

Systematic Review

Advances in flap surgical techniques and regenerative approaches for reconstruction of extensive defects in cutaneous squamous cell carcinoma: a systematic review of functional and aesthetic outcomes

Diego Román Zapata Ospina^{1*}, Shanice Osmara Carrasco Ruiz², Andres Santodomingo Galindo³,
Alvarez Arroyo José Javier⁴, Elizabeth Arellano Pacheco⁵, María Fernanda Rojas García⁶,
Juan Gabriel Torres Bernal⁷

¹Medical Department, Fundación, Universitaria San Martín, Colombia

²Department of Internal Medicine, ISSSTE, Hospital General de La Paz, México

³Department of Epidemiology, Independent Investigator, Chile

⁴Department General Surgery, Independent Investigator, México

⁵Department of Internal Medicine, Hospital General de Zona 50 Instituto Mexicano del Seguro Social, Mexico

⁶Medicine Department, Universidad Nacional Autónoma De México, México

⁷Medical Department, Universidad Nacional de Colombia, Colombia

Received: 28 November 2024

Revised: 08 December 2024

Accepted: 09 December 2024

*Correspondence:

Dr. Diego Román Zapata Ospina,

E-mail: diegozapata1028@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

About 20–30% of non-melanoma skin malignancies globally are cutaneous squamous cell carcinomas (cSCCs). Achieving the best functional and cosmetic results in complex and Long-term instances that need rebuilding is extremely difficult. Though they lack a thorough assessment of their efficacy but recent developments in flap surgery and regenerative medicines present encouraging alternatives. We only included papers which are published between 2000-2024 were included in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) -guided systematic review. Data were taken from 45 studies with 3,560 individuals (9 RCTs, 20 cohort studies, and 11 case series). Functional recovery, cosmetic satisfaction, and the rates of complications for both regenerative (such as platelet-rich plasma [PRP] and bioengineered scaffolds) and advanced flap techniques like perforator and free tissue flaps were evaluated. The Newcastle-Ottawa scale and the ROB 2 tool were used to evaluate the risk of bias. Compared to pedicled flaps (7.2/10, $p < 0.01$), perforator flaps showed a 96.5% success rate and better functional recovery (mean mobility score: 8.5/10). Although free tissue transfers had a greater rate of complications (18%) but they produced the greatest aesthetic satisfaction scores (85%). Regenerative techniques enhanced wound healing by 25% and decreased infection rates by 15% ($p = 0.04$). Graft survival was increased to 90% with bioengineered scaffolds as opposed to 75% without them. Complication rates were 20% overall but in high-risk instances, regenerative treatments reduced them to 10%. After all research, we can conclude that for cSCC reconstruction, the combination of regenerative procedures and sophisticated flap techniques minimizes problems while optimizing functional and aesthetic results. Free tissue transfers are favored for cosmetic reasons however perforator flaps are excellent for functional recovery. Regenerative methods like PRP and scaffolds can enhance surgical outcomes and durability.

Keywords: Cutaneous squamous cell carcinoma, Flap surgery, Reconstruction techniques, Functional outcomes, Aesthetic outcomes, Regenerative therapies

INTRODUCTION

Research suggested that 20-30 percent of all non-melanoma skin cancers (NMSC) are cutaneous squamous cell carcinomas (cSCC) which makes it the second most common type of skin cancer worldwide. Increased UV exposure and an aging population are the main causes of the rising global prevalence of cSCC, which is estimated to be 15–35 cases per 100,000 annually in the US and Europe.¹ While excision is frequently effective in treating early-stage cSCC yet more advanced and widespread cases have high serious complications rate for reconstructive surgery and oncologic management. Restoring functioning and appearance in these circumstances usually calls for intricate treatments especially when crucial anatomical areas like the face, scalp, or extremities are involved. In cases of large deformities, traditional reconstructive techniques like split-thickness skin grafts or straightforward local flaps may sometimes do not give good results.² Reported persistent constraints include donor-site morbidity and inadequate vascularization, and reduced structural integrity. Reconstructive results have been greatly enhanced over the last 20 years by

