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Impact of age on the overall survival benefits of anti-EGFR-containing regimens in head and neck squamous cell carcinoma: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: We conducted a meta-analysis to examine the associations of age, human papillomavirus (HPV) infection, and performance status with the overall survival (OS) benefits of patients with head and neck squamous cell carcinoma (HNSCC) after treatment with versus without epidermal growth factor receptor (EGFR) inhibitors.

Methods: We systematically searched literature for randomized controlled trials comparing chemotherapy or radiotherapy with versus without EGFR inhibitors in locoregionally advanced, recurrent, or metastatic HNSCCs. Hazard ratios (HRs) for OS were calculated using random-effects models for patient groups according to age (younger vs. older), HPV infection status (p16-positive vs. p16-negative), and performance status score (better vs. poorer).

Results: Five phase III trials with 2653 patients were included. EGFR inhibition was associated with a greater OS benefit in younger patients than in older counterparts (HR 0.70 vs. 1.05, $P < 0.001$). There were no apparent differences in OS based on HPV status ($P = 0.860$) or performance status score ($P = 0.235$). Largely consistent results were obtained following stratification by treatment strategy (i.e., chemotherapy and radiotherapy).

Conclusions: Patient age appears to impact OS independent of HPV infection and performance status after adding EGFR inhibitor agents during HNSCC treatment. This finding may help design relevant clinical trials.

1. Background

Targeting the epidermal growth factor receptor (EGFR) in patients with head and neck squamous cell carcinoma (HNSCC) produces a modest benefit (National Comprehensive Cancer Network, 2017; Cohen, 2014). Predictive markers such as *RAS* mutations, which are associated with patient responsiveness in colorectal cancer, have never been established in patients with HNSCC (Stransky et al., 2011; Licitra et al., 2011, 2013).

Post-hoc analyses from randomized trials have suggested that age might be a prognostic factor in patients with HNSCC in whom anti-EGFR therapy is included in their treatment regimens (Vermorken et al., 2008; Bonner et al., 2010; Argiris et al., 2013; Vermorken et al., 2013; Ang et al., 2014). In the pivotal phase III EXTREME trial that demonstrated a survival benefit following the addition of cetuximab to chemotherapy in recurrent or metastatic disease, a subgroup analysis showed an increased overall survival (OS) rate in younger but not older patients (Vermorken et al., 2008). Additionally, while the SPECTRUM trial demonstrated no OS benefit from adding panitumumab to chemotherapy for recurrent or metastatic disease, a subgroup analysis demonstrated an improved OS in younger patients (Vermorken et al., 2013). To date, no studies with a suitable design or adequate statistical power have been performed to detect the differences in OS benefits between younger and older patients.

Underlying causes for the differences in outcomes associated with age might be related to human papillomavirus (HPV) infection and performance status. Increasing age and the concomitant decline in performance status are major determinants of health. Additionally,

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younger age and higher performance status scores are characteristics of HPV-positive disease (Gillison et al., 2008). To clarify these associations, we conducted a meta-analysis of treatment with versus without EGFR inhibition in patients with locoregionally advanced, recurrent, or metastatic HNSCC.

2. Methods

This meta-analysis was conducted in conformance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Liberati et al., 2009).

2.1. Selection criteria

Studies eligible for inclusion were required to meet all the following criteria: 1) the EGFR antagonists, whether tyrosine kinase inhibitors (TKIs) or antibodies, selectively targeted EGFR and not any other member of the human epidermal growth factor receptor family; 2) the study was a phase III or phase IV randomized controlled trial; 3) patients had cytologically or histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; 4) the studied disease was locoregionally advanced or recurrent and/or metastatic; 5) the study compared chemotherapy, radiotherapy, or concurrent chemoradiotherapy in the presence versus absence of an EGFR inhibitor; and 6) the study provided hazard ratios (HRs) with 95% confidence intervals (CIs) for OS according to patient age groups, or else provided sufficient information to calculate these values.

Studies were excluded if they were reported solely in an abstract or if surgery was used as a curative treatment. If multiple publications were available for a given trial, only the most updated results were included. There were no language restrictions.

2.2. Identification of eligible trials

We performed a comprehensive search of papers published before March 13, 2018. The computerized bibliographic databases included: PubMed, ClinicalTrials.gov, EMBASE, Web of Science, and Chinese databases (Chinese Biomedical Literature Database, Chinese Wanfang Database, China Scientific and Technical Papers and Citations, and Chinese National Knowledge Infrastructure databases). For comprehensive exploration, the search string was "(EGFR OR HER1 OR ErbB1 OR epidermal growth factor receptor OR human epidermal growth factor receptor-1) AND (head and neck OR oral cavity OR oropharynx OR hypopharynx OR larynx) AND (trial)". We also manually searched the reference lists of the retrieved review articles and primary studies to ensure complete coverage.

2.3. Data extraction

Two investigators independently extracted the following data from each trial: study design, inclusion and exclusion criteria, patient characteristics, number of patients, histologic type, TNM stage, follow-up, EGFR inhibitors, compliance with treatment, major clinical end points, exclusion from trial analyses and reasons for such exclusions, and failure patterns. HRs and their 95% CIs were directly used if reported, and corresponding authors were contacted via e-mail to request any missing information. If the corresponding authors were unreachable, the data were calculated according to the method of Parmar et al (Parmar et al., 1998).

