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Original Article

High-Grade Gastrointestinal Neuroendocrine Carcinomas: Multidisciplinary Approach Can Improve Survival Outcomes

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Abstract

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Purpose There is limited evidence for the presentation patterns and outcomes of patients with high-grade gastrointestinal neuroendocrine carcinomas (HG-NEC).

Methods Patients diagnosed with HG-NEC, defined as having a pathological diagnosis of neuroendocrine cancer with an epicenter of cancer in the gastrointestinal tract and Molecular Immunology Borstel-1 index $\geq$ 20% between May 2014 and May 2022 were retrospectively analyzed for demographic variables, survivals, and prognostic parameters. The primary endpoint of the study was the estimation of median overall survival (OS) by the Kaplan–Meier method.

Results A total of 336 patients were included in the analysis, of whom 283 patients (84%) were started on cancer-directed treatment while 53 patients (16%) were planned for best supportive care. The most common sites of the primary were gallbladder (45%), colorectal (19%), and pancreas (13%), with 253 patients (75%) having metastatic NEC. All treated patients received systemic therapy (commonly platinum and etoposide), while 64 patients (23%) underwent resection of the primary. With a median follow-up of 65.4 (45.6 -85.3) months, the median OS of the entire cohort was 15.8 months. The prospective multidisciplinary tumor (MDT) board decision of classifying patients into resectable, unresectable, and metastatic HG-NEC was prognostic for OS (26.8 vs. 21.1 vs. 13.5 months; $p = 0.001$). Patients who were able to undergo multimodality therapy (resection and systemic therapy) had improved OS compared with patients on systemic therapy alone (23.1 vs. 14.9 months; $p = 0.003$).

Keywords
- gallbladder NEC
- high-grade gastrointestinal neuroendocrine carcinoma
- MDT
- multidisciplinary tumor board
- NEC

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Conclusion A majority of patients with HG-NEC present with advanced disease. An MDT is essential to deciding initial therapeutic strategies in these patients, with patients undergoing resection and systemic therapy having improved OS.

Introduction

High-grade gastrointestinal neuroendocrine carcinomas (HG-NEC) are the most common sites of extrapulmonary NEC. Since these cancers comprise a rare cohort, the management paradigms derive primarily from the management of small cell lung cancers (SCLCs), experiences from large databases such as Surveillance, Epidemiology, and End Results, and small single-institution studies.[1–3] A majority of these cancers present in the advanced stage and are treated with a combination of etoposide-platinum with overall survivals (OSs) approximating 12 months.[4,5] A proportion of patients with HG-NEC present without distant metastases and such patients are treated with multimodality therapy, resulting in improved survivals.

There is limited data in the Indian scenario concerning management strategies in patients with HG-NEC. With this background, we conducted a retrospective analysis of patients with HG-NEC from a prospectively maintained neuroendocrine tumor (NET) database to evaluate presentation patterns, common primary tumor sites, and survival outcomes.

Materials and Methods

Patient Selection

A retrospective study of patients diagnosed with gastrointestinal (GI)-NEC between May 2014 and May 2022 was conducted at the Tata Memorial Hospital (TMH), Mumbai, Maharashtra, India after approval for the study was obtained from the Institutional Ethics Committee at TMH (IEC Project 900658). The investigators evaluated retrospective data accrued from a prospectively maintained database of patients diagnosed with NET. From this database, patients satisfying the following criteria were included—histopathological diagnosis of NEC with Molecular Immunology Borstel (MIB) index >20 or histopathological diagnosis of small-cell cancer, epicenter of tumor in any of the following regions—gallbladder (GB), colorectal, pancreas, gastric/gastroesophageal, ampulla, duodenum, and intrahepatic NEC (without any other identifiable primary), and radiological evidence of cancer. Patients not included for analysis were those with non-GI NECs, MIB index $\leq 20\%$, and inadequate staging at baseline.

Data collected were demographic and clinical variables, including stage (resectable cancer, unresectable cancer without distant metastases, and metastatic cancers), details of locoregional therapy and systemic therapy, as well as details of recurrence (or progression) and survival. The initial decision on resectability was based on a multidisciplinary tumor board (MDT) assessment by dedicated GI surgeons, radiologists, radiation oncologists, and medical oncologists, though patients with initially unresectable disease were reevaluated for resection on a case-to-case basis if they had exceptional clinical and radiological response to systemic therapy.