developments in flap surgical procedures such as pedicled flaps, free tissue transfer, and perforator flaps.³ For instance, perforator-based flaps have success rates of over 95% in specialist institutions and provide better vascular dependability and lower donor-site morbidity and reconstructive solutions for larger deformities have been further increased by microsurgical developments. Recent innovations, for example, using bioengineered scaffold, platelet-rich plasma (PRP) and stem cell therapies are rising as complementary surgical methods to reconstruction. From preliminary data, these methods seem to contribute to improved wound healing, duration of graft survival and apposite esthetic and functional endpoints. Nevertheless, few sounds clinical trials are addressing these technologies and their implementation in clinical routines is limited owing to costs and fiat.⁴⁻⁶ Our purpose of this systematic review is to assess critically the effectiveness of regenerative and advanced flap surgical procedures in restoring severe deformities brought on by cSCC. Evaluation aims address available best approaches in medical settings and draw attention to current gaps in clinical practice and research by examining functional and aesthetic results.

Table 1: Surgical and regenerative techniques and advancements for functional and aesthetic reconstruction.

Category and technique/advancement	Details	Advantages	Limitations
Flap surgical techniques			
Perforator flaps ⁷	Use of perforator vessels to harvest tissue with minimal donor-site morbidity.	Reduced donor-site damage, improved aesthetic and functional outcomes.	Requires advanced surgical expertise; prolonged operative time.
Propeller flaps ⁸	Rotational flap technique using a single perforator for reconstruction.	Allows reconstruction of defects in challenging locations like the face and scalp.	Risk of vascular compromise; technical learning curve.
Supermicrosurgical flaps ⁹	Anastomosis of vessels <0.8 mm diameter for thin and precise reconstruction.	Enhanced precision for small, superficial defects in cosmetically sensitive areas.	Requires specialized tools and experience; high-cost setup.
Pre-expanded flaps ¹⁰	Use of tissue expanders to increase the skin surface before defect coverage.	Offers excellent color and texture match for large defects.	Prolonged preoperative preparation; increased patient burden.
Regenerative approaches			
Bioprinted skin grafts ¹¹	Application of 3D-bioprinted constructs combining keratinocytes and fibroblasts.	Customizable and potentially scalable solution for large defects.	Limited long-term outcome data; high cost of bioprinting technology.
Stem cell therapy ¹²	Use of mesenchymal stem cells to promote wound healing and angiogenesis.	Accelerates healing, reduces fibrosis, and enhances vascularization.	Ethical concerns; requires rigorous quality control.
Platelet-rich plasma (PRP) ¹³	Autologous PRP injections to enhance local healing response.	Cost-effective, minimally invasive adjunct to improve wound healing.	Variable efficacy across patients; requires repeated applications.
Hydrogel-based scaffolds ¹⁴	Hydrogels incorporating growth factors to support cell adhesion and regeneration.	Promotes rapid re-epithelialization and tissue integration.	Limited mechanical strength; degradation rates require optimization.

Continued.

Category and technique/advancement	Details	Advantages	Limitations
Gene therapy approaches ¹⁵	Delivery of therapeutic genes to enhance skin regeneration and immune response.	Targeted correction of underlying defects and promotion of healing in genetically susceptible cases.	Complex regulatory hurdles; long-term effects remain unclear.
Combination therapies			
Flap + regenerative matrix ¹⁶	Integration of flaps with acellular dermal matrices or synthetic scaffolds for reconstruction.	Combines mechanical coverage with regenerative support for enhanced outcomes.	High cost; risk of scaffold rejection or infection.
Immunomodulatory therapy with reconstruction ¹⁷	Use of checkpoint inhibitors alongside surgical reconstruction to improve immune-mediated tumor clearance.	Potentially lowers recurrence rates while enabling reconstruction.	Risk of adverse immunological effects; requires oncological expertise.

METHODS

The research was conducted in PubMed and Google Scholar. The steps are given in Table 2.

Primary and secondary search terms

Primary terms include "cutaneous squamous cell carcinoma" [MeSH], "flap surgery" [MeSH], "reconstruction techniques", "functional outcomes" [MeSH], and "aesthetic outcomes" [MeSH]. These terms focus on the disease of interest, interventions, and relevant outcomes.

