The prognostic and predictive value of excision repair cross complementation group 1 (ERCC1) protein in 1288 patients with head and neck squamous cell carcinoma treated with platinum-based therapy: a meta-analysis

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Abstract

Excision repair cross-complementation group 1 (ERCC1) protein has been extensively investigated as a prognostic and predictive factor for platinum-based treatment in head and neck squamous cell carcinoma (HNSCC) but with inconsistent results. We performed the present meta-analysis to better elucidate this issue in advanced HNSCC.

A literature search was conducted using the PubMed and Web of Science databases. The inclusion criteria were head and neck cancer patients with platinum-based treatment and evaluation of the correlation between ERCC1 expression and clinical outcomes [objective response rate (ORR), progression-free survival (PFS), and overall survival (OS), both unadjusted and adjusted estimates].

In high vs. low pooled analyses, high ERCC1 expression was associated with unfavourable OS (hazard ratio (HR) = 1.95, 95% confidence interval (CI) 1.18 – 3.21, p=0.009), PFS (HR = 2.39, 95% CI 1.74 – 3.28, p=0.000) and ORR (OR = 0.48, 95% CI 0.23 – 0.98, p=0.044). In the subgroup analysis of adjusted OS estimates, ERCC1 was a predictor of shorter survival in Asians (HR = 3.13, 95% CI 2.09 – 4.70, p=0.000) and Caucasians (HR = 2.02, 95% CI 1.32 – 3.07, p=0.001) but of longer survival in South Americans (HR = 0.17, 95% CI 0.07 – 0.40, p=0.000). Immunohistochemistry proved to be of predictive value irrespective of used antibody (p=0.009). In the stratified analysis according to the tumor site, ERCC1 expression was associated with OS in nasopharyngeal cancer (HR = 2.72, 95% CI 1.79 – 4.13, p=0.000).

ERCC1 has a potential to become predictive and prognostic factor enabling treatment tailoring in HNSCC patients.

Key words: ERCC1, platinum-based chemotherapy, HNSCC, chemoradiotherapy, meta-analysis

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for more than 550 000 new cases annually worldwide [1]. Cisplatin-based chemoradiotherapy (CRT) is the standard treatment for locoregionally advanced disease both in case of unresectable disease as well as in case of resectable disease when organ preservation is desired [2-4]. Cisplatin is also a part of frequent induction chemotherapy schemes [4]. Besides, it is used in combination with postoperative radiotherapy (RT) in patients with high risk pathological findings [2]. Platinum agents bind to DNA and create DNA adducts which thus inhibit a cell cycle and lead to apoptosis [5]. However, platinum-based chemotherapy considerably increases treatment related toxicity. Regarding to the observation that some patients have modest response to the treatment or have no response at all, it is important to distinguish those among them who would actually benefit from the treatment. Therefore, identification of reliable biomarkers is of paramount importance for better selection of patients so that they would not be subjected to ineffective treatment and toxicity.

Excision repair cross-complementation group 1 (ERCC1) protein has been studied as a possible prognostic and predictive marker of response to platinum-based therapy since its discovery in the 1990s [6]. It belongs to the nucleotide excision repair (NER) system which has important role in repair of DNA. ERCC1 associates with xeroderma pigmentosum group F (XPF) protein to form a nuclease that function in DNA repair [7]. Besides ERCC1 plays a role in several other DNA repair pathways like homologous recombination [8], interstrand cross-link repair [9] and repair of DNA double-strand breaks (DSB) [10]. A correlation between level of ERCC1 expression and clinical outcomes of HNSCC patients treated with platinum-containing therapy has been investigated in numerous studies but the results were not consistent [11-15].

In an attempt to address this issue two meta-analyses has been published, one in the patients with HNSCC irrespective of the treatment modalities [16] and one in the patients treated with cisplatin-based concurrent CRT [17]. Since cisplatin-based chemotherapy is the part of different treatment modalities in patients with HNSCC we performed a systemic review and meta-analysis of studies outcomes to evaluate the prognostic and predictive value of ERCC1 expression in this category of patients.

