

Quantitative low-dose CT from SPECT/CT and sentinel lymph node status in head and neck melanoma: a nested case-control study

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Abstract

Background

Sentinel lymph node excision (SLNE) is the standard staging procedure in intermediate- and high-risk cutaneous melanoma, but in the head and neck it is technically demanding, carries a risk of facial nerve injury, and may fail to retrieve a preoperatively marked node, leaving the patient with the operative risk but no staging information. Non-invasive predictors of sentinel lymph node (SLN) status are therefore needed. We investigated whether quantitative computed tomography (CT) parameters from the low-dose CT component of preoperative single-photon emission computed tomography/computed tomography (SPECT/CT), already performed for SLN mapping, differ between metastatic and tumor-free SLNs.

Methods

In this retrospective single-center study, 42 SLN regions of interest (ROIs) from patients with head and neck cutaneous melanoma treated between 2014 and 2025 were analyzed: 18 with histologically confirmed metastasis and 24 tumor-free controls, selected by simple random sampling. SLN ROIs were segmented by a radiologist blinded to histopathology. Five parameters were compared using the Mann–Whitney U test, with receiver operating characteristic analysis and bootstrap confidence intervals (CIs): minimum, maximum, and mean attenuation, the standard deviation (SD) of attenuation, and mask volume. Both significant parameters were entered into a multivariable logistic regression.

Results

Metastatic ROIs were larger and showed higher mean attenuation. Mask volume discriminated best (median 397.9 versus 257.7 mm³; $P = 0.004$; area under the curve [AUC] 0.77, 95% CI 0.61–0.90), followed by mean attenuation (22.6 versus 8.2 HU; $P = 0.046$; AUC 0.68, 95% CI 0.51–0.84). The two were only weakly correlated ($\rho = 0.24$; $P = 0.129$). Entered together, mask volume remained borderline significant (odds ratio [OR] 5.26 per 1-SD increase, 95% CI 1.00–27.55; $P = 0.050$) while mean attenuation retained a comparable effect size but lost significance (OR 1.88, 95% CI 0.86–4.15; $P = 0.116$). Minimum and maximum attenuation and the SD of attenuation did not differ significantly.

Conclusions

Quantitative low-dose CT parameters distinguish metastatic from tumor-free SLN regions without additional imaging, contrast, or radiation, with nodal volume the most robust discriminator and a concordant density signal whose independence a larger sample should be able to confirm. These hypothesis-generating findings require validation in larger cohorts.

Background

Cutaneous melanoma remains a growing global health challenge, with rising incidence and disability-adjusted life-years across most regions over the past thirty years [1] and a substantial fraction attributable to ultraviolet radiation [2]. In many high-income countries, mortality has diverged from incidence, reflecting earlier diagnosis and advances in systemic therapy [3, 4].

Sentinel lymph node excision (SLNE) represents the standard staging procedure for patients with intermediate- and high-risk cutaneous melanoma and offers prognostic information that informs subsequent management strategies [5]. Following the findings of the second Multicenter Selective Lymphadenectomy Trial (MSLT-II), which demonstrated that immediate completion lymph node dissection after identification of a tumor-positive sentinel lymph node (SLN) does not enhance melanoma-specific survival compared to observation [6], the focus has transitioned from the extent of surgical intervention to the status of the SLN as the critical staging determinant, which now governs eligibility for adjuvant systemic therapy in current European guidelines [7].

Although often described as minimally invasive, SLNE carries a meaningful complication rate. A systematic review of 21 studies reported an overall rate of approximately 11%, predominantly infections, seromas, hematomas, lymphedema, and nerve injuries [8], with comparable morbidity in a recent single-center series [9]. In the head and neck region, the procedure becomes additionally complex, as SLNs frequently reside within or near the parotid gland. Their excision involves certain risks, especially to the facial nerve, even when dissection is performed with nerve-sparing techniques [10]. Preoperative marking of an SLN does not guarantee its intraoperative identification. Non-identification is more common in head and neck melanomas than at other anatomical sites and is associated with poorer nodal disease-free survival [11]. A 20-year series demonstrated improvements in detection rates, increasing from 78% to 98% between the first and second decades of experience [12]. When the node remains unidentified, the patient still bears the full risk associated with a neck or parotid incision, without gaining any staging benefit.

Non-invasive imaging modalities have yet to fully bridge this diagnostic gap. Preoperative ultrasound of the nodal basin is specific but insensitive for occult sentinel-node metastases, with reported sensitivities of 13.6% and 33.8% against specificities of 96.9% and 85.7% [13, 14]. A recent systematic review and meta-analysis has confirmed that this limitation persists in the era of neoadjuvant immunotherapy, with a pooled sensitivity of 33.6% (95% CI 23.5–45.5) [15]. The use of 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET-CT) serves as a supplementary modality, although its spatial resolution constrains its efficacy in identifying subclinical nodal disease in early-stage melanoma [16, 17]. Preoperative single-photon emission computed tomography/computed tomography (SPECT/CT), although essential for localizing the sentinel node in this setting, indicates only the node's position, not its metastatic status, leaving this gap unaddressed. The complex anatomy of the head and neck compounds the problem, as many lymph nodes lie within a confined space and lymphatic drainage from a given primary site cannot be reliably predicted. In a lymphoscintigraphic series,

agreement with the clinically expected drainage field was no better than chance (Cohen's $\kappa = 0.11$), and unexpected SLNs were found in 9% of patients [18]. This is thought to contribute to the higher false-negative rate of SLNE in this region compared with other body sites (34.5% versus 14.8% for the trunk and 10.4% for the limbs) [19].

Quantitative CT analysis provides an additional method for deriving supplementary information from images that have already been acquired for other purposes. Texture features of lymph nodes observed in preoperative CT scans have enhanced the prediction of nodal metastasis beyond mere size criteria in cases of rectal cancer [20], adenocarcinoma of the esophagogastric junction [21], and duodenal papillary carcinoma [22]. Moreover, radiomic analysis of mammography and magnetic resonance imaging (MRI) has been used to predict sentinel and axillary nodal metastasis in breast cancer [23, 24]. In the context of melanoma, CT texture parameters have demonstrated predictive value for responses to anti-programmed cell death protein 1 (PD-1) therapy [25]. A closely related approach has been applied to nodal staging in canine oral melanoma, where lymphocenter volume and attenuation were measured on contrast-enhanced CT [26]. The most relevant precedent that addresses SLN status itself is a conference abstract [27]. To our knowledge, this has not been published as a peer-reviewed study, and no published study has applied quantitative CT analysis to the sentinel node in this setting.

A practical entry point is the low-dose CT component acquired as part of SPECT/CT for anatomical localization and attenuation correction during routine preoperative lymphoscintigraphy, a dataset that already supports quantitative measurement of nodal attenuation and volume. A comparable low-dose CT component of PET-CT has previously carried useful quantitative information in lymphoma [28].

We therefore conducted an exploratory quantitative CT analysis of the SLN region utilizing the low-dose CT component of preoperative SPECT/CT in patients diagnosed with cutaneous melanoma of the head and neck. Our hypothesis posited that quantitative CT parameters, encompassing both first-order attenuation statistics and the volume of the segmented region, differ between histopathologically confirmed SLN metastases and tumor-free control SLNs. The objective was to determine which of these parameters, if any, can effectively discriminate between the two groups.

Methods

Study design

This retrospective, single-center study was conducted in the Department of Oral and Maxillofacial Surgery at University Hospital Regensburg, Germany, in accordance with the Declaration of Helsinki, and is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies (Additional file 2).

Patients and case selection

The analysis is a sub-study nested within a larger retrospective cohort of 211 consecutive patients with cutaneous melanoma who underwent SLNE at our department between July 2014 and December 2025. SLNE was indicated according to the American Joint Committee on Cancer (AJCC) staging system in force at the time of treatment (seventh edition [29]; eighth edition [30] from 2017 onwards).

