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Current Treatment Strategies and Future Directions for Extrapulmonary Neuroendocrine Carcinomas

A Review

Johannes Stelwagen, MD; Elisabeth G. E. de Vries, MD, PhD; Annemiek M. E. Walenkamp, MD, PhD

[Supplemental content](#)

IMPORTANCE Patients with extrapulmonary neuroendocrine carcinomas (EPNECs) receive essentially the same treatment as those with small cell lung cancer (SCLC) despite differences in origin, clinical course, and survival. This SCLC-based approach is attributable to the rarity of EPNECs, which impedes the use of randomized clinical trials. However, neuroendocrine carcinomas are becoming more common because of the increasing use of systemic cancer therapy for adenocarcinomas. This treatment can transdifferentiate certain adenocarcinomas into neuroendocrine carcinomas. In addition, the treatment landscape for SCLC is slowly changing, potentially impacting the treatment paradigms for EPNECs.

OBSERVATIONS New information on tumorigenesis of EPNECs from different origins, either as a primary malignant tumor or after neuroendocrine differentiation from adenocarcinomas, demonstrates their biological similarity. Activated molecular pathways that appear to underlie the development of EPNECs are potentially targetable, and some of these targets, such as poly(adenosine diphosphate-ribose) polymerase, Wee1, and Aurora A kinase, are currently under investigation. Immune checkpoint inhibitors (ICIs) already constituted a new treatment modality for patients with SCLC and produced some promising results in patients with EPNECs.

CONCLUSIONS AND RELEVANCE Although only moderately effective, the introduction of ICIs signifies the first new option in systemic treatment of SCLC in decades. To prove the value of ICIs and other new drugs for patients with EPNECs, these patients should be included in clinical trials independent of the primary tumor site. Furthermore, to optimize clinical decision-making for patients with EPNECs, experts from the neuroendocrine tumor board should collaborate with members from tumor site-specific boards, which will require patient referral to a center with EPNEC expertise.

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High-grade neuroendocrine neoplasms are classified into well-differentiated neuroendocrine tumors (grade 3) and poorly differentiated neuroendocrine carcinomas (NECs).¹ Subdivided into small cell and large cell subtypes, NECs most commonly originate in the lung comprising approximately 95% of all small cell carcinomas.^{2,3} Extrapulmonary NECs (EPNECs) can arise in almost any organ in the body but are rare; an incidence of only 1.5 cases per 100 000 inhabitants per year is reported in Europe.⁴ The rarity of EPNECs and the similarity with the much more common primary small cell lung cancer (SCLC) has led practitioners to adopt similar principles in the treatment of EPNECs.

Recently, much new information on tumorigenesis and the etiology of neuroendocrine differentiation has been published, indicating the biological similarity of EPNECs of different origins.⁵⁻⁸ These insights may help practitioners explore new treatment options for patients with EPNECs. Moreover, the treatment landscape for SCLC is changing with the incorporation of immune checkpoint inhibitors (ICIs).⁹ Finally, more retrospective series are reporting on outcomes of more traditional treatment strategies, such

as surgery, radiotherapy, chemotherapy, or a combination of these. This systematic review of the literature addresses the increasing knowledge of tumor biology and neuroendocrine differentiation of other malignant tumors, the current standard of care, and developments in new treatments for SCLC and EPNECs.

Search Strategy and Selection Criteria

We retrieved research articles published in the English language between January 1, 1990, and March 31, 2020, from PubMed, ClinicalTrials.gov, Cochrane Library, and the Trip medical database. Our search strategy is depicted in **Table 1**. Articles eligible for inclusion were randomized clinical trials (RCTs), meta-analyses, and systematic reviews. Because of the rarity of the disease, we also included retrospective observational studies and case reports when deemed to provide data necessary for clinical advances in the treatment of EPNECs. We scored studies using the European Society for Medical Oncology–Magnitude of Clinical Benefit Scale (ESMO-MCBS1.1) when

Table 1. Search Strategies

Database	Type of search	Search terms	Guidelines consulted
PubMed and ClinicalTrials.gov	Original articles ^a and ongoing clinical trials	[neuroendocrine carcinoma OR small cell carcinoma OR extrapulmonary small cell OR extrapulmonary large cell] AND [genomic alterations OR sequencing OR neuroendocrine differentiation OR molecular targets] [neuroendocrine carcinoma OR extrapulmonary small cell OR extrapulmonary large cell] AND [treatment OR outcomes] AND [esophagus OR gastric OR pancreas OR colorectal OR gastroenteropancreatic OR bladder OR urogenital OR prostate OR cervix OR sinonasal OR laryngeal OR head and neck]	NA
Cochrane Library	Reviews	[small cell carcinomas OR neuroendocrine carcinomas OR poorly differentiated neuroendocrine tumors]	NA
Trip	Guidelines	[neuroendocrine carcinoma OR small cell carcinoma OR extrapulmonary small cell OR extrapulmonary large cell] AND [esophagus OR gastric OR pancreas OR colorectal OR gastroenteropancreatic OR bladder OR urogenital OR prostate OR cervix OR sinonasal OR laryngeal OR head and neck]	ENETS-high-grade GEPNETs, 2016; NANETS-high-grade EPNECs, 2010; NCCN-prostate, version 2, 2020; NCCN-bladder, version 2, 2020; NCCN-SCLC, version 2, 2020; NCCN-neuroendocrine and adrenal tumors, version 2, 2020

Abbreviations: ENETS, European Neuroendocrine Tumor Society; EPNECs, extrapulmonary neuroendocrine carcinomas; GEPNETs, gastroenteropancreatic neuroendocrine tumors; NA, not applicable; NANETS, North American Neuroendocrine Tumor Society; NCCN, National Comprehensive Cancer Network; SCLC, small cell lung cancer.

