

PERSPECTIVE ARTICLE

From mimicry to mechanism: Digital pathology and multi-omics perspectives on cutaneous T-cell lymphoma

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Abstract

Primary cutaneous lymphoma, particularly cutaneous T-cell lymphoma (CTCL), represents a malignancy long defined by protean manifestations, diagnostic delay, clinical deception, and therapeutic ambiguity. Despite being confined to the skin at presentation, CTCL exhibits marked biological heterogeneity and phenotypic variation. Diagnostic workflows reliant on serial biopsies and stage-based classifications fail to adequately capture this complexity, contributing to suboptimal intervention. In this perspective, we position CTCL as a discovery problem, highlighting the limitations of single-layer diagnostics in distinguishing malignant disease from inflammatory mimics. We discuss how emerging digital pathology, artificial intelligence-enabled imaging, and integrative interdisciplinary approaches can interrogate disease across spatial and molecular scales. By reframing CTCL through a systems-level lens, such strategies have the potential to enable earlier biological stratification, inform mechanism-driven therapeutic targeting, and guide the rational use of skin-directed and systemic treatments. Without such integrative frameworks, innovation in CTCL treatment risks remaining fragmented and incomplete.

Keywords: Cutaneous lymphoma; Cutaneous T-cell lymphoma; Digital histology; Artificial intelligence; Multi-omics

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1. Introduction

Primary cutaneous lymphoma (CL) imposes a disproportionate disease burden despite its orphan status, owing to chronicity, diagnostic delay, and sustained impairment in quality of life. These malignancies comprise a heterogeneous group of non-Hodgkin lymphoproliferative disorders confined to the skin at presentation, with the majority arising from mature T lymphocytes.^{1,2} Commonly known as cutaneous T-cell lymphoma (CTCL), the reported incidence estimates range from 2.9 to 8.6 cases per million population, though the true incidence is likely substantially higher.^{3,4} Among these, mycosis fungoides (MF) accounts for more than half of CLs worldwide.⁵ Some variants such as folliculotropic MF, pagetoid reticulosis, and primary cutaneous anaplastic large cell lymphoma are known for their clinical indolence, while others such as Sézary syndrome (SS) and primary cutaneous natural killer/T-cell lymphoma have a more aggressive clinical presentation.⁵

The path to diagnosis is not straightforward due to clinical heterogeneity and the absence of cutaneous hallmarks. A lack of awareness of CTCL among general practitioners and non-specialists adds to the diagnostic barriers to timely management.⁶ Records of biobank datasets show a median diagnostic latency between first symptom development and initial diagnosis of approximately three years in early MF.^{4,6} Diagnostic ambiguity contributes to prolonged misclassification, inconsistent management strategies, and missed opportunities for early intervention, underscoring persistent gaps in current diagnostic and oncology care pathways. This perspective review aims to address deficits in timely care by operationalizing machine learning-derived classifiers, risk stratification, and therapy response prediction. The prospective assignment of patients to mechanism-based treatment pathways and adaptive refinement of clinical decision models have the potential to bridge key transitional gaps in treatment options.

2. Clinical challenge: Cutaneous T-cell lymphoma as an underestimated mimicker

The medical dictum “when you hear hoofbeats, think horses, not zebras” often contributes to diagnostic delays. Over-reliance on such principles can be misleading, because early presentations often masquerade as “horses,” referring to common conditions getting priority in clinical triaging and work-up. The clinical challenges remain high—the morphological appearance of CTCLs can bear close resemblance to a broad spectrum of inflammatory dermatoses.^{4,7} Early stages (e.g., IA, IB, IIA) of MF can resemble common conditions such as psoriasis, atopic dermatitis, secondary syphilis, and dermatophytic infections, while late tumor presentations (e.g., IIB, IVB) and SS simulate primary and secondary erythroderma.

Clinical assessment is further confounded by the widespread use of topical corticosteroids, which can substantially modify lesion morphology and obscure characteristic features, limiting the reliability of bedside diagnosis.⁸ The typically indolent course of early MF often promotes a conservative “watch-and-wait” approach, accompanied by only moderate diagnostic vigilance. However, the unpredictability of treatment responses and relapse patterns adds considerable uncertainty to clinical decision-making.

