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Surgical De-escalation After Neoadjuvant Immunotherapy for Cutaneous Squamous Cell Carcinoma: Oncological Safety and Reconstructive Consequences

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Abstract

Neoadjuvant programmed cell death protein 1 (PD-1) blockade can produce substantial regression of resectable cutaneous squamous cell carcinoma (cSCC), creating opportunities to preserve threatened structures and reduce reconstructive morbidity. Whether these responses justify smaller operations or omission of local treatment remains a separate clinical question. This narrative review examines prospective trials and retrospective cohorts reporting pathological response, planned versus performed surgery, reconstruction, treatment omission, and oncological outcomes, with a targeted literature update to October 2026.

Prospective and retrospective reports document selected reductions in resection and reconstructive requirements. DISCERN directly compared pretreatment operative intent with performed surgery, whereas De-Squamate evaluated protocol-defined omission of surgery and radiotherapy with continuing pembrolizumab. These findings support feasibility, but small cohorts, response-based selection, heterogeneous postoperative treatment, and limited follow-up restrict conclusions about comparative safety. Anatomical imaging can underestimate pathological regression, while negative biopsies cannot establish clearance throughout an unsampled tumour bed. Adjuvant C-POST results inform postoperative systemic treatment and should not be extrapolated to reduced surgical margins. NRG-HN014/C-PRE evaluates an integrated perioperative strategy rather than the isolated effect of reducing surgery.

A practical approach should record pretreatment disease and operative intent, reassess each involved anatomical compartment, specify the proposed operative change, and document margins, subsequent treatment, surveillance, and salvage options. Future studies must measure durable cancer control alongside function, reconstructive morbidity, patient-reported outcomes, and total treatment burden.

Categories: Plastic Surgery, Therapeutics, Dermatology
Keywords: cemiplimab, cutaneous squamous cell carcinoma, neoadjuvant immunotherapy, pathological response, pembrolizumab, reconstructive surgery, surgical de-escalation

Introduction And Background

Surgery with histological margin assessment remains the foundation of treatment for resectable cutaneous squamous cell carcinoma (cSCC). High-risk or regionally advanced disease requires multidisciplinary planning, with postoperative radiotherapy considered according to disease features. In the head and neck, clearance may require removal of an eyelid, lip, facial nerve, orbit, or adjacent bone, followed by complex reconstruction. The 2026 European consensus guideline emphasises clear margins and individualised management of advanced disease [1].

Surgical de-escalation is a deliberate reduction in the extent of a previously intended resection or reconstructive procedure, including preservation of a threatened structure, on the basis of treatment response. Omission of surgery and omission of postoperative radiotherapy represent additional, distinct forms of treatment de-escalation and should be assessed separately.

PD-1 is an inhibitory receptor on activated T cells. Antibodies such as cemiplimab and pembrolizumab block this inhibitory signalling and can restore antitumour immune activity. Administering treatment before resection provides an opportunity to reduce tumour burden while the tumour remains available for immune recognition and subsequent pathological assessment [2,3].

Pathological complete response (pCR) means no residual viable tumour is identified in the assessed surgical specimen [3]. It is established after resection and therefore cannot, by itself, determine the preoperative boundary of a smaller operation. Even after apparent regression, the surgeon must address uncertainty about residual disease in previously involved deep tissues or regional sites. This review examines how

response has changed actual surgery and reconstruction, and what evidence is needed to judge the safety and patient benefit of those changes.

Review

Literature search and selection

The initial targeted PubMed/MEDLINE search covered database inception through September 2026. A targeted update was undertaken on 25 October 2026 using the following query, restricted to publication dates on or before that date:

("squamous cell carcinoma"[Title/Abstract] OR "Carcinoma, Squamous Cell"[MeSH Terms]) AND (cutaneous[Title/Abstract] OR skin[Title/Abstract]) AND (neoadjuvant[Title/Abstract] OR neoadjuvant-intent[Title/Abstract]) AND (immunotherapy[Title/Abstract] OR cemiplimab[Title/Abstract] OR pembrolizumab[Title/Abstract] OR nivolumab[Title/Abstract] OR ipilimumab[Title/Abstract]).

Additional targeted searches and primary publisher and trial-group sources were used to clarify response-adapted surgery, reconstruction, adjuvant cemiplimab, fluorodeoxyglucose positron emission tomography (FDG-PET), circulating tumour DNA (ctDNA), and ongoing trials. Reference lists were used to identify follow-up reports and potential cohort overlap.

