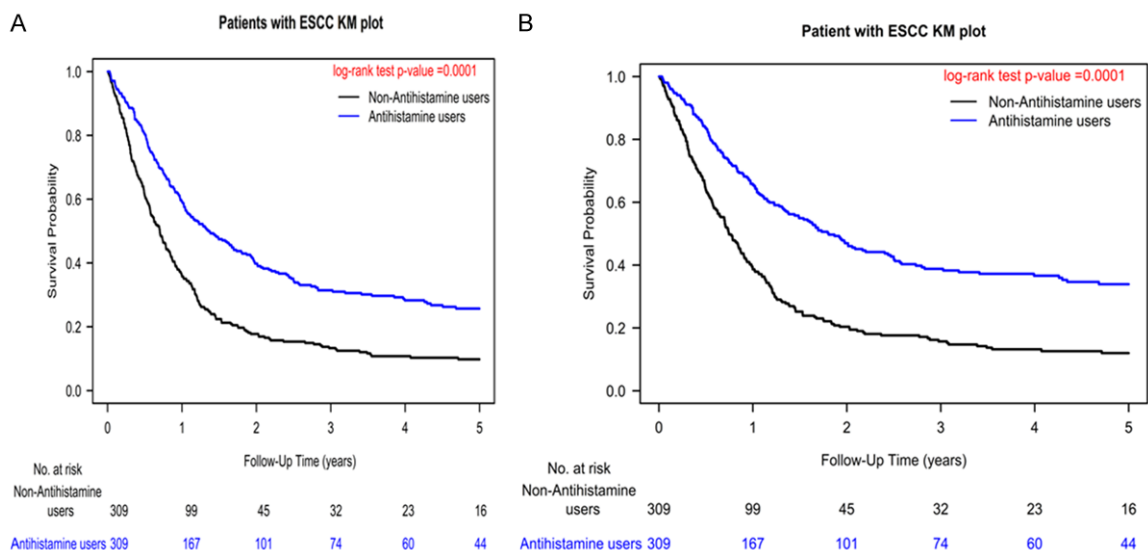Our results provide the first evidence that AH1 use during CCRT for ESCC patients can reduce

Figure 1. Kaplan-Meier analysis of overall survival curves and ESCC-specific survival curve in PSM patients with and without AH1 Use following standard definitive CCRT. A. Overall Survival curves. B. ESCC-specific Survival curve.
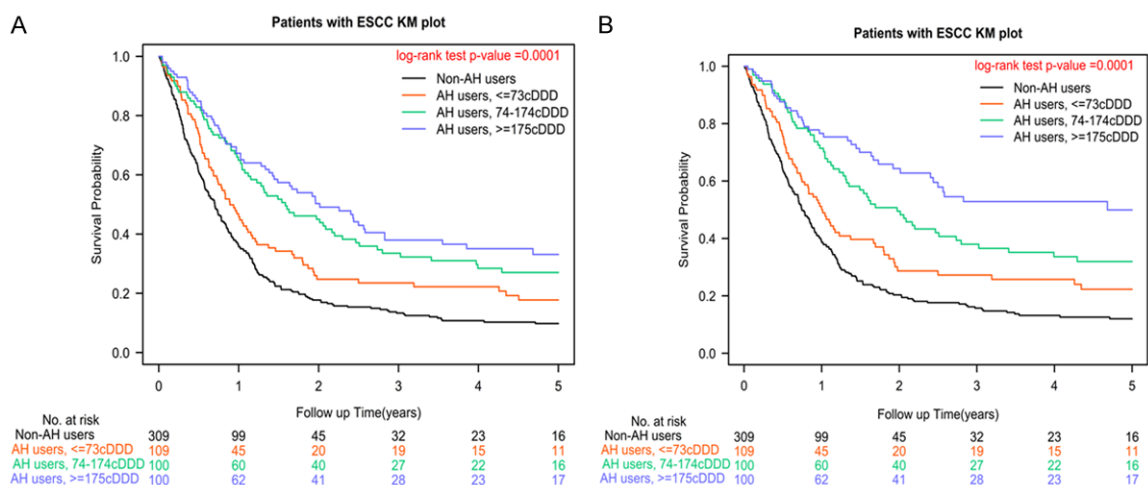

Figure 2. Kaplan-Meier curves of overall survival curves and ESCC-specific survival curves in patients with different cDDD of AH1 following standard definitive CCRT. A. Overall-survival. B. ESCC-specific Survival curve.

all-cause and ESCC-specific mortality with a dose-response relationship. Additionally, higher cDDDs of AH use were associated with lower mortality, and our study also determined the optimal daily intensity of AH1 use (0.84 DDD) for the lowest ESCC-specific mortality.

