ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 9, Issue – 2, April – 2026, Page No.: 35 – 56

Telomerase Activity and miRNAs in Oral Cancer: Molecular Mechanisms and Clinical Prospects

[1]Dr. Praveen S. Anigol, M.D.S, Professor, Department of Oral Pathology and Microbiology, P.M.N.M. Dental College and Hospital, Navanagar, Bagalkot – 587103, Karnataka, India

[2]Dr. Vijayalakshmi Kotrashetti, M.D.S, Professor & HOD, Department of Oral Pathology and Microbiology, Maratha Mandal's Nathajirao G. Halgekar Institute of Dental Sciences & Research Centre, Belagavi - 590010, Karnataka, India

[3]Dr. Kishore G. Bhat, M.D, Director, Department of Microbiology, Arihant Hospitals, Belagavi, Karnataka, India

[4]Dr. Ramakant Nayak, M.D.S., Principal and Professor, Department of Oral Pathology and Microbiology, Maratha Mandal's Nathajirao G. Halgekar Institute of Dental Sciences & Research Centre, Belagavi - 590010, Karnataka, India

[5]Dr. Bhagyashri N. Vanaki, M.D.S, Professor, Department of Periodontics, P.M.N.M. Dental College and Hospital, Navanagar, Bagalkot – 587103, Karnataka, India

Corresponding Author: Dr. Praveen S. Anigo1, M.D.S, Professor, Department of Oral Pathology and Microbiology, P.M.N.M. Dental College and Hospital, Navanagar, Bagalkot – 587103, Karnataka, India

How to citation this article: Dr. Praveen S. Anigol, Dr. Vijayalakshmi Kotrashetti, Dr. Kishore G. Bhat, Dr. Ramakant Nayak, Dr. Bhagyashri N. Vanaki, "Telomerase Activity and miRNAs in Oral Cancer: Molecular Mechanisms and Clinical Prospects", IJMACR – April – 2026, Volume – 9, Issue – 2, P. No. 35 – 56.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Oral squamous cell carcinoma (OSCC) represents a significant global health burden with poor prognosis and limited therapeutic options. Telomerase reactivation, primarily through upregulation of human telomerase reverse transcriptase (hTERT), is a hallmark of OSCC pathogenesis, enabling unlimited replicative potential and contributing to tumor progression through both canonical telomere maintenance and noncanonical signaling functions. MicroRNAs (miRNAs) have emerged as critical post-transcriptional regulators of hTERT expression and telomerase activity, with specific miRNAs demonstrating direct targeting of hTERT or indirect modulation through key signaling pathways. Among these, miR-512-5p has been validated as a direct hTERT suppressor through 3′UTR binding, while miR-31, miR-138, miR-21, and miR-155 show altered expression in OSCC with potential regulatory roles. The molecular mechanisms underlying miRNA-telomerase interactions involve complex signaling networks including AKT/ERK and Wnt/β-catenin pathways, which drive proliferation, chemoresistance, and epithelial-mesenchymal transition. Telomerase activity and hTERT overexpression demonstrate significant

prognostic value, with meta-analyses revealing hazard ratios of 3.01 for overall survival and 4.03 for disease-free survival. Diagnostic applications include tissue-based immunohistochemistry, TRAP assays, and circulating miRNA panels achieving AUC values of 0.776-0.88. Therapeutic strategies encompass siRNA-mediated telomerase inhibition, miRNA mimics and antagomiRs, and hTERT-targeted immunotherapy, with preclinical studies demonstrating tumor growth suppression and enhanced chemo sensitivity. However, clinical translation faces challenges including delivery optimization, tumor heterogeneity, and the need for prospective validation. This review synthesizes current evidence on telomerase-miRNA interactions in OSCC, highlighting molecular mechanisms, biomarker potential, and therapeutic prospects while identifying critical gaps for future investigation.

Keywords: Chemoresistance, OSCC, Oral Malignancies, Multimodal Therapy

Introduction

Oral squamous cell carcinoma (OSCC) accounts for over 90% of oral malignancies and represents the sixth most common cancer worldwide, with approximately 377,000 new cases and 177,000 deaths annually [1]. Despite advances in multimodal therapy, five-year survival remains approximately 50-60% due to late-stage diagnosis, locoregional recurrence, and therapeutic resistance [2]. Molecular pathogenesis involves genetic alterations, epigenetic modifications, and dysregulated signaling pathways [3].

Figure 1. Global OSCC Epidemiology and Survival Statistics

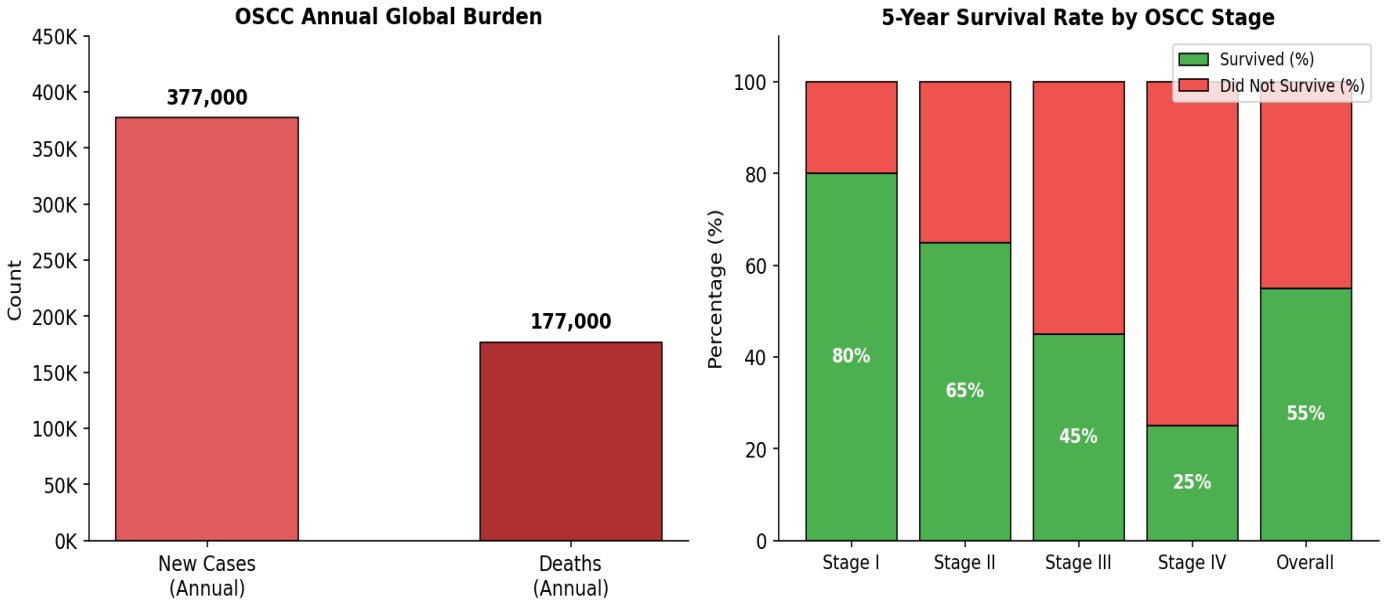

Figure 1: Global OSCC annual burden (left) and five-year survival rates by clinical stage (right). Overall five-year survival remains ~55%, with stage IV patients showing only ~25% survival.

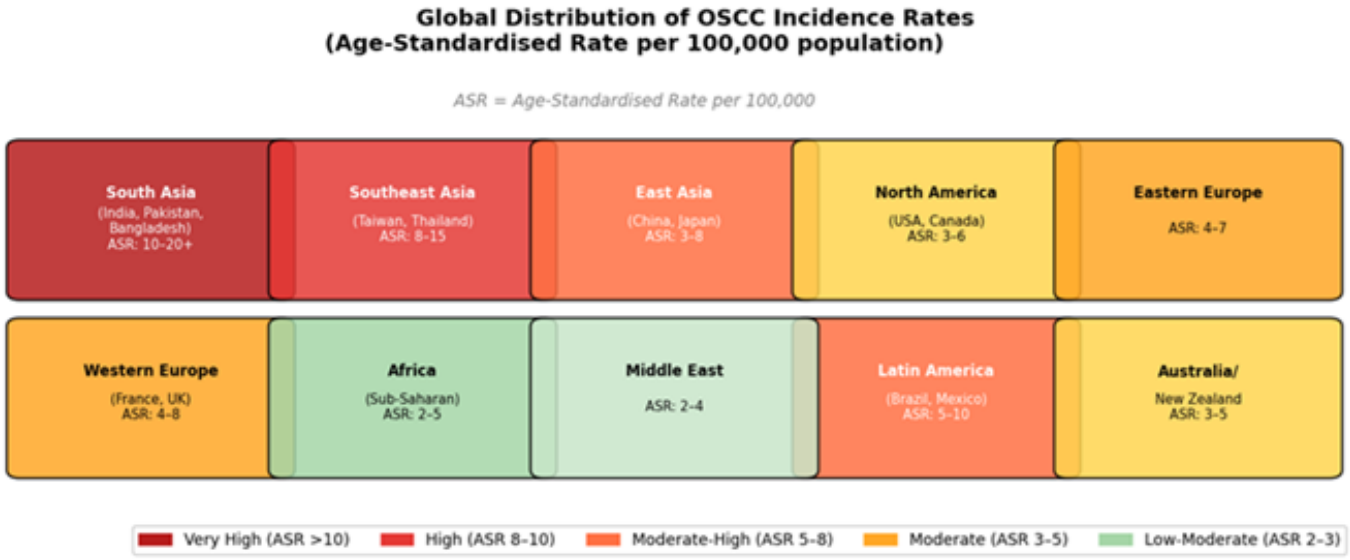

Figure 2: Schematic global distribution of OSCC incidence rates (age-standardised rate per 100,000). South and Southeast Asia carry the highest burden, driven by betel nut and tobacco use.