The principal synthesis included adult resectable or potentially resectable cSCC treated with neoadjuvant or neoadjuvant-intent PD-1-directed therapy, including combinations with cytotoxic T-lymphocyte-associated protein 4 blockade. Prospective trials and retrospective cohorts were eligible when they informed response assessment, operative modification, reconstruction, margins, treatment omission, recurrence, or survival. Selected definitive-intent and broader real-world cohorts were retained as contextual evidence and identified accordingly. Mucosal head and neck squamous cell carcinoma was excluded. Full primary reports were preferred; conference evidence was retained only where relevant results were not available as a full publication.

Selection and synthesis were narrative and were not independently duplicated. Appraisal considered study design, denominators, documentation of operative intent, response-based selection, postoperative treatment, follow-up, and ascertainment of recurrence; no formal risk-of-bias instrument was applied. Embase and Scopus were not independently searched. Sequential reports of the same trial were treated as one cohort, and institutional overlap between retrospective series could not always be excluded. No patient totals or treatment effects were pooled. Published confidence intervals and survival estimates are reported as given; the denominator example below is simple arithmetic from published counts.

Prospective evidence and documented operative modification

The cemiplimab pilot and multicentre phase II study established substantial pathological activity, with follow-up showing an association between pathological response and subsequent disease control [2-5]. Their principal purpose was to evaluate treatment activity rather than compare alternative resection boundaries. Nevertheless, the multicentre report included two illustrative patients who avoided orbital exenteration after response [3]. Table *1* summarises the main quantitative results and the surgical question each study can address.

Study and treatment	Response and outcome	Interpretation for operative decisions
Ferrarotto pilot and follow-up [2,4], Single-arm phase II, n=20. Two cemiplimab doses.	pCR in 11/20. At median follow-up of 42.3 months, 17/20 were disease-free; all three recurrences occurred in pathological nonresponders.	All underwent surgery according to original disease extent. Supports response and prognostic association; does not test reduced resection boundaries.
Gross multicentre trial and follow-up [3,5], Single-arm phase II, n=79. Up to four cemiplimab doses.	70/79 underwent surgery. pCR 40/79 (51%; 95% CI, 39-62%); MPR 10/79 (13%). Twelve-month EFS 89% (95% CI, 79-94%); median follow-up 18.7 months.	Illustrative anatomical preservation was reported. No controlled comparison of surgical extent; postoperative observation, cemiplimab, or radiotherapy was selected.
DISCERN [6] Prospective phase II, n=11. Up to four cemiplimab doses.	All underwent surgery; eight achieved pCR and three progressed, proceeding to earlier surgery. Median follow-up was approximately 10 months.	Pretreatment and performed operations were compared: all eight pCR cases had less extensive surgery; all three progressors required more. Direct operative evidence with limited precision and follow-up.
MATISSE [7] Randomised, noncomparative phase II, n=50. Nivolumab with or without ipilimumab	40 underwent surgery. MPR occurred in 9/20 and 10/20 surgical patients by regimen. Of 10 declining local therapy, nine achieved complete clinical remission and remained cancer-free at median subgroup follow-up of 34 months.	Randomisation concerned the drug regimen. Local-treatment omission was patient-selected. Overall cohort median follow-up was 31 months.
De-Squamate [8] Single-arm phase II, n=27. Pembrolizumab with maintenance.	13/27 (48%) avoided surgery and radiotherapy after complete metabolic response and negative mapping biopsies. Four additional operated patients had pCR. Combined complete response was 17/27 (63%; 95% CI, 42-80%).	No recurrence among combined complete responders at median follow-up of 18 months. Demonstrates protocol feasibility with maintenance treatment, not comparative equivalence.
Kim [9]. Two-centre retrospective cohort, n=27. Cemiplimab or pembrolizumab.	Pathology evaluable in 19: seven pCR and two MPR. Five declined planned surgery after response or stability; one did not undergo surgery because of progression. Median follow-up 9.5 months.	Shows limitations of restricting response assessment to resected patients and the importance of preserving the full neoadjuvant-intent denominator.
Yaniv [10]. Retrospective surgical cohort, n=41. Cemiplimab	17 response-adapted and 24 standard resections. Organ preservation in 4/17 and intended free flap avoided in 4/17. Clear margins 16/17 versus 22/24. Estimated two-year locoregional recurrence-free survival 95% versus 90%.	Direct evidence of operative and reconstructive modification. Small, nonrandom groups and response-based selection prevent an inference of noninferiority.
Jin [11]. Single-centre retrospective surgical series, n=18. Cemiplimab	11/18 pCR and 2/18 MPR. No complete radiographic responses. Eight of the 26 patients treated with neoadjuvant intent were excluded because they did not proceed to surgery.	Supports imaging-pathology discordance in an operated subset. Does not evaluate the entire treatment pathway or compare reduced with standard resection.
FIRST [12]. Retrospective real-world cohort, n=189. Frontline checkpoint inhibition	Objective response 119/189 (63%); complete clinical response 52/189 (27.5%). Among 50 complete responders managed without surgery, one recurrence occurred over median follow-up of 25.4 months.	Includes resectable, borderline-resectable, locally advanced, and limited metastatic disease. Response-guided treatment selection limits surgical comparisons.
Kavanagh [13]. Single-centre retrospective cohort, n=72. Cemiplimab	51 received monotherapy without surgery; 21 received neoadjuvant treatment and surgery. Two-year DSS was 90% (95% CI, 80-100%) versus 95% (95% CI, 86-100%), respectively.	Selected patients had resectable stage III/IV head and neck cSCC. Nonrandom treatment choice does not establish equivalence of surgery omission.

