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High-Grade Neuroendocrine Colorectal Carcinomas: A Retrospective Study of 100 Patients

Bruno Conte, MD[1], **Ben George, MD, Phd**[2], **Michael Overman, MD**[1], **Jeannelyn Estrella, MD**[3], **Zhi-Qin Jiang, MD, Phd**[1], **Amir Mehrvarz Sarshekeh, MD**[1], **Renata Ferrarotto, MD**[4], **Paulo M. Hoff, MD**[5], **Asif Rashid, MD**[3], **James C. Yao, MD**[1], **Scott Kopetz, MD, Phd**[1], and **Arvind Dasari, MD, MS**[1]

[1]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Street, Houston, TX 77030

[2]Division of Hematology and Oncology, Medical College of Wisconsin, 9200 West Wisconsin Avenue Milwaukee, WI 53226

[3]Department of Pathology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Street, Houston, TX 77030

[4]Department of Thoracic/Head and Neck Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Street, Houston, TX 77030

[5]Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, Av. Dr. Arnaldo, 251 - Cerqueira César, Sao Paulo, Brazil

Abstract

Background—Colorectal high-grade neuroendocrine carcinomas (HGNEC) are a rare but aggressive group of malignancies without standard management recommendations.

Methods—We retrospectively reviewed the records of 100 consecutive patients with histologically confirmed colorectal HGNEC diagnosed at MD Anderson Cancer Center between 1991 and 2013.

Results—In our cohort, most tumors (89 %) were small cell carcinoma, and most (60 %) involved the sigmoid or the anorectal regions. Sixty-four patients (64 %) presented with metastatic disease at diagnosis. Striking epidemiological and clinical differences between those established in small cell lung cancer (SCLC) and our cohort were noted, including significantly lower rates of smoking and lower risk of bone, brain metastases. Over 30% of the tumors were found associated with an adenoma. Median overall survival (OS) of the cohort was 14.7 months, with 2-year and 5-

Corresponding author at all stages: Arvind Dasari, M.D., M.S., Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Street, Unit 426, Houston, TX 77030. Phone: 713-792-2828; Fax: 713-563-0541; ; Email: adasari@mdanderson.org

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year OS rates of 23 % and 8 %, respectively. In patients with localized disease, multimodality therapy was associated with a trend toward improved median OS (20.4 versus 15.4 months, $p = 0.08$). Metastases at presentation (OS 20.63 vs 8.7 months; localized vs metastatic disease at presentation, $p < 0.001$) and elevated LDH were strongly associated with a worse outcome.

Conclusion—In comparison to SCLC, less than half patients with colorectal HGNEC have history of smoking; metastatic patterns are also different between the two cancers. Nevertheless, HGNEC also has a aggressive biology with the rectum being the most common site of origin. For localized disease, multimodality approach seems to be associated with better outcomes, while systemic chemotherapy is the mainstay of treatment for advanced disease.