Telomerase reactivation occurs in over 80-90% of oral cancers, representing a critical molecular event in OSCC development [4]. Telomeres, protective nucleoprotein structures at chromosome ends composed of TTAGGG repeats, progressively shorten with each cell division, ultimately triggering replicative senescence [5]. Cancer cells circumvent this barrier through telomerase reactivation, a specialized ribonucleoprotein reverse transcriptase that adds telomeric repeats and confers unlimited replicative potential [6]. Beyond canonical telomere maintenance, telomerase exhibits noncanonical functions including regulation of gene expression, mitochondrial function, and cellular signaling that promote tumor progression [7,8].

MicroRNAs (miRNAs) are small non-coding RNAs (19-25 nucleotides) that regulate gene expression post-transcriptionally through complementary base pairing with target mRNA 3′ untranslated regions (3′UTRs), leading to translational repression or mRNA degradation [9]. In OSCC, miRNAs function as oncogenes or tumor suppressors, modulating proliferation, apoptosis, invasion, and metastasis [10]. Emerging evidence demonstrates that specific miRNAs directly or indirectly regulate human telomerase reverse transcriptase (hTERT) expression and telomerase activity, creating a regulatory network with implications for cancer biology and therapeutics [11,12].

This review synthesizes current evidence on telomerase-miRNA interactions in OSCC, examining molecular mechanisms, diagnostic and prognostic applications, and therapeutic potential.

Telomerase Structure and Function in Oral Cancer (Table:1)

Telomerase is a specialized ribonucleoprotein complex comprising three core components essential for its function: hTERT (the catalytic subunit with reverse transcriptase activity), hTR/TERC (the RNA template component providing the template for telomeric DNA synthesis), and dyskerin (a protein component that stabilizes the complex and ensures proper assembly) [13]. Among these components, hTERT represents the rate-limiting determinant of telomerase activity, with its expression tightly regulated in normal tissues and typically absent or expressed at very low levels in most

somatic cells. However, hTERT is reactivated in approximately 85-95% of human cancers, making it one of the most consistent molecular alterations in malignancy [14].

Table 1. Core Components of the Telomerase Complex and Their Roles in OSCC

Component	Type	Function	Status in OSCC
hTERT	Catalytic Protein Subunit	Reverse transcriptase; adds TTAGGG repeats; noncanonical gene regulation	Overexpressed in 85–95% of cases; rate-limiting subunit
hTR / TERC	RNA Template	Provides RNA template for telomeric DNA synthesis	Constitutively expressed; not rate-limiting
Dyskerin (DKC1)	Structural Protein	Stabilises hTR; ensures proper complex assembly	Occasionally overexpressed; associated with poor prognosis
TCAB1 / WDR79	Accessory Protein	Localises telomerase to Cajal bodies; facilitates telomere access	Dysregulated in several cancer types including OSCC
TERT Promoter Mutations (C228T/C250T)	Genomic Alteration	Creates de novo ETS-binding sites; drives hTERT transcription	Present in ~5–10% of OSCC; correlates with aggressive phenotype

Table 1: Core components of the human telomerase complex and their functional roles and status in OSCC

In OSCC, telomerase reactivation represents an early and critical molecular event in the multistep process of carcinogenesis. Multiple studies have demonstrated elevated telomerase activity in premalignant oral lesions including oral leukoplakia and erythroplakia, suggesting that telomerase activation precedes frank malignant transformation [15]. Importantly, telomerase activity increases progressively from normal oral mucosa through various grades of dysplasia to invasive carcinoma, showing strong correlations with histological grade, clinical stage, and tumor aggressiveness [16]. Comprehensive meta-analyses have confirmed that hTERT overexpression in OSCC tissues associates with significantly poor prognosis, with hazard ratios of 3.01 for overall survival and 4.03 for disease-free survival, establishing telomerase as a robust prognostic biomarker [17].

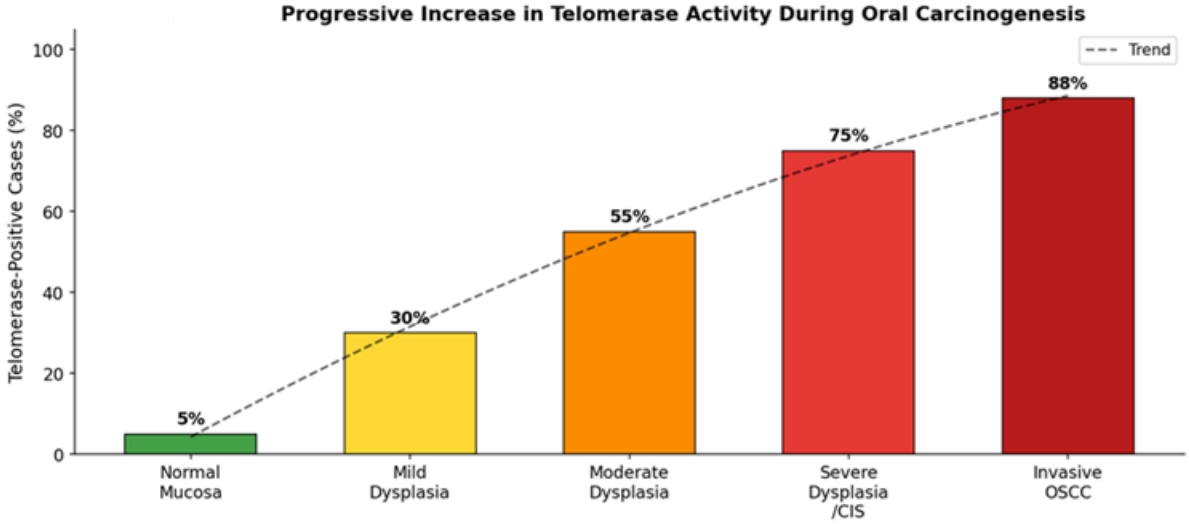

Figure 3: Progressive increase in telomerase-positive cases (%) from normal oral mucosa through dysplasia grades to invasive OSCC, illustrating telomerase reactivation as an early carcinogenic event.

Beyond its canonical role in telomere maintenance, hTERT exhibits diverse noncanonical functions that are critical for OSCC pathogenesis and progression. Nuclear hTERT functions as a transcriptional cofactor, directly modulating the expression of genes involved in cell proliferation, apoptosis resistance, and epithelial-mesenchymal transition (EMT) [18]. Specifically, hTERT interacts with the Wnt/β-catenin signaling pathway, physically associating with β-catenin and chromatin at target gene promoters to enhance β-catenin-mediated transcription of oncogenic targets including c-Myc and cyclin D1 [19]. Additionally, mitochondrial localization of hTERT provides protection against oxidative stress-induced damage and apoptosis, contributing significantly to chemoresistance observed in OSCC [20]. These pleiotropic functions position telomerase as a central hub regulating multiple malignant phenotypes in OSCC beyond simple telomere length maintenance.

hTERT Regulation Mechanisms (Table:2)

hTERT expression is regulated through transcriptional control, epigenetic modifications, alternative splicing, and post-transcriptional regulation [21]. Understanding these regulatory layers is essential for developing targeted therapeutic strategies.

Table 2. Mechanisms of hTERT Regulation in OSCC

Regulatory Level	Mechanism	Key Regulators	Effect on hTERT	Therapeutic Relevance
Transcriptional Activation	Transcription factor binding to hTERT promoter	c-Myc, Sp1, NF-κB, ETS	Upregulation	c-Myc inhibitors; NF-κB antagonists
Transcriptional Repression	Tumor suppressor binding to hTERT promoter	p53, WT1, CTCF	Downregulation	p53 restoration strategies
Promoter Mutation	De novo ETS binding sites (C228T / C250T)	ETS transcription factors	Constitutive activation	Mutation-specific targeting
Epigenetic	DNA methylation & histone modification	DNMTs, HDACs, H3K4me3	Context-dependent activation	HDAC / DNMT inhibitors
Alternative Splicing	Dominant-negative isoform generation	SR proteins, splicing factors	Reduced net activity	Splice-switching oligonucleotides
Post-transcriptional (miRNA)	miRNA binding to hTERT 3′UTR	miR-512-5p, miR-138, miR-21, miR-155	Direct suppression or indirect activation	miRNA mimics / antagomiRs

Table 2: Multi-level regulatory mechanisms governing hTERT expression in OSCC, including transcriptional, epigenetic, splicing, and miRNA-mediated control

Transcriptional Regulation

The hTERT promoter contains binding sites for numerous transcription factors. Oncogenic transcription factors including c-Myc, Sp1, and NF-κB activate hTERT transcription in cancer cells [22,23]. Conversely, tumor suppressors such as p53 and WT1 repress hTERT expression [24]. In OSCC, dysregulation of these transcription factors contributes to telomerase reactivation. Notably, hTERT promoter mutations (C228T and C250T) create de novo ETS transcription factor binding sites, occurring in approximately 5-10% of OSCC cases and correlating with aggressive phenotypes [25,26].

Epigenetic Modifications

Epigenetic mechanisms profoundly influence hTERT expression through DNA methylation and histone modifications. Promoter hypermethylation paradoxically associates with increased hTERT expression in some cancers through complex chromatin remodeling [27]. Histone modifications, including H3K4 trimethylation and H3K9 acetylation at the hTERT promoter, correlate with transcriptional activation [28]. DNA methyltransferases and histone deacetylases represent

potential therapeutic targets for modulating telomerase activity [29].