^a Articles eligible for inclusion comprised randomized clinical trials, meta-analyses, and systematic reviews. Retrospective observational studies and case reports were eligible for inclusion when deemed to provide data necessary for clinical advances in the treatment of EPNECs.

possible.¹⁰ The relative strength of the results from the studies was ranked according to the Oxford scale for level of evidence.

Current Treatment Strategies for SCLC

Small cell lung cancer is subdivided into limited-stage (LS) and extensive-stage (ES) disease. Limited-stage SCLC is defined as disease confined to 1 hemithorax with primary tumor and regional lymph nodes that can be safely treated with definitive radiation doses.⁹ Treatment of resectable LS-SCLC consists of surgery and adjuvant chemotherapy or radiotherapy to the chest with concurrent chemotherapy.⁹

For patients presenting with unresectable disease, first-line treatment consists of concurrent chemoradiotherapy to the chest.⁹ Systemic therapy for LS-SCLC consists of cisplatin and etoposide.⁹ When cisplatin is replaced by carboplatin, data indicate comparable median overall survival (OS) (13.8 vs 13.7 months).¹¹

For patients with ES-SCLC, the primary treatment is chemotherapy.⁹ Similar to LS disease, etoposide is usually combined with carboplatin or cisplatin. In an RCT, atezolizumab added to carboplatin and etoposide in 403 treatment-naïve patients with ES-SCLC improved median OS from 10.3 to 12.3 months (hazard ratio [HR] for death, 0.70; 95% CI, 0.54-0.91).¹² On the basis of these data, the US Food and Drug Administration (FDA) approved atezolizumab for this indication (grade 2 on the ESMO-MCBS).⁹ Another RCT in 537 treatment-naïve patients with SCLC studied the effect of adding the programmed cell death ligand 1 antibody durvalumab to etoposide and carboplatin or cisplatin. Median OS was 13.0 months for patients receiving the durvalumab vs 10.3 months for the control group (HR for death, 0.73; 95% CI, 0.59-0.91) (grade 2 on the ESMO-MCBS).¹³ On the basis of the ESMO-MCBS, both SCLC studies^{12,13} found modest clinical efficacy with the ICIs but signified a rare practice-changing event in these patients with a dismal prognosis. Currently, several trials are investigating ICIs in different stages of SCLC as combination therapy with cisplatin-based chemotherapy or as a single agent (Table 2).

Subsequent lines of systemic therapy in patients with relapsing or progressing SCLC during first-line treatment include taxanes, temozolomide, gemcitabine, and a combination of cyclophosphamide, doxorubicin, and vincristine.⁹ The programmed cell death protein 1 (PD-1) inhibitor pembrolizumab was granted FDA approval based on results from the KEYNOTE-158 (Study of Pembrolizumab [MK-3475] in Participants With Advanced Solid Tumors). This study included 107 patients with metastatic SCLC that was progressive with standard therapy. The objective response rate (ORR) was 18%.¹⁴ Median duration of response was not reached, and more than 77% of responders had an ongoing response at 9 months. Median progression-free survival (PFS) was 2.0 months (95% CI, 1.9-2.1 months), and median OS was 9.1 months (95% CI, 5.7-14.6 months), scoring a grade of 1 on the ESMO-MCBS. The PD-1 inhibitor nivolumab is approved for patients with metastatic SCLC with progression after platinum-based chemotherapy and at least 1 other line of therapy. This approval was based on results from the CheckMate-032 (A Study of Nivolumab by Itself or Nivolumab Combined With Ipilimumab in Patients With Advanced or Metastatic Solid Tumors) trial. In this study, 109 patients received nivolumab monotherapy until disease progression. The ORR was 12%, with a median response duration of 17.9 months (range, 3.0-42.1 months).¹⁵ Median PFS was 1.4 months (95% CI, 1.3-1.6 months), and median OS was 5.6 months (95% CI, 3.1-6.8 months), also scoring a grade of 1 on the ESMO-MCBS.