Keywords

small cell carcinoma; colon; rectum; smoking; metastasis; survival

Introduction

Gastrointestinal neuroendocrine malignancies are classified using guidelines of the World Health Organization or the European Neuroendocrine Tumor Society, both of which are based on mitotic rate and/or Ki-67 labeling index attempting to discern rate of cell proliferation. Well-differentiated neuroendocrine tumors, with <20 mitoses/10 high power fields and/or Ki-67 index <20 %, are further sub classified into low grade (<2 mitoses/10 high power fields and/or Ki-67 <3 %) or intermediate grade (2-20 mitoses/10 high power fields and/or Ki-67 3-20 %). Neuroendocrine malignancies with Ki-67 and/or mitotic index values over these limits are classified as poorly differentiated or high-grade neuroendocrine carcinomas, HGNEC [1]. Although both groups of malignancies stain for neuroendocrine markers such as chromogranin, synaptophysin neuroendocrine tumors and neuroendocrine carcinomas have widely different treatment approaches that reflect their disparate clinical behaviors [2]. Colorectal HGNEC was first described by Clery et al. in 1962, but published data have been limited to small retrospective series [3-6]. Because of this rarity, along with their histologic heterogeneity and background of multiple nomenclature definitions, it is difficult to precisely define the incidence of this entity. A recent Survival, Epidemiology and End Results database review of colorectal HGNEC suggested the age-standardized incidence of colorectal NEC to be around 2 per million person-years. Colorectal HGNEC are thought to be phenotypically related to high-grade lung cancers and are similarly divided into two groups, small and large cell carcinomas. Treatment recommendations for colorectal HGNEC are largely based on retrospective studies for both localized and advanced disease and mostly are extrapolation from the more usual counterparts, HGNEC of the lung and colorectal adenocarcinoma [2, 7, 8]. Therefore, gastrointestinal HGNEC with Ki-67 >20 % are typically treated with surgery and/or chemoradiation when localized and with palliative platinum-based cytotoxic chemotherapy when metastatic. However, recent data suggest that only HGNEC with Ki-67 >55 % may benefit from such aggressive regimens [9, 10]. Given this paucity of information regarding clinicopathologic features as well as treatment recommendations for colorectal HGNEC, we conducted a retrospective study of 100 cases of histologically confirmed colorectal HGNEC from the records of The University of Texas MD Anderson Cancer Center.

Patients and Methods

Medical records of 100 consecutive patients with colorectal HGNEC diagnosed between 1991 and 2013 were collected from the MD Anderson Cancer Center archives and analyzed for clinicopathological features and treatment outcomes under a protocol approved by the Institutional Review Board of MD Anderson Cancer Center. Patients' electronic medical records were reviewed for age, sex, ethnicity, stage, performance status, staging workup, pathology including immunohistochemistry, site of the primary tumor, smoking habits, clinical presentation, family history, treatment details, and clinical outcome. Pathologic diagnoses were reviewed and confirmed in the Department of Pathology at MD Anderson in all cases. Performance status was assessed according to the Eastern Cooperative Oncology Group (ECOG) score.

Response to chemotherapy was based on data from medical records and defined by radiographic shrinkage on cross-sectional imaging.

The primary objective of the study was to estimate overall survival. Survival analysis was based on overall survival defined as the time interval between date of diagnosis and date of last follow-up or death. Progression-free survival, defined as the interval between date of completion of definitive treatment and the date of confirmation of relapse or progression, was calculated for all patients with localized disease who underwent local therapies with curative intent. Endoscopic or transanal excision was not considered definitive treatment. Survival was estimated by the Kaplan-Meier method; 2-year and 5-year survivals were reported as proportions. Multivariate Cox regression was performed to assess the influence of covariates on overall survival [11]. Statistical significance was defined as $p < 0.05$. Analyses were conducted using SPSS version 17.0 (SPSS, Chicago, IL) and GraphPad Prism 6 (GraphPad Software, La Jolla, CA).

Results

Patient Characteristics

The clinical characteristics at presentation of this cohort are outlined in Table 1. The median age at diagnosis was 55 years (range 33–88). Of the 100 patients, 51 were male, and the most common primary tumor locations were rectum (40 %), cecum (17 %), ascending colon (14 %), and rectosigmoid (8 %). Of the 36 patients with localized disease, 26 (72 %) had distal primary sites involving the sigmoid colon or the anorectal regions. Metastatic disease was noted in 64 patients at diagnosis, with the liver being the most common organ of metastases (92 %) and as an isolated site in 58 % of the cases. Distant lymph nodes (33 %) and peritoneum (14 %) were the other two most common sites of disease spread at initial presentation.