In the realm of ESCC treatment, the potential anti-cancer effects of AH1 have emerged as a topic of considerable interest [12, 15, 21, 26-32]. AH1, primarily known for its anti-allergic properties, may offer a multifaceted approach to improve oncologic outcomes in ESCC pa-

tients undergoing CCRT [9-20]. This class of antihistamines demonstrates promise through its mechanisms that encompass anti-allergic, anti-inflammatory, and immune-modulating effects [12, 15, 21, 26-32]. By mitigating allergic reactions, AH1 can enable patients to better tolerate the rigors of chemotherapy and radiation therapy, ensuring continuous, uninterrupted treatment. Additionally, AH1's anti-inflammatory attributes create a less conducive environment for tumor growth [12, 15, 21, 26-32], addressing the chronic inflammation often associated with ESCC. These antihista-

mines also hold potential in modulating the immune system, strengthening the body's ability to recognize and combat cancer cells [33]. Moreover, by inhibiting autophagy and activating mitogen-activated protein kinases (MAPK) [34-36], AH1 may sensitize ESCC cells to treatment-induced cytotoxicity and suppress their growth [37]. Their role in promoting anti-inflammatory responses further underscores the potential of AH1 in reducing the adverse impact of inflammation on cancer progression [33]. While these mechanisms are supported by existing research, further investigations are needed to elucidate their precise roles in the context of ESCC and CCRT [33-37]. The combined effects of AH1 on allergies, inflammation, and immune responses represent a promising avenue for enhancing the therapeutic outcomes of ESCC patients. Ongoing studies in this domain aim to provide comprehensive insights into the mechanisms and clinical benefits of AH1 in the treatment of ESCC within the context of CCRT.

The prognosis for patients with ESCC undergoing CCRT in Taiwan or in the world remains poor [8]. While the use of neoadjuvant CCRT followed by thoracic surgery has been shown to improve survival outcomes [1], not all patients are able to tolerate this approach, and some studies have found no significant survival benefits from trimodality therapy compared to CCRT alone [38]. Furthermore, the impact of dose escalation on survival outcomes for ESCC patients receiving CCRT is still a subject of debate [39]. Thus, the identification of safe and long-term medications that can enhance survival outcomes for patients with poor prognoses from ESCC receiving definitive CCRT is crucial. Our study is the first to demonstrate that the use of AH1 during CCRT for ESCC is associated with improved overall survival and ESCC-specific survival.

In **Tables 2** and **3**, a Cox proportional hazard model was used to identify independent poor prognostic factors for all-cause mortality and ESCC-specific mortality in patients with ESCC receiving standard CCRT. The results revealed that advanced age (greater than 70 years), stages IIIA, IIIB, IVA, and CCI score greater than or equal to 1 were identified as independent poor prognostic factors. These findings are consistent with previous researches [3] and have

been adjusted for potential confounding variables. These independent poor prognostic factors should be taken into consideration by physicians and patients when assessing the prognosis of standard CCRT for ESCC patients. Additionally, the study suggests that the addition of AH1 to standard CCRT may be associated with improved overall survival and ESCC-specific survival. Furthermore, the results indicate that an optimal daily dose of AH1 of 0.84 DDD, and higher cumulative dose (cDDD) after starting CCRT may be beneficial for survival outcomes in ESCC patients with higher poor prognostic factors (Supplementary Figures 1 and 2).

The relationship between dosage of AH1 and its effects on patients with ESCC receiving CCRT has not been previously investigated. This study is the first to examine the dose-response relationship of AH1 use in patients with ESCC receiving CCRT. The study evaluated the relationship between AH1 use, in terms of cumulative dose (cDDD) and daily intensity (DDD), and ESCC-specific mortality. A literature review revealed that no previous studies have investigated the relationship between cDDD, DDD, and mortality in patients with ESCC receiving CCRT. The study results demonstrated that higher cDDD of AH1 use after starting CCRT (**Figure 2** and Supplementary Figure 1), and an optimal daily intensity of 0.84 DDD were associated with the lowest ESCC-specific mortality (Supplementary Figure 2). These findings suggest that a sufficient cumulative dosage and optimal daily intensity of AH1 may be necessary for patients with ESCC receiving CCRT to enhance its anticancer effects in conjunction with CCRT.