Statistical Analysis

Clinical and pathological variables were compared between patients undergoing resection followed by adjuvant therapy or observation. Categorical variables were compared using the chi-square test while continuous variables were compared by the *t*-test if normally distributed and a nonparametric Mann–Whitney test if not. The primary endpoint of the study was OS, which was calculated from the date of diagnosis to the date of death or loss to follow-up, whichever was earlier. Event-free survival (EFS) was calculated from the date of diagnosis to the date of recurrence (in patients with nonmetastatic disease undergoing definitive surgery or concurrent chemoradiation), progression (in patients undergoing systemic therapy for metastatic disease), and loss to follow-up or death, whichever was earlier. EFS and OS were calculated using the Kaplan–Meier method.

OS and EFS were estimated using the Kaplan–Meier curves and compared with log-rank tests for variables. The hazard ratios were calculated using a Cox proportional hazards model. In this study, two-sided *p*-values of ≤ 0.05 were considered statistically significant. Analyses were conducted using SPSS version 24.

Results

Baseline Clinical Characteristics of the Entire Patient Cohort

A total of 336 patients were available for inclusion in the study, of whom 283 patients (84%) were planned for cancer-directed therapy while 53 patients (16%) were planned for best supportive care alone and referred for palliative care. Of the 283 patients planned for cancer-directed therapy, briefly, the common sites of the primary tumor were GB (45%), colorectal (19%), pancreas (13%), and gastric/gastroesophageal adenocarcinomas (12%), respectively. The majority of patients presented with distant metastases (72%) and had small cell histology (54%) on pathology (►Table 1)

Details of Treatment

All patients received systemic therapy, with the most common regimens used being a combination of cisplatin-etoposide (74%) and carboplatin-etoposide (18%). Sixty-four patients (23%) underwent resection of primary while a minority of patients received concurrent chemoradiation

Table 1 Baseline demographic and clinical characteristics of entire cohort

Characteristic	Treated cohort (%) ($n = 283$)	Best supportive care cohort (%) ($n = 53$)	Overall cohort ($n = 336$)
Median age, y (range)	50 (20–75)	53 (32–85)	51 (20–85)
Gender			
• Female • Male	127 (45) 156 (55)	26 (49) 27 (51)	153 (46) 183 (55)
Site of primary			
• Gallbladder • Colorectal • Pancreas • Gastric/gastroesophageal • Ampulla • Duodenum • Intrahepatic primary	126 (45) 55 (19) 36 (13) 35 (12) 18 (6) 10 (4) 2 (1)	21 (40) 20 (38) 5 (9) 6 (11) 0 1 (2) 0	147 (44) 75 (22) 41 (12) 41 (12) 18 (5) 11 (3) 2 (1)
Histology			
• Small cell histology • Large cell neuroendocrine • Mixed • NOS	154 (54) 29 (10) 27 (10) 73 (26)	43 (81) 6 (11) 0 4 (8)	197 (59) 35 (10) 27 (8) 77 (23)
MIB1 index			
• < 55 • ≥ 55 • Not specified	102 (36) 159 (56) 22 (8)	18 (34) 35 (66) 0	120 (36) 194 (58) 22 (7)
History of transformation to higher grade	6 (2)	1 (2)	7 (2)
Disease status			
• Resectable • Locoregionally unresectable • Presence of distant metastases	47 (17) 32 (11) 204 (72)	1 (2) 3 (6) 49 (93)	48 (14) 35 (10) 253 (75)
Sites of metastases			
• Liver • Lung • Peritoneal • Osseous • Brain • Others	172 (61) 13 (5) 42 (15) 20 (7) 2 (< 1) 136 (48)	46 (79) 4 (8) 9 (17) 7 (13) 3 (6) 33 (62)	218 (65) 17 (5) 51 (15) 27 (8) 5 (2) 169 (50)

Abbreviations: MIB1, Molecular Immunology Borstel 1; NOS, not otherwise specified.

(6%). A small proportion of patients also underwent peptide receptor radionuclide therapy (►**Table 2**).