Post-transcriptional Regulation

Alternative splicing generates multiple hTERT transcript variants with distinct functional properties [30]. Full-length hTERT exhibits telomerase activity, while splice variants lacking critical reverse transcriptase domains act as dominant-negative inhibitors [31]. The balance between active and inactive isoforms influences net telomerase activity in OSCC cells [32]. Post-transcriptional regulation by miRNAs adds another regulatory layer, with specific miRNAs directly targeting hTERT mRNA or modulating upstream signaling pathways controlling hTERT expression [33].

miRNA-Telomerase Interactions (Table-3)

MicroRNAs regulate telomerase through direct targeting of hTERT mRNA or indirect modulation of signaling pathways and transcription factors controlling hTERT expression. Several miRNAs demonstrate altered expression in OSCC with functional roles in telomerase regulation.

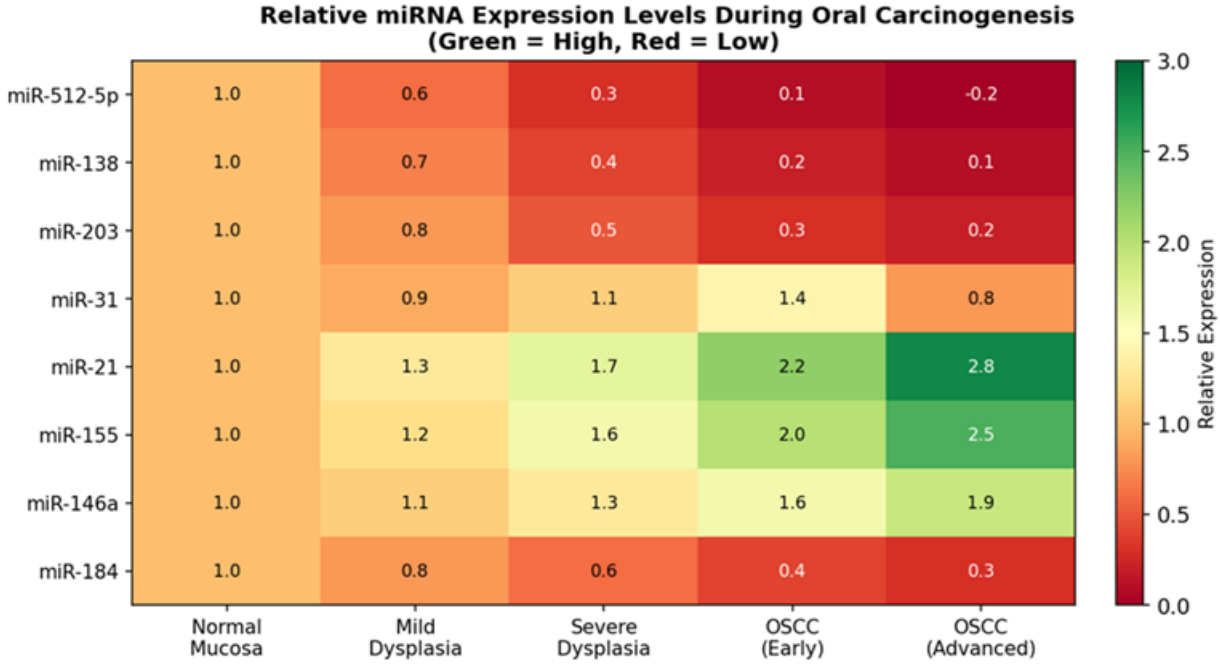

Figure 4: Relative expression levels of key miRNAs during oral carcinogenesis. Tumor suppressor miRNAs (miR-512-5p, miR-138, miR-203) progressively decrease, while oncogenic miRNAs (miR-21, miR-155) increase from normal mucosa to advanced OSCC.

Table 3. Key miRNAs Regulating Telomerase Activity in OSCC

miRNA	Expression in OSCC	Regulation Type	Target / Mechanism	Effect on Telomerase	Therapeutic Potential
miR-512-5p	Downregulated	Direct	Binds hTERT 3′UTR; mRNA destabilisation	Suppression of hTERT expression & activity	miRNA mimic restoration therapy
miR-138	Downregulated	Indirect	Targets c-Myc, β-catenin; ERK pathway inhibition	Reduced hTERT transcription	miRNA mimic; anti-invasion
miR-21	Upregulated	Indirect (oncomiR)	Suppresses PTEN; activates AKT/ERK	Enhanced hTERT transcription	AntagomiR-21 targeting
miR-155	Upregulated	Indirect (oncomiR)	PI3K/AKT, NF-κB, TRF1 targeting	Enhanced telomerase activity; telomere fragility	AntagomiR-155 therapy
miR-31	Context-dependent	Indirect	Multiple invasion/ proliferation targets	Variable; pathway-dependent modulation	Biomarker; context-specific therapy
miR-1182	Downregulated	Direct (predicted)	Putative hTERT 3′UTR binding	Potential suppression (validation needed)	Investigational

Table 3: Key miRNAs regulating telomerase activity in OSCC: expression status, regulatory mechanism, effect on telomerase, and therapeutic potential.

Direct hTERT-Targeting miRNAs

miR-512-5p represents the most extensively validated and well-characterized direct hTERT suppressor in human cancers. This miRNA binds specifically to conserved sequences within the hTERT 3′UTR, inducing translational repression and mRNA destabilization through canonical miRNA-mediated regulatory mechanisms [34]. In OSCC, miR-512-5p expression is significantly downregulated compared to normal oral mucosa, and this downregulation correlates strongly with hTERT overexpression and enhanced telomerase activity in tumor tissues [35]. Functional studies involving experimental restoration of miR-512-5p in OSCC cell lines through transfection of synthetic miRNA mimics demonstrate substantial reductions in hTERT expression at both mRNA and protein levels, accompanied by significant inhibition of cell proliferation, colony formation capacity, and induction of apoptotic cell death [36]. These findings establish miR-512-5p as a critical tumor suppressor in OSCC through direct telomerase regulation. Additional miRNAs including miR-1182, miR-1207-5p, and miR-1266 have been computationally predicted or experimentally validated as hTERT regulators in various cancer types, though their specific functional roles in OSCC require further investigation [37, 38].

Indirect Regulatory miRNAs

Multiple miRNAs indirectly regulate telomerase activity by targeting upstream signaling components, transcription factors, and pathway modulators that control hTERT expression. miR-138 functions as a tumor suppressor by directly targeting and suppressing c-Myc, one of the most potent transcriptional activators of the hTERT promoter, as well as other oncogenic transcription factors involved in telomerase regulation [39]. In OSCC tissues and cell lines, miR-138 expression is significantly downregulated compared to normal controls, and this down regulation associates with increased hTERT levels, enhanced telomerase activity, and aggressive tumor behavior including increased invasion and metastatic potential [40]. Conversely, miR-21, one of the most frequently and consistently upregulated miRNAs in OSCC, promotes telomerase activity through activation of the AKT and ERK signaling pathways by targeting and suppressing PTEN and other negative regulators of these pathways [41,42]. The resulting hyperactivation of AKT/ERK signaling enhances hTERT transcription through multiple downstream

effectors. Similarly, miR-155 modulates telomerase through complex effects on multiple interconnected signaling networks including the PI3K/AKT pathway, NF-κB signaling, and other oncogenic cascades that converge on hTERT transcriptional regulation [43]. These indirect regulatory mechanisms create intricate feedback loops between miRNA networks and telomerase regulation in OSCC.

miR-31 in OSCC

miR-31 exhibits complex, context-dependent roles in OSCC. Studies report both upregulation and down regulation depending on tumor stage, anatomical subsite, and patient population [44,45]. miR-31 targets multiple genes involved in proliferation, invasion, and metastasis, with potential indirect effects on telomerase through signaling pathway modulation [46]. The precise relationship between miR-31 and telomerase activity in OSCC warrants further investigation.

Circulating miRNAs

Circulating miRNAs in blood, saliva, and other body fluids represent promising non-invasive biomarkers for OSCC detection and monitoring [47]. Specific miRNA signatures, including panels incorporating miR-31, miR-21, and miR-184, achieve diagnostic accuracy with AUC values of 0.776-0.88 for distinguishing OSCC from healthy controls [48,49]. While direct correlations between circulating miRNA levels and telomerase activity require validation, these biomarkers offer potential for early detection and treatment monitoring.

Molecular Mechanisms and Pathways

The interplay between miRNAs and telomerase in OSCC involves complex signaling networks that regulate proliferation, survival, invasion, and therapeutic resistance.

