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The efficacy of chemotherapy and operation in patients with colorectal neuroendocrine carcinoma

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ABSTRACT

Background: Colorectal neuroendocrine carcinoma (CRNEC) is a rare type of malignancy and is quite aggressive with dismal prognosis. Neither large-scale retrospective studies nor prospective studies have been performed to evaluate the prognostic value of adjuvant chemotherapy in patients with CRNEC.

Methods: Using the Surveillance, Epidemiology, and End Results-Medicare database, 318 elderly patients who were diagnosed with high-grade colorectal neuroendocrine tumors were included. The survival benefit was evaluated using a Cox proportional hazards model and propensity score-matched techniques.

Results: Among patients with stage I-III CRNEC, there was also no significant difference in cancer-specific survival (CSS) ($P = 0.898$) or overall survival (OS) ($P = 0.539$) between the 5-fluorouracil (5-FU) and the no chemotherapy groups. Meanwhile, the etoposide + platinum (EP) regimen showed no improved survival in patients with stage I-III CRNEC compared with the no chemotherapy group. For stage IV CRNEC, there was no significant difference between operation group and no operation group in CSS ($P = 0.317$) or OS ($P = 0.385$). Both 5-FU and EP regimens improved the CSS (for 5-FU, hazard ratio [HR] = 0.257, 95% confidence interval [CI] = 0.134-0.491, $P < 0.001$; for EP, HR = 0.348, 95% CI = 0.192-0.631, $P = 0.001$) and OS (for 5-FU, HR = 0.274, 95% CI = 0.149-0.502, $P < 0.001$; for EP, HR = 0.345, 95% CI = 0.194-0.612, $P < 0.001$) of patients in stage IV CRNEC.

Conclusions: Our findings demonstrated that neither the 5-FU based nor EP chemotherapy regimens improved the CSS or OS for patients with stage I-III CRNEC. And for stage IV CRNEC, chemotherapy is an independent prognostic factor for CSS and OS, while operation could not improve the CSS or OS for patients with stage IV CRNEC.

Introduction

Neuroendocrine neoplasms of the colon and rectum are neoplasms originating from the diffuse neuroendocrine system in the midgut or hindgut.[1] According to the current World Health Organization 2010 Classification, neuroendocrine neoplasms are classified histologically into three categories: well-differentiated, low grade (G1); well-differentiated,

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Table 1 – The baseline characteristics of CRNEC patients.

Characteristics	Number of patients	Proportion (%)
Gender		
Male	131	41.2
Female	187	58.8
Age at diagnosis (y)		
66 to 72	102	32.1
72 to ≤76	62	19.5
76 to ≤82	85	26.7
>82	69	21.7
Residence location		
Big metro	182	57.20
Metro or urban	85	26.70
Less urban or rural	16	5.00
Others	35	16.40
Year of diagnosis		
1992-1999	142	44.6
2000-2004	121	38.1
2005-2009	55	17.3
Histologic grade		
Well	26	8.2
Moderate	30	9.4
Poor	156	49.1
Undifferentiated	54	17
Unknown	52	16.4
pT category		
T1	24	7.5
T2	13	4.1
T3	115	36.2
T4a	21	6.6
T4b	35	11
pN category		
N0	56	17.6
N1a	15	4.7
N1b	43	13.5
N2a	48	15.1
N2b	72	22.6
Unknown	84	26.4
pN category		
M0	74	23.3
M1	95	29.9
Unknown	149	46.9
TNM stage		
I	13	4.1
II	32	10.1
III	87	27.4
IV	186	58.5
Intestinal obstruction		
No	277	87.1
Yes	41	12.9
HCC risk score		
1st quartile	83	26.1
2nd quartile	83	26.1
3rd quartile	73	23
4th quartile	79	24.8
Number of examined lymph node		
<12	180	56.6
≥12	138	43.4
Level of education		
1st quartile	79	24.8
2nd quartile	80	25.2
3rd quartile	80	25.2
4th quartile	79	24.8
Level of income		
1st quartile	80	25.2
2nd quartile	79	24.8
3rd quartile	80	25.2
4th quartile	79	24.8
Primary site		
Rectum	63	19.8
Left-sided colon	41	12.9
Right-sided colon	214	67.3
Tumor size		
≤2 cm	23	7.2
>2 cm	232	73

intermediate grade (G2); and high grade (G3). High-grade neuroendocrine neoplasms, also called neuroendocrine carcinomas (NECs), present with a high mitotic rate (over 20/10 HPF) and Ki-67 proliferation index (over 20%).[2,3]

Although colorectal neuroendocrine carcinoma (CRNEC) is a rare type of malignancy accounting for approximately 0.6% of colon cancers,[4,5] it is often diagnosed at an advanced stage and is quite aggressive with dismal prognosis.[6] Because many cases of NEC histologically resemble small cell lung cancer, most extrapulmonary NEC usually follows a therapeutic paradigm parallel to the treatment for small cell lung cancer.[7,8] The National Comprehensive Cancer Network guideline for high-grade NEC advises combined surgical resection and chemotherapy with or without radiotherapy for resectable NEC, similar to the treatment guidelines for small cell lung cancer.[9] Based on these guidelines, a chemotherapy regimen involving platinum-based chemotherapy combined with etoposide, frequently used in small cell lung cancer, is commonly administered.[8,10,11] Other case report studies have determined that conventional adjuvant chemotherapy regimens such as 5-fluorouracil (5-FU)–based therapy and capecitabine-based therapy may also be beneficial for CRNEC patients.[12,13] Recently, a study on large-cell neuroendocrine lung carcinoma observed a potential benefit from adjuvant chemotherapy using a retrospective database designed by the European Society of Thoracic Surgeons,[14] indicating the