Materials and Methods

The present meta-analysis was performed according to PRISMA guidelines [18].

Search strategy

PubMed and Web of Science databases were searched until January 4th, 2015. The keywords used in the online search were: “head and neck cancer”, “nasopharyngeal cancer”, “laryngeal cancer”, “oropharyngeal cancer”, “oral cavity cancer”, “hypopharyngeal cancer” and “ERCC1”. Only full-text papers written in English were included.

Eligibility criteria were:1) human-based studies; 2) pathologically confirmed head and neck cancer; 3) platinum-based chemotherapy; 4) results of objective response rate (ORR), progression-free survival (PFS) and unadjusted and/or adjusted hazard ratio (HR) estimates for overall survival (OS) stratified by ERCC1 expression.

Data extraction

The following data were extracted from the selected studies: the first author's name, year of publication, country of origin, ethnicity, sample size, stage of disease, tumor site, treatment, chemotherapy regimen, detection method of ERCC1 expression, number of ERCC1 high expression patients, number of ERCC1 low expression patients, clinical outcomes, covariates utilized in multivariate analyses of OS. When the direct HRs and their 95% CIs were not reported in the studies they were estimated using the method of Tierney et al. [19].

Statistical analysis

The odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to estimate the association between ERCC1 status and the ORR to treatment containing platinum-based chemotherapy in head and neck patients. The hazard ratios (HRs) and 95% CIs were employed to evaluate the relationship between ERCC1 expression and PFS and OS. Heterogeneity between studies was assessed by the I^2 statistics. In the presence of heterogeneity between studies, a random-effect model was used instead of a fixed model [20-21]. Subgroup analyses by ethnicity (Asian, Caucasian and South American), detection method [8F1, other immunohistochemistry (IHC), reverse transcription-polymerase chain reaction (RT-PCR)] and tumor site (nasopharynx, mixed tumor sites not including nasopharynx and mixed tumor sites including nasopharynx) were also performed. Publication bias was tested by Beggs's and Egger's tests. All statistical analyses were carried out using STATA version 12 (Stata Corporation, College Station, TX, USA).

Results

Eligible studies

One hundred and twenty-seven potentially relevant articles were identified with keywords in the initial search (Supplementary Fig. 1). Ten articles were excluded because they were duplicates, and 41 after reading the titles and abstracts: 76 full-text articles were assessed for eligibility. Among them further 7 articles were excluded because of the following reasons: insufficient data (n = 3); without platinum-based chemotherapy (n = 2); highly selected population of patients (n = 2) i.e. ERCC1 expression stratified by human papillomavirus (HPV) status in head and neck cancers. At the end, 17 studies containing 1288 patients were included in meta-analysis [11-15, 22-33].

Baseline characteristics of included studies were presented in details in Table 1. Studies were published between 2007 and 2014 and sample sizes of datasets ranged from 26 to 176. Nine studies were conducted in Caucasian patients [13-15, 23-25, 27-28, 30], seven studies in Asian patients [22, 26, 28-29, 32-33] and one in South American patients [11].

In 4 studies ERCC1 expression was determined by more than one method of detection in the same population of patients [11, 14-15, 23]. Three studies employed RT-PCR along with IHC [11, 15, 23]. Among IHC employing studies distinction was made between the most frequently used 8F1 antibody and other IHC methods. In two studies other IHC methods were employed along with 8F1 [14, 15] and in two further studies other antibodies were used alone [27, 30]. In this meta-analysis different methods of detection of the ERCC1 expression were treated as separate datasets leading thus to the total number of 1427 analyzed tissue samples. Marked heterogeneity was observed between thresholds used to separate high and low ERCC1 expression (Table 1).

