Effect of Long Term Prediagnostic Aspirin Intake on the Prognosis of Esophageal Squamous Cell Carcinoma Receiving Radical Surgery

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Research Article

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Abstract

Background:

The effect of long term prediagnostic aspirin intake on the prognosis of esophageal squamous cell carcinoma (ESCC) is unclear. We aimed to reveal the effect of long term prediagnostic aspirin intake on survival of ESCC patients receiving radical surgery.

Methods:

147 eligible ESCC patients who received radical surgery for primary treatment were enrolled in this study. Patients who had used aspirin regularly for more than 3 months before diagnose were classified as aspirin group and patients who had never used aspirin before diagnose and surgery were served as non-aspirin group. The recurrence rate, disease-free survival (DFS) and overall survival (OS) were compared between the two groups to verify the effect of aspirin.

Results:

Patients were clarified into aspirin group (n=57) and non-aspirin group (n=90). The DFS and OS were both significantly shorter in aspirin group than non-aspirin group (DFS: 23.1±18.0 months vs. 30.9±19.8 months, P=0.018; OS: 29.8±17.4 months vs. 35.2±18.2 months, P=0.082). Survival analysis revealed that OS decreased in aspirin group than in non-aspirin group, however, it did not reach significance (P=0.074). DFS decreased significantly in aspirin group than non-aspirin group in both univariate (P=0.007) and multivariate (P=0.002) survival analysis. Subgroup analysis revealed that in pTNM stage 2, OS and DFS were reduced in non-aspirin group compared with aspirin group (P=0.048 and P=0.003, respectively), while no difference was found in stage 3.

Conclusions:

Long term prediagnostic aspirin intake may cause poor DFS in ESCC patients receiving radical surgery, especially for those in pTNM stage 2.

Background

Esophageal cancer is a major health problem all over the world. The estimated new cases and deaths of esophageal cancer are 572,034 and 508,585 respectively in the worldwide in 2018 [1]. Esophageal cancer is the top 10 most frequently cause of cancer death in both male and female [1]. In China, esophageal cancer turned out to be the top 10 most commonly diagnosed cancer in both men and women (3rd in men and 6th in women) [2]. Esophageal squamous cell carcinoma (ESCC) is the major type and accounts for more than 90% of esophageal cancer in China [3]. The effective preventive methods and prognostic indicators are very necessary for ESCC.

Aspirin is an analgesic and antipyretic agent which is widely used. Studies have indicated aspirin may reduce the incidence and mortality of certain cancers [4, 5]. It was observed that the anti-tumor mechanisms of aspirin include COX dependent and COX independent pathways through inhibition of angiogenesis [6], induction of autophagy and apoptosis [6–9], anti-proliferative activity [10], and inhibition of metastasis [11–13]. U.S. Preventive Services Task Force has recommended aspirin as a primary preventive agent of cardiovascular disease and colorectal cancer in adults in 2016 [14]. However, increasing studies indicated the possible risk of clinical aspirin use which make the role of aspirin uncertain. A study including 6694 endometrial cancer patients with a maximum follow-up of 13 years did not found indication that pre- or post-diagnostic low-dose aspirin use reduced mortality for endometrial cancer [15]. Previous studies suggest that aspirin may reduce prostate cancer risk, while recent studies found aspirin was not associate with reduced prostate cancer risk [16, 17]. A large Asian cohort study did not find impact of aspirin on pancreatic cancer development [18]. Besides, there was no evidence that low-dose aspirin use before or after diagnosis was associated with a reduced risk of adverse outcomes overall in breast cancer [19, 20].

It was reported aspirin could be used in esophageal cancer patients as an adjuvant chemotherapy following the standard surgery [21, 22]. However, two large cohort studies in England contained 4654 esophageal cancer patients and 3833 gastric cancer patients showed that the cancer mortality proportions of participants surviving 1 year were similar in aspirin users versus non-users after diagnosis with cancer [23]. Another cohort of esophageal cancer patients indicated pre-diagnosis aspirin use was not associated with all-cause or cancer-specific mortality but could increase the risk of interval metastatic disease [24]. Considering the conflicting results of aspirin on esophageal cancer, this study aimed to investigate the effect of long term pre-diagnostic aspirin intake on the prognosis of ESCC.