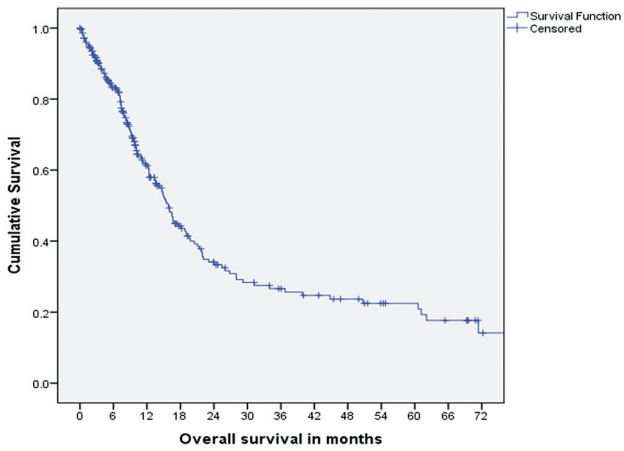
Survival Data and Prognostic Factors

With a median follow-up of 65.4 (45.6–85.3) months, the median OS for the entire cohort was 15.8 months (95% confidence interval [CI]: 13.87–17.74) (►**Fig. 1**). Of the factors evaluated as prognostic for OS, the MDT classification based on resectability status and distant metastases ($p = 0.001$) and absence of liver metastases ($p = 0.007$) predicted superior OS (►**Fig. 2**). Patients with GB NEC tended to have inferior OS compared with patients with other GI-NEC, but this did not receive statistical significance ($p = 0.054$) (►**Table 3**).

The median EFS of the entire cohort was 8.3 months (95% CI: 7.28–9.21). Of the factors evaluated as prognostic for EFS, the MDT classification based on resectability status and

Table 2 Characteristics of therapy

Characteristics	Number (percentage where applicable) ($n = 283$)
Systemic therapy	
• Cisplatin-etoposide • Carboplatin-etoposide • Capecitabine-temozolomide • Cisplatin-etoposide-durvalumab • Carboplatin-etoposide-durvalumab • Others	209 (74) 50 (18) 9 (3) 3 (1) 1 (< 1) 11 (4)
Concurrent chemoradiation	16 (6)
Resection of primary	64 (23)
Peptide receptor radionuclide therapy	16 (6)



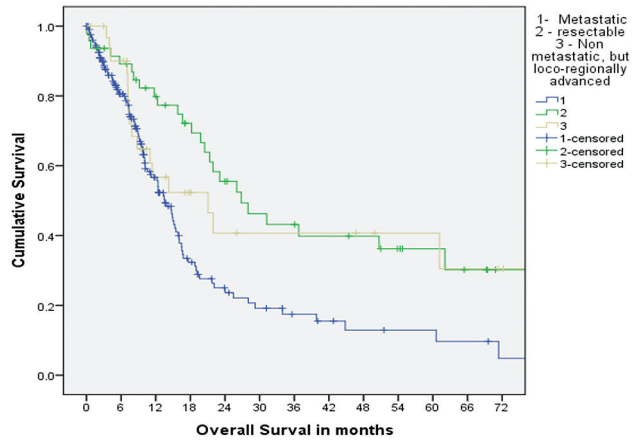


Fig. 2 Overall survival of resectable vs. locally advanced (LA).

Table 3 Factors affecting overall survival (OS)

Characteristic	OS, mo (95% CI)	*p*-Value (univariate analysis)
Age		0.92
• > 65 • ≤ 65	19.6 (7.4–31.9) 15.5 (13.5–17.5)	
Site of primary		0.054
• Gallbladder • Others	13.3 (9.5–17.2) 17.7 (14.0–21.4)	
MIB index		0.67
• < 55 • ≥ 55	17.7 (14.4–20.9) 14.8 (11.7–17.8)	
Liver metastases		0.007
• Yes • No	13.4 (11.3–15.6) 21.1 (15.7–26.5)	
Stage		0.001
• Resectable • Locally advanced unresectable • Metastatic	26.8 (16.2–37.5) 21.1 (7.8–34.3) 13.5 (11.5–15.5)	
Histology		0.27
• Large cell NEC • Small cell	19.8 (6.9–32.7) 14.8 (12.1–17.4)	