Objective response rate

Tumor response stratified by ERCC1 expression was reported by 10 datasets containing 587 head and neck patients, of whom 332 (57%) had high ERCC1 expression [12-13, 22-26, 29-30, 32]. In the pooled analysis, low ERCC1 expression was associated with better ORR to the treatment containing platinum-based chemotherapy (OR = 0.48, 95% CI = 0.23 – 0.98; I^2 = 56.5%, p = 0.014 for heterogeneity; Table 2 and Fig. 1). No significant bias was found by the Begg's (p = 0.79) and Egger's test (p = 0.53) (Supplementary Fig. 2). In the sensitivity analysis, no individual study significantly affected the OR.

Subgroup analyses were done according to ethnicity, method of the detection and tumor site. Six studies were performed in Asians containing 357 patients [12, 22, 26, 29-30, 32], while four studies were conducted in Caucasians containing 230 patients [13, 23-25]. Low ERCC1 was associated with better ORR in Asian patients (OR = 0.29, 95% CI = 0.17 – 0.52; I^2 = 31.7) while there was no association between ERCC1 expression and response to chemotherapy containing treatment in Caucasian patients (OR = 0.81, 95% CI = 0.40 – 1.67; I^2 = 65.3 %) (Table 2 and Fig. 2). In eight datasets the ERCC1 expression was detected by IHC – 8F1 [12-13, 20-21, 23-24, 27, 30], in one by some other IHC method [28] and in another one by RT-PCR [21]. Low ERCC1 expression identified by IHC-8F1 was associated with better ORR (OR = 0.38, 95% CI = 0.23 – 0.61; I^2 = 35.3%) (Table 2). The association between low ERCC1 expression and better ORR was not influenced by tumor site since low ERCC1 expression was found to be a predictor of better ORR both in nasopharyngeal cancer group and in group of mixed tumor sites without nasopharyngeal cancer (Table 2).

Progression-free survival

The association between ERCC1 expression and PFS was explored in seven datasets containing 430 patients, of whom 226 (53%) had high ERCC1 expression [12, 14, 22, 24, 30]. The pooled analysis showed that high ERCC1 expression was associated with shorter PFS for head and neck patients receiving platinum-based chemotherapy (HR = 2.39, 95% CI = 1.74 – 3.28; I^2 = 0.0%, p = 0.47 for heterogeneity) (Table 2, Fig. 2). No significant bias was found by the Begg's test (p = 0.88) and Egger's test (p = 0.42) (Supplementary Fig. 3).

High ERCC1 expression was associated with unfavorable PFS both in Asians (HR = 3.33, 95% CI = 2.04 – 5.44; I^2 = 0.0%) and Caucasians (HR = 1.89, 95% CI = 1.25 – 2.85; I^2 = 0.0%). Moreover, in all subgroup analyses high ERCC1 expression was associated with shorter PFS in HNSCC patients receiving platinum-based chemotherapy irrespective of the ERCC1 expression detection method and tumor site (Table 2).

Overall survival

Fifteen studies composed of 940 patients, of whom 530 (56%) were with high ERCC1 expression, reported data on adjusted estimates of OS (Table 2) [11-13, 15, 22, 24-26, 28-30, 32-33]. The covariates reported in included studies were: age and TNM stage in all studies, site [11-13, 15, 25], sex [11, 22, 26, 30], tumor differentiation [11, 13, 25, 30], performance status [28, 30], histologic type [29, 33], smoking [15, 22], alcohol drinking [22], betel nuts chewing [22], HPV status [15], treatment methods [28, 33], resection margin [11], extracapsular spreading [11], previous RT [30], relapse interval [30] and phosphor-mTOR expression [28]. The