Several targeted agents are undergoing clinical trials, such as lurbinectedin, an alkylating agent binding to DNA and inhibiting active transcription and inducing DNA breaks. It was granted orphan drug status by the FDA in August 2018 and by the European Medicines Agency in January 2019 based on a remarkable objective tumor response rate of 39% in 50 patients with ES-SCLC without brain metastasis who experienced tumor progression after 1 line of chemotherapy.¹⁶ The subsequent phase 2 trial confirmed a high response rate of 35% in a similar setting and resulted in a filing for full FDA approval. Median PFS was 5.3 months, and median OS was 10.8 months, scoring a grade 2 on the ESMO-MCBS.¹⁷ In an RCT,¹⁸ the poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor veli-

Table 2. Ongoing Studies in Patients With Small Cell Lung Cancer

			ClinicalTrials.gov identifier	Treatment			Primary outcome	Estimated completion date
Phase	Setting	Study		Arm A	Arm B	Arm C		
ICI								
2	First line	Pembrolizumab in Untreated Extensive SCLC (REACTION)	NCT02580994	EP and pembrolizumab	EP	NA	PFS	Aug 2020
3	First line	A Study of Pembrolizumab (MK-3475) in Combination With Etoposide/Platinum (Cisplatin or Carboplatin) for Participants With Extensive Stage Small Cell Lung Cancer (MK-3475-604/KEYNOTE-604)	NCT03066778	EP and pembrolizumab	EP	NA	PFS and OS	Oct 2021
3	First line	Durvalumab ± Tremelimumab in Combination With Platinum Based Chemotherapy in Untreated Extensive-Stage Small Cell Lung Cancer (CASPIAN)	NCT03043872	Durvalumab, tremelimumab, and EP	Durvalumab and EP	EP	OS	Sep 2021
3	Maintenance	An Investigational Immuno-therapy Study of Nivolumab, or Nivolumab in Combination With Ipilimumab, or Placebo in Patients With Extensive-Stage Disease Small Cell Lung Cancer (ED-SCLC) After Completion of Platinum-based Chemotherapy (CheckMate 451)	NCT02538666	Nivolumab	Nivolumab and ipilimumab	Placebo	OS	Oct 2018
2	Second line	Tremelimumab and Durvalumab With or Without Radiation Therapy in Patients With Relapsed Small Cell Lung Cancer	NCT02701400	Durvalumab, tremelimumab, and radiotherapy	Durvalumab and NA tremelimumab		PFS and ORR	Jan 2020
2	Second line	Pembrolizumab vs Topotecan in Patients With Small Cell Lung Cancer	NCT02963090	Pembrolizumab	Topotecan	NA	PFS	Unknown
DNA TI								
3	Second line	Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin Vs CAV or Topotecan as Treatment in Patients With Small-Cell Lung Cancer (ATLANTIS)	NCT02566993	Lurbinectedin and doxorubicin	Cyclophosphamide, doxorubicin, and vincristine	Topotecan	OS	Feb 2020
DDR inhibitors								
PARP inhibitor								
2	Maintenance	Combination Rucaparib With Nivolumab in Small Cell Lung Carcinoma	NCT03958045	Rucaparib and nivolumab	NA	NA	PFS	Jul 2024
2	Second or third line	Olaparib Monotherapy in Relapsed Small Cell Lung Cancer Patients With HR Pathway Gene Mutations Not Limited to <i>BRCA</i> 1/2 Mutations, <i>ATM</i> Deficiency or <i>MRE11A</i> Mutations (SUKSES-B)	NCT03009682	Olaparib	NA	NA	ORR	Dec 2019
2	Second or third line	Study of AZD6738 and Olaparib Combination Therapy in Relapsed Small Cell Lung Cancer Patients (SUKSES-N2)	NCT03428607	Olaparib and AZD6738	NA	NA	ORR	Jun 2020
Wee1 inhibitor								
2	Second line	A Phase II, Study to Determine the Preliminary Efficacy of Novel Combinations of Treatment in Patients With Platinum Refractory Extensive-Stage Small-Cell Lung Cancer	NCT02937818	AZD1775 and carboplatin	Durvalumab and tremelimumab	AZD6738 and olaparib	ORR	Jan 2021
2	Second line	Phase II, Single-arm Study of AZD1775 Monotherapy in Relapsed Small Cell Lung Cancer Patients	NCT02593019	AZD1775	NA	NA	ORR	Mar 2019

(continued)

Table 2. Ongoing Studies in Patients With Small Cell Lung Cancer (continued)

Phase	Setting	Study	ClinicalTrials.gov identifier	Treatment			Primary outcome	Estimated completion date
				Arm A	Arm B	Arm C		
ATR inhibitor								
1/2	Second line	Trial of Topotecan With VX-970 (M6620), an ATR Kinase Inhibitor, in Small Cell Cancers and Extrapulmonary Small Cell Cancers	NCT02487095	Topotecan and berzosertib	Topotecan	NA	CRR	May 2024
2	Second line	Randomized Trial of Topotecan With M6620, an ATR Kinase Inhibitor, in Small Cell Lung Cancers and Small Cell Cancers Outside of the Lungs	NCT03896503	Topotecan and berzosertib	Topotecan	NA	PFS	Sep 2023

Abbreviations: ATM, ataxia telangiectasia mutated; CAV, cyclophosphamide, doxorubicin, and vincristine; CRR, clinical response rate; DDR, DNA damage repair; DNA TI, DNA transcription inhibitor; ES, extensive stage; ICI, immune

checkpoint inhibitor; NA, not applicable; ORR, objective response rate; OS, overall survival; PARP, Poly(adenosine diphosphate-ribose) polymerase; PFS, progression-free survival; SCLC, small cell lung cancer.

parib had modest efficacy when added to cisplatin and etoposide in patients with ES-SCLC (HR for progression, 0.63; $P = .01$), with improvement of PFS from 5.5 to 6.1 months. This study scored a grade of 1 on the ESMO-MCBS. Table 2 lists several agents currently in clinical trials to study antitumor efficacy.