Two authors independently assessed the risk of bias of each eligible trial following the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Higgins and Green (2011)). The following domains were assessed as having a low, high, or unclear risk of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

Disagreements were resolved by discussion between the authors with arbitration by a third reviewer when necessary.

2.4. Credibility assessment

The credibility of subgroup analysis was determined using the criteria proposed by Sun et al. (Sun et al., 2014) in our meta-analyses. These criteria include 5 domains: (1) Can chance explain the subgroup difference? (2) Is the subgroup difference consistent across studies? (3) Was the subgroup difference one of a small number of a priori hypotheses in which the direction was accurately prespecified? (4) Is there external evidence to support the subgroup difference (biological rationale)? (5) Are subgroup differences suggested by comparisons *within* rather than *between* studies? As before, disagreements were resolved by discussion between the authors with the arbitration of a third reviewer when necessary.

2.5. Statistical analysis

All analyses were pre-specified in a protocol unless otherwise indicated. We calculated HRs and 95% CIs to assess the OS advantage of treatment that included EGFR inhibition versus treatment that did not. Because of clinical heterogeneity between trials identified a priori, the random-effects model was used to pool the data (Higgins and Green (2011)). An HR < 1 suggested an improved OS with treatment regimens containing EGFR inhibitors in relation to control (non-EGFR inhibitor-containing) regimens. The patient groups were defined based on age (younger vs. older), HPV status (p16-positive vs. p16-negative), and performance status (better vs. poorer). The cutoff points for age, performance status score, and p16 status were those provided in each trial. The Cochrane Q test and I^2 statistic were used to assess heterogeneity between trials (Higgins (2002)). The test of interaction proposed by Altman et al. (Altman and Bland, 2003) was used to compare treatment effects between groups. Stratified analyses were conducted to assess differences related to treatment strategies, including radiotherapy and chemotherapy. We conducted five sensitivity analyses by excluding: (1) trials in which control subjects did not receive the standard of care; (2) trials with a significant increase of treatment interruptions or delays owing to adding EGFR inhibitors to the regimen; (3) trials of TKIs, because their therapeutic efficacy might be different from that of antibodies; (4) trials in which the primary endpoint was not OS; and (5) trials of cetuximab, in order to test whether the efficacy of EGFR inhibition in the main meta-analysis was dependent on this antibody. We performed statistical analyses using the Stata software (StataCorp, College Station, Texas), version 12. Statistical significance was defined as a P-value of < 0.05 (two-sided).

3. Results

3.1. Summary of included trials

We identified 2838 studies from the initial search of the English-language databases (PubMed, EMBASE, ClinicalTrials.gov, and Web of Science) up to March 13, 2018. Among these, five phase III randomized controlled trials between 2005 and 2016 that met the inclusion criteria were identified (Vermorken et al., 2008; Bonner et al., 2010; Argiris et al., 2013; Vermorken et al., 2013; Ang et al., 2014). A search of Chinese-language databases (Chinese Biomedical Literature Database, Chinese Wanfang Database, China Scientific and Technical Papers and Citations, and Chinese National Knowledge Infrastructure databases) yielded 2288 publications available as of March 13, 2018. We did not identify a randomized controlled trial of EGFR inhibition for HNSCC in the latter databases; hence, the five English-language phase III trials were included in this meta-analysis (Fig. 1). One of these trials did not apply an intention-to-treat analysis and was considered to have a moderate risk of bias. The remaining trials were considered to have a

