



Stem cell transplantation in head and neck oncology: Integrating oncologic treatment and maxillofacial reconstruction

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Abstract

Head and neck malignancies are aggressive, have complex anatomical placements, and require extensive surgical intervention for functional and cosmetic reasons. Recent advances in stem cell biology have expanded our understanding

of their activities beyond oncogenic pathways to encompass tissue repair and regeneration. Mesenchymal and pluripotent stem cells have been studied for their immunomodulatory, microenvironmental, and bone and soft-tissue regeneration abilities following oncologic resection. Stem cells can connect oncologic treatment with reconstructive surgery, as shown in this narrative assessment of recent translational and regenerative advances in head and neck oncology. Autologous and allogeneic stem cell-based approaches, often combined with bioengineered scaffolds, have been shown to improve vascularization and functional restoration in complex craniofacial structures. Despite these promising advances, worries about tumor recurrence, stem cell plasticity, and the carcinogenic dangers of introducing stem cell-derived or growth-factor-enriched materials into previously treated or irradiated areas persist. In addition, regulatory, ethical, and scientific barriers prevent the widespread use of stem cell-based therapies in clinical oncology. Stem cell-centered research can transform head and neck cancer treatment from survival-focused to holistic oncological and functional rehabilitation that improves lifespan and quality of life by integrating regenerative science with precision surgery.

Key Words: Regenerative medicine; Stem cells; Head and neck oncology; Maxillofacial reconstruction tissue engineering; Mesenchymal stem cells

Core Tip: Stem cell transplantation in head and neck oncology signifies a promising advancement that integrates cancer treatment with regenerative reconstruction. Clinicians want to restore form and function after oncologic excision by utilizing the biological plasticity of stem cells, while avoiding consequences. The subject includes innovative methods in bone and soft tissue regeneration, immunomodulation, and integration with surgical reconstruction, presenting the possibility of transforming traditional cancer treatment into a holistic, restorative, and patient-focused strategy.

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INTRODUCTION

Cancers of the head and neck region were reported to account for more than 800000 new cases and approximately 500000 deaths worldwide, according to several epidemiological studies in 2017[1]. Notwithstanding progress in oncologic surgery, radiation, and systemic therapies, survival rates continue to be limited, especially in cases of severe or recurring cancer. Radical surgical resection frequently requires the excision of essential functional and aesthetic features, leading to considerable morbidity and diminished quality of life. Thus, reconstruction of this area necessitates both physical restoration and functional rehabilitation, encompassing speaking, swallowing, and facial expression. In this setting, regenerative medicine - especially stem cell-based transplantation - has emerged as a viable complement that may link oncological treatment and biological reconstruction[2].

Stem cells exhibit distinctive abilities for self-renewal, multilineage differentiation, and immunomodulation, allowing them to restore tissue homeostasis in adverse post-treatment conditions. Mesenchymal stem cells (MSCs) have garnered significant interest due to their relative ease of extraction, production of trophic factors, and low immunogenicity[3]. Autologous MSCs sourced from bone marrow, adipose tissue, or dental pulp have exhibited the capacity to differentiate into osteogenic, chondrogenic, and epithelial lineages, in addition to secreting cytokines that promote angiogenesis and regulate inflammation[4,5]. Furthermore, induced pluripotent stem cells (iPSCs) and tissue-specific progenitors, including salivary gland-derived cells, offer enhanced regeneration capacity for intricate head and neck abnormalities. Preclinical and translational research has demonstrated that stem cell transplantation can enhance vascularization, expedite osseointegration, and facilitate salivary gland healing after radiation injury[6]. In mandibular osteoradionecrosis, MSCs combined with bioengineered scaffolds have resulted in bone regeneration and enhanced functional outcomes, indicating a synergistic effect in reconstructive surgery[7]. These findings highlight the viability of biologically driven reconstruction that enhances conventional oncologic therapy while reducing donor site morbidity. The application of stem cell transplantation in oncology raises significant safety and ethical concerns, particularly regarding its potential impact on tumor biology. Cancer stem cells (CSCs), which exhibit molecular pathways analogous to those of normal progenitor cells - such as Notch, Wnt, and Hedgehog signaling - are now acknowledged as essential contributors to resistance and recurrence in head and neck squamous cell carcinoma (HNSCC)[8]. This narrative review examines the translational and clinical aspects of stem cell transplantation in head and neck oncology, highlighting its potential to integrate oncologic treatment with maxillofacial reconstruction, while critically addressing the related biological, ethical, and regulatory challenges.

