

# INPLASY PROTOCOL

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## The Prognostic Role of miR-195 and miR-34 in HNSCC: Protocol

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**Review Stage at time of this submission:** Data extraction.

**Conflicts of interest:**  
None declared.

**Review question / Objective:** The PICO question was as follows: What is the RR and HR in the prognostic survival indices among HNSCC patients with high tissue miR-195 expression compared to those with low expression? The different points studied were: (P) participants (patients with HNSCC), (I) intervention (impaired expression of miR-195 in HNSCC), (C) control (patients with HNSCC who have low expression of miR-195), (O) outcome (difference in death risk of survival prognosis between patients with low and high miR-195 expression in HNSCC).

**Main outcome(s):** The main outcomes are HR and the RR on the prognostic indices of survival including: OS, DFS, CSS and PFS.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 April 2022 and was last updated on 26 April 2022 (registration number INPLASY202240150).

### INTRODUCTION

**Review question / Objective:** The PICO question was as follows: What is the RR and HR in the prognostic survival indices among HNSCC patients with high tissue miR-195 expression compared to those

with low expression? The different points studied were: (P) participants (patients with HNSCC), (I) intervention (impaired expression of miR-195 in HNSCC), (C) control (patients with HNSCC who have low expression of miR-195), (O) outcome (difference in death risk of survival

prognosis between patients with low and high miR-195 expression in HNSCC).

**Condition being studied:** Squamous cell carcinoma of the head and neck region represents a heterogeneous group of neoplasms whose histological derivation comes from the lining epithelium of the mucous membranes: of the oral cavity (Oral squamous cell carcinoma OSCC) of the larynx (squamous cell carcinoma of the larynx, LSCC), of the hypopharynx squamous cell carcinoma of the hypopharynx, HSCC) and of the nasopharynx (nasopharyngeal carcinoma, NPC) of the oropharynx (squamous cell carcinoma of the oropharynx, OPSCC). per year with an estimated 5-year median survival for stages 3 4 of 30%. The recognized risk factors for HNSCC are smoking and alcohol which have a synergistic effect, furthermore for laryngeal carcinomas there is a correlation with HPV specifically for subtypes 16-18, generally LSCC HPV + s have a better prognosis by responding more effectively to radiotherapy. The etiopathogenetic mechanisms involving tumor genesis, including alterations in cell proliferation, apoptosis, invasion, migration and death, may involve alterations in the expression of MICRORNA. Microna are a small non-coded RNA sequence 18-22 nucleotides whose function is to regulate the gene expression of genes essential for the performance of physiological and pathological cellular activities. MicroRNAs can be found in tumor or precancerous tissues as well as upregulated (miR-21, miR-27, miR-31, miR-93, miR-134, miR-146, miR-155, miR-196a, miR-211, miR- 218, miR-222, miR-372 and miR-373) that downregulated (let-7, miR-26a, miR-99a-5p, miR-137, miR-139, miR-143, miR-184, miR-375 and miR-195). Many miRs have shown prognostic survival capabilities with potential as a biomarker. In the head and neck area, the main miR associated with a potential biomarker is miR-21 which would be upregulated in tumor tissues whose overexpression is potentially associated with a worsening of prognosis, similarly other upregulated miRs have also been investigated and among these the miR-31

and miR-155, among the downregulated miRs the focus is mainly on the Let-7 microRNA family and recently some interesting studies have turned towards miR-195. MiR-195 would be downregulated in the tissues of many cancers including bladder cancer, breast, stomach, lung, bone and liver. Its localization is on chromosome 17p13.1 and its mature form has the sequence of 5 'AGCAGCACA GAAUAUUGGC 3' MiR-195 performs various regulatory functions in the cell cycle and especially between the transition phases G2 / M and G1 \ S and also promotes apoptosis by inhibiting the expression of Bcl-2. Recent studies remaining in the vicinity of the head and neck area associated the downregulation of miR-195 in carcinomatous tissues with a worsening of prognostic survival indices in fact Sun et al. In 2014 they found how the aberrant expression of miR-195 can act as a promising poor prognostic biomarker for esophageal squamous cell carcinoma (ESCC), similarly similar results were found for LSCC in fact in 2017 Shuang on a cohort of 122 patients with carcinoma laryngeal identifies a Relative Risk (RR) of death at the end of the follow-up period between high and low expression of 0.358 indicating that there is a greater risk of death in patients with a downregulation of miR-195 in all carcinomatous. To date there are no systematic reviews with meta-analyses conducted specifically on the role of miR-195 in HNSCC, our hypothesis is that with the presence in the literature of recent studies conducted on miR-195 it is possible to clearly determine, by aggregating the results, if the aberrant expression of miR-195 in HNSCC tissues may represent a prognostic biomarker of survival through Hazard Ratio (HR) and RR analysis.