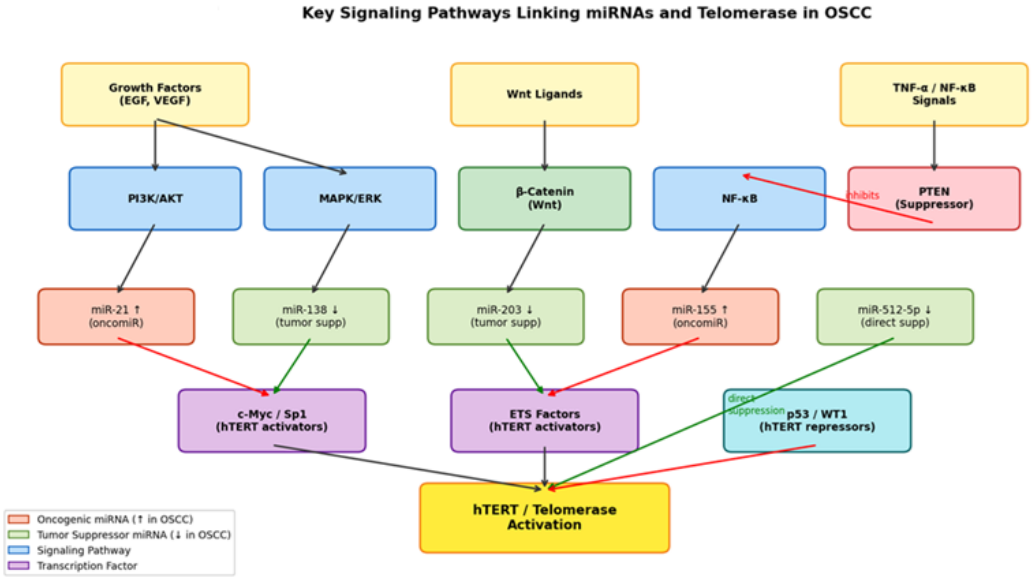

Figure 5: Integrated signaling network linking oncogenic and tumor-suppressor miRNAs to hTERT/telomerase activation in OSCC via PI3K/AKT, MAPK/ERK, Wnt/β-catenin, and NF-κB pathways.

AKT/ERK Signaling

The PI3K/AKT and MAPK/ERK signaling pathways are frequently hyperactivated in OSCC due to genetic alterations, growth factor receptor overexpression, and loss of negative regulators, and these pathways directly regulate hTERT expression through multiple

mechanisms [50]. AKT phosphorylates and activates numerous transcription factors including c-Myc, NF-κB, and others that bind to and activate the hTERT promoter, thereby enhancing hTERT transcription [51]. Similarly, ERK signaling promotes hTERT expression through phosphorylation-dependent activation of ETS family transcription factors and other transcriptional mechanisms that converge on the hTERT promoter [52]. miRNAs modulate these pathways at multiple regulatory nodes, creating complex feedback loops: miR-21 activates AKT signaling by suppressing PTEN, a critical negative regulator, while miR-138 inhibits ERK signaling through direct targeting of upstream kinases in the MAPK cascade [53,54]. This creates intricate regulatory networks where miRNA dysregulation drives telomerase activation through coordinated modulation of multiple signaling pathways.

Wnt/β-Catenin Pathway

The Wnt/β-catenin signaling pathway plays critical and multifaceted roles in OSCC development, progression, and maintenance of cancer stem cell populations [55]. Beyond its well-established role as a transcriptional regulator of hTERT, recent discoveries have revealed that hTERT physically interacts with β-catenin and associates with chromatin at Wnt target gene promoters, functioning as a transcriptional cofactor that amplifies Wnt signaling output independent of its catalytic telomerase activity [56]. This noncanonical function creates a bidirectional relationship where Wnt signaling activates hTERT expression, and hTERT protein in turn enhances Wnt-mediated transcription of proliferation-promoting genes including c-Myc, cyclin D1, and others. miRNAs including miR-138 and miR-203 suppress Wnt signaling by directly targeting multiple pathway components including β-catenin and TCF/LEF transcription factors, thereby indirectly reducing both hTERT expression levels and its transcriptional cofactor functions [57,58]. This creates a complex regulatory network where miRNA-mediated suppression of Wnt signaling simultaneously reduces telomerase expression and blocks its noncanonical oncogenic functions.

Apoptosis and Chemoresistance

Telomerase activation contributes to apoptosis resistance and chemoresistance in OSCC [59]. hTERT inhibits mitochondrial apoptosis by reducing cytochrome c release and caspase activation [60]. Telomerase-mediated upregulation of anti-apoptotic proteins including Bcl-2 and survivin enhances survival signaling [61]. miRNAs modulate these processes: tumor suppressor miRNAs promote apoptosis by reducing hTERT, while oncogenic miRNAs enhance chemoresistance through telomerase activation [62].

Epithelial-Mesenchymal Transition

EMT enables invasion and metastasis in OSCC [63]. Telomerase promotes EMT through transcriptional regulation of EMT-inducing factors including Snail, Slug, and Twist [64]. hTERT enhances mesenchymal markers (vimentin, N-cadherin) while suppressing epithelial markers (E-cadherin) [65]. miRNAs regulate EMT-telomerase interactions: miR-138 and miR-203 suppress both EMT and telomerase activity, while miR-21 promotes both processes [66,67].

Role in OSCC Pathogenesis

Telomerase reactivation and miRNA dysregulation are interconnected drivers of OSCC development, progression, and therapeutic resistance.

Tumor Initiation and Progression

Telomerase activation occurs early in the multistep process of oral carcinogenesis and is detectable in premalignant lesions with progressively increasing

frequency during malignant transformation [15]. This early reactivation of telomerase is functionally critical because it enables the accumulation of multiple genetic and epigenetic alterations by preventing replicative crisis and allowing sustained clonal expansion of cells harboring oncogenic mutations [68]. Without telomerase reactivation, pre-malignant cells would undergo senescence after a limited number of divisions. miRNA dysregulation parallels and contributes to telomerase activation during oral carcinogenesis, with progressive and coordinated changes in miRNA expression profiles observed from normal oral mucosa through various grades of dysplasia to invasive carcinoma [61]. Specifically, the coordinated downregulation of tumor suppressor miRNAs that target hTERT (such as miR-512-5p and miR-138) combined with upregulation of oncogenic miRNAs that promote telomerase activity (such as miR-21 and miR-155) facilitates the sustained proliferative capacity and genomic instability that are hallmark characteristics of OSCC development.

Metastasis and Invasion

Telomerase contributes significantly to the metastatic potential of OSCC through both its canonical telomere maintenance functions and diverse noncanonical activities [7]. Telomere maintenance enables the extensive proliferation required for successful metastatic colonization at distant sites, as metastatic cells must undergo numerous cell divisions to establish secondary tumors. Simultaneously, hTERT's transcriptional cofactor activities directly promote expression of invasion-associated genes including matrix metalloproteinases, EMT transcription factors, and other pro-metastatic factors [18]. miRNAs modulate metastatic processes through coordinated effects on telomerase and numerous other metastasis-related targets: downregulation of tumor suppressor miRNAs including miR-138 and miR-203 combined with upregulation of oncogenic miRNAs including miR-21 and miR-155 creates a permissive molecular environment that facilitates invasion, intravasation, and metastatic colonization [40,43]. This coordinated dysregulation represents a critical mechanism enabling aggressive metastatic behavior in advanced OSCC.

Therapeutic Resistance

Telomerase activation contributes to resistance against chemotherapy and radiotherapy in OSCC [59]. Mechanisms include enhanced DNA repair, apoptosis resistance, and maintenance of cancer stem cells [60, 61]. miRNA-mediated regulation of telomerase influences therapeutic sensitivity: restoration of tumor suppressor miRNAs targeting hTERT enhances chemo sensitivity, while oncogenic miRNAs promote resistance [62]. Understanding these interactions offers opportunities for combination therapies targeting telomerase and miRNA regulatory networks.

Diagnostic and Prognostic Biomarkers (Table:4)

Telomerase activity, hTERT expression, and telomerase-regulatory miRNAs demonstrate significant potential as diagnostic and prognostic biomarkers in OSCC.

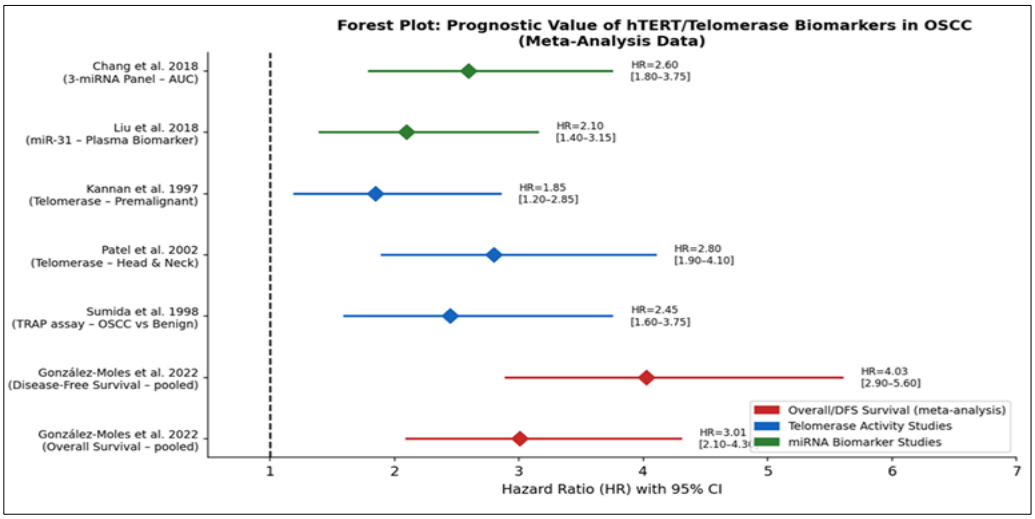

Figure 6: Forest plot of hazard ratios (HR) with 95% confidence intervals from key studies reporting the prognostic value of hTERT overexpression and telomerase activity in OSCC. HR >1 indicates increased risk of mortality/recurrence.