The findings from this study illuminate the critical importance of determining the optimal daily dosage of AH1, which was established as 0.84 DDD. This revelation provides valuable insights into the potential effectiveness of AH1 in the context of ESCC patients undergoing CCRT. Notably, our data demonstrated a clear association between higher cumulative DDD of AH1 usage and a lower ESCC-specific mortality rate, particularly when maintaining the optimal daily intensity at 0.84 DDD. These results underscore the potential necessity of achieving a sufficient cumulative dosage and adhering to the optimal daily intensity of AH1 to maximize

its anticancer effects when used alongside CCRT. While these findings are promising, it's important to acknowledge the need for further randomized controlled trials to substantiate the optimal daily dosage of AH1 for ESCC patients undergoing CCRT.

The present study has several strengths. Firstly, it is the first to investigate the relationship between cumulative and daily intensity dosage of AH1 and the outcomes of patients with ESCC receiving standard CCRT. Secondly, the study utilized a consistent treatment regimen for ESCC, rather than a mixture of adenocarcinoma and squamous cell carcinoma, and ensured that the use of AH1 was concurrent with chemotherapy and radiotherapy. Thirdly, modern radiotherapy techniques, specifically intensity modulated radiation therapy, were used consistently throughout the study. Lastly, the study employed a propensity score matching cohort design, making it the first of its kind to examine the impact of AH1 use on survival outcomes in patients with ESCC receiving standard CCRT.

This study had several limitations that should be acknowledged. Firstly, it was not able to determine the toxicity of AH1 use, which could have influenced AH1-related side effects or other underlying factors that could have biased the estimates. The study attempted to control for potential confounding factors by matching comorbidities and clinical stages according to the AJCC criteria and selecting patients with similar physical activity levels as measured by Eastern Cooperative Oncology Group performance statuses. Secondly, the study population consisted solely of Asian patients with ESCC receiving CCRT, thus the results may not be generalizable to other ethnic groups. Thirdly, diagnoses of comorbid conditions were based on International Classification of Diseases 9th and 10th revisions codes (ICD-9-CM and ICD-10-CM), which may not be entirely accurate. However, the Taiwan Cancer Registry Administration takes steps to verify the accuracy of diagnoses through chart reviews and patient interviews, and hospitals found to have discrepancies or have engaged in malpractice may face penalties. Fourthly, our study did not identify substantial differences in treatment outcomes associated with various categories of AH1. This observation is primarily attributed to the fact that different categories of AH1 primarily target histamine H1 receptors, with no

existing evidence indicating significant disparities in their effects on ESCC patients. In clinical practice, patients may frequently utilize multiple categories of AH1, complicating the determination of the specific category that might be most effective for ESCC patients. Lastly, unknown selection bias may have existed in the use of AH1 or non-AH1 use. Therefore, a large-scale randomized trial is needed to compare carefully selected patients undergoing suitable treatments in order to provide more definitive conclusions about the effectiveness of AH1 use in treating patients with ESCC receiving standard CCRT.

Conclusion

Our study results suggest that the incorporation of AH1 during the course of CCRT may enhance overall survival and ESCC-specific survival among patients receiving definitive CCRT for ESCC. Furthermore, our study revealed that a higher cumulative dose (cDDD) of AH1 use was associated with a decrease in all-cause mortality and ESCC-specific mortality. An optimal daily intensity of 0.84 defined daily dose (DDD) of AH1 use was identified as having the lowest ESCC-specific mortality. These findings provide evidence that the use of AH1 during CCRT may enhance outcomes for patients with ESCC and warrant further investigation to fully comprehend the underlying mechanisms of this association.

Acknowledgements

Disclosure of conflict of interest

None.

