

## Navigating the Diagnostic Maze of Cutaneous Squamous Cell Carcinoma Nodal Assessment

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**The global incidence** of cutaneous squamous cell carcinoma (cSCC) is rising at an alarming rate, placing a large burden on dermatological and surgical oncology services.<sup>1</sup> In this era of increasing incidence, adequate risk stratification has become essential for effective management. While risk stratification for cSCC continues to improve,<sup>2</sup> we still lack a criterion standard imaging modality for detecting occult nodal metastases—a vital missing piece given the major impact that early detection may have on treatment outcomes. This Editorial contextualizes the findings of Ferrándiz-Pulido et al<sup>3</sup> who shed light on the diagnostic performance of physical examination, ultrasonography, and computed tomography (CT) in an effort to optimize and standardize our diagnostic approach to this potentially fatal disease.

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### Comparison of Modalities for Detecting Nodal Metastasis

The lack of prior prospective studies comparing physical examination, ultrasonography, and CT speaks to both the difficulty of the task as well as the existing knowledge gap. The authors put great effort into conducting a multicenter, prospective, paired diagnostic study including 13 tertiary dermatological departments across Spain during 3 years. Also, the imaging modalities were performed in every patient in a blinded way and compared to the findings of the other modalities, an important and unique strength of this study. While the study was methodologically robust and focused on seemingly high-risk cSCCs to boost power, the low event count ( $n = 12$ ) makes it difficult to draw firm conclusions from these data alone. However, the findings reflect the general consensus of existing research: ultrasonography and CT outperform clinical examination, ie, palpation of the draining lymph nodes in the detection of nodal metastases at baseline.<sup>4,5</sup>

Whether ultrasonography and CT are interchangeable—their second major conclusion—remains an object of debate. In a previous systematic review, CT showed higher sensitivity and specificity compared to ultrasonography and in a previous meta-analysis of SCC—not limited to cSCC—only specificity was higher.<sup>6,7</sup> However, ultrasonography is more widely available and cost-effective compared to CT and, when performed by experienced and trained radiologists, the sensitivity and specificity can be as high as 91% and 78%, respectively.<sup>4</sup> Besides, ultrasonography does not have the radiation adverse effects that CT poses on patients and can be combined directly with fine-needle aspiration cytology to obtain pathological confirmation.

The main limitations of ultrasonography include its reduced efficacy in detecting deep-seated lymph nodes and

its high operator dependency and interobserver variability, all of which can compromise diagnostic consistency. However, since nodal metastases from cSCC are generally more superficial compared to non-cSCC in the head and neck region, we believe that the prior limitation is less relevant. Besides, the high level of agreement between ultrasonography and CT as found by Ferrándiz-Pulido et al<sup>3</sup> ( $\kappa = 0.87$ ) allows dermatology centers the flexibility to select the modality that best fits their specific resources and expertise. This ensures that centers lacking specialized radiologists for operator-dependent ultrasonography can confidently use CT without compromising diagnostic accuracy.

### Optimal Timing and Frequency of Surveillance Imaging

Beyond selecting the type of imaging modality, determining true high risk patients and the optimal timing for its implementation should be of equal importance. Ferrándiz-Pulido et al<sup>3</sup> conclude that sensitivity for both ultrasonography and CT at baseline declined drastically in immunosuppressed patients, from 100% for the immunocompetent group to 20% and 17%, respectively, in the immunosuppressed group.<sup>3</sup> As 83% of all nodal metastases in the immunosuppressed group became clinically apparent during the 3-month period following baseline imaging, we believe that the decline in sensitivity does not necessarily reflect a failure of these imaging modalities themselves. Rather, we propose that the rapid progression from micrometastases at baseline—undetectable by ultrasonography and CT—to clinically apparent nodal disease in these patients occurs at a very high pace in the immunosuppressed group.

Consequently, the diagnostic challenge is not the inherent resolution of ultrasonography or CT, but rather the optimal timing of their application. A retrospective study<sup>5</sup> with modalities including but not limited to ultrasonography and CT found that 56% of all subclinical nodal metastases was diagnosed using surveillance imaging during a follow-up of 2 years after baseline imaging. Another recent prospective study<sup>8</sup> showed that 19% of all subclinical nodal metastases were found with surveillance imaging, which was performed during a follow-up time of 2 years. Also, detection of subclinical nodal disease changed clinical management either fully or partly in these patients. Although 19% may seem on the low side, given that the remainder of the metastases during follow-up were detected clinically, better timing of surveillance imaging could have increased the proportion of metastases identified in the asymptomatic phase. This is underscored by a previous study<sup>9</sup> showing that 89% of all clinically detected nodal metastases were found during follow-up instead of baseline and that the lymph node sizes

of the clinically overt metastases were larger than the ultrasonography-detected nodal metastases.