Methods

Patients

We collected all newly diagnosed ESCC patients who received potential radical surgery for primary treatment in Qilu Hospital of Shandong University from 1 January 2010 to 31 December 2014. We selected all the patients who had regularly used aspirin for a long-term (≥ 3 months) before diagnose and surgery as the aspirin group and randomly chose another 90 ESCC patients who had never used aspirin or other COX-2 selective NSAIDs before diagnose and surgery as the control group. The reasons of aspirin intake were treatments for cardiovascular and cerebrovascular diseases, which were not the death reasons for the aspirin group. The American Joint Committee on Cancer TNM staging system was used in this study [25]. Undergoing radiotherapy and/or chemotherapy or not after the operation is not an exclusion criterion in this study. The exclusion criteria: lost to follow up, coexistence of other malignancies, resection not for curative intent, stage 0 disease, distant metastasis, non-cancer death. Ultimately, 147 patients were included in this study (57 in aspirin group, 90 in control group). The characteristics of patient, tumor, treatment and the final outcome were retrieved from the Medical Records Room or by phone call follow-up. During the first 2 years after surgery, follow-up visits were performed

every 3 months. After that follow-up visits were performed every 6 months up to death or the end of the study (29 November 2016).

Study design

A hospital-based retrospective cohort study was performed. Patient-related characteristics (age, gender, smoking, drinking, prediagnostic aspirin intake) and tumor-related characteristics (tumor location, tumor length, differentiation grade, pathological tumor-node-metastasis (pTNM) classification, treatment method) were investigated. We used disease-free survival (DFS) and over-all survival (OS) to evaluate the prognosis. The definition of DFS in this paper was the period of time from the radical operation to the identifiable time for first relapse or death or last follow-up, whichever firstly occurred. OS was from the radical operation date to the death date from tumor cause or last follow-up.

Statistical analysis

In data analysis of patient-related characteristics and tumor-related characteristics, Chi-square test and student's t-test were applied for categorical variables and continuous variables, respectively. Survival curves were constructed with the Kaplan Meier method to estimate the distribution of the DFS time and OS time in the two different groups. Cox proportional hazards modeling was used to investigate multiple risk factors that have been shown to influence ESCC prognosis [95% confidence intervals (CIs)]. P values less than 0.05 were considered to be statistically significant. SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Patients' characteristics

147 patients were recruited in this study, including 123 men and 24 women (49 males and 8 females in aspirin group, 74 males and 16 females in non-aspirin group, P = 0.550). Twenty patients were less than 65 years old and 37 patients were over 65 years old in aspirin group, while 47 less than 65 years old and 43 over 65 years old in non-aspirin group (P = 0.042). All other patient-related characteristics of aspirin group and non-aspirin group were not significantly different (all P > 0.05). Patients' characteristics are shown in Table 1.

Table 1
Tumor-related characteristics in aspirin and non-aspirin groups

Characteristics	Aspirin group (n = 57)	Non-aspirin group (n = 90)	P value
Age			0.042
≤65	20	47	
>65	37	43	
Gender			0.550
Male	49	74	
Female	8	16	
Smoker			0.181
Yes	38	50	
No	19	40	
Drinker			0.362
Yes	36	50	
No	21	40	
Tumor location			0.918
Neck	1	2	
Upper	4	4	
Middle	34	56	
Lower	18	28	
Tumor length			0.535
≤4cm	23	41	
>4cm	34	49	
Differentiation grade			0.692
Well	12	14	
Moderate	25	43	
Poor	20	33	
pTNM stage			0.942
I	4	5	

Characteristics	Aspirin group (n = 57)	Non-aspirin group (n = 90)	P value
II	31	46	
III	21	37	
IV	1	2	
Treatment			0.750
Surgery	24	40	
Surgery + Radiotherapy,	6	5	
Surgery + Chemotherapy	7	11	
Surgery + Radiotherapy+ Chemotherapy	20	33	

Prognostic difference between aspirin group and non-aspirin group

The recurrence rate and tumor-specific mortality rate of aspirin group were both higher than non-aspirin group (recurrence rate: 70.2% vs. 48.9%, P = 0.011 and mortality: 56.1% vs. 43.3%, P = 0.130). The DFS and OS were both significantly shorter in aspirin group than non-aspirin group (DFS: 23.1 ± 18.0 months vs. 30.9 ± 19.8 months, P = 0.018 and OS: 29.8 ± 17.4 months vs. 35.2 ± 18.2 months, P = 0.082).