A preoperative SPECT/CT was, in principle, available in this parent cohort, but a considerable proportion of the corresponding nuclear medicine examinations had already been archived by the time of data collection and could not be retrieved. All histologically confirmed SLN metastases with a retrievable SPECT/CT ($n = 18$) were included. This group was sample-size-limited, so 24 tumor-free controls were drawn from all eligible patients using computer-generated simple random sampling without replacement, yielding an approximately balanced design (ratio $\approx 1:1.3$).

Both randomization steps, control selection and, where lymphoscintigraphy had identified more than one candidate SLN, selection of a single node per patient, were run in this fixed order on data sorted by patient identifier under a single seed (20260715) in R (version 4.6.1; R Core Team, Vienna, Austria). In total, 42 regions of interest (ROIs) were analyzed (18 metastatic, 24 control; Fig. 1).

Sentinel lymph node localization and histopathological reference standard

SLNs were localized by lymphoscintigraphy with SPECT/CT, performed by the Department of Nuclear Medicine on the day before surgery. After intradermal injection of four depots of technetium-99m-labeled radiocolloid (total activity approximately 60–80 MBq) around the primary tumor site, a dynamic sequence (0–3 min) and planar scintigraphy of the head, neck and thorax at 5 min and 2 h were acquired, followed by SPECT/CT at 2 h. Over the study period, the radiotracer changed from Tc-99m-labeled nanocolloid to Tc-99m-labeled human serum albumin nanocolloid, reflecting departmental practice rather than a change in study protocol. Images were reconstructed in three planes with attenuation correction from the low-dose CT component, and SLNs were marked on the skin under probe guidance. Surgery followed the next day with intraoperative SLN detection using a hand-held gamma probe.

Excised SLNs were formalin-fixed, paraffin-embedded, and evaluated on an initial hematoxylin and eosin (H&E)-stained section. If unremarkable, additional step sections and immunohistochemistry (usually HMB45, occasionally supplemented with SOX10) were performed per current guideline recommendations [31], unless the node had not been intraoperatively marked as a sentinel node. Suspicious infiltrates were confirmed immunohistochemically (HMB45, S100, and/or SOX10 as indicated).

CT acquisition and region-of-interest segmentation

The CT data used for quantitative analysis were taken from the low-dose CT component of the SPECT/CT examination described above, acquired on a Mediso AnyScan SC SPECT/CT system (Mediso Ltd., Budapest, Hungary; model AnyScan SC-SNs-T1-123R-dcs7) without intravenous contrast, in spiral mode at a fixed tube voltage of 120 kV with the tube current–time product controlled by automatic exposure control and therefore variable between patients. Section thickness was 3.0 mm, and images were reconstructed using Tera-Tomo iterative reconstruction.

A single radiologist with more than five years of experience (G.N.), blinded to the histopathological results and to all other patient information, manually segmented the whole-organ 3D SLN ROIs using Mimics (version 26; Materialise NV, Leuven, Belgium). The workflow is illustrated in Fig. 2 in the axial plane. For each ROI, the minimum, maximum, and mean attenuation (Hounsfield units, HU), the standard deviation (SD) of attenuation, and the mask volume were extracted. The anatomical location of each ROI was also recorded. These are four first-order intensity statistics and one morphological descriptor. Higher-order texture features were deliberately not computed, given their known sensitivity to acquisition and reconstruction settings.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD where the distribution was approximately symmetrical and as median with range or interquartile range (IQR) where it was skewed. Categorical variables are given as counts and percentages.

The five CT parameters were compared between metastatic and control ROIs using two-sided Mann–Whitney U tests, with the U statistic reported. Discriminative capacity was quantified by the area under the receiver operating characteristic (ROC) curve (AUC), with metastatic status as the positive class, for a single marker, the AUC equals $U/(n_1n_2)$. Two-sided 95% confidence intervals (CIs) were obtained by group-stratified percentile bootstrap resampling (2000 resamples). Pairwise associations among the five parameters were examined with Spearman rank correlation coefficients.

As a post hoc sensitivity analysis, a binary logistic regression model was fitted with metastatic status as the outcome and mean attenuation and mask volume (both z-standardized) as simultaneous predictors, to assess whether the attenuation signal was independent of the volume signal (Table 3). With 18 events and two predictors, the model operates at approximately nine events per variable.

A P value below 0.05 was considered statistically significant. No a priori sample size calculation was performed, and power was consequently limited by the small subgroup sizes. Missing data were not imputed, and analyses were performed on complete cases, using SPSS Statistics (version 29.0.1.0; IBM Corp., Armonk, NY, USA), RStudio (version 2026.06.0 + 242; Posit Software, PBC, Boston, MA, USA), R (version 4.6.1) and Python (version 3.12; NumPy v2.4, SciPy v1.17).

Figures presenting the statistical results were generated from the SPSS output using Claude (Anthropic PBC, San Francisco, CA, USA) to ensure a consistent visual format. The underlying data and analyses

were unaffected.

Results

Cohort characteristics

Forty-two SLN ROIs from the head and neck region were analyzed, comprising 18 histologically confirmed metastatic and 24 tumor-free control SLNs. The overall median age at surgery was 71.5 years (range 28.2–85.8) and the cohort was predominantly male (30/42; 71.4%). Metastatic and control ROIs were broadly comparable in age (median 65.3 versus 73.5 years) and in the male-to-female ratio. By anatomical region, ROIs were distributed across the parotid/preauricular region (14/42; 33.3%), cervical lymph node level II (15/42; 35.7%), and the retroauricular/occipital region (7/42; 16.7%), with the remaining ROIs (6/42; 14.3%) located at other neck sites. The characteristics of the analyzed SLNs are summarized in Table 1.

Table 1
Descriptive characteristics of the 42 analyzed sentinel lymph node regions of interest

Characteristic	All ROIs (n = 42)	Metastatic (n = 18)	Control (n = 24)
<i>Age at surgery</i>			
Mean ± SD, years	67.7 ± 14.3	65.1 ± 12.3	69.7 ± 15.4
Median (range), years	71.5 (28.2–85.8)	65.3 (42.2–81.6)	73.5 (28.2–85.8)
<i>Sex, n (%)</i>			
Male	30 (71.4)	13 (72.2)	17 (70.8)
Female	12 (28.6)	5 (27.8)	7 (29.2)
<i>Anatomical region of SLN, n (%)</i>			
Parotid/preauricular	14 (33.3)	10 (55.6)	4 (16.7)
Cervical lymph node level II	15 (35.7)	6 (33.3)	9 (37.5)
Retroauricular/occipital	7 (16.7)	2 (11.1)	5 (20.8)
Other	6 (14.3)	0 (0)	6 (25.0)

Data are shown overall and by metastatic versus tumor-free control status. ROI region of interest, SD standard deviation, SLN sentinel lymph node

Comparison of CT parameters

Two of the five quantitative CT parameters differed significantly between metastatic and control SLNs in two-sided Mann–Whitney U tests: mask volume (P = 0.004) and mean attenuation (P = 0.046), both being

higher in metastatic than in control SLNs. Mask volume showed the higher discriminatory power in ROC analysis (AUC 0.77, 95% CI 0.61–0.90), while mean attenuation, although statistically significant, showed only modest discriminative capability (AUC 0.68, 95% CI 0.51–0.84; Fig. 3). Minimum attenuation, maximum attenuation, and the SD of attenuation did not differ significantly between the groups and demonstrated poor discriminative ability, with AUCs of 0.61, 0.67, and 0.42, respectively, and 95% CIs that all encompassed 0.50 (Additional file 1). Complete results are detailed in Table 2.

