The NANETS Consensus Guidelines for the Diagnosis and Management of Poorly Differentiated (High-Grade) Extrapulmonary Neuroendocrine Carcinomas

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Abstract: Extrapulmonary poorly differentiated neuroendocrine carcinomas can originate in the gastrointestinal tract, bladder, cervix, and prostate. These high-grade malignancies are characterized by aggressive histological features (high mitotic rate, extensive necrosis, and nuclear atypia) and a poor clinical prognosis. They are infrequently associated with secretory hormonal syndromes (such as the carcinoid syndrome) and rarely express somatostatin receptors.

Most poorly differentiated neuroendocrine carcinomas are locally advanced or metastatic at presentation. First-line systemic chemotherapeutic options with a platinum agent (cisplatin or carboplatin) and etoposide are recommended for most patients with metastatic-stage disease; however, response durations are often short. Sequential or concurrent chemoradiation is recommended for patients with loco-regional disease. In patients with localized tumors undergoing surgical resection, adjuvant treatment (chemotherapy or without radiation) is warranted in most cases.

Key Words: neuroendocrine carcinomas, neuroendocrine tumors, poorly differentiated, high grade

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In the jejunum and ileum, PD NECAs represent only 1% of all cases, and prostate (2% of all cases). Prognosis is poor, with median survival durations in patients with localized, regional, and distant disease of 34, 14, and 5 months, respectively.

IMAGING

Owing to the relative paucity of somatostatin receptor expression in PD NECAs, somatostatin-receptor scintigraphy (Octreoscan) is rarely useful as an imaging modality. Computed tomographic scans, magnetic resonance imaging scans, or [(18)F]-fluorodeoxyglucose positron emission tomographic scans may be used for baseline staging and for monitoring response to treatment.

MANAGEMENT OF METASTATIC (EXTENSIVE) DISEASE

Based on the established role of cisplatin and etoposide in metastatic small-cell lung cancer, this combination has been investigated in metastatic NECAs of the GI tract. The first such study explored infusional cisplatin and etoposide among 45 patients with metastatic NECAs, of whom 18 had PD tumors. A response rate of 67% was reported in patients with PD NECAs, with response duration of 8 months and a median survival of 19 months. A subsequent study of 53 patients with PD NECAs of the GI tract treated with a bolus regimen of cisplatin and etoposide reported a response rate of 42% with response duration of 9 months and a median survival of 15 months. Based on these studies, the combination of cisplatin and etoposide is recommended as first-line therapy for metastatic PD NECAs. Alternative regimens substituting carboplatin for cisplatin or irinotecan for etoposide have been validated in metastatic small-cell lung cancer and are therefore thought to be acceptable options for management of extrapulmonary PD NECAs. The optimal duration of chemotherapy has not been clearly defined, and it remains unclear whether treatment beyond 4 cycles is associated with a survival benefit.

There are no studies of salvage chemotherapy in extrapulmonary PD NECAs. Second-line chemotherapy regimens in refractory or relapsed small-cell lung cancer are typically associated with modest response rates of 0% to 20%. One study of
Based on this data, topotecan can be recommended as a salvage option for relapsed PD NECAs. Alternatively, retreatment with a platinum and etoposide or irinotecan regimen can be considered in patients who relapse more than 3 to 6 months after termination of first-line chemotherapy. Other agents with similar reported activity in small-cell lung cancer include paclitaxel, docetaxel, vinorelbine, and gemcitabine. 

**MANAGEMENT OF LOCO-REGIONAL DISEASE (LIMITED DISEASE)**

Poorly differentiated NECAs are characterized by a high proclivity for metastatic dissemination even in patients with clinically localized tumors. This principle is validated by retrospective studies confirming that surgery alone is rarely curative. Based on the treatment paradigm for limited-stage small-cell lung cancer, a course of definitive chemotherapy (cisplatin or carboplatin and etoposide for 4–6 cycles) and radiation can be considered in many patients with loco-regional extrapolmonary PD NECAs, particularly when surgical resection is difficult. Clinical trials in small-cell lung cancer suggest that concurrent chemoradiation is more efficacious than sequential treatment but at the expense of increased toxicity. The optimal sequencing of chemotherapy with radiation in extrapolmonary PD NECA is unknown. Likewise, the benefit of surgery among patients who have completed a course of chemoradiation is uncertain.

Whereas there are no studies examining adjuvant postoperative treatment in PD NECAs, their aggressive behavior warrants consideration of adjuvant therapy in most cases. Chemotherapy (4–6 cycles of cisplatin or carboplatin and etoposide) is recommended. Sequential radiation can also be considered in cases where the risk of local recurrence is thought to be higher than average (eg, carcinomas of the rectum or cervix).

The incidence of brain micrometastases in small-cell lung cancer is high, necessitating prophylactic cranial irradiation for patients with successfully treated limited-stage disease. Data on extrapolmonary PD NECAs suggest a lower frequency of central nervous system metastases. Consequently, routine prophylactic cranial irradiation cannot be recommended in this population but may be considered among patients with PD NECAs of the head and neck or unknown primary site.

**REFERENCES**


