

Clinical Practice Guideline

Gastric Carcinoma

Diagnosis, Staging, and Treatment

Yvonne Huber, Susanne Unverzagt, Petra Lynen Jansen,
Thomas Langer, Monika Nothacker, Markus Moehler

Department of Medicine I,
University Medical Center
Mainz: PD Dr. med. Yvonne
Huber, Prof. Dr. med. Mar-
kus Moehler

Institute of General Medi-
cine, University Medical
Center Halle: Prof. Dr. rer.
nat. Susanne Unverzagt

Office of the German
Society of Gastroenterol-
ogy, Digestive, and Meta-
bolic Disease (DGVS),
Berlin: PD Dr. med. Petra
Lynen Jansen

German Guideline Program
in Oncology, c/o German
Cancer Society, Berlin:
Thomas Langer

Association of the Scientific
Medical Societies in Ger-
many (AWMF), Berlin: Dr.
med. Monika Nothacker

Summary

Background: Gastric carcinoma ranks tenth in incidence among all cancers in men and women in Germany. 5565 women and 9027 men received a diagnosis of gastric carcinoma in Germany in 2022.

Methods: The German clinical practice guideline was comprehensively revised with the interdisciplinary participation of German specialty societies under the leadership of the German Society for Gastroenterology, Digestive and Metabolic Disorders, according to the methodological specifications of the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF).

Results: The new recommendations promote preventive measures in the presence of risk factors such as hereditary diseases or infection with *Helicobacter pylori*. Combinations of chemotherapy with immunotherapy, such as nivolumab, pembrolizumab, and tislelizumab, prolong median overall survival compared to chemotherapy alone (e.g., nivolumab plus chemotherapy, 14.4 vs. 11.1 months, HR 0.71) and markedly prolong 5-year survival to 16%. In patients with high claudin18.2 expression, the antibody zolbetuximab, combined with chemotherapy, prolongs median survival to 16.4 vs. 13.4 months (HR 0.77). For patients in good general health, further chemotherapy or biomarker-defined approved second-line (trastuzumab deruxtecan, pembrolizumab) or third-line treatment (e.g., trif-

luridine tipirazole) and advanced molecular-pathological diagnostic testing should be offered at centers for personalized oncology in case of treatment failure. The biomarkers HER2, PD-L1, MSI, and claudin18.2 enable new targeted therapies in palliative situations with long-term improvement in outcome.

Conclusion: The diagnostic evaluation of gastric carcinoma should include high-resolution video endoscopy, and its treatment should be stage-adapted and interdisciplinary. Monoclonal antibodies and immune checkpoint inhibitors are increasingly being used for palliative treatment. The new modifications to the clinical practice guideline will promote the use of uniform strategies for perioperative and palliative treatment and supportive measures.

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Carcinomas of the stomach and cardia are the fifth-ranking cancer-related cause of death worldwide—despite the decline in incidence and mortality rates in recent decades (1). In Germany, gastric carcinoma ranks tenth in incidence among cancers for both sexes, with 5565 cases diagnosed in women and 9027 in men in the year 2022 (2). Gastric carcinoma is often not diagnosed until an advanced stage, meaning that the prognosis is poor. There are still no biomarkers to enable early detection. It is thus essential to be familiar with the alarm symptoms, so that the diagnostic work-up can be initiated as soon as possible.

Risk factors and prevention

The principal risk factor is the bacterium *Helicobacter pylori*, which is responsible for 90% of cases of gastric carcinoma (3, 4). Infection with *H. pylori* induces chronic active gastritis, which in some persons leads, via atrophic gastritis and intestinal metaplasia, to gastric carcinoma

(5). The incidence of gastric carcinoma can therefore be reduced significantly by eradication of *H. pylori*. A meta-analysis showed that eradication treatment resulted in a 46% lower risk of developing the disease than in the control group (relative risk 0.54, 95% confidence interval [0.40; 0.72]) (6). All persons at high risk of gastric carcinoma should therefore be tested for *H. pylori*, and those with positive results should be offered eradication treatment with subsequent verification of success. The definitions of at-risk persons and constellations have been adapted in accordance with the recommendations of the German Society of Gastroenterology, Digestive, and Metabolic Disease (DGVS) in its consensus guideline on *H. pylori* and gastrointestinal ulcers (4). At-risk persons are first-degree relatives of patients with

