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Merkel cell carcinoma

# Planning study for Merkel cell carcinoma based on the relapse pattern

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ABSTRACT

*Purpose:* To develop a technique for radiation (RT) of in-transit path ways (IT) in Merkel cell carcinoma.
*Method:* In the planning study, IT were ink-marked on the skin during sentinel lymphscintigraphy and wire-marked in planning-CT. Pre- and post-operative planning-CTs were acquired. The clinical target volume (CTV) included tumor bed plus safety margin, IT and draining nodes, the planning volume (PTV) the CTV plus 0.5–1 cm margin. VMAT plans with 2–3 arcs were analyzed.
*Results:* A planning study was performed for five pts. including two pts. with primary tumor (PT) in head and neck, 1 pt. each with PT of elbow, forearm and upper leg respectively. Plans showed satisfactory PTV coverage: $D_{mean}$ 100% ± 0%, $D_{98\%}$ 92.4% ± 2.24%, homogeneity index (HI) 0.095 ± 0.01, conformation number (CN) 0.84 ± 0.01 and conformality index (CI) 0.95 ± 0.01.
*Conclusion:* The planning study confirms feasibility of highly conformal irradiation of IT pathways based on individualized target delineation. Currently, patients referred for non-metastatic MCC are encouraged to enroll in a prospective clinical study that evaluates the feasibility of radiation of IT pathways.
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Merkel cell carcinoma (MCC) is a rare aggressive cutaneous tumor. Locoregional relapse occurs in 13–29% of patients (crude incidence) [1–4]. Retrospective studies and a single randomized study have shown consistently that radiotherapy (RT) reduces the local relapse rate significantly and may improve overall survival [5–9]. Adjuvant radiation of the primary tumor (PT) region is standard practice, however the treatment of the in transit (IT) region is under debate. In transit metastases in the cutaneous draining lymph channels are well known but rarely evaluated [4,10,11]. The treatment of IT pathways is complicated by the interindividually very variable location of IT pathways that enlargens the clinical target volume.

A method to depict the draining lymph paths by lymph node scintigraphy was developed [12] and integrated into RT planning. A planning study of five patients with MCC in typical sites – extremities and head and neck – is presented.

## Material and methods

The aim was to visualize the intracutaneous lymph channels, i.e. IT regions between PT and first echelon node and study whether these can be incorporated into the clinical target volume. After informed consent was gained, five consecutive patients with tumors in the predilection sites of MCC (head and neck, upper and lower extremities) underwent the routine sentinel node lymph scintigraphy and a preoperative planning CT in treatment position with wire marking of the IT pathways (see below) (Fig. 1). After tumor resection, SNB and in case of nodal metastases, complete lymphadenectomy, patients were referred for adjuvant radiation. A planning CT with slice thickness 2 mm was acquired and therapy according to the institutional policy was applied.

Patients were immobilized according to the location of the PT, either with an individual fixation mask for PT in the head and neck or an individual vacuum cushion for PT of the extremities. Daily image guidance with portals or cone beam CT was performed.

### *Lymphoscintigraphy*

In brief, 99 m Tc nanocolloid was injected intracutaneously in usually 4 tracer depots on either side of the scar. Lymphoscintigraphy was performed in the dynamic acquisition mode for 4 min followed by static planar images over 1–2 min duration until each visualized lymph channel reached an endpoint, i.e. its putative lymph node. Lymph channels and nodes were marked on the skin using the monitor of the camera for "on-line" delineation of the radioactivity, and a small radioactive probe for directly cross-checking the position of the radioactivity in projection onto the skin [12].

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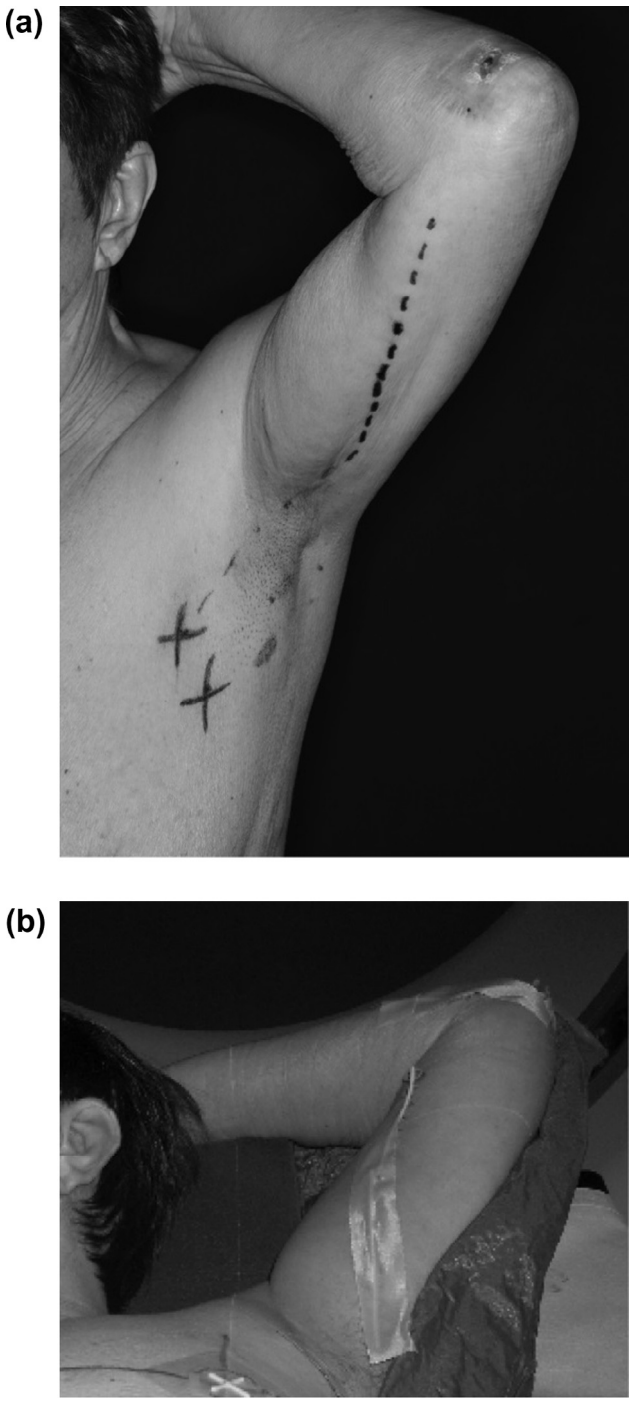


