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Review

Prognostic biomarkers in oral squamous cell carcinoma: A systematic review

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ABSTRACT

Over the years, several tumor biomarkers have been suggested to foresee the prognosis oral squamous cell carcinoma (OSCC) patients. Here, we present a systematic review to identify, evaluate and summarize the evidence for OSCC reported markers. Eligible studies were identified through a literature search of MEDLINE/PubMed until January 2016. We included primary articles reporting overall survival, disease-free survival and cause-specific survival as outcomes. Our findings were analysed using REporting recommendations for tumor MARKer prognostic studies (REMARK), QuickGo tool and SciCurve trends. We found 41 biomarkers, mostly proteins evaluated by immunohistochemistry. The selected studies are of good quality, although, any study referred to a sample size determination. Considering the lack of follow-up studies, the molecules are still potential biomarkers. Further research is required to validate these biomarkers in well-designed clinical cohort-based studies.

Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the head and neck (excluding nonmelanoma skin cancer), with more than 300,000 new cases reported annually worldwide [1]. The disease has a high morbidity rate (37.8%) five years after diagnosis (http://www.cancer.gov/statistics/find – 2003–2009 data); despite the progress in research and therapy, survival has not improved significantly in the last few decades [2]. The search for prognostic markers represents a continuing challenge for biomedical science.

A cancer biomarker may be a molecule secreted by a tumor cell or a specific response of the body to the presence of cancer [3]. Biomarkers can be used for patient assessment in multiple clinical settings, including estimating the risk of disease and distinguishing benign from malignant tissues [4]. Cancer biomarkers can be classified based on the disease state, including predictive, diagnosis and prognosis biomarkers [5]. A prognostic biomarker informs about a likely cancer outcome (e.g., overall survival, disease-free survival, and cause-specific survival) independent of treatment received [6].

According to the NCI Dictionary of Cancer Terms (https://www.cancer.gov/publications/dictionaries/cancer-terms) the overall survival (OS) corresponds to the length of time from either the date of diagnosis or the start of treatment for cancer, which patients diagnosed with the disease are still alive. Disease-free survival (DFS, also called relapse-free survival) offers the length of time after primary treatment ends that the patient survives without any signs or symptoms of that cancer. Cause-specific survival (CSS) is the length of time from either the date of diagnosis or the start of treatment for cancer to the date of death from the disease.

From the identification of a promising biomarker to its clinical use, there is a long pathway involving many complicated hurdles, such as estimating the number of patients needed for the validation phase and statistical validation, among others [7,8]. This validation and qualification are responsible for linking the promising biomarker with a biological process to clinical endpoints [9].

Considering several tumor biomarkers have been suggested to predict the prognosis of OSCC patients, we performed a systematic

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review, which is widely accepted as a "gold standard" in medicine based on evidence [10], to identify, evaluate and summarize the evidence for OSCC reported markers.

Materials and methods

We performed a systematic review to conduct this investigation. The independent variables were prognostic biomarkers; the dependent variables were OSCC outcomes.

Search strategy

A systematic review allows critical analysis of multiple research studies. Aiming to answer the question "what are the biomarkers of OSCC?", a systematic literature search based on keywords was performed. As PubMed comprises more than 26 million citations from the biomedical literature from MEDLINE, it is the search engine of choice to initiate queries in the health sciences. To identify all the primary research studies that evaluated candidate biomarkers in OSCC, we searched the MEDLINE/PubMed (http://www.ncbi.nlm.nih.gov/pubmed) medical literature database up to January 18, 2016. The search strategy was based on combinations of the following keywords: "mouth neoplasms" [MeSH] and "biomarkers" [MeSH] and (risk ratio [Title/Abstract] or relative risk [Title/Abstract] or odds ratio [Title/Abstract] or risk [Title/Abstract]) and ("humans"[MeSH Terms] and English [lang]).

Inclusion criteria

Articles were included based on a previously published protocol [11]. Briefly, studies were selected if they examined the impact of a potential biological marker on at least one of the features in OSCC patients: OS, DFS or CSS. These definitions were assessed among the selected papers. In addition, if a study was focused on isolated or combined (multiple) tumor biomarkers, it must have been subjected to multivariable analysis with one or more additional variables.

Exclusion criteria

Articles were excluded from the present review for the following reasons: (i) lack of the terms "oral cancer" and "risk" in their titles, abstracts or keywords; (ii) absence of risk ratios and (iii) unclear defining criteria for groups and variables.

Potential prognostic biomarker

To determine whether a biomarker is potentially prognostic, the selected articles showed: (i) a formal test (binary logistic regression or Cox proportional hazards model) and (ii) a statistically significantly association between the biomarker and outcome [6]. The computed risk (odds ratio, OR or hazard ratio, HR) was reported as the risk of a specific outcome from the biomarker group versus the reference group, with OR/HR > 1 indicating increased risk and OR/HR < 1 indicating decreased risk.

Data extraction

One investigator reviewed all the eligible studies and carefully extracted the study characteristics, including the article citation information, biomarker name and classification, condition or outcome, laboratory technique, sample size, number of clinical outcomes, status of biomarker expression, statistical test method, computed risk and its p-value and 95% confidence interval (CI). The main biological processes in which the biomarkers are involved were obtained using QuickGo (http://www.ebi.ac.uk/QuickGO).

Quality assessment

Quality assessment was performed in duplicate for each eligible study by three independent reviewers using operationalized prognostic biomarker reporting the REMARK guidelines [12] and extracted details on 20 items. The inter-observer agreement was evaluated using Kappa statistics.

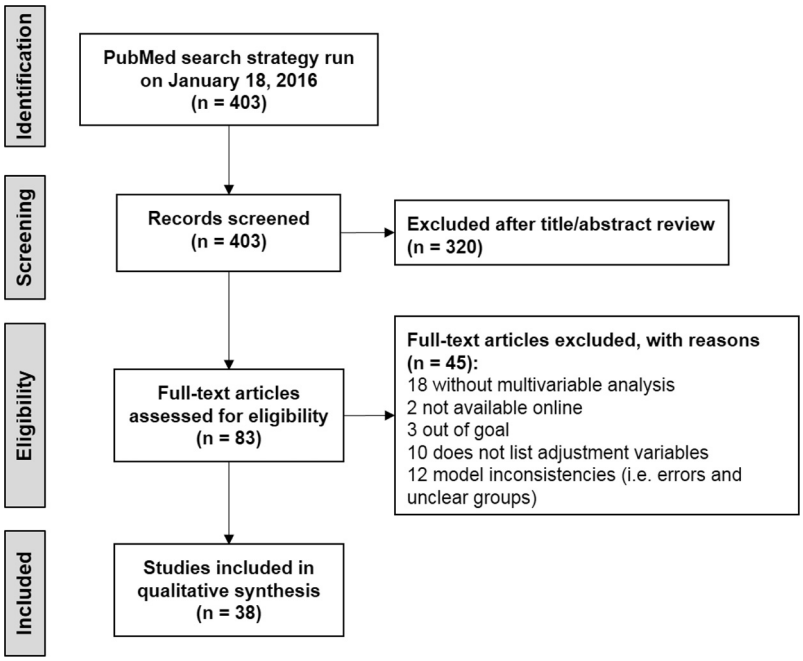

Fig. 1. Flow diagram representing systematic literature search on biomarkers and oral cancer outcomes. Studies were included if they examined the impact of a potential biomarker on at least one of overall survival, disease free survival or cause-specific survival in oral squamous cell carcinoma patients.