Although these findings highlight the pivotal role of surveillance imaging, a standard criterion has yet to be integrated into clinical guidelines. Additional well-designed studies are needed to validate the clinical benefits of cSCC surveillance imaging and to determine which patients should undergo surveillance imaging, the appropriate frequency and interval, and the total duration of the surveillance period. A clinicopathological prediction model that accurately identifies the risk of metastasis in patients with cSCC could be used to identify those who would benefit.<sup>2</sup> Also, large population-based studies could be used to pinpoint the precise times during follow-up at which metastasis becomes clinically apparent and to define a substantiated schedule for implementing surveillance imaging.

### Improving Clinical Outcomes

The primary objective of optimizing subclinical nodal imaging is to improve clinical outcomes by reducing mortality and treatment-related morbidity. Based on nationwide data from a study conducted in The Netherlands,<sup>10</sup> the 5-year disease-specific survival rates drop from 99.4% in the total cSCC group to 79.1% when metastases are detected. The disease-specific survival rates for metastatic cSCC are even lower in patients who are immunoincompetent.<sup>11</sup> Consequently, there is a strong rationale for identifying (micro)metastases before they become clinically apparent.

Currently, there is no direct evidence showing that imaging-based detection of subclinical nodal metastasis improves survival rates. To our knowledge, the only available study<sup>12</sup> on this topic was underpowered to assess the impact of imaging (either baseline or within the first few months post-operatively) on disease-specific mortality rates but did demonstrate a nonsignificant higher disease-free survival rate in the imaging group compared to the nonimaging group in their Kaplan-Meier survival analysis (73% vs 51%).

The lack of evidence regarding imaging outcomes warrants a comparison with sentinel lymph node biopsy (SLNB), a surgical technique with pathologic confirmation that serves as the established benchmark for identifying subclinical nodal metastasis in, for example, melanoma. Evaluating the prognostic impact of SLNB may provide insights into whether the early detection of occult metastases, regardless of the modality used, actually translates into superior disease-specific survival. Previous reviews<sup>13</sup> have shown a positive SLNB rate vary-

ing from 12% to 21% in cSCC and even as high as 30% for stage T2b cSCCs as classified according to the Brigham and Women's Hospital tumor staging system. A retrospective cohort study<sup>14</sup> showed a reduced risk of disease-specific mortality in patients who are immunoincompetent with high-risk cSCC (hazard ratio, 0.17; 95% CI, 0.04-0.72;  $P = .02$ ), but not in patients experiencing immunosuppression. In a relatively small retrospective study<sup>15</sup> with no stratification on immune status, a nonsignificant reduction in disease-specific mortality in the SLNB group compared to the observational group was found. In terms of overall survival, a significant benefit for the SLNB group has been shown before.<sup>16</sup>

Hence, while a potential benefit has been shown in patient with immunocompetence within a single cohort, a significant effect has not been shown in immunosuppressed populations, and broader comparative studies have shown no significant improvement in terms of disease-specific survival. Consequently, the evidence supporting SLNB—and the detection of subclinical metastasis in general—as a survival-prolonging intervention remains inconclusive and largely exploratory. However, we are confident that the identification of subclinical metastasis plays a critical role in facilitating timely intervention. Early detection could enable more refined, localized therapies such as a limited lymph node dissection instead of extensive lymph node dissections and adjuvant treatments with their associated treatment-related morbidities. Besides, identifying subclinical involvement ensures more accurate staging, allowing for a more precise prognostic assessment and personalized care, particularly in the evolving landscape of neoadjuvant immunotherapy.

Baseline nodal imaging with either ultrasonography or CT performs well in the detection of nodal metastasis whereas clinical examination can fall short. However, for certain high-risk groups such as patients who are immunosuppressed, surveillance imaging seems to have an important additional role in maximizing diagnostic yield and facilitating early identification of occult metastases, reducing the risk of extensive treatment-related morbidity. At the same time, it must be noted that definitive evidence regarding the clinical utility of detecting subclinical metastases currently remains limited. While there are indications of improved overall and disease-specific survival, appropriately targeted and timed research is required to provide a conclusive verdict. Only then can the diagnostic maze of cSCC nodal assessment be transformed into evidence-based criterion standards and benchmarks in clinical guidelines.