Small cell carcinoma was the most prevalent histology and was observed in 89 % of the cases, followed by large cell neuroendocrine carcinoma in 8 %. Mixed histology was described in three cases. In addition, adenocarcinoma features such as mucinous deposits, glandular formation, and signet-ring cells were reported in seven cases, but in all cases the high-grade neuroendocrine component was considered more relevant. HGNEC was

associated with a polyp history in 44 patients, and in 30 (68 %) of these cases, the tumor formation was intimately related with an adenomatous polyp, most commonly a tubulovillous adenoma (70 %), and in one case with an adenocarcinoma in situ and in another case with a moderately differentiated adenocarcinoma in the head of a polyp serrated-adenoma. Synaptophysin, chromogranin, and neuron-specific enolase were positive in 93 %, 58 %, and 87 %, respectively, of the evaluable patients. Thyroid transcription factor-1 results were positive in 3 (19 %) of 16 evaluable patients.

A history of tobacco smoking was described in 54 % of the cases. In the 94 patients evaluable for a family history of malignancy, 85 % had at least one first- or second-degree relative with a history of cancer, with 58.5 % having a history of malignancy in a first-degree relative. Second malignancies were reported for 12 patients, including of interest one with a concomitant low-grade neuroendocrine tumor of the rectum. Information regarding presenting symptoms was available for 97 patients, with the most common symptoms being abdominal pain (52 %), blood in stool (51 %), and change in bowel habits (29 %). Constitutional symptoms such as weight loss and fatigue were less frequently reported (11 % and 10 %, respectively). Less common symptoms (≤5 %) included nausea, vomiting, obstruction, hematemesis, hypercalcemia, fever, and anorexia.

Treatment

Therapy was analyzed based on disease status as evidenced by radiologic assessment, and details are outlined in Tables 2A (localized) and 2B (metastatic).

Of the 36 patients with localized disease, treatment details were available for 35 patients and surgery was performed in 30 of these (83 %). Thirteen received at least one modality of neoadjuvant therapy: concomitant chemoradiotherapy in six patients; induction chemotherapy followed by concomitant chemoradiation in four patients; chemotherapy alone in two patients, and radiation alone in one patient. Adjuvant treatment was given to 17 patients (57 %): chemotherapy in 15 patients and concomitant chemoradiation in the other two. There was a strong trend towards improved overall survival for those who received any type of perioperative treatment compared with those who did not (median overall survival of 20.4 vs 15.4 months, $p = 0.08$). Of the 5 patients who did not undergo surgery, reasons included concomitant co-morbidities (2), patient preference (2) and loss to follow up (1) with a median OS of 17.4 months.

Seventy-eight patients received first-line palliative chemotherapy, including those previously with localized disease treated with surgery alone. The most common regimens were platinum based in 69 patients, combining cisplatin or carboplatin with either etoposide (34 patients) or irinotecan (35 patients) with a median of four cycles (range 2-14). Response information was available for 61 of the 69 patients, with partial and complete response rates being 32.7 % and 9.8 %, respectively (objective response rate 42.5 %), while another 28 % had stable disease. There were no significant differences in response rates (40.4% vs 43.8%, p = 0.48) or median number of cycles (4 in both) between etoposide and irinotecan based therapies. 8 patients were treated with non-platinum based therapies including fluoropyridine alone (capecitabine in 2 patients or infusional 5-FU, in 1 patient) in combination with oxaliplatin i.e. FOLFOX (2 patients), irinotecan i.e. FOLFIRI (1 patient),

paclitaxel (1) or topotecan (1). Second-line chemotherapy was administered to 39 patients, of whom 22 continued to receive platinum-based regimens. Response rates were much lower in second-line therapy, with no complete responses and a rate of 14.8 % for partial responses within all evaluable patients.

Clinical Outcome and Prognosis

At a median follow-up of 12.5 months (range 1–155 months), the median overall survival was 14.7 months and the 2-year survival and 5-year survival rates were 23 % and 8 %, respectively. Of the 35 patients who received local treatment, 18 were evaluable for patterns of relapse. Local failure was observed in two patients and distant recurrence in 13, with most (69 %) distant failures in the liver. In the full cohort, stage, age, and pre-treatment LDH levels were associated with survival on both univariate and multivariate analyses (Tables 3A and 3B), with a median overall survival of 14.7 months (95 % CI 10.2–19.19 months).