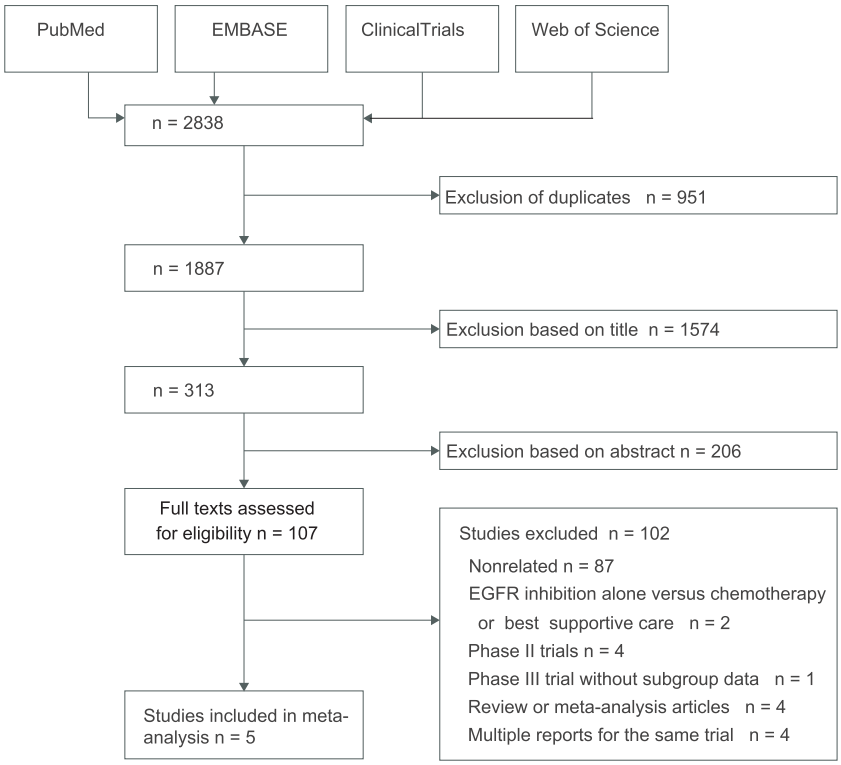

Fig. 1. Flow diagram of study selection[a].
[a] The search of the Chinese databases yielded 2288 publications dated until March 13, 2018. We did not identify any randomized controlled trial of epidermal growth factor receptor (EGFR) inhibition for locoregionally advanced, recurrent, or metastatic head and neck squamous cell carcinoma (HNSCC).

low risk of bias, although investigators and patients were not blinded to the assigned treatment arms (Supplementary Table S1).

The details of the trials are shown in Table 1. In total, 2653 patients were randomly assigned to the control group (no EGFR inhibition) (n = 1326) and the investigation group (with EGFR inhibition) (n = 1327). Three EGFR inhibitors were investigated: gefitinib in one trial (Argiris et al., 2013), panitumumab in one (Vermorken et al., 2013), and cetuximab in three (Vermorken et al., 2008; Bonner et al., 2010; Ang et al., 2014). Three trials involving 1338 patients investigated chemotherapy with or without an EGFR inhibitor in patients with recurrent and/or metastatic HNSCC (Vermorken et al., 2008; Argiris et al., 2013; Vermorken et al., 2013). Two trials involving 1315 patients investigated radiotherapy or chemoradiotherapy with or without an EGFR inhibitor for patients with locoregionally advanced HNSCC (Bonner et al., 2010; Ang et al., 2014). All these trials compared an experimental group with a control group that received standard of care treatment except for the IMCL-9815 trial (Bonner et al., 2010), in which the control arm received radiotherapy alone while concurrent chemoradiotherapy was the recognized standard of care.

The age cutoffs between young and old patients were 50 years in the RTOG 0522 trial (Ang et al., 2014), 55 years in the SPECTRUM trial (Vermorken et al., 2013), and 65 years in the EXTREME (Vermorken et al., 2008), IMCL-9815 (Bonner et al., 2010), and ECOG-E1302 (Argiris et al., 2013) trials. The performance score was assessed using the Karnofsky performance status (KPS) scale in the EXTREME (Vermorken et al., 2008) and IMCL-9815 (Bonner et al., 2010) trials, where the cutoff score for good versus poor performance was 80. In the remaining trials, the Eastern Cooperative Oncology Group performance status (ECOG PS) scale was used. The cutoff point was 1 in the SPECTRUM (Vermorken et al., 2013) and RTOG 0522 (Ang et al., 2014) trials, and 2 in the ECOG-E1302 (Argiris et al., 2013) trial. For comparison, KPS sores were converted to ECOG PS scores by considering a KPS score of 100 equal to an ECOG PS score of 0, KPS scores of 80–90 equivalent to an ECOG PS score of 1, and KPS score of 70 or less equivalent to ECOG PS scores of 2 or greater (Ma et al., 2010; Buccheri et al., 1996). HPV status was evaluated using immunohistochemical detection of the p16 protein in four trials; p16 positivity was defined by p16 staining in 10% or more of the tumour cells in the SPECTRUM trial (Vermorken et al., 2013) and in 70% or more of tumour cells in the EXTREME (Vermorken et al., 2008), IMCL-9815 (Bonner et al., 2010), and RTOG 0522 (Ang et al., 2014) trials.

3.2. OS as related to age, HPV status, and performance status

In terms of OS, there were 1430 (54%) deaths among the 2653 patients (Fig. 2). An OS benefit from adding EGFR inhibitors was associated with younger age (n = 1241; HR 0.70, 95% CI 0.61–0.80; $P <$ 0.001), p16-negative disease (n = 877; HR 0.79, 95% CI 0.67–0.92); $P =$ 0.002), and a better performance status score (n = 1511; HR 0.81, 95% CI 0.66–0.99; $P =$ 0.039). In contrast, patients with older age (n = 1412; HR 1.05, 95% CI 0.91–1.21; $P =$ 0.467), p16-positive disease (n = 450; HR 0.83, 95% CI 0.51–1.35; $P =$ 0.456), and poorer performance status scores (n = 1096; HR 0.94, 95% CI 0.82–1.08; $P =$ 0.381) did not obtain an OS benefit from EGFR inhibition. The improvement in OS after treatment with versus without EGFR inhibition differed by age ($P <$ 0.001) but not by p16 status ($P =$ 0.860) or performance status score ($P =$ 0.235). Obvious heterogeneity in performance status score and p16 status was present in the meta-analyses, but not in age.