3. Diagnostic and discovery frameworks in cutaneous T-cell lymphoma

3.1. Digital histology support

Diagnosing CTCL, especially in early stages, is challenging because histologic findings (e.g., epidermotropism, atypical

lymphocytes, Pautrier microabscesses) are not individually pathognomonic and may be absent or subtle, leading to equivocal biopsy results and potential sampling error.^{9,10} The information obtained via traditional microscopic analysis is limited and time-consuming for detailed interpretation. Digital pathology data consist of curated repositories of annotated digital slides linked to clinical metadata and can transform diagnostic histopathology from a descriptive discipline to a discovery platform. Whole-slide imaging addresses limitations inherent to conventional glass-slide review, including piecemeal assessment and cross-sectional sampling bias, by producing high-resolution images of entire tissue sections.¹¹ This forms the substrate for advanced computational analysis by aggregating large numbers of CTCL cases across cohorts, enabling the mechanistic linking of tissue and tumor characteristics.¹²

Initiatives such as the Cutaneous Lymphoma International Digital Pathology Registry serve as resource centers that support the development of predictive models for disease evolution and therapeutic responsiveness.¹³ It was founded with the goal of providing a platform for the development and validation of artificial intelligence (AI)-based models to improve clinical care and outcomes in patients with CLs. The Registry is governed by a Joint Data Registry Agreement, which defines the legal, ethical, and operational framework for the collaborative collection, management, and use of data within the platform. This framework is particularly important for rare diseases such as CTCLs, where the development and validation of robust AI models require large, multicenter datasets. Accordingly, the Cutaneous Lymphoma International Digital Pathology Registry serves as a structured collaborative consortium that enables the development and validation of AI-driven models based on shared real-world data from CL patients. Such approaches pave the way toward personalized pathology in CTCL, where histological complexity can be systematically quantified and correlated with molecular and clinical outcomes.¹⁴

However, the diagnostic interpretation of CLs remains critically dependent on clinical context and the consideration of inter-regional variations. Global, multicenter datasets are required to increase the performance and generalizability of models. Whole-slide imaging files are large and require computational infrastructure for high-throughput analysis. Care is also needed to ensure consistency in pathology workflow systems.

In cases where histology remains inconclusive but the clinical index of suspicion is high, establishing a diagnosis beyond histology and immunophenotyping requires additional tools. *TCRG* gene rearrangement analysis

using polymerase chain reaction for clonality assessment is a useful adjunct.¹⁵ Multiple studies have reported that a majority of cases demonstrate T-cell monoclonal rearrangements in 52–90% of well-established CTCL cases.¹⁶

Therefore, the real-world utility for mechanistic inference is contingent not just on access to subvisual morphometric phenotypes and high-quality image datasets but also on the integration with other “layers” (Figure 1).

3.2. The need for multi-omics profiling in cutaneous T-cell lymphoma

The factors influencing disease progression are not well understood. Around 20–30% of MF cases progress to more advanced disease, which is associated with worse five-year survival rates.¹⁷ This is signaled by a transition from a T helper 1-predominant toward a T helper 2-predominant immune profile, and the loss of specific T-cell markers (e.g., CD2, CD3, CD5, CD7).^{18,19} Rindler *et al.*²⁰ observed consistent downregulation of six cutaneous biomarkers (*CXCR4*, *CD69*, *HSPA1A*, *ZFP36*, *IL7R*, and *TXNIP*) in lesions associated with disease progression or advanced-stage progression.

The response rates of immunotherapy in advanced MF and SS remain unpredictable, reflecting the heterogeneous disease processes at local, cellular, and systemic levels. In advanced CTCL, a computational multi-omics framework

identified molecular features that distinguished responders from non-responders to monotherapy (anti-programmed cell death protein 1) and combination therapy (anti-programmed cell death protein 1 + interferon- γ therapy).²¹ Non-responders showed an enrichment of regulatory CLA⁺CD39⁺ T-cell subsets.²¹ Serum levels of circulating cell-free DNA in CTCL patients were found to be significantly higher than in healthy controls and were associated with a significantly worse prognosis.²²