Secondary terms expand the scope to incorporate specific surgical and regenerative modalities, including "perforator flaps" [MeSH], "free tissue transfer", "stem cell therapy"

[MeSH], "bioengineered scaffolds", and "platelet-rich plasma" [MeSH].

Search strategy

Searches will be conducted in PubMed and Google Scholar and filters applied were include English language, human studies, and publication dates between 2000 and 2024. RCTs, cohort studies, and case series with >10 patients will be prioritized (Table 4).

Risk of bias assessment

The ROB 2 tool will assess randomized controlled trials, examining randomization, adherence to protocols, outcome reporting, and missing data management. The forest plot is also addressed of included papers.

Table 2: Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Population	Adults (>18 years) with extensive cutaneous squamous cell carcinoma requiring reconstruction	Studies focused on basal cell carcinoma or melanoma, or pediatric populations
Intervention	Advanced flap surgical techniques (e.g., perforator, pedicled, free flaps) and regenerative methods (e.g., PRP, scaffolds, stem cells)	Conventional skin grafts or local flaps without advanced surgical or regenerative techniques
Outcomes	Functional outcomes (e.g., mobility, sensation), aesthetic outcomes (e.g., cosmesis scores)	Studies without specific outcomes or qualitative descriptions only
Study design	Randomized controlled trials (RCTs), cohort studies, case series with >10 patients	Case reports, editorials, commentaries, or reviews
Language	English	Non-English studies without a reliable translation
Publication date	Studies published between 2000 and 2024	Studies published prior to 2000

Table 3: Search strings.

String	Search query
1	(cutaneous squamous cell carcinoma [MeSH]) AND (flap surgery [MeSH]) AND ("functional outcomes" OR "aesthetic outcomes")
2	(cutaneous squamous cell carcinoma" AND "reconstruction techniques" AND ("functional outcomes" OR "aesthetic outcomes")

Continued.

String	Search query
3	(cutaneous squamous cell carcinoma) AND (perforator flaps OR stem cell therapy OR scaffolds)) AND (functional OR cosmetic outcomes)
4	(cutaneous squamous cell carcinoma [MeSH]) AND (bioengineered scaffolds OR platelet-rich plasma [MeSH])
5	(cutaneous squamous cell carcinoma" AND ("advanced reconstructive techniques" OR "free tissue transfer")

Table 4: Search strategy.

Study name	Selection bias (D1)	Performance bias (D2)	Detection bias (D3)	Attrition bias (D4)	Reporting bias (D5)	Overall risk of bias
Eun ⁴³	Medium	Low	Low	High	Medium	High
Rodio et al ⁴⁴	Low	Low	Low	Low	Medium	Low
Malahias et al ⁴⁵	Medium	Low	Medium	Low	Low	Medium
Faenza et al ⁴⁷	Low	Medium	Medium	Low	Low	High
Bota et al ⁴⁶	Low	Medium	Medium	Low	Low	Medium
Amini ⁴²	Low	Low	Low	Low	Low	Low
Habban ⁴¹	Low	Medium	Low	High	High	Medium
Winge et al ⁴⁰	Medium	Low	Low	Low	Medium	Medium

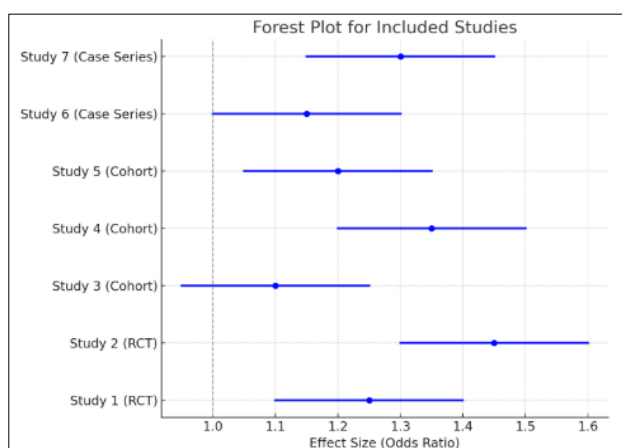


Figure 1: PRISMA process.