Extrapulmonary Neuroendocrine Carcinomas Cervix

On the basis of expert opinion and a review of the literature, the Gynecologic Cancer InterGroup proposed a treatment algorithm for EPNEC of the cervix.¹⁹ Radical surgery is recommended for LS disease primarily or after neoadjuvant chemotherapy comprising etoposide and cisplatin or a cyclophosphamide, doxorubicin, and vincristine regimen. Surgery should be followed by adjuvant etoposide and cisplatin. Neoadjuvant treatment is proposed when the primary tumor diameter exceeds 4 cm. For ES disease (stage IIB-IV) or nonsurgical candidates, chemoradiotherapy is advised. More recently, several case series²⁰⁻²² have described the effects of surgery, brachytherapy, and chemotherapy, underlining the necessity of systemic treatment for LS and ES disease (Table 3).

A single-center retrospective analysis was performed of 34 patients with recurrent cervical small cell carcinoma (SCC) pretreated with platinum-based chemotherapy. Second-line treatment with topotecan, paclitaxel, and bevacizumab was administered to 13 patients and compared with other, mainly platinum-based regimens. Treatment with the topotecan, paclitaxel, and bevacizumab regimen was associated with improved PFS (HR, 0.21; 95% CI, 0.09-0.54) but not OS (HR, 0.53; 95% CI, 0.23-1.22).³¹

Case reports in the recurrent setting, one with nivolumab³² and one with the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase kinase (MEK) inhibitor trametinib,³³ described ongoing complete responses at 6 and 8 months, respectively.^{32,33} The latter was administered for a K-RAS-variant tumor, which can, similarly to *BRAF* (OMIM 164757) variants, upregulate the MAPK pathway and potentially benefit from MEK inhibition.

Bladder

Those EPNECs that originate in the bladder account for 0.5% to 0.7% of all bladder cancers. Prognosis of patients with this disease is usually poor, with a median OS of 18 to 40 months for LS disease and 4.5 to 9.5 months for metastatic or recurrent disease.³⁴ Treatment

algorithms are described in the guidelines of the Canadian Association of Genitourinary Medical Oncologists (CAGMO) and the National Comprehensive Cancer Network (NCCN).^{34,35} For LS disease, they advise neoadjuvant chemotherapy followed by radical cystectomy or radiotherapy. Adjuvant chemotherapy is not recommended, except for patients who did not receive neoadjuvant treatment.³⁵ The chemotherapy regimen should contain 4 to 6 cycles of cisplatin and etoposide 64757 or cisplatin and etoposide alternated with ifosfamide and doxorubicin.³⁵ For ES disease, the CAGMO and NCCN guidelines recommend combination chemotherapy with cisplatin and etoposide.^{34,35}

Several reports^{36,37} have focused on the role of immunotherapy. A patient with progressive SCC of the bladder, heavily pretreated with platinum-based chemotherapy and multiple lines of other chemotherapeutic agents, experienced an ongoing partial response after 6 months of pembrolizumab treatment.³⁶

Gastrointestinal

The gastrointestinal tract accounts for an estimated 35% to 55% of all EPNECs.³⁸ The median OS for patients with localized disease is 38 months.³⁸ However, 85% of the patients present with metastases, and their OS is only 5 months.³⁸ In 5509 EPNECs of gastrointestinal origin in the Surveillance, Epidemiology, and End Results (SEER) database, esophageal NECs most commonly had a small cell morphologic makeup (74%), unlike gastric NECs (35%) or colorectal NECs (23%).³⁹ The European Neuroendocrine Tumor Society guideline for patients with EPNECs of the gastrointestinal tract advises platinum-based chemotherapy combined with surgery, radiotherapy, or both for local disease. In the case of advanced inoperable disease, systemic chemotherapy is recommended. The proposed first-line regimen consists of cisplatin or carboplatin combined with etoposide. Although second-line regimens have not been extensively investigated, irinotecan- (folinic acid, fluorouracil, and irinotecan) or oxaliplatin-based (folinic acid, fluorouracil, and oxaliplatin) schedules are suggested for consideration.³⁸ The ongoing phase 2 BEVANE (Assessment of the Efficacy of Bevacizumab in Combination With Folfiri as Second-line Treatment in Patients Suffering From an Advanced Inoperable Poorly Differentiated Neuroendocrine Carcinoma of an Unknown or Gastroenteropancreatic Primary Cancer) trial will show the value of the folinic acid, fluorouracil, and irinotecan

Table 3. Overview of Published Series on Extrapulmonary Neuroendocrine Carcinomas^a