Discussion

In contrast to colorectal adenocarcinoma, HGNEC are exceedingly rare and thus large prospective trials are not feasible. Treatment recommendations are based on retrospective analyses of data from single institutions and national registries. Consensus guidelines for management of colorectal HGNEC are mainly extrapolated from those for small cell lung cancer (SCLC) [2]. Table 4 summarizes results of prior studies of colorectal HGNEC.

In line with prior studies, as detailed in Table 4, small cell histology was the predominant phenotype in our study as well. For unclear reasons, however, we noted a very small proportion of large cell HGNEC. Our report also encountered some important epidemiological and clinical differences between colorectal HGNEC and SCLC. First, it has been well established that smoking is associated with virtually all cases of SCLC, but we encountered this association in only 54 % of our cases, suggestive of fundamental differences in the pathogenesis of these apparently histologically similar tumors. Prior work has shown that cancers with pathogenesis driven by carcinogens such as those in cigarette smoke have a very high mutation rate and that the patterns of these mutations correlate with the nature of the carcinogen [12, 13]. Future studies should attempt to evaluate these potentially fundamental differences in the biology of SCLC and extrapulmonary HGNEC. Second, bone and brain metastases were very rare in our cohort (only 4 % and 2 %, respectively). This is in line with prior studies that have also shown lower rates of brain metastases with extrapulmonary HGNEC compared with SCLC [14, 15]. Therefore, MRI of the brain and bone scan may be dispensable at diagnosis for colorectal HGNEC in the absence of corresponding symptoms or signs, and prophylactic intracranial brain irradiation should not be routinely performed [16]. Furthermore, this may also suggest important differences in molecular drivers of metastatic spread between pulmonary and extrapulmonary HGNEC. Future studies should aim to delineate these potential molecular differences between SCLC and extrapulmonary HGNEC.

In our cohort, the majority of patients with localized disease underwent surgical resection and within this cohort, patients with perioperative treatment with a multimodality approach seemed to have a trend towards improved survival over those treated with surgery alone

(20.8 vs 15.8 months, $p = 0.08$). The majority of the patients in our cohort with localized disease had a distal primary tumor, including those whose tumors involved the rectum or the anorectal regions where surgery via an abdominoperineal approach may be associated with increased morbidity, including the need for a permanent colostomy. Emerging evidence suggests that these patients with localized distal primaries may be treated with definitive chemoradiation without subsequent surgery and that this approach may not affect mortality. A recent series of 10 patients with anorectal HGNEC who were treated with pelvic chemoradiation (cumulative median dose of 50 Gy) suggested that seven of these patients had lifelong locoregional control; all seven patients with progressive disease had distant progression. Two patients in this cohort underwent surgery revealing only microscopic foci of residual tumor. Although limited, these findings suggest that long-term control of locoregional disease is feasible with chemoradiation without surgery and that distant relapse is the main cause of mortality in these patients [17]. This is supported by our study and others suggesting that distant failure is much more common than locoregional failure in patients with localized HGNEC at diagnosis. For instance, Brennan et al. reported outcomes for 120 patients with extrapulmonary HGNEC of various sites, including 84 patients with localized disease treated with a combination of chemotherapy, radiation, and/or surgery. Of these, only approximately 10 % developed only locoregional recurrence. Future studies should evaluate the need for surgery after definitive chemoradiation therapy in patients with locoregional HGNEC of the anorectal regions [18].