Table 4. Diagnostic and Prognostic Biomarker Performance in OSCC

Biomarker	Sample Type	Detection Method	Sensitivity	Specificity	AUC / HR	Clinical Application
hTERT protein	Tissue biopsy	Immunohistochemistry (IHC)	82–91%	78–88%	HR = 3.01 (OS)	Prognosis; treatment stratification
Telomerase activity	Tissue biopsy	TRAP assay	85–93%	80–92%	HR = 2.45–2.80	Diagnosis; malignancy grading
miR-31	Plasma / Saliva	qRT-PCR	76–84%	72–80%	AUC = 0.78–0.82	Early detection; recurrence monitoring
miR-21	Plasma / Tissue	qRT-PCR / ISH	80–87%	74–82%	AUC = 0.80–0.85	Diagnosis; chemoresistance prediction
3-miRNA Panel (miR-31/21/184)	Saliva	qRT-PCR multiplex	83–88%	80–86%	AUC = 0.776–0.88	Non-invasive early detection
miR-138	Tissue	qRT-PCR / IHC	72–80%	70–78%	Prognostic (inverse)	Invasion / metastasis prediction
hTERT + Telomerase (Combined)	Tissue biopsy	IHC + TRAP	90–95%	85–92%	HR = 4.03 (DFS)	Comprehensive prognostic model

Table 4: Performance characteristics of telomerase and miRNA biomarkers for OSCC diagnosis and prognosis, including sensitivity, specificity, AUC, and clinical applications.

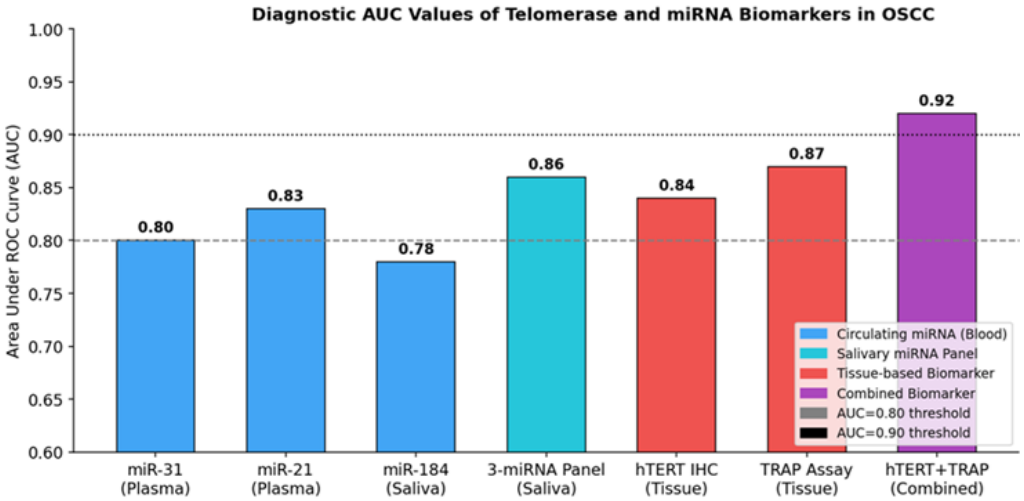

Figure 7: Diagnostic AUC values of circulating miRNA, salivary miRNA panel, tissue-based telomerase, and combined biomarkers for OSCC detection.

Tissue-Based Biomarkers

Immunohistochemical detection of hTERT protein expression in OSCC tissue specimens correlates significantly with multiple adverse clinicopathological parameters including tumor grade, clinical stage, depth of invasion, lymph node metastasis, and overall prognosis [69]. Comprehensive meta-analyses pooling data from multiple independent studies demonstrate that hTERT overexpression in OSCC tissues associates with substantial increases in mortality risk, with hazard ratios of 3.01 for overall survival and 4.03 for disease-free survival, establishing hTERT as a robust independent prognostic biomarker [17]. Telomerase activity measured by the TRAP (Telomeric Repeat Amplification Protocol) assay, which quantitatively assesses the functional enzymatic activity of the telomerase complex, effectively distinguishes malignant oral lesions from benign conditions with high sensitivity and specificity [16]. Importantly, combined assessment integrating both hTERT expression levels and functional telomerase activity measurements improves prognostic stratification compared to evaluation of either biomarker alone [69].

Circulating Biomarkers

Circulating miRNAs detected in blood, saliva, and other readily accessible body fluids offer significant promise as non-invasive biomarkers for OSCC detection, risk stratification, and treatment monitoring [47]. Salivary miRNA panels incorporating specific combinations of miRNAs including miR-31, miR-21, and miR-184 achieve impressive diagnostic accuracy with area under the receiver operating characteristic curve (AUC) values ranging from 0.776 to 0.88 for distinguishing OSCC patients from healthy controls, demonstrating clinically relevant sensitivity and specificity [48,49]. Plasma-based miRNA signatures demonstrate similar diagnostic performance and additionally correlate with tumor burden, treatment response, and disease recurrence [47]. While direct measurement of circulating telomerase activity in body fluids faces technical challenges, combined biomarker panels integrating circulating miRNA measurements with other molecular markers may enhance diagnostic accuracy.

Prognostic Stratification

Integration of telomerase biomarkers with clinical parameters improves prognostic models for OSCC. High telomerase activity combined with advanced stage and lymph node metastasis identifies patients at highest risk for recurrence and mortality [17]. miRNA expression profiles, particularly those involving telomerase-regulatory miRNAs, provide additional prognostic information [61]. Multi-marker panels incorporating telomerase activity, hTERT expression, and key miRNAs may enable personalized treatment strategies.

Therapeutic Strategies (Table:5)

Targeting telomerase and its miRNA regulators represents a promising therapeutic approach for OSCC, with multiple strategies under investigation.

Table 5. Therapeutic Strategies Targeting Telomerase and miRNA Regulators in OSCC

Strategy	Agent / Approach	Target	Preclinical Evidence	Clinical Status	Key Challenges
siRNA-mediated Telomerase Inhibition	hTERT-targeting siRNAs (e.g., si-hTERT)	hTERT mRNA	Apoptosis induction; reduced proliferation in OSCC xenografts	Preclinical only (OSCC)	Delivery to tumor; off-target effects
Small Molecule Inhibitors	Imetelstat (GRN163L); MST-312	hTR template; hTERT catalytic site	Tumor growth inhibition in multiple cancer models	Phase II (non-OSCC); no OSCC trials	Efficacy in solid tumors; resistance via ALT
miRNA Mimics (Tumor Suppressor)	miR-512-5p mimic; miR-138 mimic	hTERT 3'UTR; c-Myc / ERK	Reduced hTERT; inhibited growth & invasion in OSCC	Investigational	Delivery; stability; off-target effects
AntagomiRs (Oncogenic miRNA)	Anti-miR-21; anti-miR-155	miR-21; miR-155	Enhanced apoptosis; chemosensitisation in OSCC	Phase I (non-OSCC)	Immune activation; tissue specificity
Telomerase Peptide Vaccines	GV1001; GRNVAC1	hTERT immunogenic epitopes	Immune activation; tumour regression in models	Phase I–III (non-OSCC cancers)	Patient selection; immune tolerance
Combination Therapy	hTERT siRNA + cisplatin / 5-FU / RT	hTERT + DNA damage	Synergistic apoptosis; overcome chemoresistance	Preclinical only (OSCC)	Toxicity; optimal dosing & sequencing

Table 5: Summary of therapeutic strategies targeting telomerase and miRNA regulators in OSCC: agent, target, preclinical evidence, clinical status, and key challenges.

Direct Telomerase Inhibition

RNA interference-mediated knockdown of hTERT using specifically designed small interfering RNAs (siRNAs) effectively suppresses telomerase activity and potently inhibits OSCC cell proliferation in both in vitro cell culture systems and in vivo xenograft tumor models [70,71]. hTERT-targeting siRNAs induce multiple anti-tumor effects including apoptotic cell death, reduced invasive capacity, and enhanced sensitivity to conventional chemotherapeutic agents in preclinical OSCC models [70]. Small molecule telomerase inhibitors including imetelstat (GRN163L), a lipid-conjugated oligonucleotide that targets the RNA template component of telomerase, demonstrate significant antitumor activity in various cancer types, though systematic clinical evaluation specifically in OSCC remains limited [75]. Alternative therapeutic strategies include modulation of alternative splicing patterns to favor production of catalytically inactive hTERT isoforms that can act as dominant-negative inhibitors [72].

miRNA-Based Therapeutics

Restoration of tumor suppressor miRNAs that directly or indirectly target hTERT offers significant therapeutic potential for OSCC treatment. Synthetic miR-512-5p mimics, which are chemically modified double-stranded RNA molecules designed to recapitulate endogenous miRNA function, effectively reduce hTERT expression and inhibit OSCC cell growth and tumor development in preclinical studies [36]. Similarly, delivery of miR-138 mimics suppresses both proliferation and invasion through combined effects on hTERT and other oncogenic targets including components of invasion-promoting signaling pathways[40]. Conversely, antagomiRs (chemically modified antisense oligonucleotides designed to specifically inhibit oncogenic miRNAs) targeting miR-21, miR-155, and other oncogenic miRNAs that promote telomerase activity demonstrate significant antitumor effects in preclinical models [41,43]. Combination approaches using multiple miRNA therapeutics simultaneously targeting different nodes in telomerase regulatory networks may achieve synergistic efficacy. However, challenges including efficient delivery to tumor cells, minimizing off-target effects, and achieving sufficient intracellular concentrations must be addressed for clinical translation.

Immunotherapy

hTERT represents an attractive immunotherapy target due to its cancer-specific expression and immunogenic

epitopes [74]. Telomerase peptide vaccines including GV1001 and GRNVAC1 have been evaluated in clinical trials, demonstrating acceptable safety and immune responses [74,77]. hTERT-specific T cell therapies and CAR-T approaches are under development [74]. While clinical data in OSCC are limited, the high frequency of telomerase reactivation makes immunotherapy appealing.