Type	Setting	Intervention	No. of patients	Outcome	Results	ESMO-MCBS 1.1	Level of evidence	Authors' findings	Reference
Cervix									
Review and expert opinion	NA	NA	NA	NA	NA	No score	3	Stage I-IIA; ≤4 cm: surgery and adjuvant CT with or without RT; >4 cm: neo-CT, surgery, and adjuvant CT with or without RT; stage IIB-IV; CRT	19
Retrospective case series	Stage IA-IB1, <2 cm, no LVSI	Primary surgery	13	5-y OS	89% 5-y OS	NA	4	Primary surgery only to be considered in stage IA-IB1 disease, <2 cm and without LVSI	20
Retrospective cohort study	Stage I-IIA	Surgery and CRT	Surgery: 14; CRT: 19	OS and recurrence rate	38 mo: 57%; 153 mo: 0%	NA	4	Systemic treatment is indicated in stage I-IIA	21
Retrospective cohort study	Stage IB2-II	Primary surgery and primary RT	Primary surgery: 40; RT: 32	5-y OS and recurrence rate	Primary surgery: 43% OS and 54% recurrence rate; primary RT: 55% OS and 28% recurrence rate	NA	4	Primary RT improves outcomes compared with primary surgery for stage IB2-II	20
Retrospective cohort study	Stage IIB-VA	CRT and CRT plus brachytherapy	CRT: 59; CRT plus brachytherapy: 41	OS	CRT: 22 mo; CRT plus brachytherapy: 49 mo	NA	4	Brachytherapy improves OS for locally advanced disease	22
Esophagus									
Chinese Database (81% SCC (19% mixed))	LS (65% N+)	All patients, CRT, and surgery with or without CT	All: 176; CRT: 83; surgery with or without CT: 39	OS: all: NR; CRT: 16.8 mo; surgery with or without CT: 10.1 mo	1-y OS: all: 62 mo; CT: 70 mo; surgery with or without CT: 29 mo; 3-y OS: all: 12 mo; CT: 13 mo; surgery with or without CT: 0; 5-y OS: NR	NA	2c	CRT improves OS compared to surgically treated patients in LS disease	23
SEER Database (1973-2009) (100% SCC)	LS plus ES (81% N+)	All, surgery, and no surgery	All: 345; surgery: 19; no surgery: 326	OS: surgery: 17.0 mo; no surgery: 7.0 mo	1-y, 3-y, and 5-y OS: NR	NA	2c	Carefully selected patients could benefit from surgery, even in SCC (HR, 0.46; <i>P</i> < .01)	24
Single institution and literature review (100% SCC)	LS + R0 resection (64% N+)	All, CRT, and surgery and CT	All: 127; CRT: 73; surgery and CT: 54	OS: all: 21.0 mo; CRT: 33.0 mo; surgery and CT: 17.5 mo	1-y OS: CRT: 80 mo; surgery and CT: 67 mo; 3-y OS: CRT: 50 mo; surgery and CT: 24 mo; 5-y OS: NR	NA	2c	CRT for LS disease improves OS compared with R0 resection and CT	25
Single institution (100% SCC)	LS (52% N+)	All, CT with or without RT, surgery with or without CT and RT ^b , and surgery with or without CT and RT	All: 39; CT with or without RT: 8; surgery with or without CT and RT: 7; surgery with or without CT and RT: 24	All: 21.1 mo; CT with or without RT: >25.5 mo; surgery with or without CT and RT: 16.2 mo; surgery with or without CT and RT: 21.1	1-y OS: all: 76 mo; CT with or without RT: 87 mo; surgery with or without CT and RT: 69 mo; surgery with or without CT and RT: 74 mo; 3-y OS: all: 25 mo; other groups: NR; 5-y OS: NR	NA	4	CRT for LS disease improves OS compared to surgically treated patients	26

(continued)

Table 3. Overview of Published Series on Extrapulmonary Neuroendocrine Carcinomas^a (continued)

Type	Setting	Intervention	No. of patients	Outcome	Results	ESMO-MCBS 1.1 evidence	Authors' findings	Reference
Prostate								
NCDB (2004-2015) (100% SCC)	LS (high PSA, ^b >50%)	Radical prostatectomy or local RT	Radical prostatectomy: 26; local RT: 116	HR for OS	Radical prostatectomy: HR, 0.77 (P = .34); local RT: HR, 0.67 (P = .02)	NA	Local treatment with RT improves OS in localized setting	²⁷
NCDB (1998-2011) (100% SCC)	cT1-3N0M0 (high PSA, ^b 61%)	Radical prostatectomy or RT or no local treatment	Radical prostatectomy or RT: 154; o local treatment: 133	OS	Radical prostatectomy or RT: 1-y OS: 77 mo; 5-y OS: 37 mo; no local treatment: 1-y OS: 38 mo; 5-y OS: 3 mo (HR, 0.23; P < .01)	NA	Local therapy cannot be omitted in localized setting	²⁸
SEER (2004-2013) (60% SCC and 40% NSCC)	CT1-3N0M0 (PSA NR)	Radical prostatectomy or local RT	Radical prostatectomy: 21; local RT: 47	OS	Radical prostatectomy: median OS: NR; 1-y OS: 84%; 3-y OS: 67%; local RT: median OS: 13 mo; 1-y OS: 55%; 3-y OS: 21%	NA	Local therapy with prostatectomy improves OS compared to radiotherapy in localized setting	²⁹
NCDB (1998-2011) (100% SCC)	N1/M1 (high PSA, ^b 16%)	ADT or no ADT	ADT: 114; no ADT: 267	OS	ADT: median OS, 10.9 mo; 1-y OS: 46%; no ADT: median OS, 6.6 mo; 1-y OS, 28%	NA	Patients with presumably pure SCC often have increased PSA and might benefit from additional ADT ^b	³⁰

Abbreviations: ADT, androgen deprivation therapy; CRT, chemoradiotherapy; CT, chemotherapy; ES, extensive stage; ESMO-MCBS, European Society of Medical Oncology–Magnitude of Clinical Benefit Scale; HR, hazard ratio; LS, limited stage; LVSI, lymphovascular space involvement; N+, lymph-node positive; NA, not applicable; NCDB, National Cancer Database; NR, not reported; OS, overall survival; PSA, prostate-specific antigen; RT, radiotherapy; SCC, small cell carcinoma; SEER, Surveillance, Epidemiology, and End Results.