The use of single-cell RNA sequencing with T-cell receptor profiling, together with clustering methods—such as graph-based clustering and dimensionality reduction—can reveal both intertumoral and intratumoral heterogeneity.²³ Markers (e.g., *CCR4*, *KIR3DL2*, *DUSP2*) indicative of established MF and expressed among CD4⁺ MF central memory malignant cells suggest that early therapeutic strategies may need to focus on central/systemic routes, as opposed to tissue-resident phenotypes of CD4⁺ CTCL.²⁴

Image-based biomarkers using mathematical models to extract semi-quantitative and quantitative data for radiomic analysis represent an additional emergent tool. In inflammatory skin conditions such as Hansen's disease, lesions may show increased 18F-fluorodeoxyglucose uptake because of hypermetabolic inflammatory activity, potentially resulting in false-positive positron emission tomography-computed tomography findings.²⁵ Radiomic

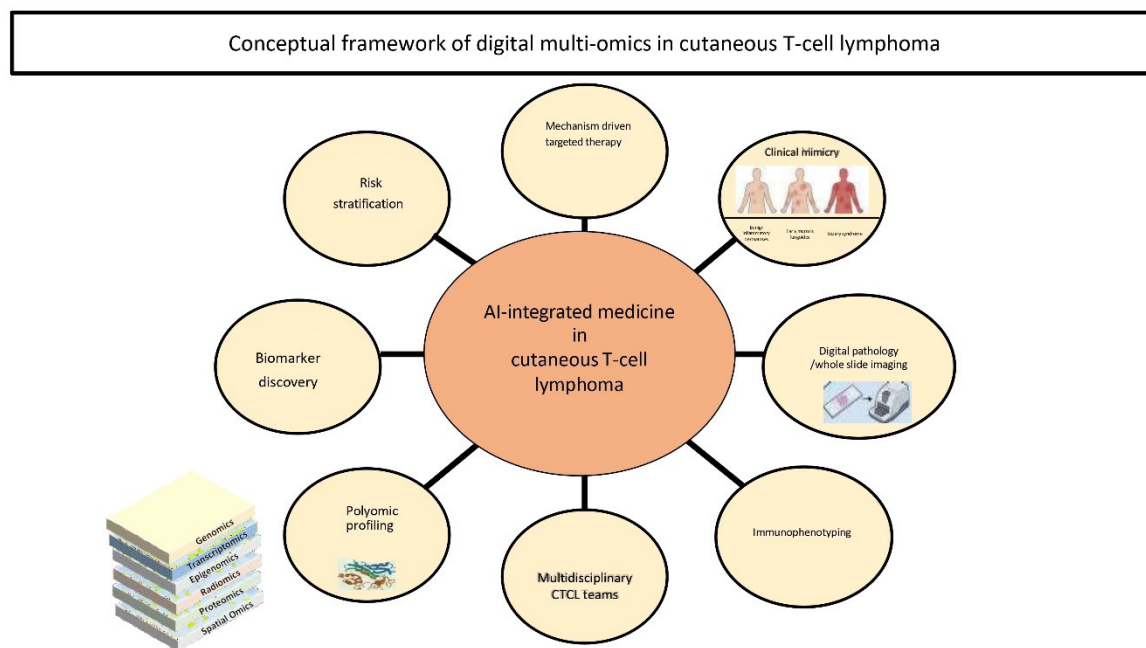


Figure 1. Diagram illustrating the integrative diagnostic pathway from biopsy to mechanism-driven therapy in cutaneous T-cell lymphoma. Image created by the authors.

data alone, or in combination with clinical and genetic profiles, may enable better classification and staging, as well as the assessment of the need to escalate or de-intensify treatment.²⁶

3.3. Epigenetic plasticity and its role in tumor development

An exciting paradigm lies in controlling the behavior of the tumor microenvironment. By shifting immune pathways, epigenetic restructuring could realign transformed T cells.²⁷ To date, several malignancy-related epigenetic pathways, such as DNA methylation and microRNAs (miRNAs)/onco-miRNAs (e.g., miR-155 overexpression in advanced CTCL), have been elucidated.^{27,28} miRNAs are non-coding RNAs that regulate post-transcriptional gene expression by binding to target mRNAs. Their dual mechanistic action on oncogenic (onco-miRNA) drivers and tumor-suppressive (anti-miRNA) RNAs has important therapeutic implications for the development of miRNA mimics and anti-miRNA-based therapies.²⁹ These agents enable the regulation of tumor activity by “silencing” the overexpression of onco-miRNAs and restoring the reduced function of anti-miRNAs. An example is Cobomarsen (MRG-106), which targets miR-155, a miRNA that utilizes locked nucleic acid antisense oligonucleotide technology and has been shown to restore gene expression and control tumor progression.³⁰