Univariate and multivariate survival analysis results

In the univariate survival analysis, we used Kaplan-Meier curves to identify the effect of long term prediagnostic aspirin intake on OS and DFS. OS decreased in aspirin group than in non-aspirin group, however, it did not reach significance (P = 0.074). DFS decreased significantly in aspirin group than in non-aspirin group (P = 0.007). Significant factors of univariate survival analysis were included in the Cox proportional hazards model (Table 2). The results showed that only pTNM stage was significant predictor for OS (2.496(1.742–3.575); P < 0.001). For DFS prediction, aspirin intake (HR, 0.502(0.325–0.777); P = 0.002) was significant. Besides, tumor location, differentiation grade, pTNM stage and treatment methods were significant as prediction biomarkers. Subgroup analysis of aspirin intake were further conducted according to pTNM stage. In pTNM stage 2, OS and DFS were reduced in non-aspirin group compared with aspirin group (P = 0.048 and P = 0.003, respectively), while no difference was found in stage 3 (P = 0.315 and P = 0.387, respectively). Subgroup analysis were not conducted in stage 1 and 4 for the patient number was less than 10 (Fig. 1).

Table 2
Univariate and multivariate analysis of factors related with DFS and OS of ESCC

	OS			DFS		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	Log-rank P	HR(95%CI)	P	Log-rank P	HR(95%CI)	P
Age	0.762	-	-	0.416	-	-
Gender	0.444	-	-	0.611	-	-
Smoker	0.789	-	-	0.858	-	-
Drinker	0.739	-	-	0.485	-	-
Tumor location	0.005	0.834(0.578–1.205)	0.334	0.002	0.771(0.545–1.088)	0.139
Tumor length	0.985	-	-	0.206	-	-
Differentiation grade	0.063	-	-	0.035	1.346(0.985–1.839)	0.062
pTNM stage	< 0.001	2.496(1.742–3.575)	< 0.001	< 0.001	2.014 (1.417–2.861)	< 0.001
Treatment	0.078			0.008	1.004(1.000-1.0007)	0.054
Aspirin use or not	0.074	-	-	0.007	0.502(0.325–0.777)	0.002

Abbreviations: DFS, disease-free survival; OS, over-all survival; ESCC, esophageal squamous cell carcinoma; CI, confidence interval; HR, hazard ratio.

Discussion

Published evidence showed that aspirin may have protective effects for several kinds of cancers, such as lung cancer, prostate cancer, breast cancer, colon cancer, pancreatic cancer, esophageal cancer [26]. Especially in colorectal cancer, aspirin has been approved as a primary preventive agent in adults by U.S. Preventive Services Task Force in 2016 [14]. Contrary to our expected result, we observed that long term prediagnostic aspirin intake may cause poor outcome of ESCC patients who received radical surgery for the first treatment. The recurrence rate and tumor- specific mortality rate of aspirin group were both higher than non-aspirin group. The DFS and OS were both significantly shorter in aspirin group than non-aspirin group. It was observed that DFS of ESCC decreased significantly in aspirin group than non-aspirin group in both univariate and multivariate survival analysis. Long term prediagnostic aspirin intake decreased OS in univariate survival analysis while it was not significant. Subgroup analysis revealed that in pTNM stage 2, OS and DFS were significantly reduced in non-aspirin group compared with aspirin group, while

no difference was found in stage 3 group. Previous studies conclusions were not consistent on the role of aspirin in esophageal cancer. The current points of aspirin effect on tumor were different. Some studies suggested to use aspirin as an adjuvant chemotherapy following the standard surgery [21, 22], while other studies did not reveal the positive role of aspirin use [23]. Another cohort of esophageal cancer patients indicated pre-diagnosis aspirin use could increase the risk of interval metastatic disease. Multi-center prospective studies are necessary to reveal the role of aspirin plays in tumor.

Previous studies tried to investigate the potential mechanism of aspirin in cancer. It was observed that the anti-tumor mechanisms of aspirin include COX dependent and COX independent pathways through inhibition of angiogenesis [6], induction of autophagy and apoptosis [6–9], anti-proliferative activity [10], and inhibition of metastasis [11–13]. It was reported that post-diagnosis aspirin therapy improved overall survival of colorectal cancer patients, especially for patients with positive PTGS2 (COX-2) expression and mutated PIK3CA tumors[27]. Besides, aspirin suppresses growth in PI3K-Mutant breast cancer by activating AMPK and inhibiting mTORC1 signaling[28]. One study revealed the cytotoxicity and synergistic potential of aspirin and aspirin analogues towards esophageal and colorectal cancer[29]. However, we did not find the clinical positive role of aspirin in esophageal cancer. In vivo and in vitro experiments are necessary to reveal mechanisms of aspirin in esophageal cancer.