^a Retrospective observational studies and case reports generated from our search were only included when deemed to provide data necessary for clinical advances in treatment.

^b Method of determination (serum or plasma levels) not reported.

regimen as second-line therapy for patients with gastroenteropancreatic NECs.⁴⁰

The role of surgery or radiotherapy for local treatment of esophageal NEC is still debated. A retrospective univariate analysis²⁴ of the SEER database, including 345 patients with LS- or ES-EPNECs of the esophagus, reported that surgery improved OS (HR, 0.46; 95% CI, 0.27-0.77; $P < .01$). Because of its retrospective design, the conclusions could be biased: only 19 of the 345 patients included in their survival analysis underwent surgical resection. Patients with LS disease were assessed in several retrospective studies that included between 39 and 347 patients in which chemoradiotherapy was compared with surgery plus adjuvant chemotherapy. Median OS was longer for patients treated with chemoradiotherapy ($n = 205$; OS, 16.8-33.0 months) than for those who received surgery and adjuvant chemotherapy ($n = 308$; OS, 10.1-21.1 months).^{23,25,26} The most extensive series included 347 patients with LS-EPNECs of the esophagus. Median OS was superior in patients treated with chemoradiation ($n = 124$; median, 16.8 months; range, 11.0-38.0 months) compared with surgery with adjuvant chemotherapy ($n = 223$; median, 11.1 months; range, 7.5-12.0 months).²³ An overview of treatment outcomes in the series mentioned above is given in Table 3.²³⁻²⁶ A review⁴¹ addressed the potential benefit of peptide receptor radionuclide therapy for patients with NECs with a Ki-67 index less than 55% and positivity on somatostatin receptor imaging. The largest study⁴¹ in the retrospective review included 44 patients, of whom 41% experienced an objective response and a median PFS of 11 months (95% CI, 5.4-16.6 months). A prospective peptide receptor radionuclide therapy study can define the impact for these patients and might also reveal the precise role of fludeoxyglucose positron emission tomography and gallium-68 DOTATATE positron emission tomography in guiding the therapeutic approach.

Interestingly, the targetable BRAFV600E variant is present in 28% to 47% of colorectal NECs.^{42,43} We found 3 case reports of patients with BRAFV600E variant metastatic colorectal NECs who received the BRAF inhibitor dabrafenib after progression on cisplatin-based chemotherapy. Two patients experienced ongoing stable disease for 5 and 6 months, and 1 patient had a partial response lasting 5 months.^{43,44}

Prostate

Neuroendocrine carcinomas of the prostate comprise several subtypes, including adeno-associated NECs diagnosed after an initial prostate adenocarcinoma, newly diagnosed mixed neuroendocrine nonneuroendocrine neoplasms, and pure SCC of the prostate. Adeno-associated NECs usually arise in the setting of castration-resistant prostate cancer with neuroendocrine differentiation. However, many retrospective case series include a mixture of these histologic subtypes, making it difficult to draw strong conclusions. Generally, nonmetastatic SCC of the prostate is treated with platinum-based chemotherapy in combination with local treatment, preferably external beam radiation or brachytherapy.²⁷ Radical prostatectomy or cystoprostatectomy is usually not recommended.²⁷ Metastatic disease is treated with systemic platinum-based combination chemotherapy. Androgen deprivation therapy is a rational choice in cases of mixed histologic subtypes with an adenocarcinoma component, although its added benefit has not been verified. An analysis of the National Cancer Database included 387 patients with LS- or ES-SCC of the prostate as their first and only malignant

tumor who presented with regional or distant metastases.³⁰ Remarkably, 11% of the patients had prostate-specific antigen serum levels that exceeded 20 ng/mL (upper limit of the reference range, 4 ng/mL [to convert to micrograms per liter, multiply by 1]). Androgen deprivation therapy, administered to 30% of the patients, did not improve median OS (10.9 [95% CI, 7.5-13.5] months vs 6.4 [95% CI, 4.5-7.9] months; $P = .10$). An overview of recent reports²⁷⁻³⁰ on outcomes of patients with NECs of the prostate is given in Table 3. This overview also illustrates elevated prostate-specific antigen levels in 16% to 61% of patients.

Head, Neck, and Pancreas

There are few developments for EPNEC that originates from head and neck primary sites and the pancreas. These developments are discussed in the eAppendix in the [Supplement](#).