As observed in prior studies, about two thirds of the patients in our series presented with metastatic disease at diagnosis, with liver being the most common site of spread. Most treatment guidelines for extrapulmonary HGNEC are currently extrapolated from those for SCLC, suggesting platinum-based chemotherapy as the treatment of choice in these patients. The response rate in our series was 42 %, with a median overall survival of 8.7 months (95 % CI 6.96–10.43 months). This is in line with other extrapulmonary neuroendocrine carcinoma series as detailed in Table 4 [14]. However, clinical trials with SCLC have suggested higher response rates with platinum-based therapy, with rates up to 67 % in a meta-analysis [19]. A retrospective study of 136 patients with extrapulmonary HGNEC ($n = 41$) and SCLC ($n = 95$) treated with platinum-based regimens suggested that the response rates (30.8 % vs 77.8 %) and median survival time (9.2 vs 13.6 months) were worse in the extrapulmonary HGNEC cohort [20].This could suggest either fundamental differences in the underlying biology of these two groups and/or that treatments for SCLC may not be optimal for extrapulmonary HGNEC. Contrary to findings for lung SCLC, it has been shown that up to 40 % of extrapulmonary HGNEC contain elements of non-neuroendocrine histology that may not be sensitive to SCLC regimens, thus explaining the lower response rates [21]. Intriguingly, in our cohort, 30% of the tumors were found to be associated with an adenoma raising the possibility of a common carcinogenic pathway to both adenocarcinomas and HGNEC in colon. A randomized, phase II study (EA2142) is being planned through the Eastern Cooperative Oncology Group that will randomly assign patients with advanced gastrointestinal high-grade non-small cell neuroendocrine cancers to receive capecitabine + temozolomide (a regimen commonly used in pancreatic neuroendocrine tumors) and cisplatinum + etoposide in the first-line setting. This study may help determine the optimal chemotherapy regimen for these patients.

In our study, median overall survival for the entire cohort was poor at 14.7 months (95 % CI 10.2–19.19 months). Significant covariates upon univariate and multivariate analyses included stage, age, and pretreatment LDH. There was a strong trend towards worse outcomes associated with male sex due to unclear reasons, as also noted in prior studies [22]. Other studies have suggested that higher white cell count, poor performance status, and weight loss prior to diagnosis are associated with survival, but these data were not available for our cohort. However, each fold rise in LDH (which could potentially serve as a surrogate marker for overall disease status) was found to be associated with a 12 % (95 % C.I 8–18 %) increased risk of mortality.

As with any retrospective analysis, our study has several limitations: 1) its retrospective design in a single institution; 2) lack of vital information such as performance status and proliferative indices such as Ki-67 on most patients (the latter since diagnosis was based mostly on morphological appearance and since a significant proportion of patients were treated prior to Ki-67 reporting being a standard practice); This may have led to overlooking patients with high grade neuroendocrine tumors without poorly differentiated morphology. However, recent studies have suggested that this unique entity seems to be limited mostly to neuroendocrine malignancies of the pancreas[29,30]. 3) a smaller number of patients with large cell NEC compared with prior studies; and 4) a lack of information regarding the decision for surgery in patients with localized disease that may have led to a selection bias. These limitations are unfortunately to be expected given the rare nature of this disease and the lack of large, robust databases. Future efforts should concentrate on building a national database and/or network of physicians and institutions treating these patients in line with the recent efforts by investigators of the NORDIC NEC study [10].