**Fig. 1.** Depiction of in transit-region for planning. a: ink marking on skin during sentinel node lymph scintigraphy b: planning CT pre-surgery with wire marking.

*Treatment planning and dosimetry*

*Target volume definition*

For the planning study, the pre- and postoperative CTs were co-registered. Three CTVs were delineated:

(1) the CTV PT that included the postop scar + 2 cm or skin transplant + 1 cm to either lateral side and 2 cm in depth or to the adjoining deep fascia
(2) the CTV IT as the marked pathways + 1 cm to either lateral side and 1 cm in depth
(3) the CTV Nodes that included the anatomical nodal basin of the first draining node as depicted in the sentinel lymph node scintigraphy.

The planning target volumes (PTV) were constructed by adding 5 mm to the CTVs. In the superficial areas the nodal PTV was cropped by 5 mm to the skin surface, all other PTVs were restricted to the skin surface. A bolus of 5 mm thickness was placed during CT or virtually during planning in the IT and PT regions.

Risk organs were contoured according to the anatomical site of the PTVs. PT of the extremities: adjoining bones, body volume minus PTV and for PT in head and neck the ipsilateral eye and lacrimal gland, parotids, submandibular glands, oral cavity, spinal cord and larynx.

*Planning procedure*

Treatment plans using 6 MV photons were generated with a commercial 3D treatment planning system (Eclipse™ v.11, Varian Medical Systems) that could be treated with a DHX™ Clinac (Varian Medical System) equipped with a 120 Leaf multi leaf collimator and on board imaging. Dose distribution was calculated using the Anisotropic Analytical Algorithm (AAA).

In order to find a treatment setup other than an opposing open static fields, in a first step intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) techniques were compared. Both were able to create nearly equivalent conformal dose distributions. Because IMRT plans needed a higher total number of monitor units (MU) and an increased overall treatment time, we focused on VMAT.

Prescription dose was 50 Gy, treated in 25 fractions with 2 Gy single fraction dose. Plans were normalized to target mean dose equal to prescription dose for the overall PTV (PT + IT + Nodes), while the encompassing isodose should be the 95% isodose.

VMAT plans consisted of 3 partial arcs (pts 1–3) or 2 partial arcs (pts 4 and 5). Details of gantry rotation range and values for angles and jaw openings are shown in Supplement Fig. 3 (upper part) and Supplement Table 1. Basically, one partial arc with collimator angle 0° is used with leaves moving in medial–lateral direction. A second arc is added with collimator angle 90°. Here leaves move in cranial-caudal direction. Due to a leaf span of 15 cm (maximum distance from the tip of the most extended leaf to the tip of the most retracted leaf), the jaw opening in leaf moving direction was restricted to maximum 20 cm which leads to potentially better optimization results. Therefore, the second arc with collimator 90° was split into 2 arcs for patients 1–3, both with a cranio-caudal jaw opening of 20 cm and an overlap region as large as possible. For details refer to Supplement Table 1 and Supplement Fig. 3 (lower part).

VMAT plans were optimized using the Progressive Resolution Optimizer (PRO) v3 in Eclipse™ TPS. Optimization constraints were upper limits (0 vol-% – 52.5 Gy/2 vol-% – 51 Gy) and lower limits (98 vol-% – 49 Gy/100 vol-% – 47.5 Gy) for the overall PTV with priorities set to 600. The dose fall-off outside the target was realized using the automatic Normal Tissue Constraint (NTC) with priority 450. OARs received upper limits that left the dose burden below desired values using priorities between 400 and 600, depending on their importance.

Fig. 2 shows typical examples of dose distributions in the primary tumor (PT), in-transit (IT), and lymph nodes region (Nodes), respectively for pt. 1–5 from left to right. The depicted 95% isodose fits very conformally to the PTV, although the PTV shape varies very much between shell-like and bulk-like in cranio-caudal direction for most of the patients.