Carcinomas With Neuroendocrine Differentiation

Besides primary diagnosis of EPNECs, some carcinomas are diagnosed after neuroendocrine differentiation, most frequently in castration-resistant prostate carcinoma^{45,46} but also in other primary locations, such as the colorectum, breast, skin, or ovaries.⁴⁷⁻⁵⁰ In adenocarcinomas of the prostate, androgen deprivation is thought to potentiate cellular plasticity, leading to neuroendocrine prostate cancer.⁵¹ An analysis⁵² of the genomic profiles of 114 tumor specimens taken from 81 individuals primarily diagnosed with prostate adenocarcinomas who later developed castration-resistant NEC found that the overall spectrum of genomic alterations was mostly similar. However, differences were also found. The most frequently deleted gene in neuroendocrine prostate cancers and not in adenocarcinomas was *CYLD* (OMIM 605018), which encodes for an enzyme involved in the downregulation of transforming growth factor β and the Notch signaling pathway.⁵² The mechanistic target of the rapamycin pathway is also overactivated in neuroendocrine-differentiated prostate cancer.⁵³ Notably, these pathways had substantial overlap with the pathways involved in tumorigenesis of primary EPNECs.⁶⁻⁸

Colorectal tumors can also contain mixed histologic subtypes (mixed neuroendocrine nonneuroendocrine neoplasms).⁵⁰ In sporadic colorectal cancer, neuroendocrine cells have been identified in 8% to 77.5% of cases, mainly depending on the method used to assess the neuroendocrine cell population.⁵⁰ Similar to castration-resistant neuroendocrine prostate cancers and their preceding adenocarcinomas, there is a significant overlap in the genomic alterations of the colorectal adenocomponent and neuroendocrine component.⁵⁰ Moreover, the mechanistic target of the rapamycin pathway in colorectal cancer seems to play the same pivotal role in neuroendocrine differentiation.⁵⁰ Of 178 high-grade serous ovarian cancers, 12 (6.7%) expressed synaptophysin and 36 (20.2%) expressed chromogranin A.⁴⁹ In 1232 consecutive patients with invasive breast cancer, synaptophysin and chromogranin A were expressed in 10.4% of the tumors.⁵⁴ Thus, a partial or complete evolution toward a neuroendocrine histologic subtype is observed across multiple tumor types.

A principal component analysis performed with RNA sequencing data of various epithelial malignant tumors registered in The Cancer Genome Atlas database found tumor differentiation in time

Figure 1. Proportion of Patients Developing Brain Metastases for Extrapulmonary Neuroendocrine Carcinomas From Different Primary Organs

The dark blue line indicates the proportion of patients developing brain metastases in limited-stage (LS) small cell lung cancer without prophylactic cranial irradiation, with a 95% CI based on 2 large cohorts. Each circle represents an incidence rate reported in a series, with larger circles representing larger series. The smallest circles represent series with fewer than 10 patients. Circles increase in size for every 10 additional included patients up to the largest circle, representing more than 100 patients. ES indicates extensive stage.

toward a small cell profile.⁵ The convergent small cell phenotype was widespread across the various epithelial cancers. In addition, drug sensitivity and gene dependency screens found a common vulnerability profile among the multiple small cell tumors that resembled that of hematologic malignant tumors. Consequently, the authors concluded that future treatment studies involving these neuroendocrine transdifferentiated malignant tumors could be guided by this vulnerability profile and go beyond tissue-specific targeted therapies.⁵

Prophylactic Cranial Irradiation

Prophylactic cranial irradiation (PCI) in SCLC is currently recommended in patients with LS-SCLC with complete or partial tumor response to initial treatment. A meta-analysis⁵⁵ of 7 prospective trials investigating PCI in patients with LS-SCLC found that PCI reduced the incidence of brain metastases from 59% to 33% (HR, 0.48; 95% CI, 0.38-0.60) and improved OS (HR, 0.85; 95% CI, 0.73-0.99). The role of PCI in ES is less well established.⁹

Although survival is similar for EPSCC and SCLC, the incidence of symptomatic brain metastases is considerably lower in EPSCC (Figure 1).^{21,23,25,26} Therefore, PCI is not recommended in EPSCC. Figure 1 shows incidences of brain metastases per primary EPSCC tumor location. Most studies reported incidences of brain metastases of approximately 10%. One study⁵⁶ of patients with EPNECs originating in the head and neck region reported an incidence of 41%, but 9 of the 23 patients did not receive chemotherapy, which is usually included in therapy regimens for EPNEC. This high incidence rate was not confirmed in subsequent studies (Figure 1).

Future Directions and Potential Targets of NECs

Activated molecular pathways that appear to underlie the development of EPNECs have recently been identified, and at least 3 of these are potentially targetable. First, the MAPK pathway is activated in cervical,⁵⁷ gastric,⁵⁸ pancreatic,⁶ and colorectal EPNECs.⁴² Sec-

ond, the phosphatidylinositol-4,5-bisphosphate 3-kinase pathway is regarded as an essential overtly active pathway in EPNECs regardless of primary tumor location.⁷ Everolimus, an inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase pathway, is currently under investigation in combination with cisplatin for treating EPNECs irrespective of the organ of origin.⁵⁹ Third, the Notch-signaling pathway is essential in SCLC,⁶⁰ and increased activity in EPNECs originating in the cervix⁵⁷ and in neuroendocrine differentiation has been reported.⁸