Table

Risk factors for the development of gastric carcinoma

<i>Helicobacter pylori</i>	Non-cardial carcinoma:
Gastroesophageal reflux disease (GERD)	• Age • Male sex • Overweight • Low socioeconomic status • Life in a high-risk population • Tobacco smoking • High alcohol intake • Family history • Previous gastric surgery
Nutritional factors: high intake of foods preserved in salt, high intake of processed meats, low consumption of fruit	

Box

Alarm symptoms that should prompt immediate further investigation by means of esophagogastroduodenoscopy with biopsies (7, 35)

- Dysphagia
- Recurring vomiting
- Loss of appetite
- Weight loss of unknown origin
- Gastrointestinal bleeding
- Iron deficiency anemia of unknown origin
- Vitamin B₁₂ deficiency of unknown origin

gastric carcinoma, persons born/resident in high-prevalence regions (Asia, eastern Europe, Central and South America), patients who already have advanced, corpus-predominant atrophic gastritis with or without intestinal metaplasia, and patients with previous gastric neoplasms (adenoma, early carcinoma) post endoscopic resection or partial gastrectomy (7).

The risk factors for gastric carcinoma are listed in the *Table*. Nutritional factors, such as high intake of foods preserved in salt, high intake of processed meats, and low consumption of fruit, have been added to the guideline.

The family history is an increasingly important factor. Up to 3% of patients have an underlying germline mutation and their gastric carcinoma is therefore hereditary (7). In the autosomal dominant form (hereditary diffuse gastric carcinoma, HDGC), there is often a mutation in the *CDH1* gene, which codes for E-cadherin. Another genetic alteration in HDGC is a germline mutation in *CTNNA1*, which codes for α -E-catenin. In 5–8% of cases gastric carcinomas may occur together with other hereditary tumors, e.g., with Lynch syndrome (hereditary non-polyposis colorectal cancer, HNPCC) or with microsatellite instability (MSI/dMMR). Recommendations for the prevention and treatment of hereditary gastric carcinomas have been incorporated into the guideline, because genetically unstable tumors can be more effectively managed with immunotherapy (7).

Population-based screening cannot be recommended in Germany owing to the relatively low incidence of gastric carcinoma and the low prevalence of *H. pylori*. However, systematic reviews have shown that

if cost/efficiency analyses incorporate the complications of *H. pylori* infection beyond carcinoma, such as peptic ulcers, then screening can be cost effective with low incidence, particularly in patients >50 years of age (8, 9). For this reason, the guideline now includes the recommendation that asymptomatic patients can be offered testing for *H. pylori* together with screening colonoscopy (7).

As recommended in international guidelines, patients with confirmed advanced preneoplastic lesions, such as marked atrophy and/or intestinal metaplasia (classification: OLGA 3/4 or OLGIM 3/4), should be monitored by endoscopy and biopsy, because successful *H. pylori* eradication does not exclude progression to gastric carcinoma. For instance, a prospective cohort study found an elevated 5-year risk of neoplasia: 36.5 per 1000 patient years for OLGA III, 63.1 for OLGA IV (10). In this situation European guidelines recommend gastroscopy (esophagogastroduodenoscopy, EGD) with biopsies at 3-year intervals in accordance with the Sydney protocol (11). EGD with biopsy for histological assessment of gastric mucosa should also be performed in patients with newly diagnosed pernicious anemia. If they are found to have autoimmune atrophic gastritis, they should be regularly monitored by endoscopy every 3–5 years, also because of the elevated risk of gastric neuroendocrine neoplasms (NEN), which have an incidence of 2.8% per person per year (7, 12).

There have been multiple reports that hypergastrinemia increases the risk of gastrointestinal tumor development. A slight increase in the serum concentration of gastrin has been demonstrated in patients being treated with proton pump inhibitors (PPI), leading to suggestions that long-term PPI intake elevates the risk of gastric carcinoma. Revision of the clinical practice guideline therefore incorporated a systematic literature survey and evaluation of the studies that have been conducted. The common factor was found to be a high degree of heterogeneity and failure to take account of other risks and parameters, such as *H. pylori* status, previous PPI treatment, tobacco consumption, and family history. In summary, although these studies show an association between gastric carcinoma risk and long-term PPI intake (i.e., 8 weeks or longer), causality has not been proved (7). In any event the indication for PPI administration should be reviewed critically at regular intervals. Especially patients with severe reflux and complications depend on adequate acid blockade. They can be prescribed a lower dosage of PPI for long-term management. Otherwise, a trial discontinuation should take place after no more than 6 months.