4. Choosing the right treatment: An integrative approach

4.1. Better cutaneous and extracutaneous targets

The conventional dichotomy of skin-directed therapy for early disease and escalated chemotherapy for tumor stages reflects a phenotypic heuristic that risks obscuring early biological aggressiveness in CTCL.³¹ Attaining durable remission states may require rethinking traditional, compartmentalized treatment paradigms in favor of early, concurrent modulation of cutaneous and hematologic disease axes. Skin-directed approaches typically involve topical agents, phototherapy, photodynamic therapy, and total skin electron beam therapy for extensive areas. Technical refinements in total skin electron beam therapy that allow real-time motion control using optical surface monitoring systems enable more rapid segmentation and higher beam output, thereby improving treatment efficiency.³²

A modular and integrative approach using multidimensional datasets—including digital histopathology, somatic genomic alterations, T-cell receptor clonality, transcriptomic cytokine networks, and epigenomic features (e.g., DNA methylation and chromatin

accessibility)—can reflect dominant biological states, such as T helper 2 cell polarization or immune regulatory suppression. Computational inference using network-based analyses and multimodal machine learning can then classify patients into mechanistically defined subgroups with distinct therapeutic susceptibilities. Such an approach can herald a shift away from a conventional reductionist framework toward integrative, mechanism-informed models that move beyond single-analyte-dependent treatment decisions (e.g., reliance on biomarkers alone).

4.2. Challenges in integrating care pathways and the need for multidisciplinary cutaneous T-cell lymphoma teams

A major challenge of multi-omics technologies is cost, because they require specialized instrumentation and computational infrastructure for data processing and storage. In addition, the lack of standardized protocols for sample collection, processing, and data analysis can lead to variability across studies, making results difficult to reproduce or compare. Data integration also remains complex, as combining diverse datasets requires advanced bioinformatics tools and expertise that are not widely available in clinical settings.

There is also a limited availability of large, well-annotated patient cohorts needed to validate multi-omic biomarkers. Translating multi-omics findings into clinically actionable targets requires extensive validation studies and regulatory approval, which can slow implementation. With a multidisciplinary CTCL team comprising dermatologists, histopathologists, oncologists, nuclear medicine specialists, and digital pathology support staff, the management of CLs may witness a paradigm shift in protocols, leading to superior clinical outcomes, beyond “watch–control–care.”

5. Conclusion

Cutaneous lymphomas epitomize the challenge of rare cancers. They remain diagnostically elusive and evade timely detection, making therapeutics uncertain. Synergy among interdisciplinary teams, digital pathology, multi-omics approaches, and epigenetic targeting offers a reframed perspective and a pivot toward management of this challenging hematological malignancy involving the skin. This premise could shift CTCL care from early-stage diagnostic ambiguity to biologically informed strategies that not only improve remission rates and symptom control but also provide greater clarity toward curative potential.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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References