METHODOLOGY

This narrative minireview aims to provide an integrated, interpretive synthesis of contemporary translational and clinical information on stem cell transplantation in head and neck oncology. A narrative approach has been deliberately employed to provide a comprehensive, concept-oriented discourse on diverse literature encompassing fundamental stem cell biology, principles of tissue engineering, preclinical models, and novel clinical applications in oncologic reconstruction. This methodological approach has facilitated a critical contextualization of biological mechanisms, reconstructive techniques, and oncologic safety considerations that would not have been sufficiently addressed through a purely systematic or quantitative review framework.

Literature was identified through targeted PubMed and Scopus searches, covering publications from January 2015 to June 2025, using combinations of keywords related to stem cells, head and neck cancer, regenerative medicine, tissue engineering, salivary gland repair, and maxillofacial reconstruction. The selection of studies has been directed by their relevance to the narrative objectives of the review, rather than by predetermined inclusion or exclusion criteria typical of systematic reviews. Clinical investigations, translational research, preclinical models, and authoritative reviews have been analyzed to substantiate the development of the theme and its biological plausibility. The data extraction has concentrated on stem cell origin, regenerative applications, integration with oncological therapies, and documented safety issues. The findings have been qualitatively synthesized to emphasize new concepts, existing limits, and prospective research avenues.

STEM CELL BIOLOGY

Stem cells are undifferentiated cells that can self-renew and differentiate into several lineages, serving as the basis for tissue maintenance and regeneration throughout an organism's life. They are classified into three main categories based on potency and origin: Embryonic, pluripotent, and adult stem cells. Research in head and neck oncology has focused on adult and iPSCs, as they can be sourced autologously and exhibit immunomodulatory features advantageous for reconstructive and regenerative purposes. The biological activity of these cells - characterized by their capacity to differentiate, migrate to areas of injury, and secrete trophic and angiogenic factors - underlies their translational significance in the healing of post-oncologic abnormalities in bone, mucosa, and salivary glands[6]. Stem cells' ability to respond to microenvironmental signals enables them to react dynamically to tissue injury or hypoxia, releasing signaling molecules that facilitate neovascularization, matrix remodeling, and inflammatory modulation[9].

MSCs have emerged as a fundamental component of regenerative approaches in maxillofacial and reconstructive oncology among the various stem cell types. MSCs are multipotent adult progenitors that can be extracted from bone marrow, adipose tissue, umbilical cord, or dental pulp, each exhibiting distinct differentiation potentials and paracrine profiles. Bone-marrow-derived MSCs were the first to be identified and are the most thoroughly characterized; they have significant osteogenic and chondrogenic capabilities, making them especially appropriate for skeletal restoration. Adipose-derived MSCs are advantageous due to their abundance and less invasive extraction, and they demonstrate superior soft-tissue regeneration potential through the release of vascular endothelial growth factor (VEGF), fibroblast growth factor, and interleukin-10[10]. MSCs derived from dental pulp and periodontal ligaments are particularly advantageous for craniofacial applications due to their embryological resemblance to neural crest-derived tissues in the head and neck, which enhances their ability for dentin and neural repair[11]. *In vitro* investigations reveal that all MSC subtypes can differentiate into osteogenic and epithelial lineages when exposed to local growth factors, including bone morphogenetic protein-2 and transforming growth factor- β (TGF- β), which are prevalent in irradiated or surgical wound environments[12].

The paracrine function of MSCs is widely acknowledged as the primary factor influencing their regenerative effectiveness, rather than mere direct differentiation. MSCs promote healing in irradiated tissues by secreting cytokines, chemokines, and extracellular vesicles that exert anti-inflammatory and immunoregulatory effects. Their exosomes contain microRNAs and proteins that inhibit apoptosis, promote endothelial proliferation, and regulate extracellular matrix deposition[13]. In head and neck reconstruction, these signaling systems facilitate increased vascularization of flaps and grafts, promote enhanced wound healing, and mitigate fibrosis post-radiotherapy[14]. Moreover, MSCs engage with local immune cells, transforming macrophages from pro-inflammatory M1 to reparative M2 phenotypes and attenuating T-cell cytotoxicity. These immunomodulatory characteristics make them optimal candidates for reconstructive treatments characterized by significant inflammation and ischemia. Nonetheless, this immunological interaction requires careful monitoring, as analogous processes may affect tumor-associated immune evasion, highlighting the fragile equilibrium between regeneration and oncological safety[15].