Combination Therapies

Combining telomerase inhibition with conventional chemotherapy or radiotherapy may overcome resistance. Preclinical studies demonstrate that hTERT knockdown sensitizes OSCC cells to cisplatin, 5-fluorouracil, and radiation [70,71]. Combining miRNA therapeutics targeting telomerase with other targeted agents (EGFR inhibitors, PI3K/AKT inhibitors) may achieve synergistic effects [50,51]. Rational combination strategies based on molecular profiling could optimize efficacy while minimizing toxicity.

Clinical Evidence and Trials

While preclinical evidence strongly supports telomerase and miRNA targeting in OSCC, clinical translation remains in early stages.

Table 6. Key Clinical Trials Involving Telomerase-Targeted Therapies

Trial / Agent	Phase	Cancer Type	Intervention	Primary Outcome	Key Findings
Imetelstat (GRN163L)	Phase II (Randomised)	NSCLC (maintenance)	Imetelstat vs placebo post-chemotherapy	PFS	Acceptable safety; limited PFS benefit
GV1001 (TeloVac)	Phase III	Pancreatic cancer	GV1001 + gemcitabine vs gemcitabine alone	Overall survival	No survival benefit; immune responses observed
GRNVAC1	Phase I/II	NSCLC	hTERT peptide vaccine + adjuvant	Safety; immune response	Well tolerated; T-cell responses in 75%
MRX34 (miR-34a mimic)	Phase I	Advanced solid tumors	Liposomal miR-34a mimic IV	Safety; dose-finding	Terminated: immune-related adverse events
OSCC-specific telomerase trials	None completed	OSCC	—	—	High unmet need; clinical trials urgently required

Table 6: Key clinical trials evaluating telomerase-targeted therapies, highlighting outcomes and the absence of completed OSCC-specific trials

Telomerase Inhibitor Trials

Imetelstat, a lipid-conjugated oligonucleotide targeting the hTR template region, has been evaluated in phase II trials for hematologic malignancies and solid tumors [76]. A randomized phase II trial in non-small cell lung cancer demonstrated acceptable safety but limited efficacy as maintenance therapy[76]. No completed trials specifically in OSCC have been reported, though the high telomerase activity in oral cancers provides rationale for clinical investigation.

Telomerase Vaccine Trials

GV1001, a 16-amino acid hTERT peptide vaccine, has been tested in multiple cancer types [77]. A phase III trial in pancreatic cancer failed to demonstrate survival benefit when combined with chemotherapy [77]. A phase I/II trial in non-small cell lung cancer showed immune responses and acceptable toxicity [74]. These results highlight challenges in telomerase immunotherapy, including patient selection, combination strategies, and immune response optimization. OSCC-specific trials are needed to evaluate efficacy in this indication.

miRNA Therapeutic Development

miRNA therapeutics are advancing through clinical development for various diseases, though none specifically target OSCC or telomerase regulation. MRX34, a liposomal miR-34a mimic, reached phase I trials in solid tumors before termination due to immune-related adverse events [62]. This experience underscores

delivery and safety challenges for miRNA therapeutics. Next-generation delivery systems including nanoparticles and exosomes may improve therapeutic index [62].

Biomarker Validation Studies

Multiple studies have validated telomerase activity and hTERT expression as prognostic biomarkers in OSCC cohorts [17,69]. However, prospective validation in large, multi-center trials is needed for clinical implementation. Circulating miRNA biomarkers show promise in retrospective studies [48,49], but require prospective validation with standardized protocols. Integration of telomerase and miRNA biomarkers into clinical decision algorithms awaits completion of these validation studies.

Challenges and Future Directions

Despite promising preclinical data, several challenges must be addressed to translate telomerase-miRNA targeting into clinical practice for OSCC.

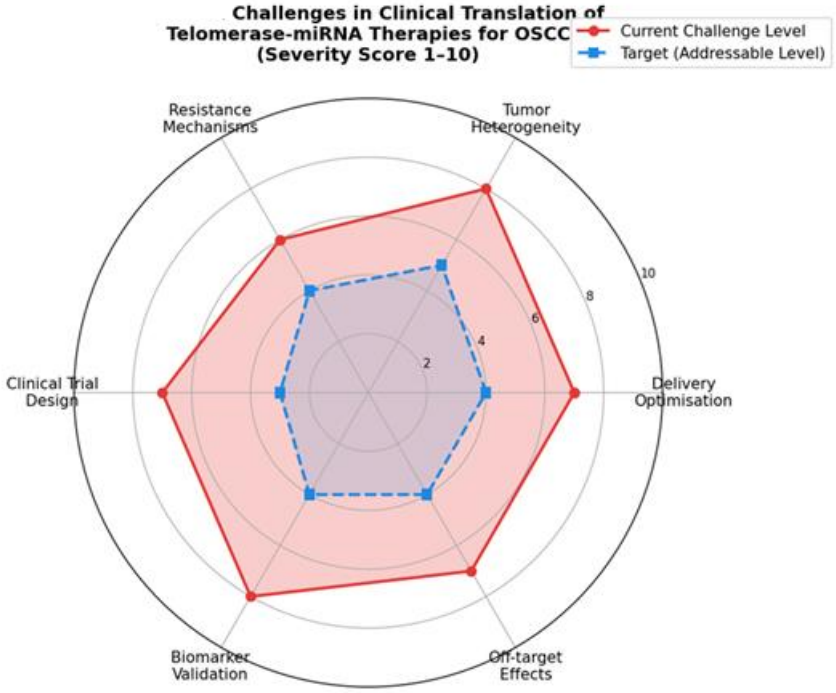

Figure 8: Radar chart depicting the severity of key challenges (scored 1–10) in translating telomerase-miRNA therapies from preclinical to clinical practice in OSCC, alongside target levels addressable through future research.

Delivery and Specificity

Efficient delivery of siRNAs, miRNA mimics, and antagomiRs to tumor cells remains a major challenge. Systemic delivery faces barriers including rapid degradation, immune recognition, and off-target accumulation [62]. Tumor-targeted delivery systems using nanoparticles, liposomes, or exosomes may improve specificity and reduce toxicity [62]. Local delivery approaches for OSCC, including direct injection or topical application, may circumvent systemic delivery challenges.

Tumor Heterogeneity

OSCC exhibits substantial intra-tumoral and inter-patient heterogeneity in telomerase activity, hTERT expression, and miRNA profiles [78]. This heterogeneity may limit single-target approaches and necessitate combination strategies. Single-cell analyses and spatial profiling can characterize heterogeneity and identify resistance mechanisms [78]. Adaptive treatment strategies

based on biomarker monitoring may address evolving tumor biology.

Resistance Mechanisms

Cancer cells may develop resistance to telomerase inhibition through alternative lengthening of telomeres (ALT), a recombination-based mechanism [75]. While ALT is rare in OSCC, monitoring during telomerase-targeted therapy is important. Resistance to miRNA therapeutics may occur through mutations in binding sites, altered miRNA processing, or compensatory pathway activation [62]. Understanding and preventing resistance requires mechanistic studies.

Clinical Trial Design

Optimal clinical trial design for telomerase-targeted therapies in OSCC requires careful consideration of patient selection, endpoints, and combination strategies. Biomarker-driven trials enrolling patients with high telomerase activity may enrich for responders [75]. Neoadjuvant trial designs in resectable OSCC enable assessment of biological activity and identification of response biomarkers [78]. Adaptive trial designs can accelerate development.

Future Research Priorities

Key research priorities include: (1) comprehensive characterization of miRNA-telomerase regulatory networks using multi-omics approaches; (2) development of improved delivery systems for nucleic acid therapeutics; (3) identification of predictive biomarkers for telomerase-targeted therapies; (4) mechanistic studies of resistance mechanisms and combination strategies; (5) prospective validation of telomerase and miRNA biomarkers in large cohorts; and (6) early-phase clinical trials evaluating telomerase inhibitors, miRNA therapeutics, and immunotherapies in OSCC patients.

Conclusion

Telomerase reactivation through hTERT upregulation is a hallmark of OSCC pathogenesis, occurring in over 80-90% of cases and conferring unlimited replicative potential through canonical telomere maintenance and noncanonical signaling functions. MicroRNAs have emerged as critical regulators of telomerase activity, with miR-512-5p directly targeting hTERT mRNA and other miRNAs (miR-138, miR-21, miR-31, miR-155) modulating telomerase through signaling networks including AKT/ERK and Wnt/β-catenin pathways. These interactions drive proliferation, invasion, metastasis, and therapeutic resistance.

Telomerase activity and hTERT expression demonstrate robust prognostic value, with hazard ratios of 3.01 for overall survival and 4.03 for disease-free survival. Diagnostic applications include tissue-based immunohistochemistry and TRAP assays, as well as circulating miRNA panels achieving AUC values of 0.776-0.88. These biomarkers offer potential for early diagnosis, prognostic stratification, and treatment monitoring.

Therapeutic strategies targeting telomerase and its miRNA regulators show promise in preclinical studies. siRNA-mediated hTERT knockdown, miRNA mimics and antagomiRs, and hTERT-targeted immunotherapy demonstrate tumor growth suppression and enhanced chemosensitivity. However, clinical translation faces challenges including delivery optimization, tumor heterogeneity, resistance mechanisms, and the need for prospective validation.