pooled analysis showed that high ERCC1 expression was associated with shorter OS (HR = 1.95, 95% CI = 1.18 – 3.21, I^2 = 70.8%, p = 0.000 for heterogeneity) (Table 2). No significant bias was found by the Begg's test (p = 0.22) and Egger's test (p = 0.84) (Supplementary Fig. 4). High ERCC1 expression was a predictor of shorter OS both in Asians and Caucasians (HR = 3.13, 95% CI 2.09 – 4.70; I^2 = 0.0% and HR 2.02, 95% CI 1.32 – 3.07; I^2 = 23.7% respectively) (Table 2, Fig. 3a). On the contrary, the study conducted in South America [11] in which ERCC1 expression was identified by IHC and RT-PCR, revealed that high ERCC1 expression was associated with better OS (HR = 0.17, 95% CI 0.07 – 0.40; I^2 = 0.0%).

Subgroup analysis based on a detection method showed association between better survival and low ERCC1 expression determined by 8F1 and other immunohistochemistry methods while it was not the case with RT-PCR (Table 2). In the stratified analysis according to tumor site ERCC1 expression was related to OS in nasopharyngeal cancer, but not in the group of mixed head and neck tumors with or without nasopharyngeal cancer (Table 2, Fig. 3b).

Fourteen studies composed of 952 patients, of whom 463 (49%) were with high ERCC1 expression, reported data on unadjusted estimates of OS (Table 2) [11-13, 15, 22, 27, 29-30, 32-33]. In the pooled analysis of unadjusted HR estimates of OS no association was found between ERCC1 expression and OS (HR = 1.10, 95% CI 0.76 – 1.59; I^2 = 55.9, p = 0.01 for heterogeneity) (Table 2). No significant bias was found by the Begg's test (p = 0.27) and Egger's test (p = 0.08) (Supplementary Fig. 5). However, in subgroup analysis based on ethnicity, low ERCC1 expression was predictor of better OS in Asians but not in Caucasians (HR = 2.13, 95% CI 1.27 – 3.59; I^2 = 0.0% and HR = 1.03, 95% CI 0.70 – 1.52; I^2 = 42.8%) while in South Americans high ERCC1 expression was a predictor of better survival (HR = 0.36, 95% CI 0.20 – 0.65; I^2 = 0.0%) (Table 2, Fig. 4). Even when the South American study with two datasets [11] was excluded from the analysis, there was still no association between ERCC1 expression and OS in the meta-analysis of unadjusted estimates. In the stratified analysis according to detection method and tumor site, no association was found between OS and ERCC1 expression (Table 2).

In the sensitivity analysis no individual study significantly affected the pooled OR in ORR and HR in PFS and OS.

Discussion

The ERCC1-XPF heterodimer is a structure-specific endonuclease that is involved in several DNA repair mechanisms like interstrand cross-link repair, repair of DNA DSB and NER system. ERCC1 mediates DNA binding and protein-protein interactions of the ERCC1-XPF complex while XPF provides the endonuclease activity. Besides its important role in the multiple repair mechanisms the ERCC1-XPF is also involved in telomere maintenance. As the part of NER system the ERCC1-XPF incises the damaged DNA strands 5' and 3'. In the DSB repair the ERCC1-XPF removes non-homologous 3' single-strands flaps at broken ends before they are rejoined. The ERCC1-XPF incises both sides of interstrand cross-links (34). On the other hand, platinum based chemotherapy and radiotherapy which are basics of the treatment of HNSCC patients exert their cytotoxic effect through formation of DNA damages. Therefore, due to the important role in the DNA repair mechanisms the expression of the ERCC1 and its correlation with clinical outcomes of HNSCC patients

treated with platinum-containing therapy has been studied in large number of studies but with inconsistent results.

Results of present meta-analysis of 1288 patients and 1427 tissue samples indicated that high ERCC1 expression was significantly associated with shorter PFS and OS (when adjusted for covariates) in patients with HNSCC treated with cisplatin-based therapy. Low ERCC1 expression was also a significant predictor of better ORR. However, ethnicity and tumor site arose as important factors. Interestingly ERCC1 expression was not a predictor of OS in the analysis of unadjusted HR estimates.