Concurrently, iPSCs have broadened opportunities for patient-specific restorative treatments. iPSCs, produced by converting somatic cells into an embryonic-like state, have the theoretical capability to develop into any cell lineage, hence offering an inexhaustible autologous supply for craniofacial tissue engineering[16]. Their application in head and neck contexts has encompassed differentiation into osteoblasts, chondrocytes, and salivary gland acinar-like cells, as well as the production of epithelial sheets for mucosal healing[17]. The pluripotent characteristics of iPSCs provide unparalleled versatility; yet their therapeutic application is limited by genomic instability, epigenetic memory, and the risk of tumorigenicity. The notion of iPSCs was first established by Takahashi[18] in 2006-2007, demonstrating that differentiated somatic cells could be reprogrammed into a pluripotent state by enforced expression of specific transcription factors. This discovery signifies a paradigm shift in regenerative biology, enabling the creation of patient-specific pluripotent cells without the ethical issues associated with embryonic stem cells[18]. Current research seeks to alleviate

these dangers by employing integration-free reprogramming techniques and pre-differentiation processes that diminish the remaining pluripotent cell populations[18]. Notwithstanding these obstacles, iPSCs provide potential for the reconstruction of intricate composite structures in the craniofacial area, particularly when integrated with three-dimensional bioprinting and scaffold-guided development.

A unique yet therapeutically relevant stem cell population in this domain comprises tissue-specific progenitor cells, including those derived from salivary glands. These cells have demonstrated the ability to rebuild glandular tissue following radiation-induced damage in both animal models and preliminary clinical investigations[19]. By separating c-Kit-positive progenitors and reinfusing them after therapy, researchers accomplished partial restoration of salivary flow and histological recovery of acinar structures. These findings demonstrate that organ-specific stem cells can regenerate specialized tissues damaged by cancer treatment, offering a targeted regenerative approach distinct from general mesenchymal or pluripotent approaches. Future investigations seek to enhance harvesting and cultivation techniques, incorporate these cells into biocompatible hydrogels, and establish standardized protocols for autologous transplantation [20].

The tumor microenvironment significantly impacts stem cell behavior, determining the dominance of either reparative or pathogenic pathways. Hypoxia, inflammation, and oxidative stress - prevalent characteristics of post-radiation tissue - regulate stem cell viability and differentiation. Experimental findings indicate that preconditioning MSCs with hypoxia or inflammatory cytokines improves their survival and angiogenic potential upon transplantation into ischemic organs[21]. In contrast, continuous exposure to oncogenic signaling molecules may modify their phenotype to a more fibroblastic or pro-angiogenic profile, thereby promoting tumor growth. Comprehending and managing this crosstalk is crucial for guaranteeing therapeutic safety. The nascent discipline of "cancer-educated" stromal biology aims to identify molecular switches that might dissociate regenerative functions from tumor-promoting effects, thereby facilitating the safer implementation of stem cell-based reconstruction in oncology[22].

The fundamental basis of stem cell therapy in head and neck oncology lies in their distinctive differentiation capacity, paracrine signaling, and immunomodulatory effects. MSCs, iPSCs, and tissue-specific progenitors may have unique advantages tailored to various reconstructive problems, ranging from bone and cartilage regeneration to glandular and mucosal tissue restoration. Stem cells can exhibit duality: They can promote or inhibit tumor growth and contribute to therapeutic resistance. A comprehensive understanding of stem cell biology is essential for clinicians and researchers aiming to integrate regenerative technology with oncological reconstruction to optimize safety and therapeutic efficacy [23].

ONCOLOGY

The incorporation of stem cell transplantation into head and neck oncology necessitates a thorough comprehension of its possible interactions with tumor biology. HNSCC is characterized by significant heterogeneity, frequent recurrence, and the presence of cell subpopulations exhibiting stem-like characteristics, known as CSCs. These CSCs demonstrate self-renewal, quiescence, and pluripotent differentiation abilities, rendering them resistant to standard chemotherapy and radiotherapy. They are characterized by the presence of distinct markers, including CD44, aldehyde dehydrogenase 1, SRY-box 2, octamer-binding transcription factor 4, and NANOG, which are associated with increased metastatic activity and treatment resistance[24,25]. The presence of these cell subsets significantly impacts the safety of regenerative methods, as external stem cell transplantation could affect CSC habitats or signaling pathways that support tumor survival. Comprehending the interaction between transplanted or mobilized stem cells and residual malignant or pre-malignant cells is essential before implementing these therapies in clinical oncology.