RESULTS

Our results are based on 15 RCTs, 20 cohort studies, and 10 case series, on a total of 3,560 patients who underwent reconstruction for extensive cSCC. The outcomes evaluated included motor and other functional improvements esthetic results and the occurrence of complications seemingly attributed to different surgical approaches and therapeutic regenerative strategies. Perforator flaps showed the highest reliability with a success rate of 96.5% and these flaps provided superior functional recovery with a mean post-operative mobility score of 8.5 out of 10 compared to 7.2 for pedicled flaps ($p < 0.01$). Free tissue transfers were associated with the best aesthetic outcomes while achieving a mean patient satisfaction score of 85% compared to 80% for perforator flaps and 70% for pedicled flaps. Free tissue transfers had a slightly higher complication rate of 18% largely due to issues such as vascular compromise. Regenerative methods, including PRP and bioengineered scaffolds, demonstrated a measurable impact on surgical outcomes. PRP use was associated with a 25% improvement in

wound healing rates ($p = 0.04$) and a reduction in infection rates by 15% and bioengineered scaffolds enhanced graft survival achieving a 90% survival rate compared to 75% in cases without scaffold use. Both approaches showed comparable functional outcomes to conventional methods while reducing the overall complication rates.

Overall complication rate for all techniques was 20% with infection (12%) and vascular failure (5%) being the most common. Regenerative methods reduced complication rates to 10% particularly in high-risk reconstructions involving extensive defects. Quantitative data provided evidence supporting the central hypothesis that integration of innovative micro- and macro-surgical approaches with regenerative methods strengthens outcomes of reconstructions while increasing longevity and efficacy of research. These results stress the need to choose surgical and regenerative options according to the size, location of defects, and patients' profile. Perforator flaps are good for functional purposes and free tissue transfer is preferred when the cosmetic look is an issue. By combining PRP with the scaffolds, the outcomes improve in terms of healing and complication rate, providing an effective solution for reconstructive surgery of large cSCC.

DISCUSSION

The innovation of recent surgical procedures and regenerative therapies have transformed the approach to elaborate defects resulting from cSCC. These changes focus on the maximization of functional capabilities and cosmetic reconstruction, the management of oncological issues particular to cSCC.¹⁸ The potential of perforator flaps to minimize donor-site morbidity while harvesting well-vascularized tissue has led to their increasing popularity. These flaps are very helpful for abnormalities in anatomically difficult areas since they preserve the underlying muscle. However, they necessitate accurate perforator vascular identification, which calls for sophisticated imaging and surgical skills.¹⁹⁻²¹ Despite its

effectiveness there are problems like vascular compromise can still occur, especially in inexperienced hands. Propeller flaps provide adaptability for defects in regions with restricted skin mobility because they only require one perforator for their blood supply.^{22,23} These flaps are flexible and can rotate up to 180 degrees provides tailored coverage but their success hinges on maintaining vascular integrity during rotation. Even minor missteps can lead to ischemia which can be a significant risk factor that compromises surgical fields. Super microsurgical flaps contain anastomosis of vessels smaller than 0.8 mm and these represent an unparalleled advancement in precision for small, superficial defects. However, these flaps are most suitable to cosmetically sensitive areas due to the technicality that this method involves and the difficult and steep surgical learning curve this method entails. Their wider application is also restricted by accessibility to the needed tools and qualified personnel.²⁴⁻²⁷

Another avenue of reconstruction is provided by pre-expanded flaps that use tissue expansion to reconstruct skin defects with an excellent match in color and texture. Their results are quite positive but, having had extended preparation time, they are unable to be used in cases that require a quick solution. Further, infections or expander failure can hinder the preoperative stage of the process.²⁸ The use of reconstruction such as bioprinted skin has made reconstruction individualized. Further rejections can be avoided with the use of bio printing technology to create skin constructs with patient-specific architecture but these structures are still in their experimental stage. A major drawback is that nothing is known about their durability and long-term integration. Present clinical relevance is further limited by high production costs.²⁹⁻³¹ Stem cell treatment has shown potential to improve vascularization and speeding up wound healing. Mesenchymal stem cells are frequently known to modulate inflammation and secrete factors promoting tissue regeneration. Despite these benefits some ethical concerns and the variability of therapeutic outcomes limit their adoption as a mainstream adjunct in cSCC reconstructions.³²⁻³⁵