- Lu Y, Zhang L, Ying X. Emerging epidemiological trends in primary cutaneous lymphomas: A population-based analysis. *Clin Exp Dermatol*. 2025;51(4):620-625. doi: 10.1093/ced/llaf535
- Kaufman AE, Patel K, Goyal K, *et al*. Mycosis fungoides: developments in incidence, treatment and survival. *J Eur Acad Dermatol Venereol*. 2020;34(10):2288-2294. doi: 10.1111/jdv.16325
- Campbell BA, Miles HM, Prince M, *et al*. Breaking down the barriers for patients with cutaneous T-cell lymphoma: current controversies and challenges for radiation oncologists in 2024. *Semin Radiat Oncol*. 2025;35(1):110-125. doi: 10.1016/j.semradonc.2024.08.005
- Hodak E, Geskin L, Guenova E, *et al*. Real-life barriers to diagnosis of early mycosis fungoides: An international expert panel discussion. *Am J Clin Dermatol*. 2023;24(1):5-14. doi: 10.1007/s40257-022-00732-w
- Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, *et al*. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-3785. doi: 10.1182/blood-2004-09-3502
- Scarisbrick JJ, Quaglino P, Prince HM, Papadavid E, Hodak E, Bagot M, *et al*. The PROCLIP international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients. *Br J Dermatol*. 2019;181(2):350-357. doi: 10.1111/bjd.17258.
- Sokołowska-Wojdyło M, Olek-Hrab K, Ruckemann-Dziurdzińska K. Primary cutaneous lymphomas: diagnosis and treatment. *Postepy Dermatol Alergol*. 2015;32(5):368-383. doi: 10.5114/pdia.2015.54749
- Huang L, Tang WH, Attar R, Gore C, Williams HC, Custovic A, Tanaka RJ. Remote assessment of eczema severity via AI-powered skin image analytics: a systematic review. *Artif Intell Med*. 2024;156:102968. doi: 10.1016/j.artmed.2024.102968
- Olsen EA, Whittaker S, Kim YH, *et al*. Cutaneous T-cell lymphoma treatment (PDQ®)—Health professional version. *National Cancer Institute*. Updated 2025. Accessed February 27, 2026. <https://www.cancer.gov/types/lymphoma/hp/mycosis-fungoides-treatment-pdq>
- Doeleman T, Hondelink LM, Vermeer MH, van Dijk MR, Schrader AMR. Artificial intelligence in digital pathology of cutaneous lymphomas: a review of the current state and future perspectives. *Semin Cancer Biol*. 2023;94:81-88. doi: 10.1016/j.semcancer.2023.06.004
- US Food and Drug Administration. FDA allows marketing of first whole slide imaging system for digital pathology. Published April 12, 2017. Accessed August 31, 2025. <https://www.fda.gov/news-events/press-announcements/fda-allows-marketing-first-whole-slide-imaging-system-digital-pathology>
- Höhn J, Kriehoff-Henning E, Jutzi TB, *et al*. Combining CNN-based histologic whole slide image analysis and patient data to improve skin cancer classification. *Eur J Cancer*. 2021;149:94-101.. doi: 10.1016/j.ejca.2021.02.032
- Schrader A, Valkema P, Rocuzzo G, *et al*. A-179 The Cutaneous Lymphoma International Digital Pathology (CLIDIPA) Registry - a multi-center, collaborative initiative to facilitate Artificial Intelligence-driven research within Cutaneous Lymphomas. *Eur J Cancer*. 2024;211:114433. doi: 10.1016/j.ejca.2024.114433
- Bera K, Schalper KA, Rimm DL, *et al*. Artificial intelligence in digital pathology—new tools for diagnosis and precision oncology. *Nat Rev Clin Oncol*. 2019;16(11):703-715. doi: 10.1038/s41571-019-0252-y.
- Klai S, Helal I, Jouini R, *et al*. Diagnostic utility of molecular analysis in cutaneous T-cell lymphoma: Tunisian series on clonality of TCRG gene rearrangement. *South Asian J Cancer*. 2025;14(3):627-631. doi: 10.1055/s-0045-1805056
- Gibbs J, Ma S, Kim A, *et al*. Utility of flow cytometry and gene rearrangement analysis in tissue and blood of patients