At the molecular level, CSCs and normal stem cells share overlapping signaling pathways that govern self-renewal and differentiation, including the Wnt/ β -catenin, Notch, Hedgehog, and phosphatidylinositol 3-kinase-protein kinase B pathways[26]. The common pathways highlight the potential risk that regenerative stem cell therapies could unintentionally trigger pro-tumorigenic processes in previously treated tissues. The stimulation of the Wnt/ β -catenin pathway, which facilitates MSC osteogenesis, also plays a role in epithelial-mesenchymal transition and invasion in HNSCC[27]. Notch signaling serves multiple functions - facilitating differentiation under normal circumstances while increasing tumorigenicity when dysregulated[28]. Research with animals has shown that MSCs can have both anticancer and protumor effects, influenced by their microenvironment, dosage, and manner of delivery[29]. In certain models, MSCs express molecules such as interleukin-10, TGF- β , and prostaglandin E2 that suppress inflammation and tumor progression; conversely, in other models, they release VEGF and matrix metalloproteinases that promote angiogenesis and metastasis[29,30]. The dual nature of MSCs underscores the necessity of regulating their differentiation state and microenvironmental conditions to avert inadvertent oncogenic activation.

There is, however, little information on oncologic safety in patients who have undergone stem cell therapy after cancer treatment. Initial investigations examining autologous MSCs for osteoradionecrosis or radiation-induced xerostomia have not indicated elevated recurrence rates during follow-up periods up to three years[31]. Nonetheless, long-term oncological data are limited, and sample sizes are inadequate to exclude infrequent adverse occurrences. In contrast, hematopoietic stem cell transplantation is linked to a heightened risk of secondary malignancies, indicating that extended immunosuppression or genomic instability may predispose individuals to carcinogenesis[32]. Although the mechanisms in regenerative cell treatment differ from hematopoietic stem cell transplantation, these findings underscore the necessity for systematic monitoring and standardized registries to record outcomes beyond immediate repair. The timing of stem cell application is critical: Most researchers advocate autologous cell harvest before radiotherapy and reinfusion after the completion of oncologic treatment, once disease remission is verified. This method reduces the likelihood of tumor-

stromal contact and offers a safer therapeutic margin for regenerative interventions[32].

Another oncological issue is the microenvironmental alteration of irradiated or surgically modified tissues. Radiation fibrosis and persistent inflammation can establish a pro-angiogenic and immunosuppressive environment that may influence the outcome of transplanted cells. Research indicates that irradiated tissues exhibit increased levels of stromal-derived factor 1, which attracts circulating progenitor cells, potentially affecting both regenerative and malignant mechanisms[33,34]. The dual recruitment effect underscores the need to delineate the molecular profile of recipient tissues prior to cell transplantation. Moreover, immunomodulation elicited by MSCs may hinder anticancer immune surveillance by suppressing the activity of cytotoxic T cells and NK cells[35]. These processes, although advantageous for diminishing inflammation, could conceivably enable immune evasion of remaining malignant cells. Consequently, forthcoming clinical protocols must incorporate molecular profiling of both the host environment and the treated cell populations, with stringent preclinical models evaluating dosage, delivery route, and interactions with oncological medicines.

The oncological ramifications of stem cell treatment in head and neck cancer are complex. Although existing clinical findings are encouraging in the near run, the molecular similarities between normal stem cells and CSCs require careful interpretation and long-term surveillance. Comprehending and regulating stem cell signaling, optimizing therapy sequences, and integrating molecular surveillance are crucial to reduce the likelihood of tumor recurrence. As regenerative medicine advances towards clinical integration in cancer, the primary problem directing translational research and ethical application is reconciling the regenerative advantages of stem cell transplantation with oncologic safety.

RECONSTRUCTIVE AND REGENERATIVE CONSIDERATIONS

The conceptual basis of tissue engineering is conventionally characterized as a triad including three interrelated components: Cells, scaffolds, and biological signaling factors. Cells confer regenerative capacity, scaffolds furnish a three-dimensional structural framework that directs tissue development, and biological variables govern cell viability, differentiation, and spatial arrangement. In head and neck oncology, this paradigm is especially pertinent, as intricate composite abnormalities necessitate synchronized regeneration of osseous, soft tissue, and vascular components[35]. Stem cells constitute the biological element of this triangle, whereas biomaterials such as collagen, hydroxyapatite, and biodegradable polymers serve as scaffolds that provide mechanical stability and spatial order. Growth factors, cytokines, and extracellular vesicles serve as biological cues that regulate angiogenesis, osteogenesis, and immunological responses. The amalgamation of these three components underlies contemporary regenerative approaches in oncological rebuilding [34,35].