Xuelei et al. [16] reported that ERCC1 expression was associated with OS in the pooled HRs analysis and in Asians while ERCC1 expression was not a predictor of the ORR in the whole cohort of patients except in Asians. Low/negative expression of ERCC1 was associated with longer OS and PFS in patients treated with cisplatin-based CRT, but there was no significant difference in ORR between low/negative and high/positive ERCC1 expression [17]. What are differences and similarities between these two meta-analyses and our meta-analysis? Firstly, the relationship between high ERCC1 expression and resistance to platinum-based chemotherapy has been better established for lung and ovarian cancer than for head and neck cancer. There is a considerable heterogeneity between reported results in head and neck patients. Whereas the literature on ERCC1 and radiotherapy is very scarce and the evidence for that relation has not been robust especially in clinical settings, we think it is of great importance to analyze separately treatments including platinum-based chemotherapy and radiotherapy alone [35-37]. Besides it was reported that although ERCC1 positive cells showed increased chemoresistance they might have been particularly radiosensitive and less hypoxic [38]. Xuelei et al. [16] included in their meta-analysis all studies irrespective of treatment modality, while Gao et al. [17] included studies dealing with cisplatin-based chemoradiotherapy. We included all the studies with treatments containing platinum-based chemotherapy. Moreover, we presume that there may be a difference between ERCC1 expression and clinical outcome in neaodjuvant and adjuvant treatment. Namely, results of the study from South America with two datasets [11] quite differ from results of the majority of other studies and the reason for that may be ethnicity but also the fact that it was the only study with adjuvant treatment.

Secondly, wide heterogeneity of detection methods has been reported in studies under consideration [11-15, 22-33]. It has been shown that ERCC1 immunodetection faces several methodological challenges including tissue processing, rates of interobserver agreement, geographic variation in protein expression and, most importantly, lack of the standardized cutoff value in semi-quantitative IHC [39-41]. It has been also reported that the most frequently used antibody 8F1 has not been specific for ERCC1 [42]. It also tags a spurious 45 kDa band on immunoblotting, a cross reaction that results in ERCC1-XPF deficient cells being falsely characterized as having ERCC1-XPF expression [43], and the unrelated nuclear membrane protein choline phosphate cytidylyltransefrase-α (PCYT1 α) [44-45]. Fiboulet et al. [46] reported that the major limitation to ERCC1 employment in guiding the treatment decision was the lack of ERCC1 antibodies that would detect functionally different ERCC1 isoforms. The ERCC1-202 was identified as the unique functional isoform of ERCC1. Therefore, in our meta-analysis stratification according to detection method was applied. ERCC1 immunodection was associated with ORR, PFS and OS (adjusted HR estimates) irrespective of different antibodies and different cutoff values. However, no association was found for RT-PCR. It is in accordance with the report of Friboulet et al. [46]. Despite the fact that RT-PCR was more quantitative analysis of ERCC1 than IHC, a predictive potential of ERCC1 appeared to be stronger at a protein level [46].

Thirdly, in our meta-analysis we performed subgroup analysis based on tumor site which was not a case in the meta-analysis of Xuelei et al. [16]. Low ERCC1 expression was associated with better ORR in nasopharyngeal cancer and in the group of mixed head and neck cancers without nasopharyngeal cancer but ERCC1 expression was associated with overall survival (adjusted HR estimates) only in nasopharyngeal cancer group. Probably, high heterogeneity (I^2 = 80.5%) of the mixed head and neck cancer group was responsible for the lack of the association between ERCC1 expression and OS in that group. Gao et al.[17] also reported that ERCC1 expression was a predictor of OS in patients with nasopharyngeal carcinoma.

Fourthly, Xuelei et al. [16] used multivariate and univariate data together while we performed separate meta-analyses of univariate and multivariate data for OS. We used only univariate data for PFS since multivariate data are scarce.