We conducted prespecified subgroup analyses by treatment strategy (chemotherapy and radiotherapy) and un-prespecified subgroup analyses using available cutoffs for age (at 50, 55, and 65 years), performance status score (ECOG PS score of 1 and 2), and p16 status (p16 positivity defined at ≥10% and 70%). The results of these subgroup analyses were generally consistent with the main analysis (Tables 2 and 3). Sensitivity analyses (Table 4) yielded generally consistent results.

3.3. Credibility

Supplementary Table S2 shows the credibility of evidence determined by our meta-analyses. In terms of age difference, the interaction test produced a very small P-value of < 0.001, consistent results across trials following a limited number of subgroup hypotheses with correctly specified directions, and support by external evidence. As for

Table 1
Study characteristics.

Trial	Sample size (N)	Patients with HPV status (N, %)	Age, median(range)		Performance score	Comparison	Disease pattern	Inclusion period	Primary end point
			Investigation	Control					
SPECTRUM	657	443 (67%)	58 (53–63)	59 (53 - 64)	ECOG PS (0-1)	Cisplatin plus 5-Fluorouracil with vs. without panitumumab	Recurrent and/or metastatic disease	2007-2009	Overall survival
EXTREME	442	416 (94%)	56(NR)	57(NR)	KPS (70-100)	Cisplatin or carboplatin plus 5-Fluorouracil with vs. without cetuximab	Recurrent and/or metastatic disease	2004-2005	Overall survival
ECOG-E1302	270	NR	61(42-84)	61 (28 - 87)	ECOG PS (0-2)	Docetaxel with vs. without gefitinib	Recurrent and/or metastatic disease	2004-2008	Overall survival
IMCL-9815	424	182(43%)	56 (34–81)	58 (35 - 83)	KPS (60-100)	Radiotherapy with vs. without cetuximab	Locoregionally advanced disease	1999-2002	Duration of control of locoregional disease
RTOG 0522	891	321 (36%)	57(31-79)	58 (34 - 76)	ECOG PS (0-1)	Radiotherapy plus cisplatin with vs. without cetuximab	Locoregionally advanced disease	2005-2009	Progression free survival

ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; KPS, Karnofsky performance status; NR, not reported.

the differences in HPV and performance statuses, we found inconsistent results across the trials with small interactions easily explained by chance. Therefore, the age difference was considered highly plausible, whereas genuine differences based on performance or HPV status were unlikely.

4. Discussion

Our meta-analysis supported previous observations that age influences the OS following the addition of EGFR inhibitors in patients with HNSCC. In contrast, we found no apparent differences in OS according to performance or HPV status. Controlling for all available confounders did not change these findings appreciably.

The impact of age on OS after treating with EGFR inhibitors is likely independent of HPV status. In a subgroup analysis of the IMCL-9815 trial, patients who exhibited the greatest gains had characteristics linked to oropharyngeal carcinoma, younger age, and higher performance status score (Bonner et al., 2010), which are characteristics of HPV-positive disease (Gillison et al., 2008). These findings may lead to the assumption that HPV infection might be the underlying cause for the differences in outcomes after EGFR inhibition in patients with HNSCC. However, a subgroup analysis of the EXTREME trial suggested that, although the magnitude of the survival benefit was most pronounced in the p16-negative population, HPV status did not influence the efficacy of cetuximab (Vermorken et al., 2014). Similarly, our results revealed no apparent difference in OS between patients with p16-positive vs. p16-negative disease. Significant heterogeneity was observed in most of the meta-analyses of patients with p16-positive disease, the sources of which ought to be investigated in future studies. Indeed, a recent meta-analysis showed that adding EGFR inhibitors to chemotherapy was effective against p16-negative but not p16-positive disease, whereas adding EGFR inhibitors to radiotherapy or chemoradiotherapy was not effective against either p16-negative or p16-positive disease (Su et al., 2018).

The biological process of aging causes a decline in functional capacity and an increase in comorbidities. The performance status score is a more suitable indicator of functional status, comorbidities, and physiological reserves than age. However, our meta-analysis indicates that age, not performance status, impacts the survival benefit of EGFR inhibition in patients with HNSCC, perhaps suggesting that aging-related aetiologies but not aging-related physiological changes might be the underlying causes. Compared to older patients, younger subjects appear to develop disease following a shorter exposure time to carcinogenic substances; thus, younger patients may have a greater predisposition to disease development (Popovtzer et al., 2004; Jones et al., 1989). Such a predisposition could be related to genetic defects in carcinogen metabolism, DNA repair, or immune system response (Tremblay et al., 2006; Llewellyn et al., 2003). Further studies are needed to investigate the role of such genetic defects in the efficacy of EGFR inhibition in HNSCC.