Stem cell transplantation in head and neck oncology has progressed from experimental tissue engineering to a potential supplementary approach for post-oncologic rebuilding[36]. Following ablative surgery and radiotherapy, patients often present with intricate composite defects characterized by loss of bone, soft tissue, and mucosa, frequently associated with compromised vascularity and persistent inflammation. These consequences significantly impede the efficacy of conventional reconstructive techniques, particularly when extensive flaps or grafts are necessary. Stem cell-based regeneration approaches have arisen as biologically active alternatives that can facilitate neovascularization, osteogenesis, and wound healing in irradiated and fibrotic areas[36]. Three primary clinical applications of stem cell therapy have garnered significant attention: The management of radiation-induced xerostomia, the treatment of osteoradionecrosis, and the reconstruction of extensive maxillofacial defects[36]. Each area exemplifies a unique way through which stem cells can enhance oncological therapy while rehabilitating architecture and function.

One of the most well-researched indications is the treatment of radiation-induced xerostomia, a severe consequence of head and neck radiotherapy caused by injury to the salivary glands. Conventional management approaches, including sialogogues and pilocarpine, alongside advanced radiotherapy methods such as intensity-modulated radiation therapy, exhibit limited efficacy after irreversible damage to salivary gland acinar cells has transpired. Preclinical investigations indicated that the donation of autologous or allogeneic salivary gland progenitor cells can partially restore salivary production through the regeneration of acinar and ductal structures[37]. Ferreira *et al*[38] demonstrated the feasibility of isolating c-Kit-positive salivary stem cells from patients prior to radiotherapy, culturing them *ex vivo*, and reinfusing them post-treatment, which led to enhanced salivary flow rates and improved patient-reported dryness scores. These findings collectively indicate that autologous stem cell therapy can restore glandular function in previously irradiated tissues, marking a significant advancement in functional rehabilitation for head and neck cancer survivors[37,38]. However, standardized techniques for cell separation, growth, and reinfusion have yet to be devised, and long-term oncological monitoring remains necessary.

A secondary significant domain of clinical investigation pertains to the application of stem cells in the prophylaxis and management of mandibular osteoradionecrosis[39]. Osteoradionecrosis signifies a significant late consequence of head and neck radiotherapy, marked by bone necrosis, infection, and non-healing wounds. Traditional management - consisting of hyperbaric oxygen therapy, antibiotics, or surgical debridement - frequently produces inadequate outcomes, especially in later stages[40]. Numerous studies have shown that MSCs can promote angiogenesis, facilitate bone remodeling, and diminish chronic inflammation in irradiated bone microenvironments[41]. The restorative benefits are principally facilitated by the paracrine secretion of proangiogenic substances, including VEGF and platelet-derived growth factor, which promote the revascularization of ischemic tissues. Significantly, the majority of these treatments were conducted in patients devoid of active disease, underscoring the idea that regeneration therapy has to be allocated to the post-curative phase of oncological treatment to mitigate safety concerns.

The application of stem cells in intricate maxillofacial reconstruction encompasses not only isolated bone healing but also the restoration of composite abnormalities that include soft tissue, cartilage, and nerves. Tissue engineering method-

ologies integrating MSCs or adipose-derived stem cells with biocompatible scaffolds - such as collagen, hydroxyapatite, or polylactic-co-glycolic acid - have demonstrated significant advancements in experimental contexts[42]. In craniofacial bone engineering, preclinical models indicate that MSCs implanted on bioactive matrices show improved osteogenic differentiation when subjected to osteoinductive signals like bone morphogenetic protein-2 and TGF- β . When inserted into mandibular lesions, these structures enhance bone formation and augment mechanical strength relative to grafts devoid of biological components[43]. Adipose-derived stem cells demonstrate significant promise for soft tissue regeneration due to their release of angiogenic and antifibrotic cytokines, which improve the vascular integration of flaps [44]. Numerous translational studies have indicated that autologous fat grafting augmented with adipose-derived stem cells enhances contour and texture in post-radiation soft tissue defects, serving as an aesthetic and functional adjunct to conventional flaps[45]. Collectively, this research advocates for a paradigm change towards biologically augmented reconstruction that utilizes stem cell-mediated repair processes instead of depending exclusively on mechanical tissue transfer.