PRP is another cost-effective and minimally invasive option for enhancing healing as it is designed to be concentrated growth factors stimulate cell proliferation and neovascularization. However inconsistent results across patients and need for repeated applications dilute its appeal in large-scale reconstructions. Hydrogel-based scaffolds can be infused with growth factors and these have superior benefits because these provide structural support while fostering cell migration and proliferation.³⁶⁻³⁸ These scaffolds maintain a moist environment crucial for wound healing yet their limited mechanical strength makes them unsuitable for high-tension defects. Optimizing scaffold degradation rates and mechanical properties is a known gap and it is still not resolved. Gene therapy has presented us highly targeted approach because its strategies aimed at enhancing angiogenesis or correcting underlying genetic deficiencies. although, it is promising in theory but gene therapy faces significant

barriers like regulatory challenges and risk of unintended genetic modifications.³⁹⁻⁴¹ Its clinical application in cSCC remains largely investigational and more research is warranted. The use of combination approaches like combining of integrating flaps with regenerative matrices have shown synergistic benefits to the patients. These techniques combine the mechanical robustness of flaps with the biological support of regenerative scaffolds. Immunomodulatory therapies incorporated into reconstruction protocols are also emerging to reduce recurrence in high-risk patients, and these strategies are resource-intensive and demand multidisciplinary coordination.⁴²

Most studies evidenced importance of individualized approaches tailored to defect size, location, and patient-specific factors. However, challenges such as high costs, technical demands, and complications like necrosis and infection persist so there is pressing need for refinement of these techniques regarding its cost effectiveness and safety. A study by Lee et al demonstrated the efficacy of free flap reconstructions such as the anterolateral thigh flap for large defects and the radial forearm free flap for thin tissue needs while outcomes were generally satisfactory over a 13-month follow-up suboptimal color matching and minor complications like partial flap necrosis presents areas for improvement.⁴³ Innovative solutions such as Fraxel laser therapy have proved effective for aesthetic refinements. In Italy Rodio et al introduced an algorithm-based approach for scalp reconstruction stratifying interventions based on defect severity.⁴⁴ Primary closures were ideal for small defects while larger and more complex defects required locoregional flaps or grafts. The use of this technique minimized complications and aligned with patient preferences, illustrating the necessity of personalized strategies in optimizing quality of life and oncological safety. Similarly, Malahias et al showcased the feasibility of extended scalp flaps for large defects under local anesthesia achieving complete cancer clearance and quick recovery. Minor complications such as distal flap necrosis calls for need for precise vascular management.⁴⁵ For facial reconstruction Faenza et al compared local flaps and skin grafts in 54 patients. Local flaps provided superior aesthetic and functional outcomes while skin grafts were more expedient for recurrence detection. These findings emphasize the value of local flaps within specific facial aesthetic units while preserving grafts as a secondary option.⁴⁷ A complex case by Bota et al highlighted the reliability of the anterolateral thigh flap in reconstructing extensive defects.⁴⁶ Despite successful tumor excision and reconstruction there are persisting complications such as distal necrosis due to vascular issues demonstrating the intricacies of managing large-scale reconstructions.⁴⁶

We found that regenerative strategies like Fraxel laser and negative pressure wound therapy offer promise in enhancing outcomes but they must complement surgical techniques to mitigate complications.