The results of meta-analysis do not support the hypothesis that the differential survival benefits according to age were caused by more treatment interruptions or delays in older patients than younger patients owing to the toxic sequelae of adding EGFR inhibitors. First, any such treatment interruptions or delays occurred in only two of the five included trials. One was the RTOG 0522 trial (Ang et al., 2014) comparing the presence vs. absence of cetuximab in patients undergoing concurrent chemoradiotherapy; the other was the ECOG 1302 trial (Argiris et al., 2013) that investigated docetaxel with versus without gefitinib. However, the latter comprised a far greater proportion of patients with ECOG PS scores of 2 (n = 150) than all the other trials. In contrast, adding EGFR inhibitors did not affect the tolerability to radiotherapy in the IMCL-9815 trial (Bonner et al., 2010), or to chemotherapy in the EXTREME (Vermorken et al., 2008) and SPECTRUM (Vermorken et al., 2013) trials. Moreover, we conducted a planned sensitivity analysis by excluding trials that had significant increases in treatment interruptions or delays caused by adding EGFR inhibitors

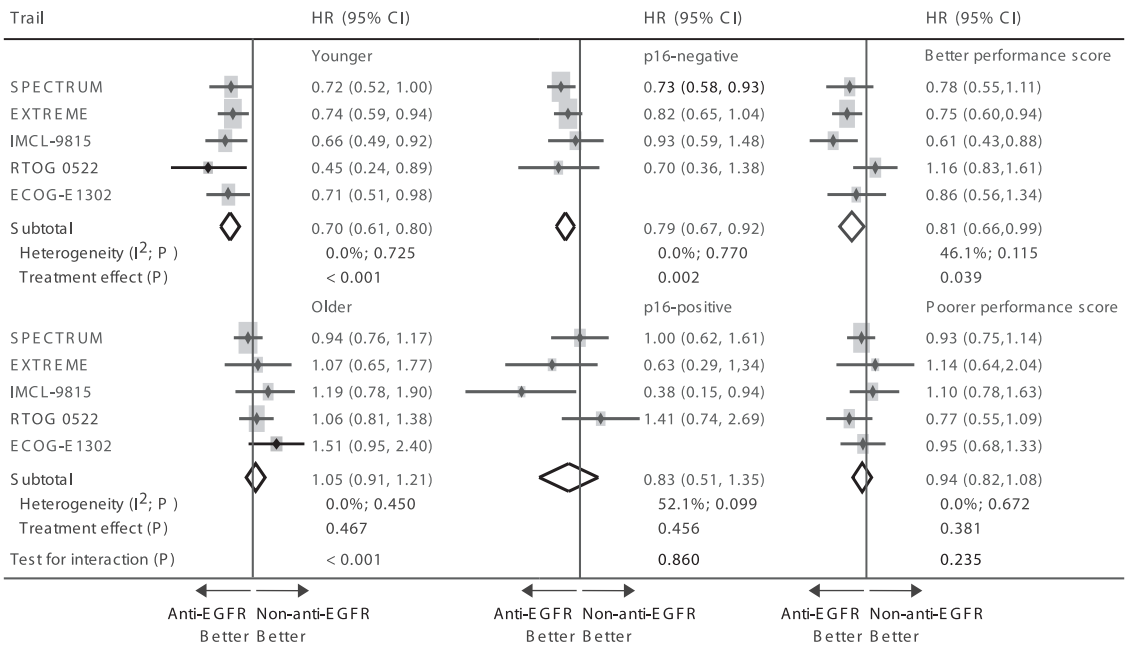

Fig. 2. Forest plot of the treatment effect on overall survival according to age, human papillomavirus status, and performance status score.
CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio.

(the RTOG 0522 [Ang et al., 2014] and ECOG 1302 [Argiris et al., 2013] trials), and observed results similar to those of the primary analysis. Taken together, treatment interruptions or delays due to toxicities following the incorporation of EGFR inhibitors do not explain the negative results observed in older patients.

The results of this study have clinical implications. (1) The age related phenomenon in outcome following EGFR inhibitors observed in our meta-analysis might not be limited to HNSCC. Indeed, evidence is also shown in advanced KRAS wild-type colorectal cancer. Guidelines recommend adding an anti-EGFR antibody to an infusional fluorouracil based chemotherapy regimen in the first-line treatment of the metastatic disease (National Comprehensive Cancer Network, 2018). Among 4 trials (Grothey and Lenz, 2012; Van Cutsem et al., 2009; Douillard et al., 2010; Bokemeyer et al., 2009; Maughan et al., 2011) that demonstrated an efficacy of this setting, two trials (Douillard et al., 2010; Bokemeyer et al., 2011) reported subgroup analyses based on age, with a trend toward greater benefits in patients younger than 65 years compared with patients 65 and older. (2) The use of radiotherapy and concurrent cetuximab has been considered to be a more tolerable alternative compared to platinum-based chemoradiation for older patients with locally advanced HNSCC (Baxi et al., 2016). However, our meta-analysis was against the therapeutic option in patients older than 65 years of age. This was supported by a recent Surveillance, Epidemiology, and End Results–Medicare database analysis that compared radiotherapy with concurrent cetuximab versus radiotherapy with or without concurrent chemotherapy in patients over 65 yeas of age. The results showed that radiotherapy with concurrent cetuximab was associated with similar OS to radiotherapy alone, and worse OS compared to radiotherapy with concurrent chemotherapy (Zandberg et al., 2018). Due to the respective nature, we advise cautious interpretation of the findings on radiotherapy and concurrent anti-EGFR therapy for patients over 65 yeas of age. (3) Our results should help in the design of prospective trials. We recommend 65 years as the age cut-off and cetuximab as the EGFR inhibitor.

