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REVIEW

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Head and neck cancer organoids as a promising tool for personalized cancer therapy: A literature review

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Abstract

Background and Aim: Chemotherapy and targeted therapy are used in treating head and neck cancers (HNCs) either alone or in combination with surgery, especially in advanced tumors but these treatments have resulted in variable outcomes in different patients. This, along with the introduction of new therapies to improve the survival of patients makes it necessary to search for models that can predict the response to treatment among different patients. Organoids, as three-dimensional culture models, have been studied more widely in non-HNCs and to a lesser extent in HNCs as tools to predict treatment outcomes. We aimed to conduct a review to validate the use of organoids as a preclinical tool for the treatment of HNCs patients.

Methods: A comprehensive literature search was separately performed by both authors in PubMed and google scholar databases, using the following keywords: "organoid," "head and neck cancer," "personalized medicine," "chemotherapy," and "targeted therapy." The articles published up to September 2021 were included in this review and selected according to a quality appraisal method.

Results: Examination of HNC-derived organoids made in various studies showed that these organoids had the ability to recapitulate original tumor features, including histopathological properties, functional characteristics, and expression of molecular markers in almost all of the studies. Differential sensitivity to chemotherapy drugs similar to in vivo was observed in sensitivity testing. Epidermal growth factor receptor (EGFR) expression levels were different between organoids from different patients and EGFR expression level was found to correlate with the response to anti-EGFR targeted therapy. A similar result was reported for organoids derived from salivary adenoid cystic carcinoma.

Conclusion: Since HNC-derived organoids seem to recapitulate characteristics of original tumors and to show differential responses to different chemotherapy and targeted therapy agents, these organoids might have the potential to be used as preclinical prediction tools for the treatment of HNC patients.

KEYWORDS

head and neck neoplasms, head and neck cancer, organoids, precision medicine

1 | INTRODUCTION

Head and neck cancers (HNCs) are the seventh most common cancer in the world and the 5-year survival rate is around 25%–60%.[1,2] Many efforts and research have been done to increase the 5-year survival rate of these cancers. Although targeted therapy has been developed in recent years to improve prognosis in HNC patients, chemoradiotherapy is still the mainstay of HNC treatment, especially in unresectable ones, which has been associated with variable individual clinical outcomes.[3,4] In some cases, even the addition of a chemotherapeutic agent has led to toxicity and increased microscopic grade.[5] One of the challenges in HNC therapy is also the introduction of new drugs to treat patients, the response to which is unknown in different people.[6,7]

To ensure the success of chemotherapy or targeted therapy, we need models that can predict the response to treatment among different patients. Culture models are one of such models. If a culture model is to be used as a preclinical predictive tool, it must determine the response to treatment in a short period of time and be similar to the patient's tumor. For example, Xenograft mouse models are long-term tools that require 20–40 weeks to obtain the results of chemotherapy sensitivity tests; tumor cells also adapt to the mouse environment, which leads to genetic alteration of tumor cells. These mouse models are not suitable as they are expensive, and are not appropriate for multidrug testing.[6,8] Cell culture models provide an opportunity to fill this gap; tumor tissue can be cultured and various treatment methods can be evaluated to predict the outcome of treatment before trying them on patients.[7] Two-dimensional (2D) cell culture models are one of such models; however, 2D cultures have many limitations like the absence of natural structure of the tumor, disturbance of interactions between the cellular and extracellular environments and changes in cell morphology and polarity.[1] So, to overcome these limitations, special attention has been paid to three-dimensional (3D) ones. Evaluating the response of 3D culture models for chemotherapy, radiotherapy, immunotherapy, and targeted therapies helps us a lot in formulating personalized medicine through preclinical prediction of therapeutic response. There are several 3D culture models for HNCs, including multicellular spheroids, cancer stem cells-enriched spheroids, organoids, histocultures, patient-derived xenografts (PDXs), and microdevices.[1,6,7]

An organoid is a 3D structure that recapitulates morphological, functional, and genetic characteristics of the tissue of origin.[9] The development of organoid technology has given a lot of hope for the evaluation of different drugs effects in the preclinical setting.[8]

We aimed to conduct a review to validate the use of organoids as a preclinical prediction tool for the treatment of HNCs patients.