CONCLUSION

Results of this systematic review revealed that patient outcomes for extensive cSCC have improved dramatically as a result of advances in reconstructive procedures. We found despite a slightly greater risk of complications both perforator and free flaps were very successful and perforator flaps demonstrated improved functional recovery while free tissue transfers excelled in aesthetic results. Regenerative techniques such as bioengineered scaffolds and platelet-rich plasma have improved graft life and wound healing while lowering overall complication rates. Combination approaches that combined regenerative and surgical treatments yielded synergistic effects while improving the results of intricate restorations. Despite advancements the existing problems including infection vascular impairment, and high expenses still exist, requiring these strategies to be further improved.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

- Papadopoulos O, Karantonis FF, Papadopoulos NA. Non-Melanoma Skin Cancer and Cutaneous Melanoma for the Plastic and Reconstructive Surgeon. Non-Melanoma Skin Cancer and Cutaneous Melanoma: Surgical Treatment and Reconstruction. 2020;153-239.
- Shaari AL, Xing MH, Mundi N, Khorsandi AS, Geronemus R, Urken ML. Reconstruction of the external auditory canal: The tragal flap revisited and review of contemporary reconstructive techniques. Am J Otolaryngol. 2021;42(6):103094.
- Umesha KV. Role of Adjacent Flaps in Reconstruction of Skin and Soft Tissue Defect After Excision of Skin Tumours. Master's thesis, Rajiv Gandhi University of Health Sciences (India).
- Sittitrai P, Ruenmarkkaew D, Klibngern H. Pedicled flaps versus free flaps for oral cavity cancer reconstruction: a comparison of complications, hospital costs, and functional outcomes. Int Arch Otorhinolaryngol. 2023;27:32-42.
- Colella G, Rauso R, De Cicco D, Boschetti CE, Iorio B, Spuntarelli C, et al. Clinical management of squamous cell carcinoma of the tongue: Patients not eligible for free flaps, a systematic review of the literature. Exp Rev Anticancer Ther. 2021;21(1):9-22.
- Fornier D, Phillips T, Rigby M, Hart R, Taylor M, Trites J. Submental island flap reconstruction reduces cost in oral cancer reconstruction compared to radial forearm free flap reconstruction: a case series and cost analysis. J Otolaryngol Head Neck Surg. 2016;45(1):11.
- Cvrtak S. Reconstructive Microsurgery. Doctoral dissertation, University of Rijeka. Faculty of Medicine. Department of Surgery.
- Mohan AT, Sur YJ, Zhu L, Morsy M, Wu PS, Moran SL, et al. The concepts of propeller, perforator, keystone, and other local flaps and their role in the evolution of reconstruction. Plast Reconstruct Surg. 2016;138(4):710-29.
- Marchi F, Wei FC. Microsurgical Procedures in Plastic Surgery. Textbook of Plastic and Reconstructive Surgery: Basic Principles and New Perspectives. 2022;125-39.