Although sharing some similarities with the meta-analysis of Gao et al. [17] our analysis of adjusted OS estimates included larger sample size of 940 patients from 15 studies while the study of Gao et al. [17] included 568 patients from 9 studies.

Both meta-analyses, that of Xuelei et al. [16] and the present one, found strong association between ERCC1 expression and ORR and OS in Asian population. Gao et al. [17] also reported that ERCC1 expression was a predictor of OS in Asians but not in non-Asians. In our analysis of unadjusted and adjusted HR estimates, ERCC1 expression was significantly associated with OS in Asians while in Caucasians significant association was found only in the analysis of adjusted HR estimates. In the analysis of Xuelei et al. [16] ERCC1 expression was not associated with OS in Caucasians. Low ERCC1 expression was strong prognostic factor of better PFS in all three meta-analyses.

Our meta-analysis has several limitations. Firstly, the included studies differed considerably in study design, cutoffs in ERCC1 expression, treatment scheme and chemotherapy regimen contributing thus to the observed heterogeneity. Secondly, 8F1 was the most frequently used antibody for ERCC1 expression, and in the light of new knowledge about this antibody caution is needed not only in the interpretation of results of the study, but also in its possible implementation in the clinical setting. Thirdly, the majority of included studies are of small sample size with only 4 of them having more than 100 patients, which may contribute to the heterogeneity. Only one randomized study and one extension of the randomized study were identified. Fourthly, it is possible that calculations of HR estimates and corresponding 95% CIs from Kaplan Mayer's curves also contributed to heterogeneity and bias.

The results of this meta-analysis provided evidence that ERCC1 has a potential to become predictive and prognostic factor enabling tailoring of treatment in patients with HNSCC. However, considering limitations of this analysis and rapidly expending scientific knowledge about the ERCC1, our findings need to be interpreted with caution. The standardized methodology of ERCC1 expression determination and well-designed prospective randomized studies are needed before its implementation in everyday clinical practice.

Conflict of interest: None

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Fig. 1 Forest plot for the association between ERCC1 expression and objective response rate (ORR) in patients with head and neck cancer receiving platinum-based therapy. Results are stratified by ethnicity.

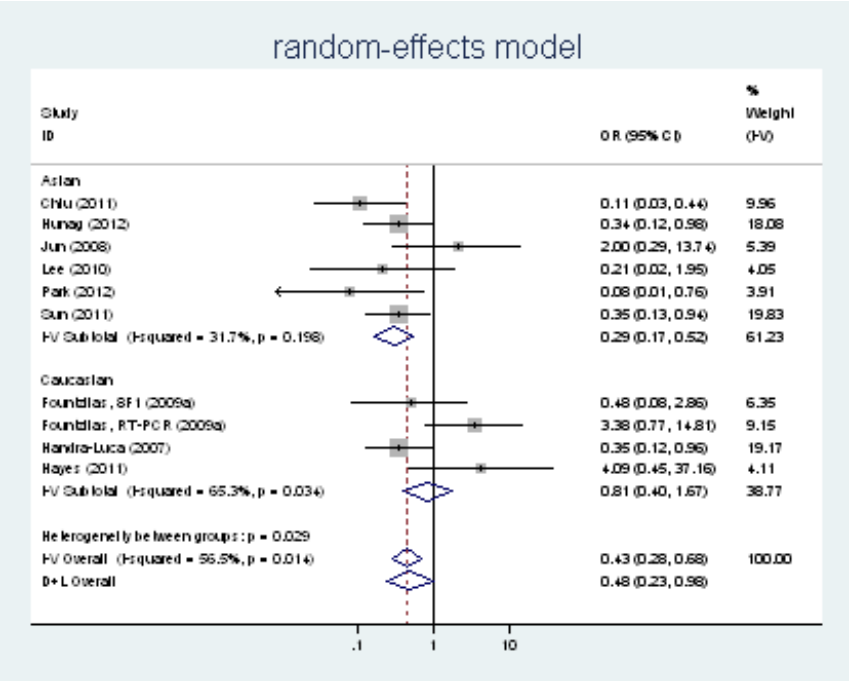


Fig. 2 Forest plot showing the meta-analysis of unadjusted hazard ratio estimates for progression-free survival (PFS) in patients with head and neck cancer receiving platinum-based therapy.