### ARTICLE INFORMATION

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### REFERENCES

1. Tokez S, Hollestein L, Louwman M, Nijsten T, Wakkee M. Incidence of multiple vs first cutaneous squamous cell carcinoma on a nationwide scale and estimation of future incidences of cutaneous squamous cell carcinoma. *JAMA Dermatol*. 2020; 156(12):1300-1306. doi:10.1001/jamadermatol.2020.3677
2. Rentroia-Pacheco B, Tokez S, Brammer EM, et al. Personalised decision making to predict absolute metastatic risk in cutaneous squamous cell carcinoma: development and validation of a

clinico-pathological model. *EClinicalMedicine*. 2023; 63:102150. doi:10.1016/j.eclinm.2023.102150

3. Ferrándiz-Pulido C, Gómez-Tomás Á, Siurana S, et al. Diagnostic modalities and nodal staging in high-risk cutaneous squamous cell carcinoma. *JAMA Dermatol*. Published online April 22, 2026. doi:10.1001/jamadermatol.2026.0803

4. Tokez S, Koekelkoren FHJ, Baatburg de Jong RJ, et al. Assessment of the diagnostic accuracy of baseline clinical examination and ultrasonographic imaging for the detection of lymph node metastasis in patients with high-risk cutaneous squamous cell

- carcinoma of the head and neck. *JAMA Dermatol.* 2022;158(2):151-159. doi:10.1001/jamadermatol.2021.4990
5. Maher JM, Schmults CD, Murad F, Karia PS, Benson CB, Ruiz ES. Detection of subclinical disease with baseline and surveillance imaging in high-risk cutaneous squamous cell carcinomas. *J Am Acad Dermatol.* 2020;82(4):920-926. doi:10.1016/j.jaad.2019.10.067
6. Libson K, Sheridan C, Carr DR, Shahwan KT. Use of imaging in cutaneous squamous cell carcinoma to detect high-risk tumor features, nodal metastasis, and distant metastasis: a systematic review. *Dermatol Surg.* 2024;50(8):705-709. doi:10.1097/DSS.0000000000004191
7. Liao LJ, Lo WC, Hsu WL, Wang CT, Lai MS. Detection of cervical lymph node metastasis in head and neck cancer patients with clinically NO neck—a meta-analysis comparing different imaging modalities. *BMC Cancer.* 2012;12:236. doi:10.1186/1471-2407-12-236
8. Davis M, Connolly K, Dusza S, Lee E, Nehal K, Barker C. Surveillance imaging detects subclinical recurrence in very high-risk cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 2025;SO190-9622(25)03423-1. doi:10.1016/j.jaad.2025.12.042
9. Eggermont C, Nené LEH, Koekelkoren FHJ, et al. The impact of routine ultrasonography on nodal metastasis in head and neck cutaneous squamous cell carcinoma: a retrospective multicentre cohort study. *J Eur Acad Dermatol Venereol.* 2023;37(9):e1136-e1140. doi:10.1111/jdv.19150
10. Tokez S, Wakkee M, Kan W, et al. Cumulative incidence and disease-specific survival of metastatic cutaneous squamous cell carcinoma: a nationwide cancer registry study. *J Am Acad Dermatol.* 2022;86(2):331-338. doi:10.1016/j.jaad.2021.09.067
11. Wackel M, Plampton K, Georgesen C, Wysong A, Whitley MJ. Metastatic squamous cell carcinoma is associated with a lower disease-specific survival in immunosuppressed patients: a matched case-control study. *J Am Acad Dermatol.* 2022;87(6):1410-1411. doi:10.1016/j.jaad.2022.08.042
12. Ruiz ES, Karia PS, Morgan FC, Schmults CD. The positive impact of radiologic imaging on high-stage cutaneous squamous cell carcinoma management. *J Am Acad Dermatol.* 2017;76(2):217-225. doi:10.1016/j.jaad.2016.08.051
13. Schmitt AR, Brewer JD, Bordeaux JS, Baum CL. Staging for cutaneous squamous cell carcinoma as a predictor of sentinel lymph node biopsy results: meta-analysis of American Joint Committee on Cancer criteria and a proposed alternative system. *JAMA Dermatol.* 2014;150(1):19-24. doi:10.1001/jamadermatol.2013.6675
14. Tejera-Vaquero A, Gómez-Tomás Á, Jaka A, et al. Sentinel lymph node biopsy versus observation in high-risk cutaneous squamous cell carcinoma in immunosuppressed and immunocompetent patients: an inverse probability of treatment weighting study. *J Eur Acad Dermatol Venereol.* 2024;38(8):1588-1598. doi:10.1111/jdv.20051
15. Kofler L, Kofler K, Schulz C, Breuninger H, Häfner HM. Sentinel lymph node biopsy for high-thickness cutaneous squamous cell carcinoma. *Arch Dermatol Res.* 2021;313(2):119-126. doi:10.1007/s00403-020-02082-1
16. Roberts KA, Chen K, Wahle BM, Nguyen SA, Moore MG, Yesensky JA. Management of regional lymph nodes in clinically node-negative cutaneous squamous cell carcinoma of the head and neck: a systematic review & meta-analysis. *Cancers (Basel).* 2025;17(20):3335. doi:10.3390/cancers17203335