A systematic literature survey was conducted to identify studies testing the use of other substance groups for prevention. Randomized controlled trials found no reduction in the risk of gastric carcinoma development in patients who took statins regularly. The evidence from observational studies in Asia showed a benefit with regard to the incidence and mortality of gastric carcinoma, but in western populations the measured effect was more limited. Owing to the heterogeneous nature of the data, general administration of statins for gastric carcinoma prophylaxis therefore cannot be recommended. NSAID and ASA should also not be used for prophylaxis (7).

Diagnosis and staging

The alarm symptoms that should prompt immediate further investigation are listed in the *Box*. Vitamin B₁₂ deficiency of unknown origin has been added to the alarm symptoms to diagnose causal autoimmune atrophic gastritis (*Box*).

The primary diagnostic work-up for detection of adenocarcinoma of the stomach or the cardia (AEG) should feature high-resolution EGD, backed up by magnifying endoscopy and computer-assisted virtual chromoendoscopy to improve the detection rate and aid treatment planning (*Figure 1*). Biopsy samples should be obtained from all suspicious lesions. If the gastric neoplasm seems potentially amenable to endoscopic resection, only two samples should be taken from the most suspicious segments of the lesion to confirm the diagnosis, so as not to endanger endoscopic resection by inducing submucosal fibrosis.

In the case of a non-endoscopically resectable advanced gastric neoplasm, a sufficient number of tissue samples should be harvested (8–10 biopsies). This will provide four or five samples of vital tumor tissue, enabling not only diagnosis but also determination of molecular biomarkers, which are important for treatment planning. To ascertain whether infection with *H. pylori* is present, biopsy samples should be taken from areas of gastric mucosa that appear free of tumor on endoscopy.

Staging sonography, thoracic computed tomography (CT), and abdominopelvic CT should be carried out to exclude distant metastases. If curative treatment is intended, the primary tumor should be examined by endoscopic ultrasonography (EUS) to determine the local infiltration depth (T stage). EUS is significantly more sensitive than CT for assessment of the N stage, but has lower specificity with regard to the discrimination of lymph nodes affected by inflammatory enlargement or malignant infiltration. There is no evidence that determination of serum tumor markers in the primary diagnostic work-up is beneficial (7).

In locally advanced gastric carcinomas (principally cT3, cT4) that are classified as potentially resectable, a diagnostic laparoscopy with peritoneal lavage should be performed to rule out occult peritoneal metastasis before starting neoadjuvant therapy (see below, “Personalized treatment”). Because the treatment plan will change considerably if peritoneal carcinosis is demonstrated, it should be performed before the start of neoadjuvant therapy according to a standardized protocol with assessment of the peritoneal carcinomatosis index (PCI) according to Sugarbaker (13). Completion of neoadjuvant treatment must be followed by restaging with CT and EGD to evaluate the treatment response. In patients with gastric carcinoma amenable to curative treatment, surgery can be preceded by CT-assisted determination of muscle mass at the level of the L3 vertebra to estimate the risk of postoperative complications (7). This serves to identify the presence of sarcopenia, which is associated with increased overall and disease-specific mortality, reduced recurrence-free survival, and a higher overall rate of perioperative complications. Timely inclusion of nutritional therapists in the multidisciplinary management team is therefore advisable in the curative scenario (7).



Figure 1: Endoscopic image of a case of gastric carcinoma

At the time of diagnosis, about 20% of patients have a stage I tumor, around 45% are at stage II–III, and approximately 38% have reached stage IV (14). In the presence of locally advanced, unresectable gastric carcinoma or metastasized disease, patients eligible for treatment should undergo determination of their MSI, PD-L1, and HER2 status as well as claudin 18.2, owing to the importance of these factors for the prognosis and/or the nature of medicinal tumor treatment.