Table 2

Comparison of quantitative CT parameters between metastatic and tumor-free sentinel lymph nodes

CT parameter	Metastatic (n = 18), median (IQR)	Control (n = 24), median (IQR)	U	P	AUC (95% CI)
<i>Attenuation-based parameters</i>					
Minimum attenuation (HU)	–53.5 (– 64.5 to – 39.0)	–64.0 (– 79.8 to – 40.3)	262	0.247	0.61 (0.43–0.78)
Maximum attenuation (HU)	82.0 (50.8 to 92.8)	65.5 (45.5 to 72.3)	290	0.062	0.67 (0.49–0.83)
Mean attenuation (HU)	22.6 (6.4 to 43.5)	8.2 (– 5.6 to 22.9)	295	0.046	0.68 (0.51–0.84)
SD of attenuation (HU)	29.2 (23.3 to 30.4)	30.3 (23.8 to 33.7)	183	0.409	0.42 (0.25–0.61)
<i>Volume-based parameter</i>					
Mask volume (mm ³)	397.9 (335.5 to 738.0)	257.7 (168.1 to 367.2)	331	0.004	0.77 (0.61–0.90)
Metastatic status was the positive class throughout; AUC values below 0.50 therefore indicate a difference in the direction opposite to that expected. U Mann–Whitney U statistic, P two-sided Mann–Whitney U test P value, AUC area under the receiver operating characteristic curve with 95% group-stratified percentile bootstrap confidence interval (2000 resamples), CI confidence interval, HU Hounsfield units, IQR interquartile range, SD standard deviation					

Correlation structure of the CT parameters

Pairwise Spearman rank correlations among the five CT parameters, computed across all 42 ROIs, showed that the attenuation-based parameters conveyed partly overlapping information (Fig. 4). Mean and maximum attenuation were strongly correlated ($\rho = 0.85$), consistent with the mean being mathematically constrained by the maximum within the same ROI, and minimum attenuation correlated with mean attenuation ($\rho = 0.61$) and inversely with the SD of attenuation ($\rho = -0.54$). Mask volume, by contrast, was largely independent of the attenuation domain: its correlation with mean attenuation was weak and not statistically significant ($\rho = 0.24$; $P = 0.129$), and only the association with maximum attenuation reached nominal significance ($\rho = 0.33$; $P = 0.034$). The two parameters that discriminated

between groups therefore capture largely non-redundant information, whereas a multivariable model incorporating all four attenuation-based parameters would be over-parameterized at the present sample size.

To evaluate whether the observed attenuation difference was independent of the volume signal, mean attenuation and mask volume were entered simultaneously into an exploratory logistic regression model. Mask volume remained associated with metastatic status at the threshold of significance (odds ratio [OR] 5.26 per 1-SD increase, 95% CI 1.00–27.55; $P = 0.050$), and mean attenuation retained an effect size comparable to its univariable estimate (OR 1.88, 95% CI 0.86–4.15; $P = 0.116$, versus OR 2.21, 95% CI 1.03–4.70; $P = 0.041$ univariably) but was no longer statistically significant (Table 3). Rather than being explained away by volume, the attenuation signal was thus only modestly reduced by mutual adjustment, with CIs too wide at this sample size to establish independence.

Table 3
Exploratory logistic regression of metastatic status on mean attenuation and mask volume

Model	Predictor	OR (per 1-SD)	95% CI	P
Univariable	Mask volume	6.61	1.34–32.76	0.021
Univariable	Mean attenuation	2.21	1.03–4.70	0.041
Multivariable	Mask volume	5.26	1.00–27.55	0.050
Multivariable	Mean attenuation	1.88	0.86–4.15	0.116
Binary logistic regression with metastatic status (metastatic versus control) as the outcome; $n = 42$ regions of interest (18 metastatic, 24 control). Mean attenuation and mask volume were z-standardized (mean attenuation: SD = 28.8 HU; mask volume: SD = 458.7 mm ³), so odds ratios are expressed per 1-SD increase. OR odds ratio, CI confidence interval, SD standard deviation				

Discussion

In this exploratory cohort comprising 42 excised SLNs, two of the five quantitative CT parameters successfully differentiated histologically confirmed metastatic SLNs from tumor-free control SLNs. Mask volume was the stronger discriminator (medians 397.9 versus 257.7 mm³; $P = 0.004$; AUC 0.77, 95% CI 0.61–0.90), correctly ranking a metastatic against a control SLN in roughly three out of four pairwise comparisons. Mean attenuation was also higher in metastatic SLNs (medians 22.6 versus 8.2 HU; $P = 0.046$; AUC 0.68). Critically, these two measures were only weakly correlated ($\rho = 0.24$; $P = 0.129$), so they do not simply restate one another, and in a joint model the attenuation estimate was reduced only modestly rather than abolished. The higher density of metastatic nodes is biologically plausible: in vitro CT–histology correlation of excised nodes has shown that the low-attenuation central hilum corresponds to adipose tissue, blood vessels, and lymphatic sinuses, whereas the higher-attenuation peripheral cortex aligns with densely cellular lymphoid tissue [32]. Metastasis-suspicious SLN regions therefore present a larger, denser profile on CT, with volume currently the more reliable of the two indicators. To the best of our knowledge, this is the first study to demonstrate that quantitative features

derived from the low-dose CT component of preoperative SPECT/CT imaging can distinguish SLN status in cutaneous melanoma.

The only prior attempt we could identify to link SPECT/CT imaging characteristics to SLN malignancy in melanoma exists as a conference abstract [27], and the closest precedent for exploiting the low-dose component of a hybrid acquisition comes from lymphoma rather than melanoma, where texture analysis of the low-dose CT of PET-CT yielded prognostic information complementary to interim FDG-PET [28]. Radiomic prediction of nodal metastasis, by contrast, is well established across diverse tumor entities [20–24], supporting the premise that quantitative nodal imaging carries diagnostic information. Our attenuation values fall within that literature: Urata and colleagues reported mean non-enhanced nodal attenuation of 7.83 HU for tumor-free and 29.17 HU for metastatic axillary nodes in breast cancer [33], remarkably similar to the 8.2 and 22.6 HU medians observed here, and attenuation has since informed a preoperative nomogram for cervical cancer [34]. The most direct precedent comes from the SLN setting itself, as Zhang and colleagues discriminated metastatic from non-metastatic axillary SLNs using contrast-enhanced dual-energy CT, achieving 90.5% per-node accuracy [35]. Although reliant on intravenous contrast and spectral post-processing and therefore not directly comparable, this supports the premise that nodal attenuation may provide staging information beyond nodal size. Within melanoma itself, CT analysis has otherwise been applied only to known metastatic deposits [25]. The closest parallel is veterinary, as nodal volume on contrast-enhanced CT was significantly greater in dogs with metastatic oral melanoma, but discrimination remained only moderate [26].

Our approach also belongs within a broader shift. Several complementary approaches are being investigated to refine patient selection and planning for SLN biopsy. In head and neck melanoma, quantitative SPECT/CT has been investigated not only for SLN localization but also for refining the surgical selection of nodes for removal [36]. In melanoma, gene-expression profiling of the primary tumor using the clinicopathologic and gene expression profile (CP-GEP) “Merlin” assay can reclassify a substantial proportion of patients as low risk [37], while measurement of invasive tumor area has outperformed Breslow thickness alone in predicting SLN status [38]. These rest on different data sources, whereas our study interrogates the suspect node itself, at the moment of staging, using data already acquired. They are therefore complementary rather than competing, and the more interesting question is whether nodal CT parameters add incremental information once combined with them, as clinical and radiomic features have been combined into single nomograms elsewhere [23, 39].

More broadly, head and neck oncology is being reshaped by digital and additive technologies whose common thread is a fuller use of imaging data. In radiotherapy planning, integrating 18F-FDG PET-CT with the planning CT improves target-volume delineation and refines nodal staging in head and neck cancer [40], mirroring benefits reported in other tumor entities such as non-small-cell lung cancer [41]. Additive manufacturing extends the same idea into three dimensions, because the segmentation that yields our quantitative parameters can equally be exported as a printable mesh, so that a single delineation produces both numerical descriptors and a patient-specific anatomical model [42]. In a region where sentinel nodes lie close to the facial nerve and major vessels, such 3D-printed models

could support preoperative rehearsal, intraoperative orientation during nerve-sparing dissection, and patient education, applications for which additive manufacturing is increasingly adopted in surgical planning and training [42]. Care is also moving beyond the operating room. Concepts grouped under the “Internet of Surgical Things”, meaning networked sensors and wearables that stream physiological and wound data, are being explored to extend perioperative and postoperative monitoring, including surveillance of reconstructive flaps, and, looking further ahead, connected follow-up could help flag the late locoregional or distant recurrences to which melanoma is prone [43].