- with suspected cutaneous T-cell lymphoma. *Oncol Rep.* 2021;45(1):349-358.
doi: 10.3892/or.2020.7865
17. Scarisbrick JJ, Prince HM, Vermeer MH, Quaglino P, Horwitz S, Porcu P, *et al.* Cutaneous lymphoma international consortium study of outcome in advanced stages of mycosis fungoides and Sezary syndrome: effect of specific prognostic markers on survival and development of a prognostic model. *J Clin Oncol.* 2015;33(32):3766-3773.
doi: 10.1200/JCO.2015.61.7142
 18. Krejsgaard T, Lindahl LM, Mongan NP, Wasik MA, Litvinov IV, Iversen L, *et al.* Malignant inflammation in cutaneous T-cell lymphoma-a hostile takeover. *Semin Immunopathol.* 2017;39(3):269-282.
doi: 10.1007/s00281-016-0594-9
 19. Pulitzer M. Cutaneous T-cell lymphoma. *Clin Lab Med.* 2017;37(3):527-546.
doi: 10.1016/j.cll.2017.06.006
 20. Rindler K, Jonak C, Alkon N, Thaler FM, Kurz H, Shaw LE, *et al.* Single-cell RNA sequencing reveals markers of disease progression in primary cutaneous T-cell lymphoma. *Mol Cancer.* 2021;20:124.
doi: 10.1186/s12943-021-01419-2
 21. Glass DR, Mayer-Blackwell K, Ramchurren N, Parks KR, Duran GE. Multi-omic profiling reveals the endogenous and neoplastic responses to immunotherapies in cutaneous T-cell lymphoma. *Cell Rep Med.* 2024;5(5):101527.
doi: 10.1016/j.xcrm.2024.101527
 22. Mizuno Y, Shibata S, Miyagaki T, *et al.* Serum cell-free DNA as a new biomarker in cutaneous T-cell lymphoma. *J Dermatol.* 2022;49(11):1124-1130.
doi: 10.1111/1346-8138.16520
 23. Liu, X., Jin, S., Hu, S. *et al.* Single-cell transcriptomics links malignant T cells to the tumor immune landscape in cutaneous T cell lymphoma. *Nat Commun.* 2022;13(1):1158.
doi: 10.1038/s41467-022-28799-3
 24. Chennareddy S, Rindler K, Ruggiero JR, *et al.* Single-cell RNA sequencing comparison of CD4+, CD8+, and T-cell receptor $\gamma\delta$ + cutaneous T-cell lymphomas reveals subset-specific molecular phenotypes. *Br J Dermatol.* 2024;192(2):269-282.
doi: 10.1093/bjd/ljae313
 25. Shao D, Deng YT, Shao FQ, Liang JW, Wang SX. 18F-FDG PET/CT imaging findings of leprosy. *Clin Nucl Med.* 2020;45(5):e236-e238.
doi: 10.1097/RLU.0000000000002935
 26. Chauvie S, Ceriani L, Zucca E. Radiomics in malignant lymphomas. In: *Lymphoma*. Brisbane City, Australia: Exon Publications; 2021:71-82.
doi: 10.36255/exon-publications.lymphoma.2021.radiomics
 27. Lai P, Wang Y. Epigenetics of cutaneous T-cell lymphoma: biomarkers and therapeutic potentials. *Cancer Biol Med.* 2021;18(1):34-51.
doi: 10.20892/j.issn.2095-3941.2020.0216.
 28. Tahir M, Norouzi M, Khan SS, Davie JR, Yamanaka S, Ashraf A. Artificial intelligence and deep learning algorithms for epigenetic sequence analysis: a review for epigeneticists and AI experts. *Comput Biol Med.* 2024;183:109302.
doi: 10.1016/j.compbimed.2024.109302
 29. Di Martino MT, Tagliaferri P, Tassone P. MicroRNA in cancer therapy: breakthroughs and challenges in early clinical applications. *J Exp Clin Cancer Res.* 2025;44(1):126.
doi: 10.1186/s13046-025-03391-x
 30. Seto AG, Beatty X, Lynch JM, *et al.* Cobomarsen, an oligonucleotide inhibitor of miR-155, co-ordinately regulates multiple survival pathways to reduce cellular proliferation and survival in cutaneous T-cell lymphoma. *Br J Haematol.* 2018;183(3):428-444.
doi: 10.1111/bjh.15547.
 31. Hristov AC, Tejasvi T, Wilcox RA. Cutaneous T-cell lymphomas: 2021 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2021;96(10):1313-1328.
doi: 10.1002/ajh.26299.
 32. Schöpe M, Sahlmann J, Lorenz K, *et al.* Sweeping-beam technique with electrons for large treatment areas as total skin irradiation: dosimetric and technical aspects of a modified Stanford technique. *Strahlenther Onkol.* 2021;198(1):47-55.
doi: 10.1007/s00066-021-01859-1.