There are several limitations in this meta-analysis. First, publication bias was not assessed, as any findings would be unreliable given the low number of included studies (Ioannidis and Trikalinos, 2007). Second, we adopted the methods provided by the investigators in each individual trial to classify age, HPV status, and performance status. These classifications varied between trials, which in turn may have diluted HR

Table 2
Stratified analyses according to treatment strategy.

Covariate	Chemotherapy with vs. without EGFR inhibitors			Radiotherapy with vs. without EGFR inhibitors		
	HR (95%CI)	*P* effect	I^2 (%)	HR (95%CI)	*P* effect	I^2 (%)
Age						
Younger	0.73 (0.62,0.86)	< 0.001	0.0	0.61 (0.46,0.82)	0.001	1.8
Older	1.09 (0.83,1.44)	0.556	39.9	1.09 (0.87,1.37)	0.436	0.0
Interaction test (*P*)	0.014			0.002		
HPV status						
p16 positive	0.88 (0.58,1.32)	0.531	0.8	0.76 (0.21,2.75)	0.399	80.9
p16 negative	0.77 (0.66,0.91)	0.003	0.0	0.85 (0.58, 1.24)	0.680	0.0
Interaction test (*P*)	0.585			0.886		
Performance score						
Better	0.77 (0.65,0.92)	0.004	0.0	0.84 (0.45,1.58)	0.593	84.9
Poorer	0.95 (0.80,1.13)	0.567	0.0	0.92 (0.65,1.29)	0.622	46.1
Interaction test (*P*)	0.092			0.814		

CI, confidence interval; EGFR, epidermal growth factor receptor; HPV, human papillomavirus; HR, hazard ratio; I^2, I-squared for heterogeneity.

Table 3
Stratified analyses according to different cutoff points for age, human papillomavirus status, and performance status score.

Covariate	Cutoff point	HR(95%CI)	*P* effect	I^2 (%)	*P* heterogeneity	Interaction test (*P*)
Age (years)						
	Categorization 1	3 trials with 1105 patients				< 0.001
	Younger (< 65)	0.71(0.60,0.84)	< 0.001	0.0	0.849	
	Older (≥ 65)	1.18(0.95,1.47)	0.128	0.0	0.469	
	Categorization 2	1 trial with 657 patients				0.182
	Younger (< 55)	0.72(0.52,1.00)	0.049	NA	NA	
	Older (≥ 55)	0.94(0.76,1.17)	0.574	NA	NA	
	Categorization 3	1 trial with 889 patients				0.017
	Younger (≤ 50)	0.45(0.23,0.87)	0.017	NA	NA	
	Older (> 50)	1.06(0.81,1.38)	0.668	NA	NA	
Performance status						
	Categorization 1	2 trials with 1542 patients				0.702
	Better (ECOG PS = 0)	0.96(0.65,1.41)	0.818	61.5	0.107	
	Poorer (ECOG PS = 1)	0.88(0.74,1.06)	0.173	0.0	0.356	
	Categorization 2	2 trials with 681 patients				0.159
	Better (ECOG PS = 0, 1)	0.77(0.63,0.94)	0.011	0.0	0.585	
	Poorer (ECOG PS = 2)	0.99(0.74,1.33)	0.970	0.0	0.594	
HPV status						
	Categorization 1	1 trial with 443 patients				0.247
	p16 positive (≥ 10%)	1.00(0.62,1.61)	0.998	NA	NA	
	p16 negative (< 10%)	0.73(0.58,0.93)	0.012	NA	NA	
	Categorization 2	3 trials with 884 patients				0.773
	p16 positive (≥ 70%)	0.73(0.34,1.57)	0.425	65.9	0.053	
	p16 negative (< 70%)	0.83(0.68,1.01)	0.064	0.0	0.782	

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HPV, human papillomavirus; HR, hazard ratio; I^2, I-squared for heterogeneity; NA, not applicable.

estimates and led to obscuring the differences between groups. However, a difference in OS was consistently observed between younger and older patients, with sensitivity analyses indicating the robustness of these results. Based on these outcomes, it was entirely appropriate to pool these trials together, and the variability may be considered a strength of our study. Third, our study was based on summarized data rather than individual patient data; however, results derived from both these types of studies are often consistent (Steinberg et al., 1997; Baujat et al., 2006). Fourth, this meta-analysis had a small number of studies (n = 5), which included locally advanced, recurrent, and metastatic diseases, as well as 3 different EGFR inhibitors whereas only cetuximab has been approved for routine clinical care. Because of the above limitations, our findings should be considered preliminary proof-of-concepts that require prospective trials for confirmation.

Table 4
Sensitivity analyses.