TABLE 1: Principal clinical studies and their implications for surgery

CI: confidence interval; cSCC: cutaneous squamous cell carcinoma; DSS: disease-specific survival; EFS: event-free survival; MPR: major pathological response; pCR: pathological complete response.

MPR categories are reported according to the individual study. Trial follow-up reports are combined in the same row; cohorts are not pooled. The table is an original synthesis of the cited studies.

DISCERN prospectively recorded the intended operation before immunotherapy and compared it with the surgery performed. All eight patients with pCR underwent less extensive surgery than initially planned, while all three patients with progression required more extensive surgery. One patient initially planned for total lower-lip resection, free-flap reconstruction, and bilateral levels I-III neck dissections instead underwent lip wedge resection with limited nodal surgery. The statement that immunotherapy did not otherwise alter surgical execution concerns intraoperative handling, not the absence of operative modification. This small cohort and short follow-up cannot establish the long-term safety of the reductions [6].

MATISSE randomised the immunotherapy regimen, not the local-treatment strategy. Its nonoperative group comprised patients who declined planned local treatment; most complete clinical remissions developed during follow-up rather than being established at the scheduled operation [7]. This is an important organ-preservation observation, but it is vulnerable to patient selection and cannot identify a routine omission rule.

De-Squamate more directly tested feasibility of a defined response-adapted pathway. Patients with complete metabolic response and negative mapping biopsies avoided planned surgery and radiotherapy; those undergoing surgery could omit radiotherapy after pCR. The protocol included 13 additional cycles of maintenance pembrolizumab [8]. Thus, local-treatment omission was part of a continuing systemic-treatment strategy. The combined clinical or pathological complete-response endpoint should not be interpreted as a resection-confirmed pCR rate.

Retrospective surgical and nonoperative evidence

The Kim cohort demonstrates the difference between neoadjuvant intent and completed surgery: several patients declined the planned operation, and pathological response was assessable in only a subset [9]. The Yaniv comparison is more directly relevant to operative extent, reporting organ preservation and avoidance of intended free flaps after response-adapted surgery [10]. These outcomes describe actual treatment changes, although retrospective allocation leaves uncertainty about why particular patients received smaller operations.

Jin et al. reported 18 patients who underwent surgery among 26 treated with neoadjuvant intent. Eleven achieved pCR and two achieved a major pathological response, despite no complete radiographic responses. The eight nonoperated patients were excluded from that analysis, including three with a complete clinical response [11]. This adds evidence of imaging-pathology discordance while illustrating that an operated cohort may omit both favourable responders and patients unable or unwilling to proceed to surgery.

FIRST extends the evidence to a heterogeneous population receiving frontline immunotherapy with response-guided subsequent treatment. It reports durable control in selected complete responders managed without surgery, but includes disease beyond the uniformly resectable setting [12]. Kavanagh et al. provide a further 2026 comparison of cemiplimab monotherapy with neoadjuvant cemiplimab followed by surgery in resectable stage III/IV head and neck cSCC [13]. Its nonrandom treatment selection and differing patient characteristics limit causal comparisons. Neither series defines a prospectively validated threshold for safely withholding surgery. Table *1* summarises the clinical studies and their implications for surgery.