The stakes of that surveillance are illustrated by the unpredictable natural history of melanoma. In a recent report, a cutaneous melanoma recurred seven years after excision and presented as metastatic disease of initially unknown primary, with synchronous brain, lung, and pancreatic lesions. The pancreatic deposit, a site involved in only a small minority of disseminated melanomas and readily mistaken for a primary pancreatic tumor, required multidisciplinary and endoscopic-ultrasound-guided work-up before its melanocytic origin was confirmed [44]. Trajectories in which disease re-emerges late and at unexpected visceral sites underline why accurate stratification at the moment of sentinel-node staging, which remains the pivotal determinant of adjuvant-therapy eligibility and surveillance intensity, is so consequential.

The rationale rests on an asymmetry specific to the head and neck. SLNE here is a distinct procedure with real anatomical risks and an intrinsic failure rate [10–12], so a failed intraoperative identification leaves the patient with the full risk of the incision but no staging return. Preoperative characterization cannot yet replace surgical exploration, but even partial information obtained beforehand would mean that a failed exploration is no longer the only chance to stage the node, and it would come at no additional imaging, contrast, or radiation, because the signal derives from a CT already acquired.

Several limitations follow from one underlying constraint: this is a retrospective, hypothesis-generating pilot analysis nested within a larger surgical cohort, not a purpose-designed diagnostic accuracy study. Most consequentially, the sample is small (42 ROIs, 18 metastatic, 24 control), which limits power and the stability of the observed differences. The CIs around the odds ratios in the joint model are correspondingly wide, and the volume estimate sits at the threshold of significance. We therefore deliberately report the AUC as a continuous measure of discrimination rather than deriving optimal cut-off values, because Youden-optimized thresholds obtained in a sample of this size are prone to substantial optimism bias and would convey a false impression of clinical applicability that these exploratory data cannot support. The measure carrying the strongest signal is a volume descriptor, so its association with metastatic status partly re-expresses the established relationship between nodal size and metastatic probability. Whether higher-order texture features would add information beyond the first-order parameters analyzed here remains untested. Mean attenuation was less affected by mutual adjustment, since it correlated only weakly with volume, but we cannot claim on these data that nodal density carries staging information independent of nodal volume. Establishing this will require a larger, pre-specified adjusted analysis. Further, all ROIs were segmented by a single, though blinded, radiologist, so inter-observer reproducibility, a recognized and non-trivial source of uncertainty in quantitative CT

analysis, could not be assessed directly. Its magnitude is both feature-dependent and tumor-site-dependent, and reported findings conflict. Some CT studies report first-order and simple morphological measures to be among the more reproducible descriptors and higher-order texture features the least [45], whereas in head and neck tumors specifically the overall stability of features under inter-observer delineation variability has been found to be only moderate, at 59% of features versus 90% in lung, with shape features among the least stable [46]. Because the reproducibility of the two parameters that carried signal here, namely mask volume and mean attenuation, cannot be assumed, quantifying it directly is a priority for confirmatory work. The CT data were acquired as the low-dose, attenuation-correction component of a SPECT/CT rather than as a diagnostic examination and therefore carry more noise, which may disproportionately affect attenuation-based parameters. Finally, this is a single-center study, and the scanner, reconstruction procedures, and other in-house standards may limit the generalizability of absolute parameter values.

The logical next step is external, ideally multicenter validation in a larger, prospectively defined cohort enriched for metastatic nodes, using an image biomarker standardization initiative (IBSI)-compliant and fully documented acquisition and segmentation protocol [47, 48] with independent segmentation by several radiologists, which will allow the inter-observer reproducibility of mask volume and mean attenuation to be quantified formally, for example by intraclass correlation, rather than assumed. Such a study should be powered specifically for the volume-adjusted attenuation effect, since this is the comparison on which the incremental value of quantitative CT beyond conventional size assessment ultimately depends. Any combined model will also need to account for the collinearity within the attenuation domain shown in Fig. 4, selecting a single representative parameter from that cluster rather than entering all of them.

Conclusions

Quantitative CT parameters extracted from the low-dose CT component of a preoperative SPECT/CT distinguished metastatic from tumor-free SLNs in cutaneous melanoma of the head and neck, with mask volume the strongest single discriminator (AUC 0.77) and a concordant, only weakly correlated increase in mean attenuation that persisted in effect size but not in statistical significance after mutual adjustment. These results are hypothesis-generating rather than diagnostic, and the contribution of nodal density beyond nodal volume remains to be established in an adequately powered, adjusted analysis. What the study does establish is that a clinically relevant nodal signal can be recovered from a low-dose, contrast-free acquisition these patients already undergo for SLN mapping, in a setting where SLNE in the head and neck carries genuine anatomical risk and can return no diagnostic material at all. This warrants larger, multicenter validation.

Abbreviations

AJCC

American Joint Committee on Cancer

AUC

area under the receiver operating characteristic curve

CI

confidence interval

CP-GEP

clinicopathologic and gene expression profile

CT

computed tomography

FDG

fluorodeoxyglucose

GDPR

General Data Protection Regulation

HU

Hounsfield units

IBSI

Image Biomarker Standardization Initiative

IQR

interquartile range

MBq

megabecquerel

MRI

magnetic resonance imaging

MSLT-II

Second Multicenter Selective Lymphadenectomy Trial

OR

odds ratio

PD-1

programmed cell death protein 1

PET-CT

positron emission tomography-computed tomography

ROC

receiver operating characteristic

ROI

region of interest

SD

standard deviation

SLN

sentinel lymph node

SLNE

sentinel lymph node excision

SPECT/CT

single-photon emission computed tomography/computed tomography

STROBE

Strengthening the Reporting of Observational Studies in Epidemiology

Tc-99m

technetium-99m

Declarations

Ethics approval and consent to participate

The study was reviewed by the Ethics Committee of the University of Regensburg (*Ethikkommission bei der Universität Regensburg*; reference number 23-3446-104, 10 July 2023) and was conducted in accordance with the Declaration of Helsinki and its later amendments. Following its assessment under § 15 of the Professional Code for Physicians in Bavaria (*Berufsordnung für die Ärzte Bayerns*), the committee raised no professional-ethical or legal objections to the conduct of the study. The requirement for written informed consent was waived because the study was purely retrospective and based exclusively on the evaluation of existing medical records and imaging data, without any study-related patient contact. Clinical trial number: not applicable.

Consent for publication

Not applicable. The imaging shown in Fig. 2 does not permit identification of the individual patient.

Competing interests

R.E. has received honoraria from Roche, Eisai, Pfizer, BioNTech, Veracyte (PROCURE), Diaceutics, Mindpeak, AstraZeneca, MEDAC, Lilly, Menarini Stemline, and Novartis. The institutions of R.E. conduct research for AstraZeneca, Roche, Janssen-Cilag, NanoString Technologies, Biocartis, ZytoVision, Novartis, Cepheid, Mindpeak, MSD, Gilead, palleos healthcare, Owkin, and BioNTech. The other authors declare no competing interests.

Authors' information

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Author Contribution

F.N. contributed to the conception of the study, curated the data, performed the statistical analysis, and wrote the original draft. M.B. contributed to data acquisition and curation. G.N. performed the blinded segmentation and quantitative CT analysis of all regions of interest. Q.D.S. provided radiological expertise and methodological advice on the quantitative CT analysis, contributed to the interpretation of the results, and critically revised the manuscript. J.G.S., K.H. and J.E. contributed to data acquisition and to the interpretation of the results. T.E. contributed to the interpretation of the results and critically revised the manuscript. T.E.R. provided resources and critically revised the manuscript. R.E. contributed to the conception and design of the study, provided the histopathological expertise underlying the reference standard, reviewed the histopathological classification of the sentinel lymph nodes, and critically revised the manuscript. J.T. conceived the study, designed it, supervised its clinical conduct, provided senior supervision of the project as last author, and critically revised the manuscript. All authors read and approved the final manuscript.