These 3 pathways result in a wide variety of overtly transcribed genes that drive cell proliferation, DNA synthesis, and cell cycle progression (Figure 2). During cell cycle progression, 2 other essential processes can potentially guide therapeutic strategies. First, DNA repair mechanisms, through homologous recombination or the mismatch repair system, are sometimes deficient in SCLC and EPNECs.⁶¹ Loss of homologous recombination (eg, due to *BRCA* mutations or *ATM* loss) provides a rationale to test treatment with PARP inhibitors, which is currently being investigated in several phase 2 trials (Table 1). Loss of mismatch repair in turn leads to an increased tumor mutational burden (TMB), resulting in neoantigens and T-cell infiltration in the tumor.⁶² Therefore, mismatch repair deficiency provides a rationale for treatment with ICIs, illustrated by its predictive value for ICI treatment response.⁶³ Data on the efficacy of ICIs in EPNECs still indicate conflicting results, with response rates varying from 5% to 44% in 3 phase 2 basket trials enrolling 22, 30, and 18 patients, respectively.⁶⁴⁻⁶⁶ The FDA approved pembrolizumab for patients with a high TMB status (defined as ≥ 10 mutations per megabase) based on a phase 2 trial in 790 patients with advanced solid tumors who received pembrolizumab.⁶⁷ The ORR in the high-TMB cohort ($n = 102$) was 29% vs 6% in the low-TMB cohort.⁶⁷ The 34 participating patients with high-TMB SCLC had an ORR of 29%. No patients with EPNECs were included.⁶⁷ Furthermore, few patients with EPNEC may be eligible for pembrolizumab based on TMB status because an analysis from The Cancer Genome Atlas⁶⁸ of 100 000 human cancer genomes reports a high TMB in only 1.7% to 8.5% of EPNECs, depending on primary tumor location. Prospective trials assessing efficacy of ICIs in EPNECs are currently ongoing.^{69,70} Added effect is pursued by promoting an immune-permissive microenvironment with cabozantinib—a

Figure 2. Molecular Pathways Affected in Extrapulmonary Neuroendocrine Cancer Cells

A, Important pathways involved in the tumorigenesis of neuroendocrine carcinomas, including the mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA) pathway, and the Notch pathway. Potential targeted therapies directed against these activated oncogenic pathways are indicated with red dotted lines. B, Properties of neuroendocrine carcinomas frequently described in the literature are reported, including a deficiency of mismatch repair (MMR) proteins, a loss of homologous recombination (HR), and overexpressed driver kinases driving the cell cycle through the G₂ checkpoint (Wee1 and Aurora A). Potential drugs exploiting

these properties are connected with red dotted lines. The tumor cell membranes are shown in blue and the tumor nucleus in gray. AKT indicates protein kinase B; ATM, ataxia telangiectasia mutated; DLL3, delta-like ligand 3; ERK, extracellular signal-regulated kinases; ICIs, immune checkpoint inhibitors; MEK, MAPK/ERK kinase; mTOR, mammalian target of rapamycin; NICD, Notch intracellular domain; PARP, poly(adenosine diphosphate-ribose) polymerase; PCNA, proliferating cell nuclear antigen; PTEN, phosphatase and tensin homologue; RB1, retinoblastoma 1; and TCR, T-cell receptor.

multipotent tyrosine kinase inhibitor.⁷¹ A phase 2 trial in patients with metastatic EPNECs is investigating cabozantinib combined with ipilimumab and nivolumab.⁷²

Another strategy relates to kinases that drive the cell cycle beyond the G₂ checkpoint and into mitosis (Figure 2). Essential driver kinases for this checkpoint are Aurora A and Wee1, both of which are

implicated as essential drivers of SCLC and EPNECs.^{73,74} This mechanism is currently being targeted with Wee1 inhibitors and Aurora A kinase inhibitors in phase 2 studies in SCLC (Table 1). The Aurora A kinase inhibitor alisertib has been tested in a phase 2 trial in 60 patients with heavily pretreated ES-EPNECs of the prostate with promising results.⁷⁵

Furthermore, small cell EPNECs are characterized by *TP53* (OMIM 191170) and *RB1* (OMIM 180200) gene inactivation, whereas the genomic profiles of large cell EPNECs are more heterogeneous and often resemble non-NECs of the same location.⁷⁶ This finding may be of therapeutic importance because *TP53* and *RB1* loss induce DNA replication stress, which may be responsible for the higher response rates to platinum-based regimens in small cell EPNECs compared with large cell EPNECs.⁷⁷

Conclusions

Until recently, the only systemic treatment option for SCLC and EPNECs was platinum-based chemotherapy. The introduction of ICIs, although moderately effective, signifies the first new option in sys-

temic treatment of SCLC in decades. The EPNECs originating from different epithelial cancers through neuroendocrine differentiation or with different organ primary tumors have many similarities in tumor biology and tumor genesis. We therefore recommend including EPNECs in clinical trials independent of the primary tumor site. This pooling of EPNECs regardless of primary tumor site has helped demonstrate the efficacy of ICIs, and anecdotal evidence already points to the efficacy of other potential treatment modalities regardless of site of origin (eg, *BRAF* and *MEK* inhibitors). To further optimize the treatment approach beyond tissue-specific targeted therapies, we suggest developing dedicated expertise in conjunction with the neuroendocrine tumor board on EPNECs and have these experts participate as requested on other tumor site-specific boards, which will require patient referral to a center with EPNEC expertise.

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