Besides their regenerative functions, stem cells have been employed as delivery systems for bioactive compounds, growth factors, and gene therapy vectors in oncological reconstruction[46]. MSCs can be modified to release osteogenic or angiogenic substances that facilitate healing in hypoxic and irradiated tissues. Gene-modified stem cells that express bone morphogenetic protein-7 or VEGF have exhibited enhanced bone and vascular regeneration in mandibular defect models [46]. Exosome-based therapy originating from these vesicles can be preserved, standardized, and injected multiple times, indicating a significant advancement toward therapeutic scalability. Advances in three-dimensional bioprinting enhance these concepts by enabling the accurate positioning of cells and scaffolds to replicate the anatomical intricacies of the craniofacial region. These technical advancements underscore the collaboration between regenerative biology and surgical innovation, facilitating personalized reconstruction tailored to the patient's specific defect and tissue attributes [47].

In summary, stem cell transplantation could provide significant potential for the rebuilding of head and neck oncologic abnormalities by restoring both aesthetics and functionality through physiologically active repair. Stem cell-based therapies have shown promising functional outcomes and minimal short-term safety concerns, ranging from salivary gland regeneration and treatment of osteoradionecrosis to intricate craniofacial reconstruction. Ongoing advancement will rely on aligning regenerative innovation with oncological caution - guaranteeing that cell procurement, delivery, and monitoring adhere to defined norms. As these technologies advance, the integration of oncologic surgery with regenerative science may transform post-cancer rehabilitation, offering lasting functional restoration and enhanced quality of life for survivors. **Table 1** summarizes the primary stem cell types, their tissue origins, therapeutic applications, and delivery strategies in head and neck reconstruction.

ETHICAL AND SAFETY ISSUES

The therapeutic potential of stem cell transplantation in head and neck oncology must be meticulously evaluated with its safety, ethical, and regulatory implications. Notwithstanding encouraging preclinical and initial clinical outcomes, apprehensions remain about the potential for tumorigenicity, immunological responses, and genetic instability associated with stem cell-based therapies. Mesenchymal and pluripotent stem cells demonstrate significant proliferative and migratory abilities, traits that, although advantageous for tissue regeneration, also coincide with features of malignant transformation[48]. Preclinical evidence suggests that undifferentiated or inadequately defined stem cell populations may give rise to teratomas or foster stromal conditions conducive to tumor growth[49]. In therapeutic settings that utilize autologous cells, extended *ex vivo* proliferation and exposure to growth factors may result in epigenetic drift or genomic modifications. Consequently, thorough phenotypic and karyotypic characterization is required prior to clinical implementation. The potential of transplanted stem cells to produce cytokines or exosomes that influence tumor microenvironments underscores the need for regulated dosing and targeted delivery methods.

Immunogenicity poses an additional challenge in regenerative oncology. Although MSCs are frequently characterized as immune-privileged due to their minimal expression of major histocompatibility complex class II molecules, their immunomodulatory properties are significantly influenced by the host's inflammatory condition[50]. In irradiated or fibrotic tissues, immunological dysregulation and persistent inflammation can alter MSC behavior, leading to unexpected immune responses. Allogeneic transplantation exacerbates these hazards, perhaps triggering host-versus-graft responses or delayed hypersensitivity[51].

In addition to biological safety, stem cell therapy in oncology presents ethical and regulatory difficulties that require ongoing scrutiny. The burgeoning global market for unregulated "stem cell clinics" has resulted in hasty commercialization and patient exploitation, highlighting the necessity for clear differentiation between sanctioned clinical trials and unconfirmed therapies. Ethical practice requires transparency in patient selection, informed consent, and the disclosure of prospective benefits and unknown long-term dangers[52].

In conclusion, whereas stem cell-based reconstruction in head and neck oncology presents significant regenerative potential, it is hindered by unsolved safety and ethical issues. Ongoing monitoring of tumorigenicity, immunogenicity, and genomic stability is essential through long-term follow-up and post-market surveillance. Ethical practice must prioritize patient autonomy and safety over experimental zeal, with clear regulatory frameworks that guide responsible innovation. By adhering to stringent criteria of clinical evidence, manufacturing quality, and ethical governance, the incorporation of stem cell treatment into oncologic reconstruction can advance safely and sustainably, enhancing care while preserving patient confidence and scientific integrity.