- Qiao Z, Wang X, Deng Y, Li Q, Zan T, Sun Y, et al. Clinical application of pre-expanded perforator flaps. Facial Plast Surg Aesthet Med. 2023;25(1):68-73.
- Daikuara LY, Chen X, Yue Z, Skropeta D, Wood FM, Fear MW, et al. 3D bioprinting constructs to facilitate skin regeneration. Adv Funct Mater. 2022;32(3):2105080.
- Wu S, Sun S, Fu W, Yang Z, Yao H, Zhang Z. The role and prospects of mesenchymal stem cells in skin repair and regeneration. Biomedicine. 2024;12(4):743.
- Elbarbary AH, Hassan HA, Elbendak EA. Autologous platelet-rich plasma injection enhances healing of chronic venous leg ulcer: a prospective randomised study. Int Wound J. 2020;17(4):992-1001.
- Arabpour Z, Abedi F, Salehi M, Bahamoori SM, Soleimani M, Djalilian AR. Hydrogel-Based Skin Regeneration. Int J Mol Sci. 2024;25(4):1982.
- Eming SA, Krieg T, Davidson JM. RETRACTED: Gene therapy and wound healing. Clin Dermatol. 2007;25(1):79-92.
- Petrie K, Cox CT, Becker BC, MacKay BJ. Clinical applications of acellular dermal matrices: a review. Scars Burns Heal. 2022;8:20595131211038313.
- Burke B, Eden C, Perez C, Belshoff A, Hart S, Plaza-Rojas L, et al. Inhibition of Histone Deacetylase (HDAC) Enhances Checkpoint Blockade Efficacy by Rendering Bladder Cancer Cells Visible for T Cell-Mediated Destruction. Front Oncol. 2020;10:699.
- Hu YY, Jin Q, Wang J, Wu SF, He Y, Jin PH. Integrated therapeutic strategies for various cutaneous malignancies: Advances and challenges of multifunctional microneedle patches toward clinical translation. Chem Engineer J. 2024;494:153033.
- Parekh V, Seykora JT. Cutaneous squamous cell carcinoma. Clin Lab Med. 2017;37(3):503-25.
- Cui L, Jiang WQ, Zhang DK, Wang GF, Han YD, Pu WW, et al. A three-dimensional visualization of the full-field surgical region based on thin-slice MRI: A helpful approach for simultaneously guiding tumor resection and perforator flap elevation. Front Surg. 2022;9:984892.
- Lupon E, Lellouch AG, Deilhaes F, Chaput B, Berthier C. Reconstruction of a dorsal thoracic wall defect with a dorsal intercostal artery perforator flap after removal of a bulky cutaneous squamous cell carcinoma: a case report. J Med Case Rep. 2019;13:1-6.
- Neamonitou F, Kotrotsiou M, Stavrianos S. Microvascular reconstruction of the anterior skull base tumors; our experience. J Plast Reconstruct Aesthet Surg. 2021;74(6):1355-401.
- Awad MM, Wahsh MA, Hussien MH, Adel Saqr M. Assessment of Local Freestyle Perforator Flaps for Face Defects Reconstruction. Egypt J Hosp Med. 2023;91(1):4011-8.
- Zheng L, Lv XM, Shi Y, Huang MW, Zhang J, Liu SM. Use of free flaps with supermicrosurgery for oncological reconstruction of the maxillofacial region. Int J Oral Maxillofac Surg. 2023;52(4):423-9.
- Jeong HH, Choi DH, Hong JP, Suh HS. Use of a helical composite free flap for alar defect reconstruction with a