1.1 | Literature search

A systematic narrative review of the literature published up to September 2021 was done. Keywords were selected for each subcategory and included "organoid" as the main keyword in combination with "head and neck cancer," "personalized medicine," "normal tissue," "chemotherapy," and "targeted therapy." Keywords were searched in PubMed and Google scholar databases. Articles were selected using a quality appraisal method and the most related articles were included in the review. For this reason, the titles and abstracts of the articles were screened and the full text of relevant articles was scrutinized by both authors (Figure 1).

This review includes all original research articles (in the English language), which reported the role of organoids in HNCs. Exclusion criteria were as follows: studies evaluating cancers located in other parts of the body other than the head and neck area and studies that did not report the role of the organoids.

In this review, we used the Joanna Briggs Institute (JBI) checklist to evaluate the quality of the studies. Based on this checklist, all selected studies were scored in terms of clear criteria for inclusion, detailed description of study subject and setting, reliability, and validity of study tools, using standard criteria or objective, identifying cofounding factor, strategy dealing with cofounders, outcome measured in a valid way and using appropriate statistical analysis. The minimum acceptable score for article eligibility was 60% and articles with a score less than 60% were excluded.

2 | CENTRAL BODY/DISCUSSION

2.1 | Examples of organoids for recapitulation of normal tissues

There are dynamic tissues in the body such as the endometrium; stem cells or progenitor cells are believed to be responsible for their regenerative properties. In recent years, there has been great interest in studying the characteristics of these cells because infertility, diseases of the endometrium, and proliferative disorders, such as endometriosis and cancers, can be treated by controlling these cells. There are some studies that have been examined methods to generate organoids from the endometrium.[10,11]

2.2 | Examples of using organoids in diseases as a personalized medicine tool

Since recognizing susceptibility to cystic fibrosis (CF) and underlying defects are necessary for predicting disease prognosis and response to treatment in variants of cystic fibrosis transmembrane conductance regulator (CFTR) gene, studies have been conducted to determine the characteristics of very rare mutations in the direction of personalized medicine. In this way, these studies have used organoids to evaluate the function of CFTR and response to treatment with modulators.[12,13]

Organoid-generating methods have made it possible to study the interaction between intestinal and gastric bacteria with gastrointestinal tissue. It has been shown that gastric organoids can be used for modeling the pathophysiologic response of gastric tissue to *Helicobacter pylori* infection.[14]