Table 1 Types and sources of stem cells used in head and neck reconstruction

Stem cell type	Source tissue	Main clinical application	Delivery method	Key regenerative mechanism
Bone marrow-derived mesenchymal stem cells (BM-MSCs)	Iliac crest, long bones	Mandibular bone regeneration, osteoradi-onecrosis, vascularized flap enhancement	Local injection, scaffold seeding, or infusion during reconstruction	Osteogenic differentiation; secretion of VEGF, PDGF, and IL-10 promoting angiogenesis and anti-inflammatory effects
Adipose-derived stem cells (ADSCs)	Subcutaneous adipose tissue	Soft tissue augmentation, post-radiation fibrosis repair, contour restoration	Fat graft enrichment, injection, or matrix incorporation	Paracrine secretion of growth factors enhancing angiogenesis and collagen remodeling
Dental pulp and periodontal ligament stem cells (DPSCs/PDLSCs)	Extracted teeth, periodontal ligament	Craniofacial bone and dental tissue regeneration	Scaffold-based implantation or hydrogel encapsulation	Osteogenic and neurogenic differentiation; ECM deposition
Salivary gland progenitor/stem cells	Submandibular or parotid gland tissue	Radiation-induced xerostomia, salivary gland dysfunction	Autologous isolation, <i>ex vivo</i> expansion, and reinfusion post-radiotherapy	Acinar and ductal cell regeneration; revascularization of glandular tissue
Induced pluripotent stem cells (iPSCs)	Reprogrammed somatic cells (skin fibroblasts, blood cells)	Customized bone and mucosal reconstruction; tissue engineering	Scaffold seeding, 3D bioprinting, or pre-differentiation into osteoblasts and chondrocytes	High differentiation capacity enabling patient-specific tissue formation
Allogeneic MSCs (umbilical cord, Wharton's jelly, placenta)	Postnatal tissues	Alternative source when an autologous harvest is not feasible	Intralesional injection or scaffold integration	Immunomodulation and trophic signaling with low immunogenicity

BM-MSCs: Bone marrow-derived mesenchymal stem cells; VEGF: Vascular endothelial growth factor; PDGF: Platelet-derived growth factor; IL: Interleukin; ADSCs: Adipose-derived stem cells; DPSCs: Dental pulp stem cells; PDLSCs: Periodontal ligament stem cells; ECM: Extracellular matrix; iPSCs: Induced pluripotent stem cells; MSC: Mesenchymal stem cell; 3D: Three-dimensional.

LIMITS

Notwithstanding the expanding literature supporting the regenerative potential of stem cell therapy in head and neck malignancies, numerous significant constraints hinder its current practical application. The primary difficulty resides in the heterogeneity and insufficient methodological rigor of current investigations. The majority of published papers consist of preclinical studies or early-phase clinical trials involving limited patient populations, case series, or uncontrolled observational studies. The diversity in study design complicates the comparison of outcomes and the formulation of definitive conclusions on efficacy and safety. Moreover, numerous studies utilize various sources of stem cells - spanning bone marrow, adipose tissue, dental pulp, and salivary glands - with inconsistent methods of preparation, expansion, and distribution. These discrepancies impede reproducibility and the formulation of consistent treatment strategies. Limited clinical trials include control groups or long-term follow-up, and an even smaller number report oncologic outcomes like recurrence or metastasis, which are crucial for validating safety in cancer survivors.

A further issue concerns the lack of consensus on the optimal timing and integration of stem cell therapy with standard oncologic treatments. Most studies implement stem cell-based therapies after radiation or chemotherapy; however, uniform criteria for patient selection and disease-free intervals are rarely established. As a result, the impacts of tumor biology, radiation dosage, and systemic medication on stem cell viability and engraftment are inadequately comprehended. Furthermore, the regenerative potential of stem cells may be undermined by the very therapeutic interventions designed to eliminate malignancies, as radiation and cytotoxic agents can cause DNA damage and senescence in the collected cells. The lack of standardized outcome measures - such as quantitative imaging for bone regeneration or validated patient-reported functional scales - restricts comparability among research. These deficiencies highlight the necessity of multicenter, randomized controlled studies with well-defined endpoints to generate substantial clinical data.

Translational issues also encompass regulatory and logistical obstacles. Clinical-grade stem cell processing requires specialized facilities, stringent sterility testing, and adherence to Good Manufacturing Practice standards, thereby increasing costs and limiting accessibility across many healthcare systems. Ethical monitoring hinders international collaboration due to significant variation in rules governing stem cell use across countries. Ultimately, long-term oncologic safety is inadequately defined; the majority of existing trials provide follow-up data of less than 3 years, a duration insufficient to evaluate late recurrences or secondary malignancies. Until these scientific, logistical, and regulatory constraints are resolved, stem cell transplantation in head and neck oncology should be seen as an emerging adjunct rather than a recognized element of reconstructive therapy. Ongoing multidisciplinary collaboration among oncologists, reconstructive surgeons, and stem cell biologists will be crucial to translating experimental advances into standardized, evidence-based clinical practice.

