Clinical Practice Guidelines

NEUROENDOCRINE CARCINOMA OF THE SKIN

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Introduction

Neuroendocrine carcinoma (NEC) is often referred to as Merkel cell carcinoma of the skin, trabecular cell carcinoma, cutaneous apudoma, and primary small-cell carcinoma of the skin. NEC is derived from Merkel cells found in the hair follicles of mammals that form complexes with terminal axons to act as mechanoreceptors to pressure. Merkel cells are also found in the dermis, epidermis, and oral cavity. NEC is usually found in sun-exposed areas, with 50% in the head and neck. NEC appears most often in the white population and at an average age of 65 years. A poorer prognosis is associated with men, with younger age, with location in the head, neck, and trunk areas, and with regional or systemic disease. The disease is rare but aggressive. The one-, two-, and three-year survival rates are 88%, 72%, and 55%, respectively.2

Clinical Presentation

The local tumor presents as a rapidly growing, firm, nontender, reddish-blue dermal nodule. The overlying skin is usually intact and shiny and is rarely ulcerated. The differential diagnosis includes basal cell carcinoma, adnexal tumor, lymphoma, adult neuroblastoma, melanoma, and metastatic small-cell carcinoma. Regional metastases present as enlarged, firm, lymph nodes. Systemic disease may present as masses in the lung, liver, and other solid organs.

Pathologic Diagnosis

The diagnosis of NEC is confirmed by examination of hematoxylin–eosin-stained sections and a panel of immunohistochemical stains.3 These tumors demonstrate a characteristic trabecular or sheet-like dermal proliferation of monomorphic cells with minimal cytoplasm, hyperchromatic nuclei, frequent mitoses, and numerous apoptotic bodies. Tumor cells stain with antibodies to low-molecular-weight keratin (often in a perinuclear “dot-like” pattern) and neuroendocrine markers (e.g., neuron-specific enolase, chromogranin, synaptophysin).

Case Review and Staging

The patient history, physical examination, pathologic data, radiologic studies, and laboratory evaluation allow classification as clinical stage I (local disease only), clinical stage II (regional disease), or clinical stage III (systemic disease).

Local Disease

Clinical stage I disease is limited to the skin. It appears as a dermal nodule unless a previous excisional biopsy has been done. A larger nodule may be found following incisional biopsy, and ulceration may be present. The extent of local disease, adherence to underlying structures, and proximity to surrounding anatomical structures is assessed.

Excision includes the primary tumor with a 2-cm margin of surrounding normal-appearing skin.2,4 The margin may be modified to save surrounding structures for aesthetic and functional considerations. Two thirds of patients with local disease will develop regional nodal metastases.4 Since there are no useful, reliable factors to determine the relative risk of regional metastases, all patients are considered at high risk. Sentinel lymph node excision gives less morbidity than total lymphadenectomy. This technique includes preoperative radiolymphoscintigraphy and cutaneous tattooing of the sentinel lymph nodes, intraoperative localization of the sentinel lymph node with vital blue dye lymphazurin injection, and intraoperative radio-lymphoscintigraphic localization with preoperative radioactive sulfur colloid injection and hand-held gamma counter localization.5 As a result of the high local recurrence rate and the aggressive nature of the tumor, radiotherapy to the primary site using wide (2-5 cm) margins is recommended following excision.2,6

Regional Disease

As clinical stage II disease, 7% to 31% of patients present with enlarged nodes (>2 cm in size) in regional basins.1,6 Fine needle aspiration may be used preoperatively. The extent of regional disease and adherence to underlying structures is determined. Treatment includes total lymphadenectomy and postoperative radiotherapy. Patients with positive sentinel nodes have micrometastatic regional disease and are classified as pathologic stage II disease. They are further treated with total lymphadenectomy and postoperative radiotherapy to the regional site. Management of the regional disease with radiation alone results in a 20% survival rate at a mean of 14 months after developing regional disease, whereas treatment with surgery alone or with radiation results in a 44% survival rate at 40 months.1 If the sentinel node is negative, the patient is classified as clinical stage I. Patients not eligible for lymphoscintigraphy usually receive elective radiotherapy (44-55 Gy) to the draining lymph node basins.

Systemic Disease

Clinical stage III disease may present in the bone, abdomen, skin, mediastinum, lung, or liver.2,8 The median survival is eight months. No firmly established chemotherapy for NEC exists. Because of the neuroendocrine features of this tumor, etoposide plus cisplatin and cisplatin plus 5-fluorouracil have been tried. There are...
anecdotal reports of responses to paclitaxel. The rarity of this tumor has precluded cooperative efforts to establish a firm basis for a recommended therapy.

**Follow-up and Prognosis**

Follow-up includes a history and physical examination every three months for three years and annually thereafter. Laboratory and/or radiologic evaluation is needed only to investigate symptoms.

Within one year, 30% to 40% of patients develop local recurrence.\(^1,2,4,9\) If recurrence is confirmed, treatment consists of local excision with a margin of at least 2 cm and further radiotherapy if possible. If there is no evidence of regional and systemic disease, then patients are retreated for local disease only. Radiotherapy to nodal basins may also be applied depending on sentinel node sampling or the extent of recurrence. If not present, follow-up is continued.

The majority of regional recurrences develop within one year,\(^4\) and there is a 50% recurrence rate within two years.\(^2\) Clinically suspicious nodes at the regional disease site are diagnosed with biopsy or with fine needle aspiration of nodes. If present, they are treated with further excision, if possible, and further radiotherapy is considered. If regional recurrence is absent, follow-up is continued. Systemic metastases develop in 50% of patients with regional recurrence, and 36% develop systemic recurrence.\(^2\) Patients are diagnosed with histology if possible. Treatment may include chemotherapy.

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**Algorithm for Neuroendocrine Carcinoma of the Skin**

![Algorithm Diagram](image)

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**References**