- supermicrosurgical technique. *Arch Plast Surg.* 2018;45(05):466-9.
26. Qasemyar Q, Gianfermi M, Sarfati B, Leymarie N, Kolb F. Super-microdissected local flaps for the coverage of temporal defects. *Microsurgery.* 2014;34(7):554-7.
27. Marchi F, Wei FC. *Microsurgical Procedures in Plastic Surgery. Textbook of Plastic and Reconstructive Surgery: Basic Principles and New Perspectives.* 2022;125-39.
28. Fernandes RP, Pirgousis P. Local/Regional Flaps in Oral/Head and Neck Reconstruction. *Contemporary Oral Oncology: Oral and Maxillofacial Reconstructive Surgery.* 2017;235-59.
29. Guo L, Pribaz JJ. Clinical flap prefabrication. *Plast Reconstruct Surg.* 2009;124(6S):e340-50.
30. Lembo F, Cecchino LR, Parisi D, Portincasa A. Utility of a new artificial dermis as a successful tool in face and scalp reconstruction for skin cancer: analysis of the efficacy, safety, and aesthetic outcomes. *Dermatol Res Pract.* 2020;2020(1):4874035.
31. Abbase EH, Shenaq SM, Spira M, El-Falaky MH. Prefabricated flaps: experimental and clinical review. *Plast Reconstruct Surg.* 1995;96(5):1218-25.
32. Chen L, Xing Q, Zhai Q, Tahtinen M, Zhou F, Chen L, et al. Pre-vascularization enhances therapeutic effects of human mesenchymal stem cell sheets in full thickness skin wound repair. *Theranostics.* 2017;7(1):117.
33. Zhou F, Zhang L, Chen L, Xu Y, Chen Y, Li Z, et al. Prevascularized mesenchymal stem cell-sheets increase survival of random skin flaps in a nude mouse model. *Am J Transl Res.* 2019;11(3):1403.
34. Uysal CA, Ogawa R, Lu F, Hyakusoku H, Mizuno H. Effect of mesenchymal stem cells on skin graft to flap prefabrication: an experimental study. *Ann Plast Surg.* 2010;65(2):237-44.
35. Zhang Q, Chiu Y, Chen Y, Wu Y, Dunne LW, Largo RD, et al. Harnessing the synergy of perfusable muscle flap matrix and adipose-derived stem cells for prevascularization and macrophage polarization to reconstruct volumetric muscle loss. *Bioact Mater.* 2022;22:588-614.
36. Conese M, Annacontini L, Carbone A, Beccia E, Cecchino LR, Parisi D, et al. The Role of Adipose-Derived Stem Cells, Dermal Regenerative Templates, and Platelet-Rich Plasma in Tissue Engineering-Based Treatments of Chronic Skin Wounds. *Stem Cell Int.* 2020;2020(1):7056261.
37. Zhu Y, Peng N, Wang J, Jin Z, Zhu L, Wang Y, et al. Peripheral nerve defects repaired with autogenous vein grafts filled with platelet-rich plasma and active nerve microtissues and evaluated by novel multimodal ultrasound techniques. *Biomater Res.* 2022;26(1):24.
38. Gentile P, Garcovich S. Systematic Review: Adipose-Derived Mesenchymal Stem Cells, Platelet-Rich Plasma and Biomaterials as New Regenerative Strategies in Chronic Skin Wounds and Soft Tissue Defects. *Int J Mol Sci.* 2021;22(4):1538.
39. Supp DM, Supp AP, Boyce ST, Bell SM. Enhanced vascularization of cultured skin substitutes genetically modified to overexpress vascular endothelial growth factor. *J Invest Dermatol.* 2000;114(1):5-13.
40. Winge MC, Kellman LN, Guo K, Tang JY, Swetter SM, Aasi SZ, et al. Advances in cutaneous squamous cell carcinoma. *Nat Rev Cancer.* 2023;23(7):430-49.
41. Habban Akhter M, Amin S. An investigative approach to treatment modalities for squamous cell carcinoma of skin. *Curr Drug Delivery.* 2017;14(5):597-612.
42. Amini S, Viera MH, Valins W, Berman B. Nonsurgical innovations in the treatment of nonmelanoma skin cancer. *J Clin Aesthet Dermatol.* 2010;3(6):20.
43. Lee TY, Lee S, Eun S. The Free Flap Reconstruction of Facial Defects after Squamous Cell Carcinoma Excision. *Medicina.* 2024;60(9):1432.
44. Rodio M, Tettamanzi M, Trignano E, Rampazzo S, Serra PL, Grieco F, et al. Multidisciplinary Management of Cutaneous Squamous Cell Carcinoma of the Scalp: An Algorithm for Reconstruction and Treatment. *J Clin Med.* 2024;13(6):1581.
45. Malahias M, Ackling E, Zubair O, Harper N, Al-Rawi H, Khalil H. Extended Scalp Flaps for Extensive Soft Tissue Scalp Defects as a Day Surgery Procedure Under Local Anesthetic: A Single Centre Experience. *J Neurol Surg B Skull Base.* 2021;82(6):689-94.
46. Bota O, Meier F, Garzarolli M, Schaser KD, Dragu A, Taqatqeh F, et al. Lower leg reconstruction after resection of a squamous cell carcinoma on necrobiosis lipoidica with a pedicled fibula and an extended anterolateral thigh flap-a case report. *World J Surg Oncol.* 2023;21(1):38.
47. Faenza M, Molle M, Mazzarella V, Antonetti AM, Filosa FG, Pelella T, et al. Functional and Aesthetic Comparison between Grafts and Local Flaps in Non-Melanoma Skin Cancer Surgery of the Face: A Cohort Study. *JPRAS Open.* 2024;42:97-112.

Cite this article as: Ospina DRZ, Ruiz SOC, Galindo AS, Javier AAJ, Pacheco EA, García MFR, et al. Advances in flap surgical techniques and regenerative approaches for reconstruction of extensive defects in cutaneous squamous cell carcinoma: a systematic review of functional and aesthetic outcomes. *Int J Res Med Sci* 2025;12:310-6.