Personalized treatment

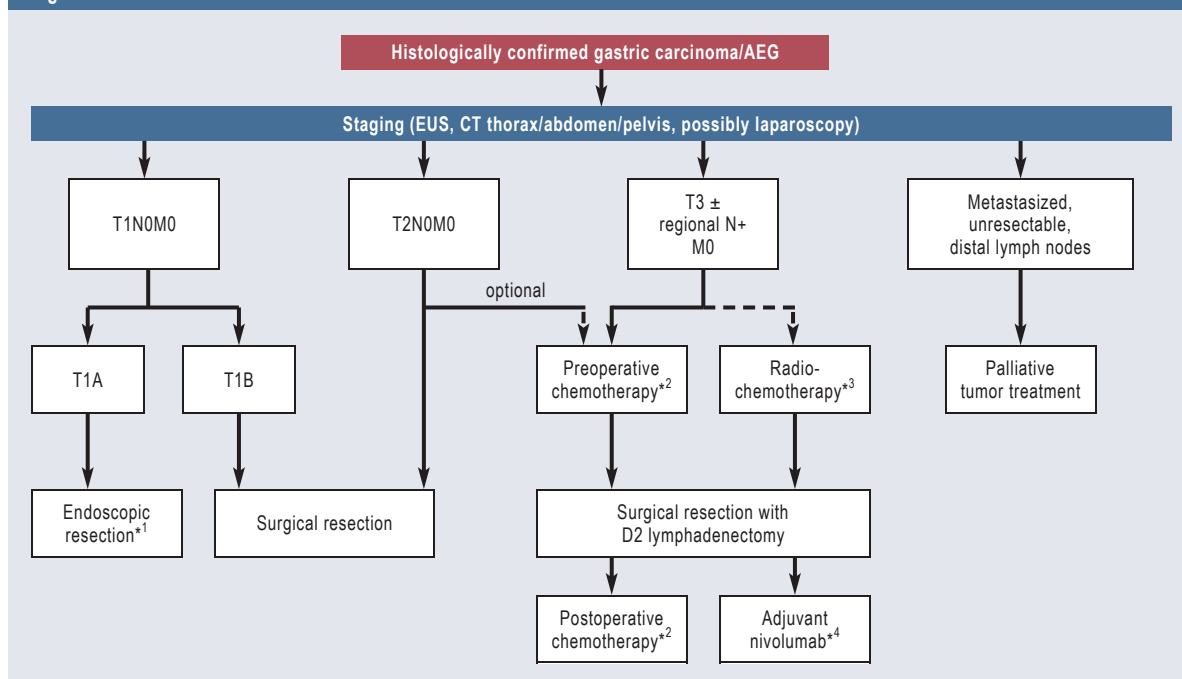
The planning and implementation of treatment requires the formation of an interdisciplinary treatment team with a holistic approach to patient care. Nutritional medicine and sports medicine are important, as is the inclusion of psycho-oncological and palliative medicine expertise. The sections of the guideline covering nutrition and quality of life have been firmed up and brought into line with the existing clinical practice guidelines on supportive therapy and palliative medicine.

The rest of this article outlines the treatment recommendations for the different stages. A more detailed description can be found in the long version of the clinical practice guideline (7). *Figure 2* shows the treatment algorithm.

In stage IA with intraepithelial neoplasia or early carcinoma, assuming certain other criteria are fulfilled, endoscopic resection can be performed. Endoscopic submucosal dissection (ESD) is superior to endoscopic mucosal resection (EMR) as standard treatment and should be carried out at a center with existing ESD expertise. Curative ESD/EMR must be followed by repeated EGD for exclusion of local recurrence or early detection of metachronous lesions (risk: circa 3.5% annually) (15). The first follow-up after R0 resection by means of ESD/EMR is recommended at 3–6 months, followed by annual visits. The local recurrence rate after ESD is <1%, and most such recurrences can again be treated endoscopically (16). As mentioned above, one should test for *H. pylori*; if found to be present, it should be eradicated to reduce the risk of metachronous neoplasia.

Surgical resection is—with the exception of endoscopically resectable early cancers—the sole option for curative

Figure 2



Treatment algorithm (from [7])

*¹ If the criteria for endoscopic resection are met

*² Licensing for combination therapy with durvalumab anticipated (MATTERHORN study)

*³ Possibly in AEG I in patients whose general health is poor

*⁴ In pathological residual disease ($\geq$ ypT1 or $\geq$ ypN1)

AEG, Cardial adenocarcinoma; CT, computed tomography; EUS, endoscopic ultrasonography