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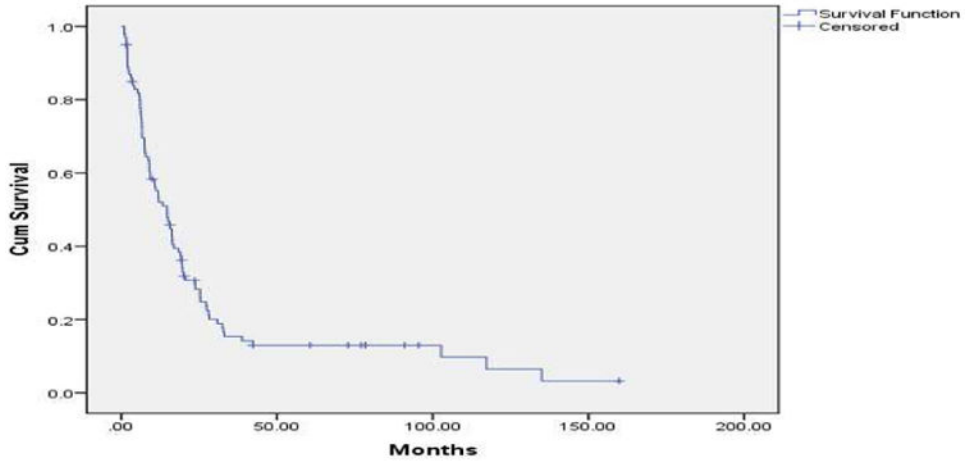
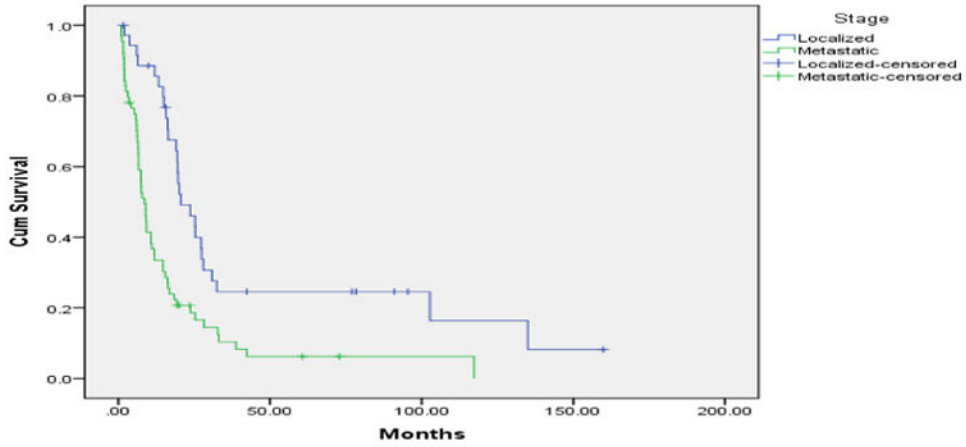


Median OS = 14.70 mos
95% CI = 10.20 – 19.19



Median Overall Survival according to stage (95% CI):
Non-metastatic: 20.63 mos (12.86 – 28.39)
Metastatic: 8.70 (6.96 – 10.43)

Figure 1.
A: Overall Survival of cohort
B: Overall Survival according to stage

Table 1

Patient characteristics

Characteristic	N (%)
Sex	
Male	51
Female	49
Age (years)	
Median	55
Range	33-88
ECOG Performance Status (n = 39)	
0-1	30 (77 %)
≥2	9 (23 %)
Prior smoking	
Yes	54
No	46
Predisposing factors	
Ulcerative colitis	2
Adenomatous polyps	44
Family history (n = 94)	
First degree	55 (58)
First and second degree	80 (85)
Presenting symptoms	
Abdominal pain	52
Hematochezia/melena	51
Altered bowel movements	29
Fatigue	10
Weight Loss	11
Histology	
Small cell	89
Large cell	8
Mixed	3
Immunohistochemistry	
Synaptophysin	93
Chromogranin	58
Neuron-specific enolase	87
Location of primary tumor	
Anus	5

Characteristic	N (%)
Rectum	40
Rectosigmoid	8
Sigmoid	7
Cecum	17
Ascending colon	14
Transverse colon	8
Descending colon	1
Stage at presentation	
Localized/locally advanced	36
Metastatic	64
Sites of metastases (n = 59)	
Liver	59 (92)
Liver only	36 (57)
Lymph nodes	21 (33)
Peritoneum	7 (14)
Lung	6 (12)
Bone	4 (6)
Brain	2 (3)

Table 2

A Treatment and outcomes (localized disease)

	n = 35	Overall Survival
Non-surgical therapy (4 with chemoradiation and 1 with chemotherapy alone)	5	17.4 months
Surgery	10	15.4 months*
Surgery + perioperative therapy	20	20.4 months*
Neoadjuvant therapy	13	
Adjuvant therapy	17	
Both	4	