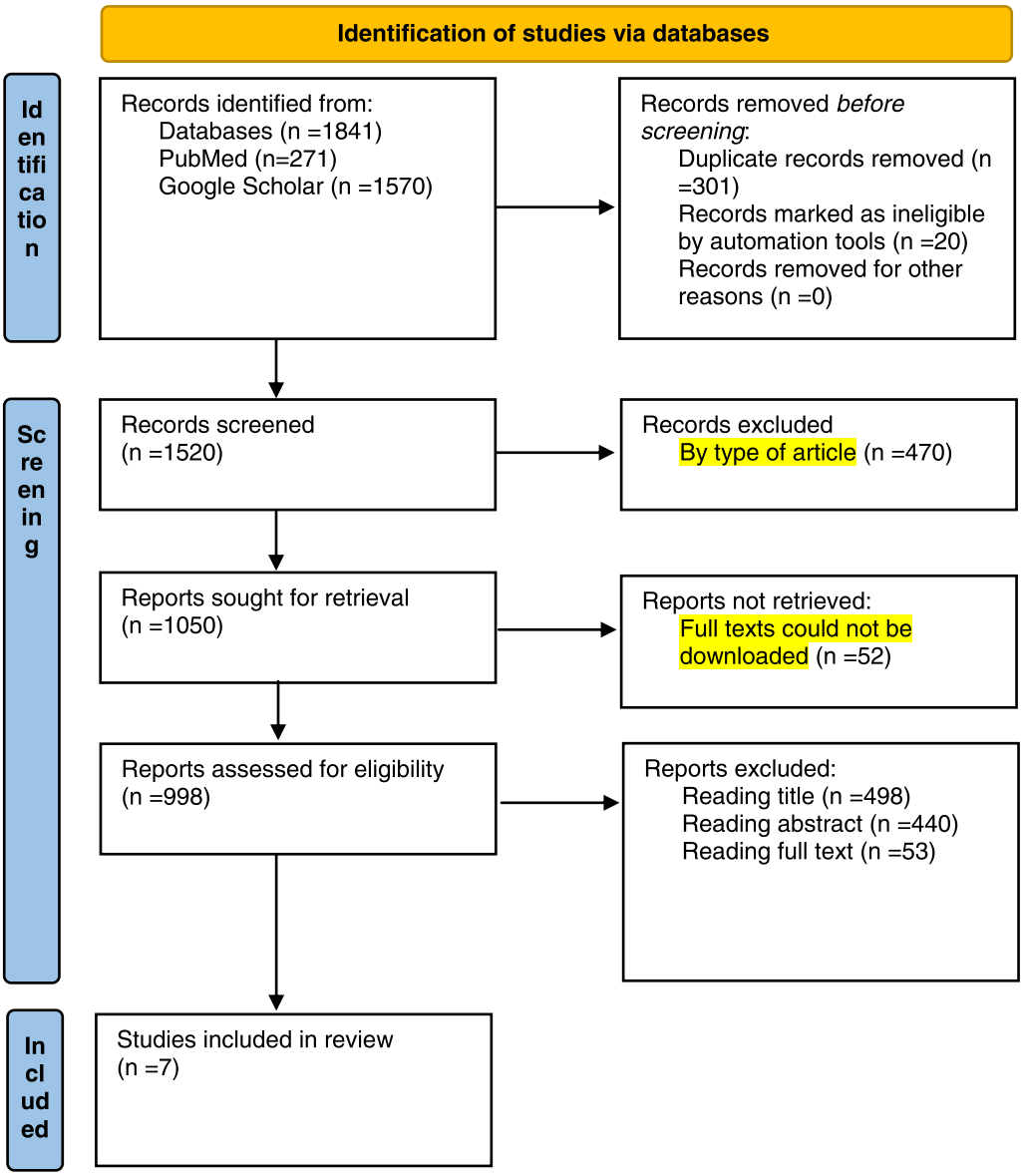

FIGURE 1 PRISMA flow diagram illustrating the process for the selection of the included studies for this review

2.3 | Examples of using organoids in non-HNCs

There are studies that describe adult stem cell-derived gastric organoid models and their characteristics and feasibility as a predicting tool for response to treatment in gastric cancer patients. They proposed that gastric organoids are in vitro models for studying gastric development and lead to precision medicine.[15]

In the case of prostate cancers, they have been very difficult to propagate in vitro, and there have been no models that can reconstruct the complex structure of prostate cancers, making it difficult to monitor disease progression and response to treatment. The use of tissue slices, monolayer cultures, mouse models, and PDXs has been unsuccessful in the reconstruction of the complex microenvironment of prostate cancers. In recent years, there have been successes in the production of patient-derived organoids in prostate cancers, which have allowed the use of these organoids to evaluate patients' therapeutic responses in a personalized medicine pathway.[16]

Although there have been challenges to establishing pure lung cancer organoids, studies to generate lung cancer organoids have been conducted; these challenges have limited the use of such organoids for personalized medicine.[17]

2.4 | Use of organoids as a preclinical prediction tool for response to chemotherapy in HNCs

Table 1 summarizes the characteristics of the studies included in this review on the use of HNC-derived organoids as a preclinical prediction tool for personalized cancer therapy (Table 1).