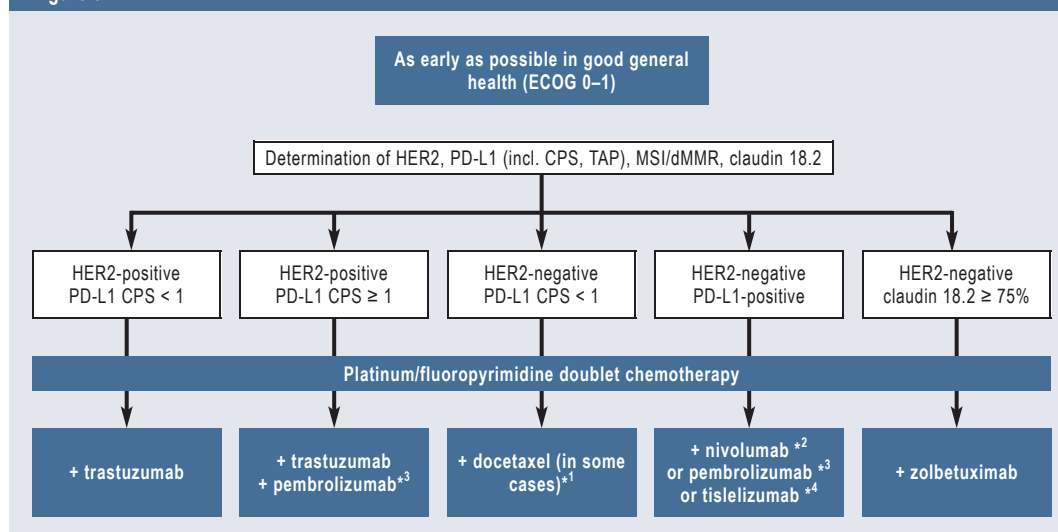
treatment of potentially resectable gastric carcinoma. In early gastric carcinoma, laparoscopic subtotal distal resection or gastrectomy can be carried out. This procedure is oncologically equivalent to open resection. The 5-year survival rate after resection of early gastric carcinoma is 96–97% (17). In contrast to minimally invasive surgery of early carcinoma, laparoscopic procedures for resection of advanced tumors ($> T2$) are still in evaluation. Effects similar to those of open surgery have been observed. Conclusive assessment of robotic surgery is also not yet possible; further studies are being conducted. The standards for surgical safety margins after initial neoadjuvant treatment are currently under discussion, with the aim of achieving preservation of gastric reservoir function by means of partial resection, thus improving the subsequent quality of life.

In localized carcinomas of the categories $\geq cT3$ and/or N+, perioperative chemotherapy should be performed (hazard ratio [HR] 0.77 [0.63; 0.94]) (18) to improve overall survival. The FLOT regime (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) represents the standard (19). Multimorbid and older adult patients with AEG-I tumors can be treated as follows with an eye to preservation of quality of life: preoperative radiochemotherapy according to the CROSS protocol followed by resection, plus adjuvant treatment with nivolumab if pathological residual disease ($\geq$ ypT1 or $\geq$ ypN1) is demonstrated (20). The German ESOPEC trial (21), the first head-to-head study, compared

the two standard treatments for esophageal and AEG adenocarcinomas and showed a significantly higher 3-year survival rate for FLOT (57.4%) than for CROSS (50.7%). It should be noted, however, that the design of the ESOPEC trial did not take account of the now validated standard immunotherapy with nivolumab for patients with postoperative residual tumor disease. The MATTERHORN trial of immunotherapy in the perioperative scenario was recently presented at the American cancer congress ASCO 2025 and published in the *New England Journal of Medicine* (22). It shows that combination of FLOT with durvalumab improves the 2-year disease- and event-free survival rate considerably, at 67.4% versus 58.5% (HR 0.71 [0.70; 1.39]). The 2-year survival rate was also much improved (75.7% versus 70.4%, $p = 0.03$). The licensing of checkpoint inhibitors for use in the perioperative scenario is expected in early 2026.

Only 10–20 years ago, most patients with metastases survived no more than a year. The new combinations of chemotherapy with targeted antibodies and immunotherapy are fortunately changing this situation, with 2-year survival rates of 31–39% and 5-year survival of 16% now being achieved (23–26). Moreover, new strategies of later local treatment (irradiation or ablation), resection of single metastases or small numbers of metastases (oligometastasis), and maintenance treatments in the presence of stable metastasis are being evaluated with regard to improvement of quality of life (27, 28).

Figure 3



First-line treatment for metastasized gastric or cardiac adenocarcinoma (from [7]); clinical re-evaluation and imaging every 6–12 weeks

^{*1} In young patients with good general health and high remission pressure: consider addition of docetaxel

^{*2} Licensing of nivolumab in PD-L1 CPS ≥ 5 (Check-Mate-649 trial)

^{*3} Licensing of pembrolizumab in PD-L1 CPS ≥ 1 (KEYNOTE-859 trial and KEYNOTE-811 trial)

^{*4} Licensing of tislelizumab in PD-L1 TAP ≥ 5% (RATIONALE-305 trial)