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The use of AI-based tools in this work is described in the Methods section. The authors critically reviewed and take full responsibility for all content of the manuscript.

Data Availability

The datasets generated and analyzed during the current study are not publicly available because of restrictions arising from European and German data-protection legislation (General Data Protection Regulation, GDPR) and institutional policy on patient-related data, but are available from the corresponding author on reasonable request.

References

1. Liu C, Liu X, Hu L, Li X, Xin H, Zhu S. Global, regional, and national burden of cutaneous malignant melanoma from 1990 to 2021 and prediction to 2045. *Front Oncol.* 2024;14:1512942. 10.3389/fonc.2024.1512942.
2. Langselius O, Rumgay H, de Vries E, Whiteman DC, Jemal A, Parkin DM, et al. Global burden of cutaneous melanoma incidence attributable to ultraviolet radiation in 2022. *Int J Cancer.* 2025;157:1110–9. 10.1002/ijc.35463.
3. De Pinto G, Mignozzi S, La Vecchia C, Levi F, Negri E, Santucci C. Global trends in cutaneous malignant melanoma incidence and mortality. *Melanoma Res.* 2024;34:265–75. 10.1097/CMR.0000000000000959.

4. Cirillo N. Global epidemiological trends in the incidence and mortality for melanoma. *Skin Health Dis.* 2025;5:84–6. 10.1093/skinhd/vzae013.
5. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370:599–609. 10.1056/NEJMoa1310460.
6. Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med.* 2017;376:2211–22. 10.1056/NEJMoa1613210.
7. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguín N, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: treatment - Update 2024. *Eur J Cancer.* 2025;215:115153. 10.1016/j.ejca.2024.115153.
8. Moody JA, Ali RF, Carbone AC, Singh S, Hardwicke JT. Complications of sentinel lymph node biopsy for melanoma - a systematic review of the literature. *Eur J Surg Oncol.* 2017;43:270–7. 10.1016/j.ejso.2016.06.407.
9. Gonzales M, Grosh K, Coster S, Hunt A, Schmitt C, Baxter M, et al. Better-defined morbidity of sentinel lymph node biopsy in patients with melanoma. *Ann Surg Oncol.* 2025;32:3198–202. 10.1245/s10434-025-16987-6.
10. Kfir U, Ronen O. Intraparotid sentinel lymph node dissection for melanoma: a systematic review and meta-analysis. *Ann Surg Oncol.* 2024;31:8245–52. 10.1245/s10434-024-15668-0.
11. Moro R, Arjona-Aguilera C, Requena C, Pont-Sanjuan V, Traves V, Manrique-Silva E, et al. Prognostic role of non-identification of sentinel lymph node in cutaneous melanoma patients: an observational retrospective study. *Cancers (Basel).* 2020;12:3151. 10.3390/cancers12113151.
12. Lükewille L, Wiegand S, Fazel A, Kähler KC, Radecker G, Hoffmann M. Diagnostic performance and clinical limitations of sentinel lymph node biopsy in head and neck melanoma: a 20-year retrospective cohort study. *J Cancer Res Clin Oncol.* 2026;152(5):114. 10.1007/s00432-026-06499-5.
13. Stoffels I, Dissemond J, Poeppel T, Klötgen K, Hillen U, Körber A, et al. Advantages of preoperative ultrasound in conjunction with lymphoscintigraphy in detecting malignant melanoma metastases in sentinel lymph nodes: a retrospective analysis in 221 patients with malignant melanoma AJCC stages I and II. *J Eur Acad Dermatol Venereol.* 2012;26:79–85. 10.1111/j.1468-3083.2011.04013.x.
14. Chai CY, Zager JS, Szabunio MM, Marzban SS, Chau A, Rossi RM, et al. Preoperative ultrasound is not useful for identifying nodal metastasis in melanoma patients undergoing sentinel node biopsy: preoperative ultrasound in clinically node-negative melanoma. *Ann Surg Oncol.* 2012;19:1100–6. 10.1245/s10434-011-2172-7.
15. van den Broek JA, Schurink AW, Leeneman B, Brabander T, van der Veldt AAM, Verhoef C, et al. Preoperative ultrasound before sentinel lymph node biopsy in melanoma in the era of neoadjuvant treatment: a systematic review and meta-analysis of diagnostic performance and cost analysis. *EClinicalMedicine.* 2026;92:103770. 10.1016/j.eclinm.2026.103770.

16. Mititelu TS, Mititelu MR, Bucurica S, Costache DO. [18F]-FDG PET-CT in malignant melanoma. *Diagnostics (Basel)*. 2025;15:1192. 10.3390/diagnostics15101192.
17. Cheng D, McNicoll CF, Kirgan D, Jones MS, Rivera MR, Doyle GM, et al. The role of FDG-PET-CT is limited in initial staging of nodal metastasis for thin cutaneous melanoma. *Am J Surg*. 2021;221:737–40. 10.1016/j.amjsurg.2020.03.031.
18. Lavelli V, Ferrari C, Santo G, Altini C, Ballini A, Sardaro A, et al. The lymphoscintigraphic study of unpredictable head and neck cutaneous melanoma lymphatic drainage. *Biomedicines*. 2020;8:70. 10.3390/biomedicines8040070.
19. Pasha T, Arain Z, Buscombe J, Aloj L, Durrani A, Patel A, et al. Association of complex lymphatic drainage in head and neck cutaneous melanoma with sentinel lymph node biopsy outcomes: a cohort study and literature review. *JAMA Otolaryngol Head Neck Surg*. 2023;149:416–23. 10.1001/jamaoto.2023.0076.
20. Nakao T, Shimada M, Yoshikawa K, Tokunaga T, Nishi M, Kashihara H, et al. Computed tomography texture analysis for the prediction of lateral pelvic lymph node metastasis of rectal cancer. *World J Surg Oncol*. 2022;20:281. 10.1186/s12957-022-02750-8.
21. Wang D, Wang M, Chen R, Song J, Su Y, Wang Y, et al. Preoperative prediction of lymph node metastasis in adenocarcinoma of esophagogastric junction using CT texture analysis combined with machine learning. *Med (Baltim)*. 2025;104:e42252. 10.1097/MD.00000000000042252.
22. Tang CT, Wu Y, Jiang L, Zeng CY, Chen YX. Radiomics analysis based on CT for predicting lymph node metastasis and prognosis in duodenal papillary carcinoma. *Insights Imaging*. 2024;15:155. 10.1186/s13244-024-01732-6.
23. Cheng Y, Xu S, Wang H, Wang X, Niu S, Luo Y, et al. Intra- and peri-tumoral radiomics for predicting the sentinel lymph node metastasis in breast cancer based on preoperative mammography and MRI. *Front Oncol*. 2022;12:1047572. 10.3389/fonc.2022.1047572.
24. Li X, Hong M, Lu Z, Liu Z, Lin L, Xu H. Radiomics models to predict axillary lymph node metastasis in breast cancer and analysis of the biological significance of radiomic features. *Front Oncol*. 2025;15:1546229. 10.3389/fonc.2025.1546229.
25. Bonnin A, Durot C, Barat M, Djelouah M, Grange F, Mulé S, et al. CT texture analysis as a predictor of favorable response to anti-PD1 monoclonal antibodies in metastatic skin melanoma. *Diagn Interv Imaging*. 2022;103:97–102. 10.1016/j.diii.2021.09.009.
26. Menghini TL, Schwarz T, Dancer S, Gray C, MacGillivray T, Blacklock KLB. Contrast-enhanced CT predictors of lymph nodal metastasis in dogs with oral melanoma. *Vet Radiol Ultrasound*. 2023;64:694–705. 10.1111/vru.13254.
27. Lipman M, Tann M, Adusumilli N. Can SPECT/CT lymphoscintigraphy help predict if a sentinel node is malignant in patients with melanoma? [abstract]. *J Nucl Med*. 2022;63.
28. Ganeshan B, Miles KA, Babikir S, Shortman R, Afaq A, Ardeshtna KM, et al. CT-based texture analysis potentially provides prognostic information complementary to interim FDG-PET for patients with