TABLE 1 Characteristics of the studies included in this review

Author (year)	Assay (assess of cell viability)	Cancer	Patient/ cases	Success rate	In vitro treatment	In vivo treatment	Duration (days)
Köpf-Maier (1992)[18]	Trypan blue (TB) exclusion assay	Human hypopharynx carcinoma	3	-	Chemotherapy (cisplatin)	Chemotherapy (cisplatin)	12
Tanaka (2018)[19]	Clonogenic survival assays	Head and neck squamous cell carcinoma	43	30.2%	Chemotherapy (cisplatin docetaxel)	Radiotherapy, cisplatin, docetaxel, and cetuximab	8
Driehuis (2018)[20]	-	Head and neck squamous cell carcinoma	-	-	Cisplatin, carboplatin and the anti-EGFR antibody cetuximab	-	-
Driehuis (2019)[21]	CellTiter-Glo 3D (promega)	Head and neck squamous	31	60%	Cisplatin, carboplatin, anti-EGFR antibody cetuximab, and radiotherapy	-	-
Driehuis (2019)[22]	CellTiter-Glo 3D reagent	Head and neck squamous cell carcinoma (tongue, larynx, parotid gland, oral cavity, gingiva)	8	-	Epidermal growth factor receptor (EGFR)-targeted photodynamic therapy	-	-
Facompre (2020)[23]	-	Head and neck Squamous cell Carcinoma	9 HPV + and 11 HPV−	-	-	-	-
Takada (2021)[24]	CellTiter-Glo 3D (promega)	Salivary adenoid cystic carcinoma	7	100%	-	-	-

Köpf-Maier et al. reported three strains of hypopharyngeal squamous cell carcinoma (HSCC) for testing chemotherapeutic agents with an organoid culture model. These three strains were highly sensitive to cisplatin chemotherapeutic agent (original strain), partially resistant to cisplatin, and highly resistant to cisplatin. Pathological evaluation of the culture models showed histological characteristics similar to the original HSCC up to 3 weeks of culturing. Organoid cultures of the original strain of HSCC were more sensitive to cisplatin than the other strains and the viability of the cultured cells was affected in clear dependence upon the drug concentration. It was demonstrated that this organoid culture assay was actually able to mirror the difference in levels of in vivo resistance to cisplatin in human carcinoma strains in in vitro conditions. It was concluded that organoids can be used as a model to determine drug sensitivity and resistance of cancers in a few days at the laboratory. Their study showed that organoids provide HNCs growth at the laboratory and retain many properties of the original tumor, including 3D and histological structure, formation of several cell types, and expression of biological markers.[18]

In Tanaka et al.'s study, the head and neck squamous cell carcinoma (HNSCC) organoids were established with a success rate of 30.2%. These organoids reconstructed many features of the original tumor, such as histological properties, expression of tissue markers, and in vitro response to therapy similar to in vivo. It was concluded that organoids can predict drug sensitivity in vitro and can be used as a preclinical tool for personalized medicine in HNCs.[19]

Driehuis et al. proposed that HNSCC-derived organoids have the potential for the prediction of patient response because they reconstructed the genetic and histological characteristics of original tumors. Also, different in vitro drug treatments demonstrated various responses.[20]

In another study by Driehuis et al., HNSCC derived organoids recapitulate genetic and molecular characteristics of HNSCCs. These organoids retained their tumorigenic potential upon xeno-transplantation. Different responses to various drugs and therapies, including cisplatin, carboplatin, cetuximab, and radiotherapy were found. These findings may indicate a personalized medicine approach to treating HNSCC and expand the range of HNSCC drugs.[21]

In Facompre et al.'s study, organoids were obtained from HPV + HNSCCs while preserving the genetic characteristics of cancer. According to the results of this study, organoids play an important role in complementing the space between in vitro and in vivo experiments to choose a suitable model for HPV+ HNCs.[23]

2.5 | Use of organoids as a preclinical prediction tool for response to targeted therapy in HNCs

In the two studies by Driehuis et al., there were differential responses to the targeted therapeutic drug (antiepidermal growth factor receptor [EGFR] antibody cetuximab). Variable sensitivities to this compound were observed.[20,21]