Abbreviations

AH1, antihistamines H1; HRH1, histamine receptor H1; ESCC, Esophageal squamous cell carcinoma; CCRT, Concurrent chemoradiotherapy; AJCC, American Joint Committee on Cancer; PSM, Propensity score matching; CI, Confidence interval; aHR, Adjusted hazard ratio; NCCN, National Comprehensive Cancer Network; TCRD, Taiwan Cancer Registry Database; CCI, Charlson comorbidity index;

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; HR, hazard ratio; NHIRD, National Health Insurance Research Database; ATC, Anatomical Therapeutic Chemical; cDDDs, cumulative defined daily doses; DDD, defined daily doses.

Address correspondence to: Dr. Szu-Yuan Wu, Division of Radiation Oncology, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, No. 83, Nanchang Street, Luodong Township, Yilan 265, Taiwan. E-mail: szuyuanwu5399@gmail.com

References

[1] Lin WC, Ding YF, Hsu HL, Chang JH, Yuan KS, Wu ATH, Chow JM, Chang CL, Chen SU and Wu SY. Value and application of trimodality therapy or definitive concurrent chemoradiotherapy in thoracic esophageal squamous cell carcinoma. Cancer 2017; 123: 3904-3915.

[2] Yen YC, Chang JH, Lin WC, Chiou JF, Chang YC, Chang CL, Hsu HL, Chow JM, Yuan KS, Wu ATH and Wu SY. Effectiveness of esophagectomy in patients with thoracic esophageal squamous cell carcinoma receiving definitive radiotherapy or concurrent chemoradiotherapy through intensity-modulated radiation therapy techniques. Cancer 2017; 123: 2043-2053.

[3] Chang CL, Tsai HC, Lin WC, Chang JH, Hsu HL, Chow JM, Yuan KS, Wu ATH and Wu SY. Dose escalation intensity-modulated radiotherapy-based concurrent chemoradiotherapy is effective for advanced-stage thoracic esophageal squamous cell carcinoma. Radiother Oncol 2017; 125: 73-79.

[4] Pennathur A, Gibson MK, Jobe BA and Luketich JD. Oesophageal carcinoma. Lancet 2013; 381: 400-412.

[5] Domper Arnal MJ, Ferrandez Arenas A and Lanas Arbeloa A. Esophageal cancer: risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol 2015; 21: 7933-7943.

[6] Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA and Kelsen DP. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002; 20: 1167-1174.

[7] NCCN Clinical practice guidelines in oncology: Uterine Neoplasms. National Comprehensive Cancer Network (NCCN) Version 1. 2023 2022; December 22, 2022:Version 1. 2023.

Available at: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf, 2022.

[8] Cheng YF, Chen HS, Wu SC, Chen HC, Hung WH, Lin CH and Wang BY. Esophageal squamous cell carcinoma and prognosis in Taiwan. Cancer Med 2018; 7: 4193-4201.

[9] Li H, Xiao Y, Li Q, Yao J, Yuan X, Zhang Y, Yin X, Saito Y, Fan H, Li P, Kuo WL, Halpin A, Gibbons DL, Yagita H, Zhao Z, Pang D, Ren G, Yee C, Lee JJ and Yu D. The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1. Cancer Cell 2022; 40: 36-52, e39.

[10] Wu SY, Chen WM, Chen YC, Chiang MF, Lee MC and Soong RS. Effects of H1-Antihistamines on hepatocellular carcinoma risk in patients with type 2 diabetes mellitus. Diabetes Metab 2023; 49: 101393.

[11] Hsieh MC, Lee WH, Wu AT, Chow JM, Chang CL, Yuan KS and Wu SY. Cyproheptadine use in hepatocellular carcinoma. Am J Cancer Res 2017; 7: 584-602.

[12] Shen YC, Hsu HC, Lin TM, Chang YS, Hu LF, Chen LF, Lin SH, Kuo PI, Chen WS, Lin YC, Chen JH, Liang YC and Chang CC. H1-antihistamines reduce the risk of hepatocellular carcinoma in patients with hepatitis B virus, hepatitis C virus, or dual hepatitis B virus-hepatitis C virus infection. J Clin Oncol 2022; 40: 1206-1219.

[13] Matsumoto N, Ebihara M, Oishi S, Fujimoto Y, Okada T and Imamura T. Histamine H1 receptor antagonists selectively kill cisplatin-resistant human cancer cells. Sci Rep 2021; 11: 1492.