Future research should focus on comprehensive characterization of miRNA-telomerase regulatory networks, development of improved delivery systems, identification of predictive biomarkers, mechanistic

studies of resistance and combination strategies, and early-phase clinical trials in OSCC patients. Addressing these challenges will advance telomerase-miRNA targeting from preclinical concept to effective clinical therapy, potentially improving outcomes for OSCC patients.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3):209-249. https://doi.org/10.3322/ caac. 21660
2. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45(4-5):309-316. https://doi.org/10.1016/ j.oraloncology. 2008.06.002
3. Bagan J, Sarrion G, Jimenez Y. Oral cancer: clinical features. Oral Oncol. 2010;46(6):414-417. https:// doi.org/10.1016/j.oraloncology.2010.03.009
4. Patel MM, Parekh LJ, Jha FP, et al. Clinical usefulness of telomerase activation and telomere length in head and neck cancer. Head Neck. 2002;24(12):1060-1067. https://doi.org/ 10.1002/ hed.10178
5. Blackburn EH. Structure and function of telomeres. Nature. 1991;350(6319):569-573. https://doi.org/ 10.1038/350569a0
6. Greider CW, Blackburn EH. Identification of a specific telomere terminal transferase activity in Tetrahymena extracts. Cell. 1985;43(2 Pt 1):405-413. https://doi.org/10.1016/0092-8674(85)90170-9
7. Artandi SE, DePinho RA. Telomeres and telomerase in cancer. Carcinogenesis. 2010;31(1):9-18. https:// doi.org/10.1093/carcin/bgp268
8. Masutomi K, Possemato R, Wong JM, et al. The telomerase reverse transcriptase regulates chromatin state and DNA damage responses. Proc Natl Acad Sci U S A. 2005;102(23):8222-8227. https:// doi. org/10.1073/pnas.0503095102
9. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281-297. https://doi.org/10.1016/s0092-8674(04)00045-5
10. Kozaki K, Imoto I, Mogi S, Omura K, Inazawa J. Exploration of tumor-suppressive microRNAs silenced by DNA hypermethylation in oral cancer. Cancer Res. 2008;68(7):2094-2105. https:// doi.org/10.1158/0008-5472.CAN-07-5194
11. Mitomo S, Maesawa C, Ogasawara S, et al. Downregulation of miR-138 is associated with overexpression of human telomerase reverse transcriptase protein in human anaplastic thyroid carcinoma cell lines. Cancer Sci. 2008;99(2):280-286. https://doi.org/10.1111/j.1349-7006.2007. 00666.x
12. Hrdličková R, Nehyba J, Bose HR Jr. Alternatively spliced telomerase reverse transcriptase variants lacking telomerase activity stimulate cell proliferation. Mol Cell Biol. 2012;32(21):4283-4296. https://doi.org/10.1128/MCB.00550-12
13. Cohen SB, Graham ME, Lovrecz GO, Bache N, Robinson PJ, Reddel RR. Protein composition of catalytically active human telomerase from immortal cells. Science. 2007;315(5820):1850-1853. https:// doi.org/10.1126/science.1138596
14. Kim NW, Piatyszek MA, Prowse KR, et al. Specific association of human telomerase activity with immortal cells and cancer. Science. 1994;266(5193):2011-2015. https://doi.org/10. 1126/ science.7605428

15. Kannan S, Tahara H, Yokozaki H, et al. Telomerase activity in premalignant and malignant lesions of human oral mucosa. Cancer Epidemiol Biomarkers Prev. 1997;6(6):413-420.
16. Sumida T, Hamakawa H, Sogawa K, et al. Telomerase components as a diagnostic tool in human oral lesions. Int J Cancer. 1998;76(3):348-352. https:// doi.org/10.1002/(sici)1097-0215(19980504)76:3<348::aid-ijc10>3.0.co;2-u
17. González-Moles MÁ, Warnakulasuriya S, López-Ansio M, Ramos-García P. Prognostic and clinicopathological significance of telomerase reverse transcriptase upregulation in oral cancer: a systematic review and meta-analysis. Cancers (Basel). 2022;14(15):3673. https://doi.org/10.3390/cancers14153673
18. Liu N, Ding D, Hao W, et al. hTERT promotes tumor angiogenesis by activating VEGF via interactions with the Sp1 transcription factor. Nucleic Acids Res. 2016;44(18):8693-8703. https:// doi.org/10.1093/nar/gkw549
19. Park JI, Venteicher AS, Hong JY, et al. Telomerase modulates Wnt signalling by association with target gene chromatin. Nature. 2009;460(7251):66-72. https://doi.org/10.1038/nature08137
20. Haendeler J, Dröse S, Büchner N, et al. Mitochondrial telomerase reverse transcriptase binds to and protects mitochondrial DNA and function from damage. Arterioscler Thromb Vasc Biol. 2009;29(6):929-935. https://doi.org/10.1161/ATVBAHA.109.185546
21. Cong YS, Wright WE, Shay JW. Human telomerase and its regulation. Microbiol Mol Biol Rev. 2002;66(3):407-425. https://doi.org/10.1128/MMBR.66.3.407-425.2002
22. Wu KJ, Grandori C, Amacker M, et al. Direct activation of TERT transcription by c-MYC. Nat Genet. 1999;21(2):220-224. https://doi.org/10.1038/6010
23. Kyo S, Takakura M, Taira T, et al. Sp1 cooperates with c-Myc to activate transcription of the human telomerase reverse transcriptase gene (hTERT). Nucleic Acids Res. 2000;28(3):669-677. https:// doi.org/10.1093/nar/28.3.669
24. Xu D, Wang Q, Gruber A, et al. Downregulation of telomerase reverse transcriptase mRNA expression by wild type p53 in human tumor cells. Oncogene. 2000;19(45):5123-5133. https://doi.org/10.1038/sj.onc.1203890
25. Horn S, Figl A, Rachakonda PS, et al. TERT promoter mutations in familial and sporadic melanoma. Science. 2013;339(6122):959-961. https:// doi.org/10.1126/science.1230062
26. Huang FW, Hodis E, Xu MJ, Kryukov GV, Chin L, Garraway LA. Highly recurrent TERT promoter mutations in human melanoma. Science. 2013;339(6122):957-959. https://doi.org/ 10.1126/science.1229259
27. Renaud S, Loukinov D, Abdullaev Z, et al. Dual role of DNA methylation inside and outside of CTCF-binding regions in the transcriptional regulation of the telomerase hTERT gene. Nucleic Acids Res. 2007;35(4):1245-1256. https://doi.org/ 10.1093/nar/gkl1125
28. Atkinson SP, Hoare SF, Glasspool RM, Keith WN. Lack of telomerase gene expression in alternative lengthening of telomere cells is associated with chromatin remodeling of the hTR and hTERT gene promoters. Cancer Res. 2005;65(17):7585-7590. https://doi.org/10.1158/0008-5472.CAN-05-1715

29. Kumari A, Srinivasan R, Vasishta RK, Wig JD. Positive regulation of human telomerase reverse transcriptase gene expression and telomerase activity by DNA methylation in pancreatic cancer. Ann Surg Oncol. 2009;16(4):1051-1059. https://doi.org/10.1245/s10434-009-0333-8
30. Saebøe-Larssen S, Fossberg E, Gaudernack G. Characterization of novel alternative splicing sites in human telomerase reverse transcriptase (hTERT): analysis of expression and mutual correlation in mRNA isoforms from normal and tumour tissues. BMC Mol Biol. 2006;7:26. https://doi.org/10.1186/1471-2199-7-26
31. Yi X, Shay JW, Wright WE. Quantitation of telomerase components and hTERT mRNA splicing patterns in immortal human cells. Nucleic Acids Res. 2001;29(23):4818-4825. https://doi.org/10.1093/nar/29.23.4818
32. Hrdličková R, Nehyba J, Bose HR Jr. Alternatively spliced telomerase reverse transcriptase variants lacking telomerase activity stimulate cell proliferation. Mol Cell Biol. 2012;32(21):4283-4296. https://doi.org/10.1128/MCB.00550-12
33. Gao L, Ma J, Mannoor K, et al. Genome-wide small nucleolar RNA expression analysis of lung cancer by next-generation deep sequencing. Int J Cancer. 2015;136(6):E623-E629. https://doi.org/ 10.1002/ijc.29169
34. Dinami R, Ercolani C, Petti E, et al. miR-155 drives telomere fragility in human breast cancer by targeting TRF1. Cancer Res. 2014;74(15):4145-4156. https://doi.org/10.1158/0008-5472.CAN-13-2038
35. Xu Y, Goldkorn A. Telomere and Telomerase Therapeutics in Cancer. Genes (Basel). 2016; 7(6):22. https://doi.org/10.3390/genes7060022
36. Khattar E, Kumar P, Liu CY, et al. Telomerase reverse transcriptase promotes cancer cell proliferation by augmenting tRNA expression. J Clin Invest. 2016;126(10):4045-4060. https://doi.org/10.1172/JCI86042
37. Hrdličková R, Nehyba J, Bargmann W, Bose HR Jr. Multiple tumor suppressor microRNAs regulate telomerase and TCF7, an important transcriptional regulator of the Wnt pathway. PLoS One. 2014;9(2):e86990. https://doi.org/10.1371/ journal.pone.0086990
38. Liang J, Zhang S, Wang W, et al. Long non-coding RNA DSCAM-AS1 contributes to the tumorigenesis of cervical cancer by targeting miR-877-5p/ATXN7L3 axis. Biosci Rep. 2020; 40(1): BSR20192061. https:// doi.org/10.1042/ BSR 20192061
39. Mitomo S, Maesawa C, Ogasawara S, et al. Downregulation of miR-138 is associated with overexpression of human telomerase reverse transcriptase protein in human anaplastic thyroid carcinoma cell lines. Cancer Sci. 2008;99(2):280-286. https://doi.org/10.1111/j.1349-7006.2007.00666.x
40. Liu X, Jiang L, Wang A, Yu J, Shi F, Zhou X. MicroRNA-138 suppresses invasion and promotes apoptosis in head and neck squamous cell carcinoma cell lines. Cancer Lett. 2009;286(2):217-222. https://doi.org/10.1016/j.canlet.2009.05.030
41. Liu M, Wu H, Liu T, et al. Regulation of the cell cycle gene, BTG2, by miR-21 in human laryngeal