## METHODS

**Search strategy:** The research was conducted on 2 databases: SCOPUs and PubMed, and a registry: Cochrane central Trial; In addition, Google scholar (keywords miR-195), gray literature sources such as Open Gray (keywords miR) and the bibliographic references of previous systematic reviews on miR and HNSCC

were consulted, Specifically below are all the keywords used on pub med: (((((((("opsc" [All Fields] OR "opscs" [All Fields]) AND "miR-195" [All Fields]) OR "HSCC" [All Fields]) AND "miR-195" [All Fields]) OR "LSCC" [All Fields]) AND "miR-195" [All Fields]) OR "OSCC" [All Fields]) AND "miR-195" [All Fields]) OR "miR-195" [All Fields]) AND ("hnsccs" [All Fields] OR "squamous cell carcinoma of head and neck" [MeSH Terms] OR ("squamous" [All Fields] AND "cell" [All Fields] AND "carcinoma" [All Fields] AND "head" [All Fields] AND "neck" [All Fields]) OR "squamous cell carcinoma of head and neck" [All Fields] OR "hnscc" [All Fields])) OR ("microrna s" [All Fields] OR "micrnas" [MeSH Terms] OR "micrnas" [All Fields] OR "microrna" [All Fields])) AND ("hnsccs" [All Fields] OR "squamous cell carcinoma of head and neck" [MeSH Terms] OR ("squamous" [All Fields] AND "cell" [All Fields] AND "carcinoma" [All Fields] AND "head" [All Fields] AND "neck" [All Fields]) OR "squamous cell carcinoma of head and neck" [All Fields] OR "hnscc" [All Fields]); Translations OPSCC: "opsc" [All Fields] OR "opscs" [All Fields]; HNSCC: "hnsccs" [All Fields] OR "squamous cell carcinoma of head and neck" [MeSH Terms] OR ("squamous" [All Fields] AND "cell" [All Fields] AND "carcinoma" [All Fields] AND "head" [All Fields] AND "neck" [All Fields]) OR "squamous cell carcinoma of head and neck" [All Fields] OR "hnscc" [All Fields]; Microrna: "microrna's" [All Fields] OR "micrnas" [MeSH Terms] OR "micrnas" [All Fields] OR "microrna" [All Fields]; HNSCC: "hnsccs" [All Fields] OR "squamous cell carcinoma of head and neck" [MeSH Terms] OR ("squamous" [All Fields] AND "cell" [All Fields] AND "carcinoma" [All Fields] AND "head" [All Fields] AND "neck" [All Fields]) OR "squamous cell carcinoma of head and neck" [All Fields] OR "hnscc" [All Fields].

**Participant or population:** Patients with HNSCC.

**Intervention:** Altered expression of miR-195 in HNSCC tissue.

**Comparator:** Overall survival hazard ratio or Risk Ratio between low and high tissue expression of miR.195 in patients with HNSCC.

**Study designs to be included:** Retrospective studies, observational studies and RTC.

**Eligibility criteria:** All retrospective, prospective and randomized trials that considered differences in miR-195 expression in patients with HNSCC in correlation with prognostic indices of survival and specific OS were taken into consideration.

**Information sources:** The research of the studies involved 2 independent reviewers (M.D. and D.S.). The research and selection phase of the articles was carried out in 3 phases, in the first phase the inclusion and exclusion criteria, the databases, the keywords to be used and the period of time in which to conduct the search were jointly decided. second phase we proceeded separately to the research and selection of the studies with the removal of the overlapps using reference management software such as EndNote 8.0 with the inclusion of the studies, in the third phase we proceeded to the comparison of the included studies and to resolve any conflicts between the 2 auditors with the help, if necessary, of a 3 auditor (G.T) to decide on doubtful situations. the keywords used were miR-195 AND HNSCC, Microrna AND HNSCC, LSCC AND miR-195, OSCC AND miR-195, OPSCC AND miR-195, HSCC AND miR-195. The research was conducted on 2 databases: SCOPUS and PubMed, and a registry: Cochrane central Trial; In addition, Google scholar (keywords miR-195), gray literature sources such as Open Gray (keywords miR) and the bibliographic references of previous systematic reviews on miR and HNSCC were consulted.

**Main outcome(s):** The main outcomes are HR and the RR on the prognostic indices of survival including: OS, DFS, CSS and PFS.

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**Quality assessment / Risk of bias analysis:**

The risk of bias in the individual studies was assessed by an Author (MD), as a tool for the evaluation parameters derived from the Reporting Recommendations for prognostic studies of markers (REMARK). Studies with a high risk of bias were excluded from the meta-analysis. The risk of bias between the studies, on the other hand, was assessed through the heterogeneity indices (Higgins index I<sup>2</sup>) and graphically through the visual analysis of the overlapping of the confidence intervals in the various forest plots and through the funnel Plot, the asymmetry of the funnel plot will be used for a publication bias assessment.

**Strategy of data synthesis:** For the meta-analysis, the Reviewer Manager 5.4 software will be used, applying fixed or random effects based on the heterogeneity of the studies.

**Subgroup analysis:** A subgroup analysis could be performed on the basis of the number of studies included as a function of tumor histological sub-types.

**Sensitivity analysis:** It could be performed in the presence of heterogeneity of the data to identify the source.

**Language:** Only clinical studies in English.

**Country(ies) involved:** Italy.

**Keywords:** miR-195, HNSCC, OSCC, LSCC, microRNA.

**Contributions of each author:**

Author 1 - Mario Dioguardi.