- Hodgkin's and aggressive non-Hodgkin's lymphomas. *Eur Radiol.* 2017;27:1012–20. 10.1007/s00330-016-4470-8.
29. Balch CM, Gershenwald JE, Soong SJ, Thompson JF. Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. *AJCC cancer staging manual*. 7th ed. New York: Springer; 2010. pp. 325–46.
 30. Gershenwald JE, Scolyer RA, Hess KR. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, editors. *AJCC cancer staging manual*. 8th ed. New York: Springer International Publishing; 2017. pp. 563–85.
 31. Cook MG, Green MA, Anderson B, Eggermont AMM, Ruiter DJ, Spatz A, et al. The development of optimal pathological assessment of sentinel lymph nodes for melanoma. *J Pathol.* 2003;200:314–9. 10.1002/path.1365.
 32. Uematsu T, Sano M, Homma K. In vitro high-resolution helical CT of small axillary lymph nodes in patients with breast cancer: correlation of CT and histology. *AJR Am J Roentgenol.* 2001;176:1069–74. 10.2214/ajr.176.4.1761069.
 33. Urata M, Kijima Y, Hirata M, Shinden Y, Arima H, Nakajo A, et al. Computed tomography Hounsfield units can predict breast cancer metastasis to axillary lymph nodes. *BMC Cancer.* 2014;14:730. 10.1186/1471-2407-14-730.
 34. Meng X, Song S, Li K, Duan Y, Zhong J, Wang J, et al. Application of CT in predicting lymph node metastasis in cervical cancer and construction of a preoperative nomogram. *Sci Rep.* 2025;15:11674. 10.1038/s41598-025-94999-8.
 35. Zhang X, Zheng C, Yang Z, Cheng Z, Deng H, Chen M, et al. Axillary sentinel lymph nodes in breast cancer: quantitative evaluation at dual-energy CT. *Radiology.* 2018;289:337–46. 10.1148/radiol.2018180544.
 36. Kwak JJ, Kesner AL, Gleisner A, Jensen A, Friedman C, McCarter MD, et al. Utility of quantitative SPECT/CT lymphoscintigraphy in guiding sentinel lymph node biopsy in head and neck melanoma. *Ann Surg Oncol.* 2020;27:1432–8. 10.1245/s10434-019-08078-0.
 37. Pazhava A, Yu WY, Jing FZ, Hill S, Rohr BR, Honda KS, et al. Enhanced risk stratification for sentinel lymph node biopsy in head and neck melanoma using the Merlin assay (CP-GEP). *Ann Surg Oncol.* 2025;32:2748–55. 10.1245/s10434-024-16551-8.
 38. Orme SE, Bamford M, O'Riordan M, Da Forno PD, Snelling A, Heaton MJ, et al. Validation of invasive area for predicting sentinel node status and survival in primary cutaneous melanoma. *Ann Surg Oncol.* 2025;32:6927–35. 10.1245/s10434-025-17442-2.
 39. Lambin P, Rios-Velazquez E, Leijenaar R, Carvalho S, van Stiphout RG, Granton P, et al. Radiomics: extracting more information from medical images using advanced feature analysis. *Eur J Cancer.* 2012;48:441–6. 10.1016/j.ejca.2011.11.036.
 40. Mulita A, Bekou E, Valsamaki P, Koukourakis IM, Mulita F, Liolis E, et al. 18F-FDG PET-CT- vs. CT-based radiotherapy treatment planning for head and neck cancer. *Life (Basel).* 2026;16:263. 10.3390/life16020263.

41. Mulita A, Valsamaki P, Bekou E, Anevlavis S, Nanos C, Zisimopoulos A, et al. Benefits from 18F-FDG PET-CT-based radiotherapy planning in stage III non-small-cell lung cancer: a prospective single-center study. *Cancers (Basel)*. 2025;17:1969. 10.3390/cancers17121969.
42. Anagnostopoulos S, Baltayiannis N, Koletsis NE, Mulita F, Spanou F, Leivaditis V, et al. 3D printing in medicine: bridging imaging, education, and practice. *Arch Med Sci Atheroscler Dis*. 2025;10:e172–88. 10.5114/amsad/209721.
43. Mulita F, Verras GI, Anagnostopoulos CN, Kotis K. A smarter health through the Internet of Surgical Things. *Sens (Basel)*. 2022;22:4577. 10.3390/s22124577.
44. Massara M, Christakos E, Mulita F, Liolis E, Leivaditis V, Tasios K, et al. An unusual case of pancreatic metastasis from malignant melanoma. The diagnostic work-up to arrive at a final diagnosis. *Prz Gastroenterol*. 2026;21:233–5. 10.5114/pg.2026.161904.
45. Haarbarger C, Müller-Franzes G, Weninger L, Kuhl C, Truhn D, Merhof D. Radiomics feature reproducibility under inter-rater variability in segmentations of CT images. *Sci Rep*. 2020;10:12688. 10.1038/s41598-020-69534-6.
46. Pavic M, Bogowicz M, Würms X, Glatz S, Finazzi T, Riesterer O, et al. Influence of inter-observer delineation variability on radiomics stability in different tumor sites. *Acta Oncol*. 2018;57:1070–4. 10.1080/0284186X.2018.1445283.
47. Aguirre-Meneses H, Stoehr-Muñoz P, Molina-Gonzalez M, Nuñez-Gaona MA, Roldan-Valadez E. Radiomics and the Image Biomarker Standardisation Initiative (IBSI): a narrative review using a six-question map and implementation framework for reproducible imaging biomarkers. *Cureus*. 2025;17:e95335. 10.7759/cureus.95335.
48. Shin HB, Sheen H, Oh JH, Choi YE, Sung K, Kim HJ. Evaluating feature extraction reproducibility across image biomarker standardization initiative-compliant radiomics platforms using a digital phantom. *J Appl Clin Med Phys*. 2025;26:e70110. 10.1002/acm2.70110.