Targeted photodynamic therapy (PDT), via a photosensitizer that is conjugated to targeted molecules, has been taken into consideration as a more personalized cancer therapy. Driehuis et al. assessed the possibility of an HNSCC organoid to evaluate targeted therapy for EGFR in the context of PDT. They found that EGFR levels were different between organoids from various patients, and were similar to in vivo levels. There was a lower level of EGFR in organoids of peripheral normal mucosa compared to neighboring cancerous tissue and this normal tissue was not affected by the treatment. From their point of view, organoids from HNCs are a good tool for testing target therapy in vitro in the field of PDT.[22]

2.6 | Use of organoids as a preclinical prediction tool for response to treatment in salivary gland cancers

In Takada et al.'s study, human organoids derived from salivary adenoid cystic carcinoma (ADCC) were created as a 3D culture model and these organoids retained their potential of tumorigenicity. Drug sensitivity tests were performed with success on organoid cultured cells using three different agents. According to the results of this study, ADCC derived-organoids provide insights into the understanding of the ADCC biology and can be used as a preclinical tool for personalized medicine in patients with ADCC.[24]

In this review, we focused on the role of organoids in HNCs and detailed their role in personalized cancer therapy.

Organoids have several favorable characteristics, which make them suitable for use as preclinical predictive tools in cancer therapy; some of these characteristics are as follows: short time to achieve results, physiological cell to cell and cell to extracellular matrix interactions, presence of a gradient of nutrient and oxygen, proper recapitulating of composition and architecture of primary tissue, the capacity of self-renewal and differentiation, the capacity of cryo-preservation, and not needing to use radioactivity for investigating the antiproliferative effects of cytostatic agents.[18,25] There has not been a significant difference between the success rate of HNC-derived organoids from patients with different gender, staging, histologic grading, invasion pattern, and primary cancer site[19]; this is another useful feature in the use of organoids as a preclinical model for HNCs.

One of the main advantages of HNC-derived organoids for personalized medicine is their high take rate and rapid growth. Other advantages include the capacity for new drugs sensitivity screening at the time of tumor recurrence. On the other hand, studying the properties of the HNC organoids that respond to these new drugs will help us identify biomarkers by which we can differentiate patients for using or not using these new drugs. The differential response of HNC organoids to different targeted therapies makes them a suitable tool for personalized medicine.[22]

Immunotherapy is currently in use for HNCs. Generation of immune organoids (combination of organoids with immune cells) may

make them suitable for immunotherapy. Early studies have shown that HNC organoids have the capacity for the generation of immune organoids.[22]

Conventional chemotherapeutic drugs have not been very successful in improving the survival of patients with recurrent or metastatic ADCCs. Due to the rarity of appropriate preclinical models so far, our understanding of the biology of these malignancies encounters challenges. The development of ADCC-derived organoids has shed light on introducing new chemotherapeutic drugs for treating these cancers.[24]

Since HPV+ oropharyngeal cancers do not grow well outside the human body and there are few preclinical models for these cancers, the development of new treatments for these cancers is hampered. The use of cell lines as a preclinical model is limited due to the loss of genetic characteristics of cancer. Organoids address deficiencies in preclinical models for HPV+ HNCs, as studies have examined the effects of the virus on host gene expression through these preclinical models, leading to the identification of new biomarkers for the treatment of these cancers.[23]

3 | CONCLUSIONS

HNC-derived organoids seem to recapitulate the morphological, functional, and genetic characteristics of these tumors. These organoids have shown differential responses to different chemotherapeutic agents and molecular targeted therapies. Overall, HNC-derived organoids might have the potential to be used as preclinical prediction tools for the treatment of HNC patients.

AUTHOR CONTRIBUTIONS

Conceptualization, formal analysis, writing—original draft, and writing—review and editing: Nooshin Mohtasham, Farnaz Mohajer Tehran, and Hamid Abbaszadeh. *Data curation*: Hamid Abbaszadeh. All authors have read and approved the final version of the manuscript. Hamid Abbaszadeh had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

ETHICS STATEMENT

This review study does not include animal or human experiments.

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