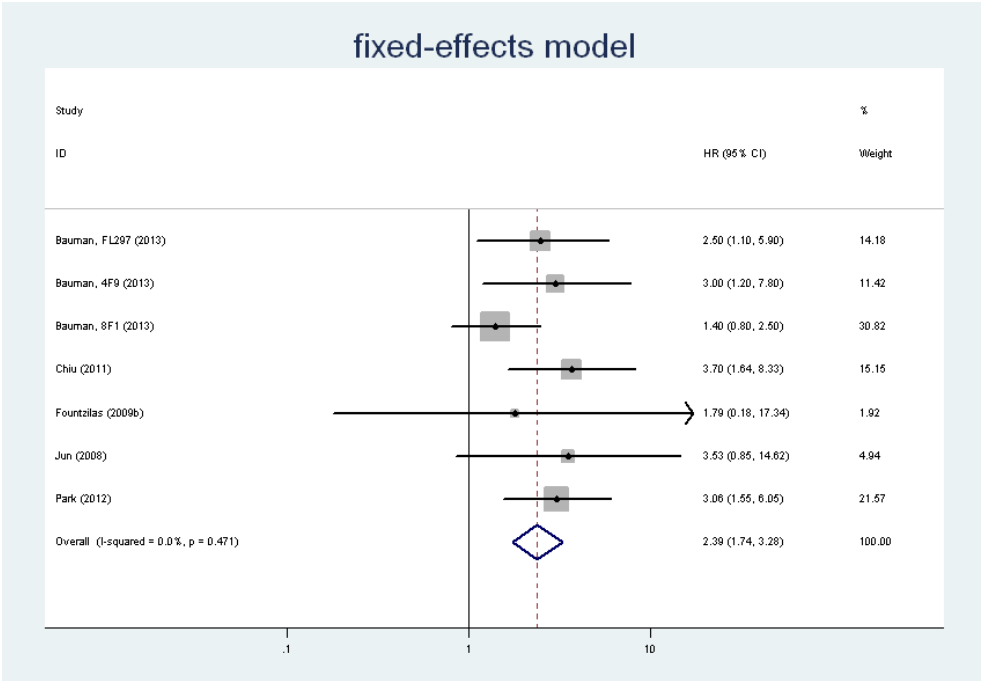
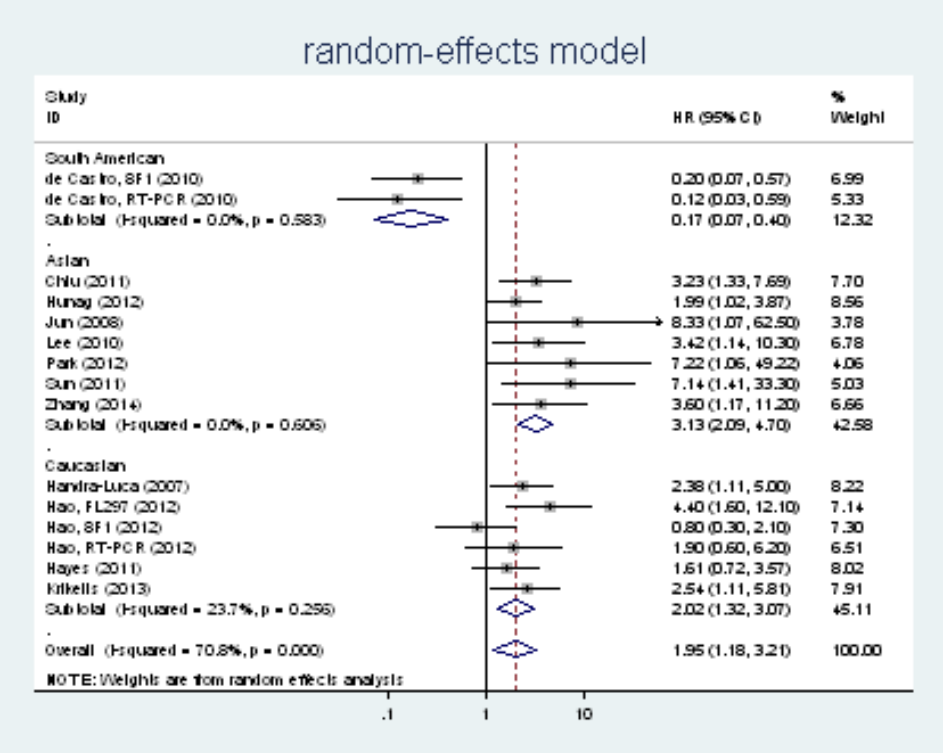