Figures

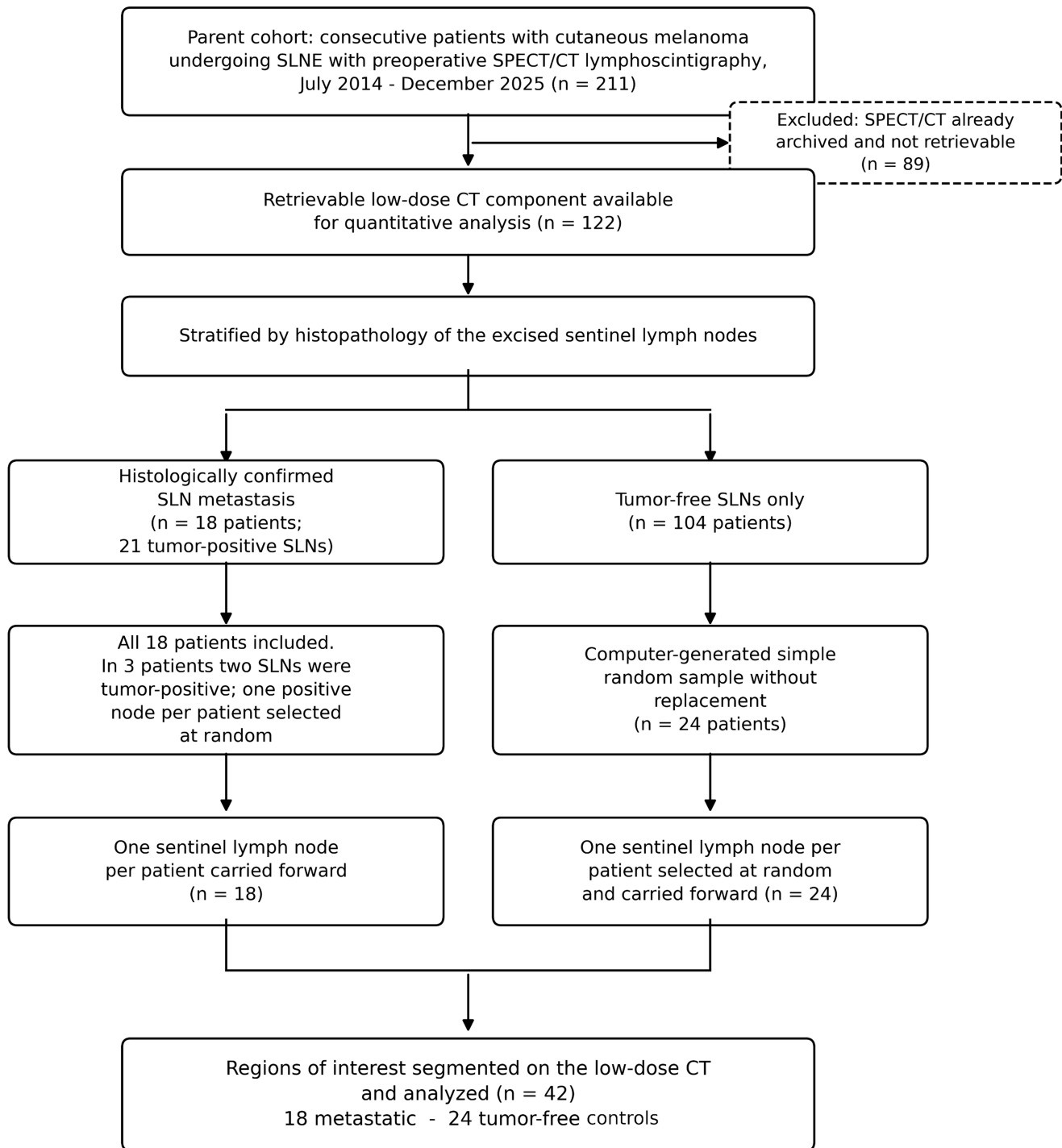


Figure 1

Flow of patients and sentinel lymph node regions of interest through the study. SLNE sentinel lymph node excision, SPECT/CT single-photon emission computed tomography/computed tomography, SLN sentinel lymph node

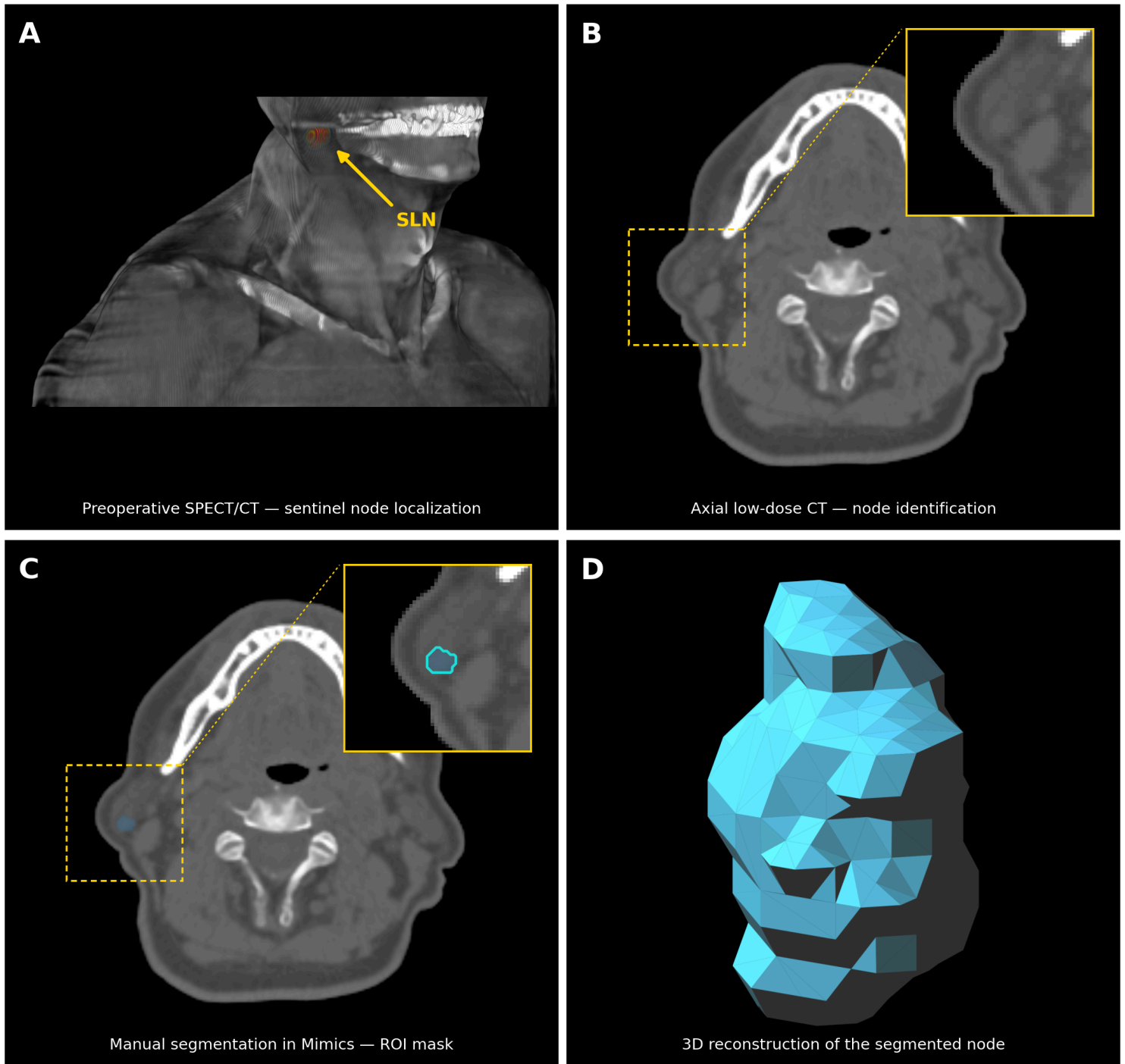


Figure 2

Workflow from sentinel lymph node localization to quantitative CT analysis, shown for one representative metastatic sentinel lymph node located at the lower pole of the right parotid gland. **A** Preoperative SPECT/CT volume rendering; the arrow indicates the radiotracer-avid sentinel lymph node. **B** Corresponding axial low-dose CT slice from the same SPECT/CT examination, shown without overlay; the dashed box marks the node and is reproduced magnified in the inset. **C** The same slice after manual segmentation in Mimics; the boundary of the resulting ROI mask is outlined in the inset. **D** Surface reconstruction of the segmented node, illustrating its three-dimensional extent