Interpreting response before choosing resection boundaries

Clinical examination, anatomical imaging, metabolic imaging, and histology measure different aspects of response. Major pathological response (MPR) generally denotes no more than 10% residual viable tumour; some reports include pCR within MPR, whereas others report the categories separately [3,7]. Definitions must therefore accompany response rates.

Quantitative discordance is clinically relevant. In the multicentre cemiplimab study, radiographic complete response occurred in 5/79 patients, compared with pCR in 40/79 [3]. In DISCERN, all eight pCR patients had partial anatomical responses; PET assessment classified six as complete metabolic responders and two as partial metabolic responders [6]. Persistent imaging abnormalities may therefore represent treatment effect as well as viable tumour. Conversely, shrinkage does not establish microscopic clearance throughout the original disease distribution.

A negative mapping biopsy establishes the absence of identified tumour in the sampled tissue. Its ability to support a smaller resection depends on sampling location, depth, distribution, and the residual-disease pattern. The De-Squamate results apply to its combined metabolic and biopsy assessment, not to appearance alone [8]. Similarly, pathological clearance in an excised specimen does not provide direct evidence about tissues left outside that specimen.

The MATISSE-associated PET analysis supports early metabolic response assessment, but was not a validation of a reduced surgical margin [14]. A 2026 ctDNA abstract reported associations between biomarker kinetics, pathological response, and postoperative recurrence, but baseline detection was imperfect and the cohort was small [15]. Neither biomarker currently supplies a sufficiently validated

negative result to certify clearance of all previously involved sites. Prospective validation should link the proposed test to mapped histology and long-term outcomes under the intended local-treatment strategy.

A practical framework for surgical and reconstructive planning

A practical framework is proposed for multidisciplinary discussion and prospective documentation, although it has not been validated as a surgical-margin algorithm. Before treatment, the primary lesion and regional disease should be mapped using examination, photographs, and appropriate imaging, with documentation of threatened structures, suspected deep or perineural extension, the intended resection, and anticipated reconstruction. A contemporaneous plan provides a more credible comparator than retrospective reconstruction of operative intent after the response is known.

Post-treatment findings should then be compared with this baseline, reassessing the primary tumour, nodal disease, and any initially suspected neural or bony involvement separately. Discordant findings should prompt targeted imaging or biopsy when appropriate, with advance agreement on how clinically important progression would trigger expedited surgery or another treatment decision.

Any proposed reduction in treatment should identify precisely which structure, resection component, or reconstructive procedure may be preserved or avoided and explain the supporting evidence. Peripheral and deep margin assessment, specimen orientation, and the ability to extend resection or revise reconstruction if residual disease is identified should be incorporated into operative planning.

Omission of surgery or radiotherapy requires separate justification and explicit discussion of uncertainty. Subsequent treatment decisions should integrate viable tumour distribution, margin status, and regional findings, while documentation should capture planned and performed reconstruction, functional outcomes, complications, patient preferences, surveillance, and feasible salvage options. Patients who do not reach surgery must remain included in outcome reporting.

Routine implementation may be limited by inconsistent documentation of surgical intent, differing reconstructive preferences, access to specialist imaging and pathology, and the workload of repeated multidisciplinary review. A short shared proforma recording the baseline plan, post-treatment modification, and rationale may improve feasibility, although its implementation requires evaluation in practice.

Measuring reconstructive benefit and treatment burden

The reconstructive endpoint should describe what changed between the intended and performed procedure. DISCERN and Yaniv provide direct examples of reduced operative or reconstructive requirements [6,10]. These observations should be recorded separately from tumour shrinkage without a documented change in reconstruction.

Avoidance of a free flap is a procedure-based outcome, not a complete measure of patient benefit. A smaller reconstruction may still produce poor oral competence, exposed bone, unstable coverage, or repeated revisions; a well-planned flap may provide more reliable function. Future comparisons should assess the consequence of reconstruction through relevant function, appearance, wound reliability, donor-site morbidity, length of admission, and revision or salvage procedures. These are proposed evaluation domains rather than demonstrated benefits of de-escalation.

Assessment must also include immunotherapy exposure, immune-related toxicity, additional investigations, and delay to definitive local treatment. Continuing systemic therapy after local-treatment omission, as in De-Squamate, can shift rather than eliminate treatment burden [8]. Progression can increase the required operation, as observed in DISCERN [6]. Existing cohorts do not establish whether neoadjuvant therapy improves or worsens free-flap failure or wound-complication rates compared with appropriately matched surgery-first care.