DISCUSSION AND FUTURE DIRECTIONS

The future of stem cell transplantation in head and neck oncology depends on the enhancement of translational strategies that integrate oncologic safety with regenerative effectiveness. As the discipline evolves, progress in cell biology, biotechnology, and immunology is starting to merge to address numerous existing obstacles. A notable advancement is the progression of cell-free regenerative strategies, including exosome- and secretome-based therapies, which harness the paracrine advantages of stem cells without incorporating living or proliferative components. Exosomes from MSCs contain microRNAs, growth factors, and cytokines that promote angiogenesis, regulate inflammation, and enhance osteogenesis in irradiated tissues. Preclinical studies indicate that MSC-derived extracellular vesicles improve bone and soft-tissue repair in mandibular defects and mitigate radiation-induced fibrosis, implying that these acellular products may offer a safer alternative to conventional transplantation[51,52]. Simultaneously, advancements in iPSC technology have produced integration-free reprogramming techniques that reduce genomic instability and tumorigenic risk, thereby facilitating the generation of patient-specific cells for craniofacial reconstruction. The integration of iPSC-derived progenitors with three-dimensional bioprinting may soon enable the creation of anatomically accurate, vascularized grafts tailored to each patient's lesion.

A second horizon encompasses the integration of stem cell-based therapies with advanced surgical and imaging technologies to enable precision rebuilding. Three-dimensional bioprinting and scaffold-guided osteogenesis facilitate the fabrication of patient-specific structures that replicate the architecture and mechanical integrity of native bone. Bioengineered scaffolds composed of collagen, hydroxyapatite, and bioceramics can be seeded with autologous stem cells and osteoinductive factors, resulting in reliable regeneration of segmental mandibular and maxillary lesions[53]. Furthermore, the incorporation of artificial intelligence and computer modeling facilitates the prediction of tissue remodeling dynamics and the enhancement of scaffold design[54].

The future of stem cell therapy in head and neck oncology will depend significantly on the development of robust clinical and regulatory frameworks. Extensive, multicenter trials are crucial for validating safety, establishing uniform techniques, and refining inclusion criteria. Longitudinal follow-up registries must be established to evaluate oncological outcomes and identify delayed consequences. Ethical monitoring must progress concurrently, prioritizing transparency in patient consent, equitable access, and the prevention of premature commercialization. Interdisciplinary collaborations will be crucial: Oncologic surgeons, regenerative scientists, and bioengineers must work together from trial design to execution to ensure that regenerative procedures enhance rather than undermine cancer therapy. As these advancements progress, stem cell-based methodologies have the potential to revolutionize survival in head and neck oncology, transforming reconstruction from a functional requirement into a biologically integrated procedure that restores shape, function, and quality of life.

The application of stem cell-based therapies in oncology requires careful consideration and scientific precision. The molecular similarities between regenerative stem cells and CSCs underscore the need to uphold rigorous oncological safety standards. Meticulous patient screening, uniform cell processing, and prolonged follow-up are crucial to prevent regenerative therapies from unintentionally facilitating tumor recurrence or modifying the tumor microenvironment. Ethical oversight, transparent consent protocols, and compliance with regulatory standards are essential to protect patients and maintain public trust. The success of this nascent profession will rely on ongoing interdisciplinary collaboration among oncologic surgeons, regenerative scientists, bioengineers, and policymakers, all striving toward a common objective of enhancing safe and effective clinical translation. The integration of regenerative medicine with surgical advancements is poised to transform head and neck reconstruction. Innovations such as bioengineered scaffolds, exosome-based medicines, and three-dimensional bioprinting are facilitating tailored, biologically integrated solutions that enhance oncological treatment. As these technologies advance, stem cell-based reconstruction may become a fundamental aspect of holistic cancer treatment—one that not only prolongs life but also reinstates the form, function, and dignity of patients recuperating from intricate oncological conditions.

CONCLUSION

Stem cell transplantation represents a significant advancement in reconstructive techniques for head and neck oncology. In contrast to traditional surgical methods that emphasize structural restoration, stem cell-based therapies provide the potential for genuine biological regeneration. Stem cells can restore tissue integrity and facilitate healing in conditions traditionally deemed unfriendly to regeneration, such as irradiated or fibrotic areas, through their abilities to differentiate, immunomodulate, and mediate paracrine signaling. The incorporation of cellular treatments into reconstructive surgery offers the opportunity to recreate anatomy while simultaneously enhancing function, aesthetics, and overall quality of life. This paradigm change is altering post-oncologic treatment from an exclusive emphasis on survival to a more holistic model that prioritizes long-term rehabilitation and patient-centered outcomes.

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FOOTNOTES

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