	Exclusion of									
	Trials in which control subjects did not receive the standard of care [a]		Trials with a significant increase of treatment interruptions or delays owing to adding EGFR inhibitors [b]		Trials of tyrosine kinase inhibitors [c]		Trials in which the primary endpoint was not overall survival [d]		Trials of cetuximab [e]	
	HR(95%CI)	I^2 (%)	HR(95%CI)	I^2 (%)	HR(95%CI)	I^2 (%)	HR(95%CI)	I^2 (%)	HR(95%CI)	I^2 (%)
Age										
Younger	0.71(0.60,0.83) **	0.0	0.71(0.61, 0.84) **	0.0	0.70(0.59,0.81) **	0.0	0.73(0.62,0.86) **	0.0	0.72(0.57,0.90) *	0.0
Older	1.05(0.89,1.24)	11.0	0.99(0.83,1.19)	0.0	1.02(0.88,1.18)	0.0	1.09(0.83,1.44)	39.9	1.14(0.72,1.79)	69.7
Interaction test (*P*)	0.001		0.006		0.001		0.014		0.07	
Performance score										
Better	0.86 (0.70,1.05)	36.9	0.72 (0.61,0.86) **	0.0	0.80 (0.63,1.02)	59.0	0.77 (0.65,0.92) *	0.0	0.81 (0.62,1.07)	0.0
Poorer	0.91 (0.79,1.06)	0.0	0.98 (0.82,1.17)	0.0	0.94 (0.80, 1.09)	0.0	0.95 (0.80,1.13)	0.0	0.94 (0.78,1.12)	0.0
Interaction test (*P*)	0.670		0.010		0.271		0.092		0.394	
HPV status										
p16 (+)	1.00 (0.68,1.48)	19.6	0.69 (0.40, 1.20)	45.8	0.83 (0.51,1.36)	52.1	0.88 (0.58,1.32)	0.8	1.00 (0.62,1.61)	NA
p16 (-)	0.77 (0.66,0.90) *	0.0	0.79 (0.68,0.93) *	0.0	0.79 (0.68,0.92) *	0.0	0.77 (0.66, 0.91) *	0.0	0.73 (0.58,0.92) *	NA
Interaction test (*P*)	0.226		0.658		0.845		0.585		0.248	

CI, confidence interval; HPV, human papillomavirus; HR, hazard ratio; I^2, I-squared for heterogeneity; NA, not applicable.
[a] Exclusion of one trial (IMCL-9815: n = 424, 16%).
[b] Exclusion of two trials (ECOG-E1302 and RTOG 0522: n = 1130, 43%).
[c] Exclusion of one trial (ECOG-E1302: n = 239, 9%).
[d] Exclusion of two trials (IMCL-9815 and RTOG 0522: n = 1315, 50%).
[e] Exclusion of three trials (EXTREME, IMCL-9815 and RTOG 0522: n = 1757, 66%).
** *P* effect < 0.001; * *P* effect < 0.05.

In conclusion, our meta-analysis found that age is a factor that influences survival following EGFR inhibition therapy in patients with HNSCC in a manner that is independent of performance and HPV statuses. These findings ought to be helpful for designing future clinical trials.

Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

Study concept and design: F. J. Han.

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Appendix A. Supplementary data

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References

Altman, D.G., Bland, J.M., 2003. Interaction revisited: the difference between two estimates. BMJ 326, 219.

Ang, K.K., Zhang, Q., Rosenthal, D.I., Nguyen-Tan, P.F., Sherman, E.J., Weber, R.S., et al., 2014. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. J. Clin. Oncol. 32, 2940–2950.

Argiris, A., Ghebremichael, M., Gilbert, J., Lee, J.W., Sachidanandam, K., Kolesar, J.M., et al., 2013. Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck Cancer: an Eastern cooperative oncology group trial. J. Clin. Oncol. 31, 1405–1414.

Baujat, B., Audry, H., Bourhis, J., Chan, A.T., Onat, H., Chua, D.T., et al., 2006. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int. J. Radiat. Oncol. Biol. Phys. 64, 47–56.

Baxi, S.S., O'Neill, C., Sherman, E.J., Atoria, C.L., Lee, N.Y., Pfister, D.G., et al., 2016. Trends in chemoradiation use in elderly patients with head and neck cancer: changing treatment patterns with cetuximab. Head Neck 38 (Suppl 1), E165–171.

Bokemeyer, C., Bondarenko, I., Makhson, A., Hartmann, J.T., Aparicio, J., de, Braud, F., et al., 2009. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J. Clin. Oncol. 27, 663–671.

Bokemeyer, C., Bondarenko, I., Hartmann, J.T., de, Braud, F., Schuch, G., Zubel, A., et al., 2011. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann. Oncol. 22, 1535–1546.

Bonner, J.A., Harari, P.M., Giralt, J., Cohen, R.B., Jones, C.U., Sur, R.K., et al., 2010. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 11, 21–28.

Buccheri, G., Ferrigno, D., Tamburini, M., 1996. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur. J. Cancer 32A, 1135–1141.

Cohen, R.B., 2014. Current challenges and clinical investigations of epidermal growth factor receptor (EGFR)- and ErbB family-targeted agents in the treatment of head and neck squamous cell carcinoma (HNSCC). Cancer Treat. Rev. 40, 567–577.

Douillard, J.Y., Siena, S., Cassidy, J., Tabernero, J., Burkes, R., Barugel, M., et al., 2010. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J. Clin. Oncol. 28, 4697–4705.

Gillison, M.L., D'Souza, G., Westra, W., Sugar, E., Xiao, W., Begum, S., et al., 2008. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J. Natl. Cancer Inst. 100, 407–420.

Grothey, A., Lenz, H.J., 2012. Explaining the unexplainable: EGFR antibodies in colorectal cancer. J. Clin. Oncol. 30, 1735–1737.