carcinoma. Cell Res. 2009;19(7):828-837. https://doi.org/10.1038/cr.2009.72

42. Chan JK, Blansit K, Kiet T, et al. The inhibition of miR-21 promotes apoptosis and chemosensitivity in ovarian cancer. Gynecol Oncol. 2014;132(3):739-744. https://doi.org/10.1016/j.ygyno.2014.01.034
43. Jiang S, Zhang HW, Lu MH, et al. MicroRNA-155 functions as an OncomiR in breast cancer by targeting the suppressor of cytokine signaling 1 gene. Cancer Res. 2010;70(8):3119-3127. https://doi.org/10.1158/0008-5472.CAN-09-4250
44. Liu CJ, Kao SY, Tu HF, Tsai MM, Chang KW, Lin SC. Increase of microRNA miR-31 level in plasma could be a potential marker of oral cancer. Oral Dis. 2010;16(4):360-364. https://doi.org/10.1111/j.1601-0825.2009.01646.x
45. Hung PS, Liu CJ, Chou CS, et al. miR-146a enhances the oncogenicity of oral carcinoma by concomitant targeting of the IRAK1, TRAF6 and NUMB genes. PLoS One. 2013;8(11):e79926. https://doi.org/10.1371/journal.pone.0079926
46. Avissar M, McClean MD, Kelsey KT, Marsit CJ. MicroRNA expression in head and neck cancer associates with alcohol consumption and survival. Carcinogenesis. 2009;30(12):2059-2063. https://doi.org/10.1093/carcin/bgp277
47. Park NJ, Zhou H, Elashoff D, et al. Salivary microRNA: discovery, characterization, and clinical utility for oral cancer detection. Clin Cancer Res. 2009;15(17):5473-5477. https://doi.org/ 10.1158/1078-0432.CCR-09-0736
48. Liu CJ, Lin SC, Yang CC, Cheng HW, Chang KW. Exploiting salivary miR-31 as a clinical biomarker of oral squamous cell carcinoma. Head Neck. 2012;34(2):219-224. https:// doi.org/10.1002/hed.21713
49. Duz MB, Karatas OF, Guzel E, et al. Identification of miR-139-5p as a saliva biomarker for tongue squamous cell carcinoma: a pilot study. Cell Oncol (Dordr). 2016;39(2):187-193. https://doi.org/10.1007/s13402-015-0259-z
50. Kang SS, Kwon T, Kwon DY, Do SI. Akt protein kinase enhances human telomerase activity through phosphorylation of telomerase reverse transcriptase subunit. J Biol Chem. 1999;274(19):13085-13090. https://doi.org/10.1074/jbc.274.19.13085
51. Akiyama M, Hideshima T, Hayashi T, et al. Nuclear factor-kappaB p65 mediates tumor necrosis factor alpha-induced nuclear translocation of telomerase reverse transcriptase protein. Cancer Res. 2003; 63(1):18-21.
52. Maida Y, Kyo S, Kanaya T, et al. Direct activation of telomerase by EGF through Ets-mediated transactivation of TERT via MAP kinase signaling pathway. Oncogene. 2002;21(26):4071-4079. https://doi.org/10.1038/sj.onc.1205509
53. Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. Gastroenterology. 2007;133(2):647-658. https:// doi.org/10.1053/j.gastro.2007.05.022
54. Guo SL, Ye H, Teng Y, et al. Akt-p53-miR-365-cyclin D1/cdc25A axis contributes to gastric tumorigenesis induced by PTEN deficiency. Nat Commun. 2013;4:2544. https://doi.org/10.1038/ncomms3544
55. Katase N, Lefeuvre M, Tsujigiwa H, et al. Knockdown of Dkk-3 decreases cancer cell

migration and invasion independently of the Wnt pathways in oral squamous cell carcinoma-derived cells. Oncol Rep. 2013;29(4):1349-1355. https://doi.org/10.3892/or.2013.2258

56. Park JI, Venteicher AS, Hong JY, et al. Telomerase modulates Wnt signalling by association with target gene chromatin. Nature. 2009;460(7251):66-72. https://doi.org/10.1038/nature08137
57. Jiang L, Liu X, Kolokythas A, et al. Downregulation of the Rho GTPase signaling pathway is involved in the microRNA-138-mediated inhibition of cell migration and invasion in tongue squamous cell carcinoma. Int J Cancer. 2010;127(3):505-512. https://doi.org/10.1002/ijc.25320
58. Boll K, Reiche K, Kasack K, et al. MiR-130a, miR-203 and miR-205 jointly repress key oncogenic pathways and are downregulated in prostate carcinoma. Oncogene. 2013;32(3):277-285. https://doi.org/10.1038/onc.2012.55
59. Hahn WC, Stewart SA, Brooks MW, et al. Inhibition of telomerase limits the growth of human cancer cells. Nat Med. 1999;5(10):1164-1170. https://doi.org/10.1038/13495
60. Del Bufalo D, Rizzo A, Trisciuoglio D, et al. Involvement of hTERT in apoptosis induced by interference with Bcl-2 expression and function. Cell Death Differ. 2005;12(11):1429-1438. https://doi.org/10.1038/sj.cdd.4401670
61. Gintoni I, Papageorgiou SG, Liakou CI, et al. Identification of Stage-Specific microRNAs That Govern the Early Stages of Sequential Oral Oncogenesis by Strategically Bridging Genetics and Epigenetics. Preprints. 2024;2024051606. https://doi.org/10.20944/preprints202405.1606.v1
62. Faraoni I, Antonetti FR, Cardone J, Bonmassar E. miR-155 gene: a typical multifunctional microRNA. Biochim Biophys Acta. 2009;1792(6):497-505. https://doi.org/10.1016/j.bbadis.2009.02.013
63. Chang KW, Liu CJ, Chu TH, et al. A Three-MicroRNA Signature as a Potential Biomarker for the Early Detection of Oral Cancer. Int J Mol Sci. 2018;19(3):758. https:// doi.org/10.3390/ ijms 19030758
64. Preprint: A novel 3-miRNA network regulates tumour progression in oral squamous cell carcinoma. bioRxiv. 2022. https://doi.org/10.1101/ 2022.05. 31.494114
65. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009;136(2):215-233. https://doi.org/10.1016/j.cell.2009.01.002
66. Polakis P. Wnt signaling in cancer. Cold Spring Harb Perspect Biol. 2012;4(5):a008052. https://doi.org/10.1101/cshperspect.a008052
67. Park JI, Venteicher AS, Hong JY, et al. Telomerase modulates Wnt signalling by association with target gene chromatin. Nature. 2009;460(7251):66-72. https://doi.org/10.1038/nature08137
68. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res. 1961;25:585-621. https://doi.org/10.1016/0014-4827(61)90192-6
69. González-Moles MÁ, Warnakulasuriya S, López-Ansio M, Ramos-García P. Prognostic and clinicopathological significance of telomerase reverse transcriptase upregulation in oral cancer: a systematic review and meta-analysis. Cancers (Basel). 2022;14(15):3673. https://doi.org/10.3390/cancers14153673

70. Zhao Y, Zhang Y, Sun H, et al. Telomerase reverse transcriptase interference synergistically promotes tumor necrosis factor-related apoptosis-inducing ligand-induced oral squamous cell carcinoma apoptosis and suppresses proliferation in vitro and in vivo. Int J Mol Med. 2018;42(3):1283-1294. https://doi.org/10.3892/ijmm.2018.3721
71. Li S, Xu Y, Chen JP, et al. Telomerase inhibition strategies by siRNAs against either hTR or hTERT in oral squamous cell carcinoma. Cancer Gene Ther. 2011;18(5):318-325. https://doi.org/10.1038/ cgt. 2010.81
72. Saebøe-Larssen S, Fossberg E, Gaudernack G. Characterization of novel alternative splicing sites in human telomerase reverse transcriptase (hTERT): analysis of expression and mutual correlation in mRNA isoforms from normal and tumour tissues. BMC Mol Biol. 2006;7:26. https://doi.org/10.1186/1471-2199-7-26
73. Wiley SR, Schooley K, Smolak PJ, et al. Identification and characterization of a new member of the TNF family that induces apoptosis. Immunity. 1995;3(6):673-682. https://doi.org/10.1016/1074-7613(95)90057-8
74. Brunsvig PF, Aamdal S, Gjertsen MK, et al. Telomerase peptide vaccination: a phase I/II study in patients with non-small cell lung cancer. Cancer Immunol Immunother. 2006;55(12):1553-1564. https://doi.org/10.1007/s00262-006-0145-7
75. Harley CB. Telomerase and cancer therapeutics. Nat Rev Cancer. 2008;8(3):167-179. https://doi.org/10.1038/nrc2275
76. Chiappori AA, Kolevska T, Spigel DR, et al. A randomized phase II study of the telomerase inhibitor imetelstat as maintenance therapy for advanced non-small-cell lung cancer. Ann Oncol. 2015;26(2):354-362. https:// doi.org/10.1093/annonc/mdu550
77. Middleton G, Silcocks P, Cox T, et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. Lancet Oncol. 2014;15(8):829-840. https://doi.org/10.1016/S1470-2045(14)70236-0
78. Leemans CR, Snijders PJF, Brakenhoff RH. The molecular landscape of head and neck cancer. Nat Rev Cancer. 2018;18(5):269-282. https://doi.org/10.1038/nrc.2018.11