Many of these treatment combinations yield a better quality of life in the long term than simple chemotherapy (29, 30). Before commencement of treatment, therefore, molecular pathological diagnosis should take place, with determination of HER2, PD-L1, MSI, and claudin 18.2. These biomarkers are fundamental to the effective use of targeted substances and immune checkpoint inhibitors. In patients with advanced, inoperable, or metastatic disease, the patient's preference, the ECOG status, and the prognosis should determine whether and to what extent palliative and supportive treatments should be used. Advanced age is not a contraindication for medicinal tumor treatment. Particularly patients with an ECOG status of 0–1 should be offered treatment to prolong survival and maintain quality of life. A meta-analysis of over 11 698 persons showed that chemotherapy prolongs overall survival by about 6.7 months compared with a pure best supportive care approach (HR 0.3 [0.24; 0.55]) (31).

In tumors with overexpression of HER2, trastuzumab should be added to the platinum/fluoropyrimidine-based first-line treatment. In PD-L1-positive tumors, the addition of immune checkpoint inhibitors to chemotherapy can further improve the likelihood of survival (Figure 3), and nivolumab, pembrolizumab, and tislelizumab have been licensed for use as first-line treatment. When using immune therapies it is important to be aware of the immune-related adverse effects and to recognize them even when they occur later, perhaps not until after conclusion of the immune treatment (32). Zolbetuximab, a monoclonal IgG1 antibody to claudin 18.2, was licensed for use in combination with first-line chemotherapy in autumn 2024. Around 30–40% of adenocarcinomas overexpress claudin 18.2 (immunohistochemically at least 75% positive tumor cells). The aggregated data from the SPOTLIGHT and GLOW approval studies show improvements in progression-free survival (9.2 versus 8.2 months, HR 0.71 [0.61; 0.83]) and overall survival (16.4 versus

13.4 months, HR 0.77 [0.67; 0.89]) compared with chemotherapy and placebo. Nausea and vomiting are relevant adverse effects, so it is necessary to give antiemetics as recommended in advance of the highly emetogenic chemotherapy (33).

After failure of first-line treatment, patients in good general health should be offered second-line chemotherapy. The treatment protocol should be selected on the basis of the prior treatment and the biomarkers, given that trastuzumab deruxtecan is licensed for HER2-positive carcinomas and pembrolizumab for MSI status. After failure of second-line treatment, patients in good general health should be offered third-line treatment, e.g., trifluridine/tipiracil. In the palliative scenario the personal treatment goal should regularly be discussed by the patient and their physician. The patient's preferences, their general health, and the medical rationale of further attempts at treatment should be weighed up with regard to risks and benefits. Moreover, the initiation of palliative (co-)care (34) should be considered.

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PLJ has received funding from German Cancer Aid in relation to the German Guideline Program in Oncology. She is the executive director of the German Society of Gastroenterology, Digestive, and Metabolic Disease.

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Clinical practice guidelines in the *Deutsches Ärzteblatt International*, as in many other journals, are not subject to a peer review process, since clinical practice (S3 level) guidelines are texts which have already been evaluated, discussed, and broadly agreed upon multiple times by experts (peers).

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Corresponding author

PD Dr. med. Yvonne Huber
Yvonne.Huber@unimedizin-mainz.de

Supplementary material

Complete list of full references, eBox:
www.aerzteblatt-international.de/m2025.0159

CLINICAL SNAPSHOT



Cutaneous *Larva Migrans* on Darker Versus Lighter Skin

Two cases of cutaneous larva migrans were diagnosed based on the clinical and morphological characteristics of the rash (itchy, serpiginous eruption migrating by 1–2 cm/day) and the context (tropical climate). A 40-year-old European male living in rural Thailand presented in 2007 with an erythematous rash on the left upper arm (Figure a). A 50-year-old female living in rural Uganda presented in 2025 with a dark black rash in the right gluteal area (Figure b). Both cases were treated with oral albendazole as per local guidelines. This self-limiting disease, which is common in tropical areas, is caused by *Ancylostoma caninum* or *Ancylostoma braziliense* larvae transmitted through soil (contaminated with dog or cat feces). Albendazole or ivermectin can accelerate healing. Inflammation appears erythematous (reddish) on lightly pigmented skin, while on darker skin tones, it can cause characteristically violaceous, gray, dark brown, or black color changes.



Lykourgos Christos Alexakis, MD, DTM, MSc; Daniel Godwin Olal, DCM; Medical Project in Uganda, German Doctors e.V., Bonn, lchalexakis@gmail.com

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Supplementary material to accompany the article

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