The current work has several limitations. Firstly, the work was a retrospective cohort study; some of the results were based on the phone-call follow-up, which may influence the accuracy. Secondly, the sample size was small which may bring bias on the results. We called on large sample, prospective, randomized controlled studies on this field. Thirdly, due to the small sample size, we did not carry out a subgroup analysis according to the dose and frequency of aspirin intake.

Conclusions

In conclusion, our work found long term prediagnostic aspirin intake caused poor outcome of ESCC and reminded that aspirin cannot benefit all cancer patients.

List Of Abbreviations

esophageal squamous cell carcinoma (ESCC)

disease-free survival (DFS)

overall survival (OS)

confidence intervals (CIs)

Declarations

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: Wenqiao Jia and Cong Wang developed the concept and design of the article. Ming Lu and Yufeng Cheng contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

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Figures

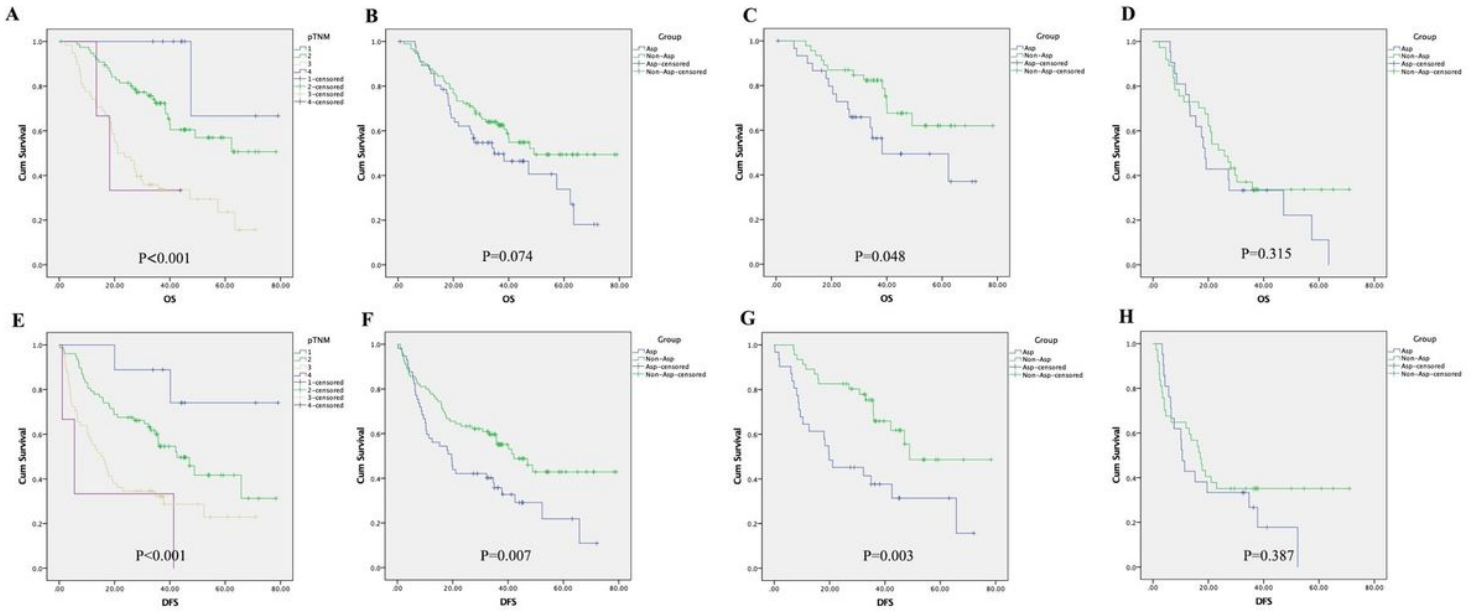

Figure 1

Kaplan-Meier survival curves of the differences of OS and DFS. (A) OS decreased significantly as pTNM stage increased; (B) OS decreased in aspirin group than in non-aspirin group although it was not significant; (C) In pTNM stage 2, OS of patients in aspirin group was worse than patients in non-aspirin group; (D) In pTNM stage 3, no significance was found between aspirin groups; (E) DFS decreased as pTNM stage increased however, it didnot reach the significance; (F) DFS decreased in aspirin group than in non-aspirin group; (G) In pTNM stage 2, DFS of patients in aspirin group was worse than patients in non-aspirin group; (H) In pTNM stage 3, no significance was found between aspirin groups.