Fig. 3 Forest plot showing the meta-analysis of adjusted hazard ratio estimates for overall survival (OS) in patients with head and neck cancer receiving platinum-based therapy.

a) Results are stratified by ethnicity



b) Results are stratified by tumor site.

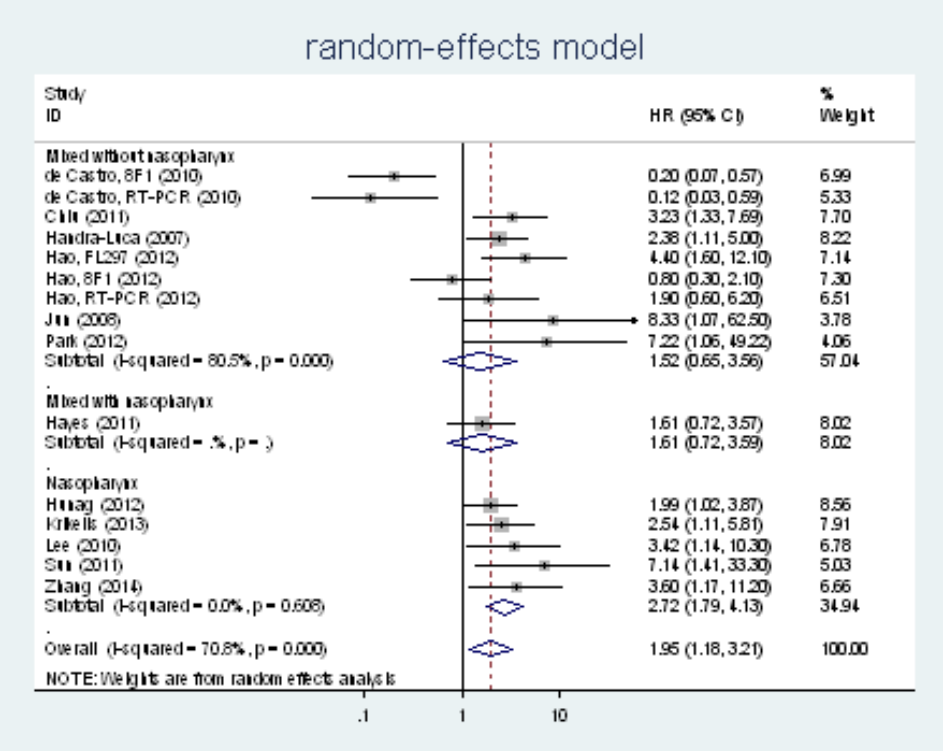


Fig. 4 Forest plot showing the meta-analysis of unadjusted hazard ratio estimates for overall survival (OS) in patients with head and neck cancer receiving platinum-based therapy. Results are stratified by ethnicity.