Higgins, J.P., 2002. Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21, 1539–1558.

Cochrane Handbook for Systematic Reviews of Interventions. In: Higgins, J.P.T., Green, S. (Eds.), Version 5.1.0 [updated March 2011]. The Cochrane Collaboration (Accessed 1 October 2017). http://handbook.cochrane.org.

Ioannidis, J.P., Trikalinos, T.A., 2007. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ 176, 1091–1096.

Jones, J.B., Lampe, H.B., Cheung, H.W., 1989. Carcinoma of the tongue in young patients. J. Otolaryngol. 18, 105–108.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 339, b2700.

Licitra, L., Mesia, R., Rivera, F., Remenar, E., Hitt, R., Erfan, J., et al., 2011. Evaluation of EGFR gene copy number as a predictive biomarker for the efficacy of cetuximab in combination with chemotherapy in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck: EXTREME study. Ann. Oncol. 22, 1078–1087.

Licitra, L., Storkel, S., Kerr, K.M., Van Cutsem, E., Pirker, R., Hirsch, F.R., et al., 2013. Predictive value of epidermal growth factor receptor expression for first-line chemotherapy plus cetuximab in patients with head and neck and colorectal cancer: analysis of data from the EXTREME and CRYSTAL studies. Eur. J. Cancer 49, 1161–1168.

Llewellyn, C.D., Linklater, K., Bell, J., Johnson, N.W., Warnakulasuriya, K.A., 2003. Squamous cell carcinoma of the oral cavity in patients aged 45 years and under: a descriptive analysis of 116 cases diagnosed in the South East of England from 1990 to 1997. Oral Oncol. 39, 106–114.

Ma, C., Bandukwala, S., Burman, D., Bryson, J., Seccareccia, D., Banerjee, S., et al., 2010. Interconversion of three measures of performance status: an empirical analysis. Eur. J. Cancer 46, 3175–3183.

Maughan, T.S., Adams, R.A., Smith, C.G., Meade, A.M., Seymour, M.T., Wilson, R.H., et al., 2011. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 377, 2103–2114.

National Comprehensive Cancer Network, 2017. Practice Guidelines in Oncology, Head and Neck Cancers–version 2. (Accessed 1 October 2017). https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.

National Comprehensive Cancer Network, 2018. Practice Guidelines in Oncology, Colon cancer-version 2. (Accessed 1 March 2018). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.

Parmar, M.K., Torri, V., Stewart, L., 1998. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat. Med. 17, 2815–2834.

Popovtzer, A., Shpitzer, T., Bahar, G., Marshak, G., Ulanovski, D., Feinmesser, R., 2004. Squamous cell carcinoma of the oral tongue in young patients. Laryngoscope 114, 915–917.

Steinberg, K.K., Smith, S.J., Stroup, D.F., Olkin, I., Lee, N.C., Williamson, G.D., et al., 1997. Comparison of effect estimates from a meta-analysis of summary data from published studies and from a meta-analysis using individual patient data for ovarian cancer studies. Am. J. Epidemiol. 145, 917–925.

Stransky, N., Egloff, A.M., Tward, A.D., Kostic, A.D., Cibulskis, K., Sivachenko, A., et al., 2011. The mutational landscape of head and neck squamous cell carcinoma. Science 333, 1157–1160.

Su, Y., Cui, J., Xu, D., Wang, M., Xu, T., Tian, H., et al., 2018. p16(INK4a) status and survival benefit of EGFR inhibitors in head and neck squamous cell cancer: a systematic review and meta-analysis. Crit. Rev. Oncol. Hematol. 124, 11–20.

Sun, X., Ioannidis, J.P., Agoritsas, T., Alba, A.C., 2014. Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. JAMA 311, 405–411.

Tremblay, S., Pintor, Dos, Reis, P., Bradley, G., Galloni, N.N., Perez-Ordonez, B., Freeman, J., et al., 2006. Young patients with oral squamous cell carcinoma: study of the involvement of GSTP1 and deregulation of the Fanconi anemia genes. Arch. Otolaryngol. Head Neck Surg. 132, 958–966.

Van Cutsem, E., Kohne, C.H., Hitre, E., Zaluski, J., Chang Chien, C.R., Makhson, A., et al., 2009. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N. Engl. J. Med. 360, 1408–1417.

Vermorken, J.B., Mesia, R., Rivera, F., Remenar, E., Kawecki, A., Rottey, S., et al., 2008. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N. Engl. J. Med. 359, 1116–1127.

Vermorken, J.B., Stohlmacher-Williams, J., Davidenko, I., Licitra, L., Winquist, E., Villanueva, C., et al., 2013. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. Lancet Oncol. 14, 697–710.

Vermorken, J.B., Psyrri, A., Mesía, R., Peyrade, F., Beier, F., De, B.B., et al., 2014. Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 25, 801–807.

Zandberg, D.P., Cullen, K., Bentzen, S.M., 2018. Goloubeva OG. Definitive radiation with concurrent cetuximab vs. Radiation with or without concurrent cytotoxic chemotherapy in older patients with squamous cell carcinoma of the head and neck: analysis of the SEER-medicare linked database. Oral Oncol. 86, 132–140.