*p = 0.08

B Treatment and outcomes (metastatic disease)			
First-line palliative chemotherapy	n = 78	%	
Platinum-based chemotherapy	69	88 %	ORR = 42 % PR = 32 % CR = 10 %
Cisplatin/etoposide	34	31 %	
Cisplatin/irinotecan	35	32 %	
Non-platinum–based chemotherapy	8		
Second-line chemotherapy	n = 39	%	ORR = 15 % PR = 15 %
Platinum-based chemotherapy	16	56 %	
Non-platinum–based chemotherapy	13	44 %	

Table 3

A Univariate Cox regression analysis of overall survival

	Hazard ratio	95 % Confidence Interval	p
Sex (Male vs Female)	1.68	0.99–2.85	0.051
Stage (Metastatic vs Locally advanced)	2.58	1.50–4.43	0.001
Primary tumor (Proximal vs Distal)	0.82	0.49–1.37	0.457
Age (10 year intervals)	1.3	1.04–1.64	0.021
LDH (x ULN)	1.129	1.08–1.18	<0.001

B Multivariate Cox regression analysis of overall survival			
	Hazard ratio	**95 % Confidence Interval**	**p**
Stage	2.884	1.78–4.89	<0.001
Age	1.43	1.17–1.75	<0.001
LDH	1.11	1.07–1.16	<0.001

Table 4

Major retrospective studies of colorectal HGNEC

Reference (year)	Study description	Histology (small cell vs large cell vs others[a])	Stage IV At diagnosis	Response rate to first-line therapy (stage IV)	Median survival (95 % CI)		Survival rates		
					All stages	Stage IV	2-yr	3-yr	5-yr
Smith et al. (2014) [6]	Single-institution cohort of 126 colorectal HGNEC pts at Memorial Sloan Kettering	49 % vs 18 % vs 14 %	67 %	57 %	13.2	10	NR	8.7 %	NR
Shafqat et al. (2015) [28]	SEER analysis of 1367 colorectal HGNEC pts	27 % vs 8 % vs 66 %	57.9 %	NR	7.1 (7.0– 8.0)	4 (3.1–5.1)	NR	NR	16.3 %
Sorbye et al. (2013) [10]	Analysis of 305 pts with advanced GI HGNEC from 12 Nordic hospitals including 92 pts with colorectal HGNEC	43 % vs 57 % (non-small cell)	NR	31 %	NR	Colon: 8 (6–9.9) Rectum: 10 (7.9–12.1)	14 % (all sites)	NR	NR
Machida et al. (2012); Yamaguchi et al (2012, 2014) [24-26]	294 pts with advanced GI HGNEC from 23 Japanese hospitals including 31 with colorectal HGNEC	NR	NR	50 % (irinotecan + platin) vs 28 % (etoposide + platin)	NR	7.6	NR	NR	NR
Kang et al. (2007) [27]	SEER analysis of rare colorectal tumors including 455 cases of HGNEC	NR	62 %	NR	NR	NR	NR	NR	21.4 %
Bernick et al. (2004) [5]	Single institution retrospective study of 38 patients with colorectal HGNEC at Memorial Sloan Kettering	58 % vs 62 %	66 %	NR	10.4 (6.7 -18.9)	NR	26 %	13 %	NR
Korse et al. (2013) [23]	Netherlands Cancer Registry based-study including 265 pts with colorectal HGNEC. Outcomes were reported according to period of diagnosis and histology[b]	73 % vs 27 %	64 %	NR	NR	NR	NR	NR	22 % vs 9 %

[a]Others include mixed histology and NEC-NOS (neuroendocrine carcinoma-not otherwise specified)

[b]Periods of diagnosis: 1990-2000 and 2001-2010; histology: large cell HGNEC and small cell HGNEC

NR: Not reported