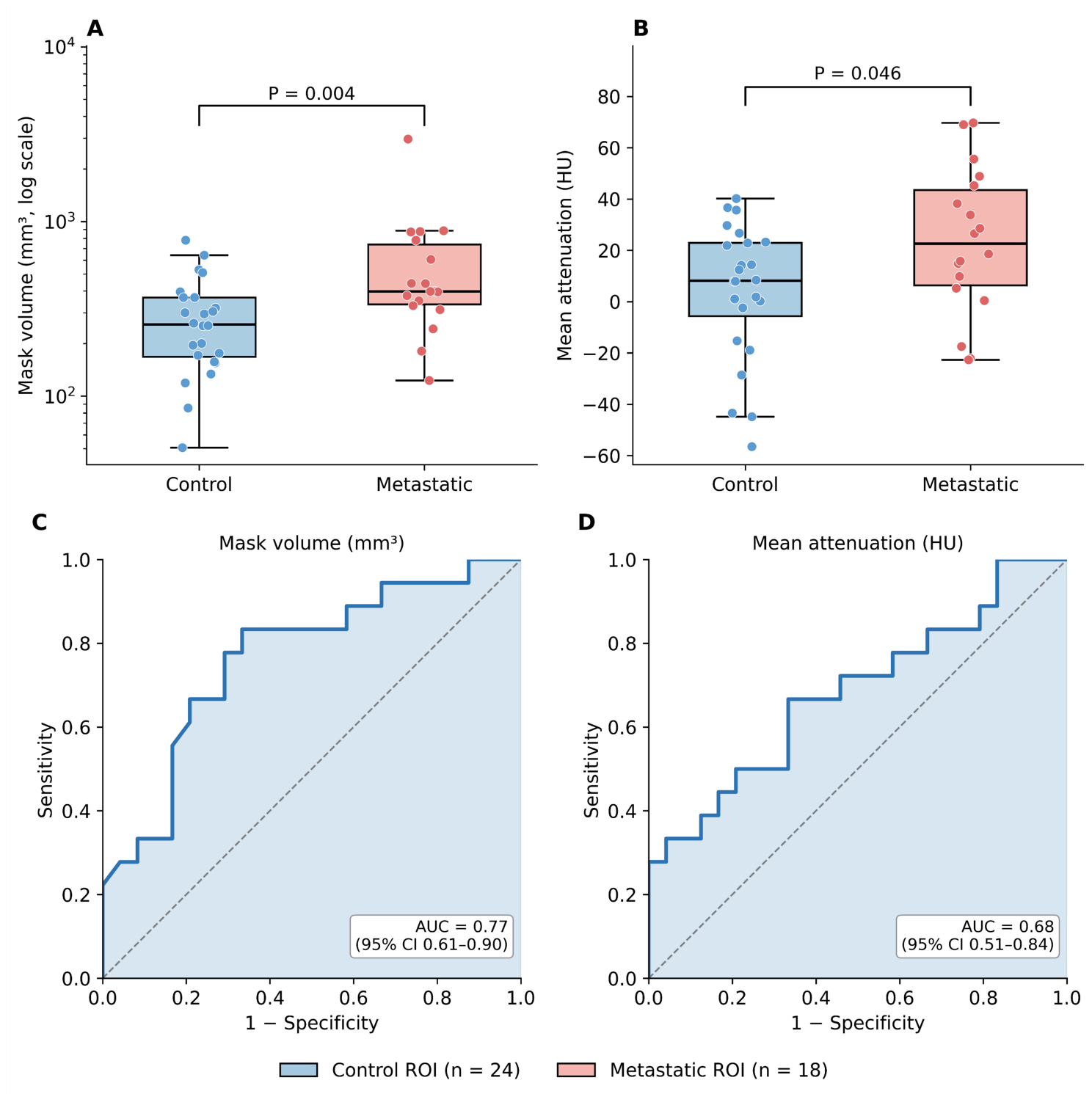


Figure 3

CT parameters that discriminate metastatic from control sentinel lymph node regions. **A, B** Box-and-whisker plots and **C, D** corresponding receiver operating characteristic (ROC) curves for the two CT parameters that differed between metastatic ROIs (n = 18, red) and control ROIs (n = 24, blue): **A, C** mask volume (log scale) and **B, D** mean attenuation. Boxes show the median and interquartile range (IQR); whiskers extend to the most extreme values within 1.5 × IQR, and individual ROIs are overlaid as points.

CT computed tomography, ROI region of interest, HU Hounsfield units, AUC area under the curve, CI confidence interval

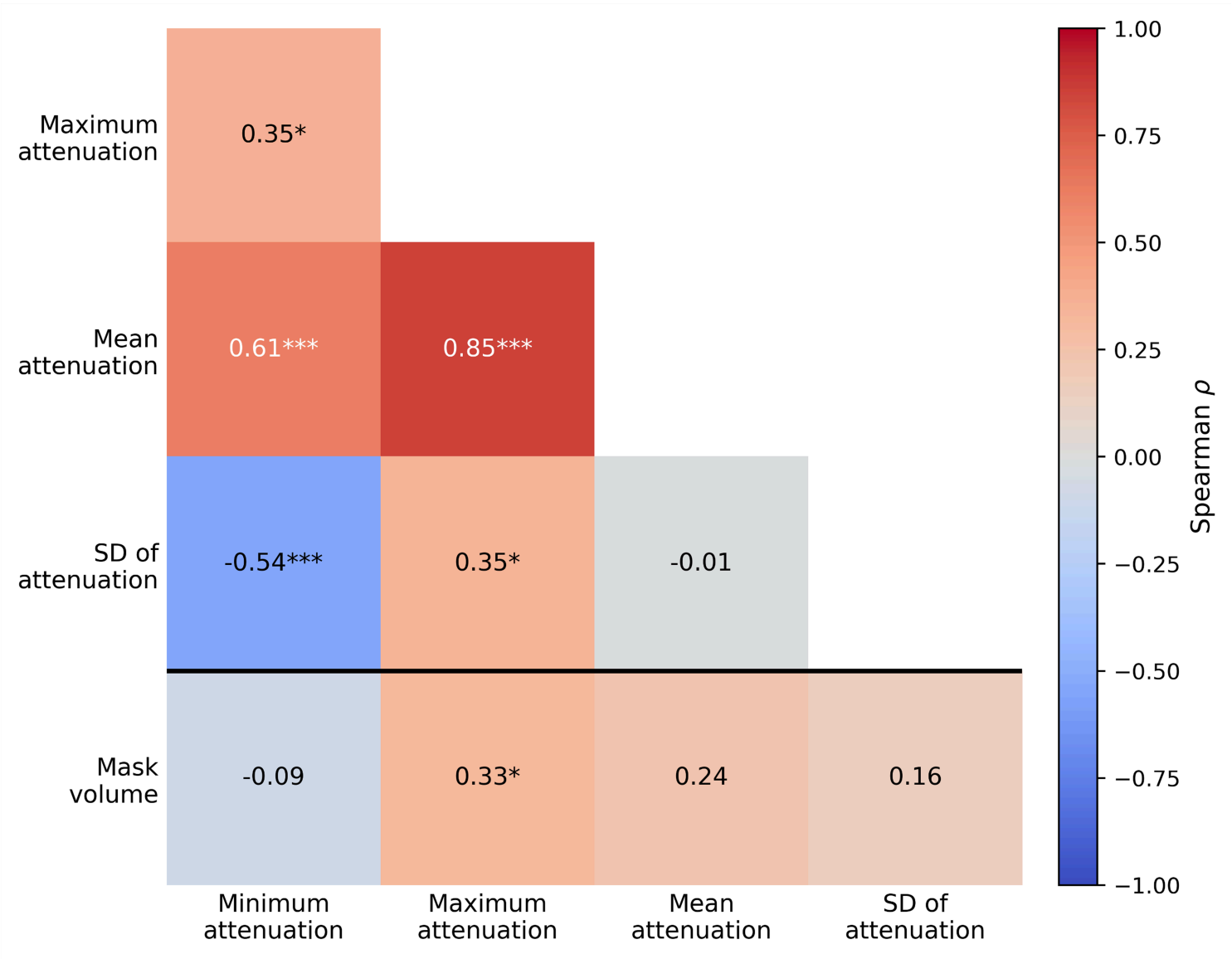


Figure 4

Correlation structure of the five quantitative CT parameters. Lower triangle of the pairwise Spearman rank correlation matrix across all 42 ROIs (18 metastatic and 24 control combined); the diagonal and the mirrored upper triangle are omitted because they carry no additional information. Coefficients are printed in each cell and additionally encoded by color. The black rule separates attenuation-based from volume-based parameters. *P < 0.05, **P < 0.01, ***P < 0.001. ROI region of interest, SD standard deviation

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