# INPLASY PROTOCOL

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**Conflicts of interest:**
**None declared.**

# Extracellular Vesicle-Based Drug Delivery Systems for Head and Neck Squamous Cell Carcinoma: A Systematic Review

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**Review question / Objective:** **This systematic review aims to identify studies investigating the membrane vesicle-based drug de-livery systems (DDS) for HNSCC and define the potential of extracellular vesicles (EVs) in the treatment of this disease according to the current state of knowledge.**
**Condition being studied:** **Head and neck squamous cell carcinoma (HNSCC), which is ranked the sixth most common malignancy worldwide, originates in the epithelium of the oral and nasal cavities, pharynx, and larynx. The treatment of HNSCC remains a challenge and requires the involvement of a multidisciplinary team. Currently available methods of treatment, such as surgery, radiotherapy, and chemotherapy, cause significant dysfunctions and toxicity, which highlights the necessity to explore new therapeutic options. One-third of patients treated with intended curative surgery and adjuvant therapy experience local or regional recurrence and/or distant metastasis.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 April 2023 and was last updated on 07 April 2023 (registration number INPLASY202340021).

## INTRODUCTION

**Review question / Objective:** **This systematic review aims to identify studies investigating the membrane vesicle-based drug de-livery systems (DDS) for HNSCC and define the potential of extracellular vesicles (EVs) in the treatment of this disease according to the current state of knowledge.**

**Rationale:** **Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy world-wide, where currently available treatments cause significant dysfunctions and toxicities, which indicates the need to search for new**

treatment options. In this article, we would like to summarize the most important information regarding the potential use of mem-brane vesicle-based DDS in HNSCC, including sources of EVs, purification, isolation, characterization, and labeling methods, modifications of EVs for DDS and therapeutic effects of membrane vesicle-based DDS in HNSCC.

**Condition being studied:** Head and neck squamous cell carcinoma (HNSCC), which is ranked the sixth most common malignancy worldwide, originates in the epithelium of the oral and nasal cavities, pharynx, and larynx. The treatment of HNSCC remains a challenge and requires the involvement of a multidisciplinary team. Currently available methods of treatment, such as surgery, radiotherapy, and chemotherapy, cause significant dysfunctions and toxicity, which highlights the necessity to explore new therapeutic options. One-third of patients treated with intended curative surgery and adjuvant therapy experience local or regional recurrence and/or distant metastasis.
New approaches to targeted cancer therapy are being intensively researched to overcome innate and acquired tumor resistance, as well as to prevent their side effects and adverse effects. In addition, therapies that are more personalized and tailored to the tumor and patient profile are increasingly being sought. Since the discovery that extracellular vesicles (EVs) carry biological information, the potential use of EVs as drug-delivery vehicles has gained scientific interest.

## METHODS

**Search strategy:**
Scopus: TITLE-ABS-KEY ((extracellular vesicle*) OR (multivesicular bodies) OR (exosome*)) AND ((squamous cell carcinoma*) AND ((head and neck) OR (larynx) OR (laryngeal) OR (nasal cavity) OR (oral) OR (pharyngeal) OR (hypopharyngeal) OR (nasopharyngeal) OR (oropharyngeal) OR (mouth))) AND ((delivery system*) AND (drug*))
Limited to: Article

Web of Science
AB=(((extracellular vesicle*) OR (multivesicular bodies) OR (exosome*)) AND ((squamous cell carcinoma*) AND ((head and neck) OR (larynx) OR (laryngeal) OR (nasal cavity) OR (oral) OR (pharyngeal) OR (hypopharyngeal) OR (nasopharyngeal) OR (oropharyngeal) OR (mouth))) AND ((delivery system*) AND (drug*)))
Pubmed
(("Extracellular Vesicles"[Mesh]) OR ("Multivesicular Bodies"[Mesh]) OR ("Exosomes"[Mesh]) AND ("Squamous Cell Carcinoma of Head and Neck"[Mesh]) AND ("Drug Delivery Systems"[Mesh])
Cochrane
#1 MeSH descriptor: [Extracellular Vesicles] explode all trees
#2 MeSH descriptor: [Multivesicular Bodies] explode all trees
#3 MeSH descriptor: [Exosomes] explode all trees
#4 MeSH descriptor: [Drug Delivery Systems] explode all trees
#5 MeSH descriptor: [Squamous Cell Carcinoma of Head and Neck] explode all trees
#6 (#1 OR #2 OR #3) AND #4 AND #5.

**Participant or population:** Full-text original research studies concerning membrane vesiclebased DDSs for HNSCC, written in English were included regardless of the publication date. Both animal and in vitro studies were included.

**Intervention:** Not reported.

**Comparator:** Not reported.

**Study designs to be included:** Original articles.

**Eligibility criteria:** Full-text original research studies concerning membrane vesicle-based DDSs for HNSCC, written in English were included regardless of the publication date. Both animal and in vitro studies were included. Review articles, book chapters, letters to the editor, expert opinions, study protocols, conference papers, case reports, case series, unpublished articles, and papers in other languages than English were excluded from further consideration.

**Information sources:** A systematic literature review carried out with the use of four databases: Pubmed/MEDLINE, Scopus, Web of Science, and Cochrane.

**Main outcome(s):** The above-described search strategy allowed the identification of 18 articles that meet all the inclusion criteria. All selected for the review papers are original studies published in the years 2019-2022, which corresponds with rapid development in this field in recent years. The majority (13) of studies were conducted in China, two in Japan, and one in Israel, France, and India. There are in vivo studies (mainly mice model), in vitro, and ex vivo studies.
In this review, we have presented perspectives on the use of new DDS in the treatment of HNSCC. Membrane vesicle-based DDSs have led to tremendous advances in cancer therapy by direct targeting of cancer cells, which improved efficacy and reduced toxicity but also by impacting tumor chemo- and radioresistance.

**Additional outcome(s):** EVs may have many advantages over currently available drug carriers. They improved the therapeutic effect by protecting, stabilizing, and delivering the drug exactly to the target. Although they face several biological barriers during transport to tissues, they have the ability to overcome them, because they are formed naturally.

**Data management:** Basic data on the research articles included in this systematic review describing type of study, type of EVs, EVs cargo, main results, and additional information are presented in tables.

**Quality assessment / Risk of bias analysis:** The risk of bias for the interpretation of the data was assessed with the use of the Office of Health Assessment and Translation (OHAT), modified by the authors for the needs of this review. Selection, performance, attrition/exclusion, detection, and selective reporting were assessed independently by two investigators using a four-point scale: "definitely low risk of bias", "probably low risk of bias", "probably high risk of bias", and "definitely high risk of bias". Any discrepancies in judgments regarding the risk of bias were resolved by discussion to reach a consensus between the two review authors.

**Strategy of data synthesis:** A customized data extraction sheet was used for the collection of the following information: first author's name, year and country of publication, study design, the aim, study population, and the main results.

**Subgroup analysis:** Type of EVs and Carcinoma Models.

**Sensitivity analysis:** Conducted by 2 authors, assessed with the use of the Office of Health Assessment and Translation (OHAT), modified by the authors for the needs of this review.

**Language restriction:** English.

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

**Keywords:** drug delivery systems; head and neck squamous cell carcinoma; exosomes; extracellular vesicles; nanoparticles.

**Contributions of each author:**
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