Oncological safety and comparative evidence

Response rates should retain their original denominators. In the multicentre trial, the same 40 pCRs represent 50.6% of 79 treated patients but 57.1% of 70 operated patients [3]. Excluding patients who progress or deteriorate before surgery can inflate an apparent response estimate by removing treatment failures. When favourable responders decline surgery, selection can also act in the opposite direction, as illustrated by the Kim and Jin series [9,11]. Operated-cohort pathology and outcomes of the complete treatment pathway answer different questions.

The reported survival after response-adapted surgery is encouraging, but small nonrandom groups cannot establish noninferiority. A nonsignificant difference between survival estimates does not demonstrate equivalence. Comparisons should begin at a common pretreatment time point, retain patients who fail to reach surgery, and account for response-dependent treatment selection, subsequent radiotherapy, and systemic therapy. The nonoperative experiences in MATISSE, De-Squamate, FIRST, and Kavanagh should be interpreted in their distinct selection and treatment contexts [7,8,12,13].

C-POST addresses a different question. Among 415 patients at high recurrence risk after surgery and postoperative radiotherapy, adjuvant cemiplimab improved estimated 24-month disease-free survival to 87.1%, versus 64.1% with placebo (hazard ratio for recurrence or death, 0.32; 95% confidence interval, 0.20-0.51; P<0.001). Grade 3 or higher adverse events occurred in 23.9% and 14.2%, respectively [16]. These findings inform adjuvant systemic treatment after definitive local therapy. They do not establish that a neoadjuvant response permits narrower resection or omission of radiotherapy.

NRG-HN014/C-PRE is a randomised phase III comparison of standard surgery-based treatment with a strategy incorporating neoadjuvant cemiplimab, response-adapted surgery, and pathological-response-guided adjuvant treatment. Its primary endpoint is event-free survival [17]. It will provide comparative evidence for the integrated treatment strategy. Because systemic exposure, surgical extent, and postoperative treatment can all differ between groups, it will not independently isolate the oncological effect of reducing surgery. Specific operative changes and functional outcomes will remain important to interpretation.

Applicability limitations and research priorities

The evidence remains concentrated in selected populations, often with head and neck disease. Older age, frailty, autoimmune disease, and different forms of immunosuppression may change eligibility, toxicity, and treatment priorities. Inclusion of patients with lymphoma in one real-world cohort does not establish applicability to all immunocompromised groups [9]. Advanced-disease decisions should therefore integrate specialist assessment and patient preferences [1].

This review is limited by targeted narrative selection, lack of independent duplicate assessment or formal risk-of-bias scoring, and incomplete ascertainment outside PubMed/MEDLINE. The studies use different response definitions, treatment exposures, anatomical populations, postoperative therapies, and follow-up periods. The pilot and multicentre follow-up papers are longitudinal reports of previously described cohorts, and retrospective series from related institutions may overlap [2-5,9,10,12]. Their sample sizes should not be added to produce an apparent independent evidence base.

The highest-priority research question is which patients can receive a defined reduction in local treatment while retaining durable cancer control. Studies should prospectively record the baseline operation, the operation performed, the tissue preserved, margins, and reasons for treatment changes. A common dataset should retain all patients starting the pathway, including progression, toxicity, patient refusal, and loss of operability. Long-term assessment should combine local and regional recurrence, survival, salvage burden, function, and patient-reported outcomes. Within suitable prospective designs, the contribution of surgical modification should be distinguished from changes in systemic and radiation treatment.

Conclusions

Neoadjuvant immunotherapy has enabled documented reductions in surgery and reconstruction in selected patients with resectable cSCC. The next requirement is comparative evidence that identifies which operative changes preserve durable cancer control and improve outcomes that matter to patients. A useful clinical record starts with pretreatment disease and operative intent, identifies the proposed change after treatment, and documents margin assessment, subsequent therapy, follow-up, and salvage. Response-adapted surgery and omission of local treatment should remain distinct decisions evaluated within multidisciplinary care and, where feasible, prospective protocols.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Daniel Gravino, Ruben Chircop

Acquisition, analysis, or interpretation of data: Daniel Gravino, Ruben Chircop

Drafting of the manuscript: Daniel Gravino, Ruben Chircop

Critical review of the manuscript for important intellectual content: Daniel Gravino, Ruben Chircop

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