[14] Kacar S, Hacioglu C, Kar F, Sahinturk V and Kanbak G. Cyproheptadine causes apoptosis and decreases inflammation by disrupting thiol/disulfide balance and enhancing the levels of SIRT1 in C6 glioblastoma cells. Toxicol In Vitro 2021; 73: 105135.

[15] Chen S and Luster AD. Antihistamines for cancer immunotherapy: more than just treating allergies. Cancer Cell 2022; 40: 9-11.

[16] Shi Z, Fultz RS, Engevik MA, Gao C, Hall A, Major A, Mori-Akiyama Y and Versalovic J. Distinct roles of histamine H1- and H2-receptor signaling pathways in inflammation-associated colonic tumorigenesis. Am J Physiol Gastrointest Liver Physiol 2019; 316: G205-G216.

[17] Hsieh HY, Shen CH, Lin RI, Feng YM, Huang SY, Wang YH, Wu SF, Hsu CD and Chan MW. Cyproheptadine exhibits antitumor activity in urothelial carcinoma cells by targeting GSK3beta to suppress mTOR and beta-catenin signaling pathways. Cancer Lett 2016; 370: 56-65.

[18] Xu J, Wang Y, Zhang Y, Dang S and He S. Astemizole promotes the anti-tumor effect of vitamin D through inhibiting miR-125a-5p-meidat-

ed regulation of VDR in HCC. Biomed Pharmacother 2018; 107: 1682-1691.

[19] Feng YM, Feng CW, Chen SY, Hsieh HY, Chen YH and Hsu CD. Cyproheptadine, an antihistaminic drug, inhibits proliferation of hepatocellular carcinoma cells by blocking cell cycle progression through the activation of P38 MAP kinase. BMC Cancer 2015; 15: 134.

[20] Cheng JS, Lee KC, Wang JL, Tseng LL, Chou KJ, Tang KY and Jan CR. Histamine-induced increases in intracellular free Ca2+ levels in hepatoma cells. Chin J Physiol 2000; 43: 165-169.

[21] Fritz I, Wagner P and Olsson H. Improved survival in several cancers with use of H(1)-antihistamines desloratadine and loratadine. Transl Oncol 2021; 14: 101029.

[22] Zhang J, Lu CY, Chen HM and Wu SY. Neoadjuvant chemotherapy or endocrine therapy for invasive ductal carcinoma of the breast with high hormone receptor positivity and human epidermal growth factor receptor 2 negativity. JAMA Netw Open 2021; 4: e211785.

[23] Chen WM, Chen M, Hsu JG, Lee TS, Shia BC and Wu SY. Use of preoperative FDG PET/CT and survival of patients with resectable non-small cell lung cancer. Radiology 2022; 305: 219-227.

[24] Liu WC, Liu HE, Kao YW, Qin L, Lin KC, Fang CY, Tsai LL, Shia BC and Wu SY. Definitive radiotherapy or surgery for early oral squamous cell carcinoma in old and very old patients: a propensity-score-matched, nationwide, population-based cohort study. Radiother Oncol 2020; 151: 214-221.

[25] Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011; 10: 150-161.

[26] Chiang CH, Chiang CH, Peng CY, Hsia YP, See XY, Horng CS, Chang YC, Shen XE, Wang SS, Tsai TC, Chen YJ, Ma KS, Chen BS, Luan YZ, Tay ST, Shen CH, Chung KC, Chiang CH and Peng CM. Efficacy of cationic amphiphilic antihistamines on outcomes of patients treated with immune checkpoint inhibitors. Eur J Cancer 2022; 174: 1-9.

[27] Chiang CH, Chiang CH and Chiang CH. Are H1-antihistamines associated with a lower risk of hepatocellular carcinoma? J Clin Oncol 2022; 40: 2389-2390.

[28] Bens A, Dehlendorff C, Friis S, Cronin-Fenton D, Jensen MB, Ejlertsen B, Lash TL, Kroman N and Mellemkjaer L. The role of H1 antihistamines in contralateral breast cancer: a Danish nationwide cohort study. Br J Cancer 2020; 122: 1102-1108.

[29] Faustino-Rocha AI, Ferreira R, Gama A, Oliveira PA and Ginja M. Antihistamines as promising drugs in cancer therapy. Life Sci 2017; 172: 27-41.

[30] Ellegaard AM, Dehlendorff C, Vind AC, Anand A, Cederkvist L, Petersen NHT, Nylandsted J, Stenvang J, Mellemgaard A, Osterlind K, Friis S and Jaattela M. Repurposing cationic amphiphilic antihistamines for cancer treatment. EBioMedicine 2016; 9: 130-139.

[31] Kalpaklioglu F and Baccioglu A. Efficacy and safety of H1-antihistamines: an update. Antiinflamm Antiallergy Agents Med Chem 2012; 11: 230-237.

[32] Simons FE and Simons KJ. H1 antihistamines: current status and future directions. World Allergy Organ J 2008; 1: 145-155.

[33] Branco ACCC, Yoshikawa FSY, Pietrobon AJ and Sato MN. Role of histamine in modulating the immune response and inflammation. Mediators Inflamm 2018; 2018: 9524075.

[34] Jakhar R, Paul S, Bhardwaj M and Kang SC. Astemizole-histamine induces beclin-1-independent autophagy by targeting p53-dependent crosstalk between autophagy and apoptosis. Cancer Lett 2016; 372: 89-100.

[35] Liang YC, Chang CC, Sheu MT, Lin SY, Chung CC, Teng CT and Suk FM. The antihistamine deptropine induces hepatoma cell death through blocking autophagosome-lysosome fusion. Cancers (Basel) 2020; 12: 1610.

[36] Shi Q, Pei F, Silverman GA, Pak SC, Perlmutter DH, Liu B and Bahar I. Mechanisms of action of autophagy modulators dissected by quantitative systems pharmacology analysis. Int J Mol Sci 2020; 21: 2855.

[37] Nguyen PL and Cho J. Pathophysiological roles of histamine receptors in cancer progression: implications and perspectives as potential molecular targets. Biomolecules 2021; 11: 1232.

[38] Best LM, Mughal M and Gurusamy KS. Non-surgical versus surgical treatment for oesophageal cancer. Cochrane Database Syst Rev 2016; 3: CD011498.

[39] Hulshof MCCM, Geijsen ED, Rozema T, Oppedijk V, Buijsen J, Neelis KJ, Nuyttens JJME, van der Sangen MJC, Jeene PM, Reinders JG, van Berge Henegouwen MI, Thano A, van Hooft JE, van Laarhoven HWM and van der Gaast A. Randomized study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer (ARTDECO Study). J Clin Oncol 2021; 39: 2816-2824.
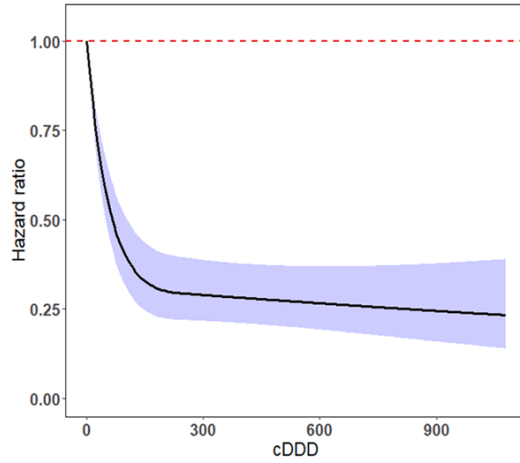
Supplementary Figure 1. The cDDD and the hazard ratio of ESCC-specific mortality in patients with and without AH1 Use following standard definitive CCRT.
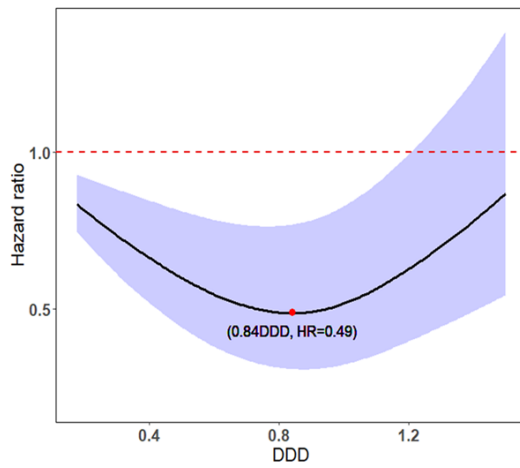
Supplementary Figure 2. Intensity of AH1 use (DDD) and the hazard ratio of ESCC-specific mortality in patients with and without AH1 use following standard definitive CCRT.