Abbreviations: CI, confidence interval; MIB1, Molecular Immunology Borstel 1; NEC, neuroendocrine carcinoma.

distant metastases (20.76 vs. 10.22 vs. 7.23; $p < 0.001$) and absence of liver metastases (10.61 vs. 7.23 months; $p < 0.001$) predicted for superior OS. Patients with large cell NEC tended to have superior EFS compared with patients with small cell NEC, but this did not receive statistical significance (9.2 vs. 8.3 months; $p = 0.06$). Elderly age ($p = 0.98$), MIB index >55 ($p = 0.7$), and presence of GB primary ($p = 0.49$) did not correlate with EFS.

In the overall cohort, patients who were able to undergo curative resection of their primary tumor and received systemic therapy ($n = 64$) had superior OS compared with patients who were not candidates for surgery ($n = 219$) (23.1 vs. 14.9 months; $p = 0.003$). Among the 79 patients without distant metastases at presentation (patients with resectable and unresectable cancers), 44 patients (56%) underwent curative resection while 35 patients did not undergo resection (44%). There was no difference in OS between the two cohorts (36.7 vs. 21.4 months; $p = 0.43$).

Discussion

The current study presents the results of a large retrospective audit in patients with HG-NEC and adds to the growing literature on this rare cohort of cancers.

HG-NECs are rare cancers and, hence, the majority of experience in treating these cancers is drawn from large retrospective studies. The data from the NORDIC-NEC study as well as the National Cancer Database (NCDB) are two of the largest about HG-NECs and have been contrasted and compared with the current study (►Table 4).[1,2] Some of the key differences between the three studies include a younger median age of patients in the TMH study (by approximately one decade), a high proportion of patients with GB cancer (GBC) primaries as opposed to colorectal and pancreas being common sites of primary in the NORDIC-NEC and NCDB data as well as the differential proportion of patients with advanced disease in the three databases. While the younger age of patients can be explained by the distribution of the population pyramid in India, the increased proportion of patients with GB primaries is likely to be unique to India.[6] This is primarily because the Northern and Northeastern parts of India have a high prevalence of GBCs per se and the increased proportion of GB NEC could be a reflection of the same. A previous study from our institution has reported extensively on outcomes of GB NEC previously.[7]

An important aspect of the current data set is that a significant proportion of patients with HG-NECs (16%) are unable to start therapy due to various factors and are planned for best supportive care alone. This is similar to the data from the NORDIC-NEC study and is indicative of the aggressive biology of these cancers. While we do not have data on the survival of patients planned for best supportive care alone, it

Table 4 Comparative analysis of studies evaluating GI-NEC

Characteristic	NORDIC-NEC	NCDB	TMH
Time period of patient assessment	2000–2009	2004–2013	2014–2022
Number of patients	305	1,861	336
Median age, y (range)	60 (24–89)	63	51
Common sites of primary			
• Cancer of unknown primary • Pancreas • Colorectal • Gallbladder • Esophagus	98 (32) 71 (23) 82 (27) NA 12 (4)	- 361 (19) 502 (27) 138 (7) 330 (18)	- 41 (12) 75 (22) 147 (44) 41 (12)[a]
Small cell morphology	117 (43)	NA	197 (59)
MIB index			
• <55 • ≥ 55 • Not specified	136 (47) 169 (53) 0	NA	120 (36) 194 (58) 22 (6)
Disease status			
• Nonmetastatic • Presence of distant metastases	4 (1) 301 (99)	659 (35) 1,202 (65)	83 (24) 253 (76)
Treatment plan			
• Supportive care • Systemic therapy/surgery/radiotherapy	53 (18) 252 (82)	NA	53 (16) 283 (84)
Resection of primary tumor	83 (27)		64 (23)
Follow-up period (mo)	NA	15 (mean)	
Median OS (treated cohort) (mo)	11	9.3	15.8

Abbreviations: GI, gastrointestinal; MIB-1, Molecular Immunology Borstel 1; NA, not available; NCDB, National Cancer Database; NEC, neuroendocrine carcinoma; OS, overall survival; TMH, Tata Memorial Hospital.
[a]Includes gastric and esophageal primary.

does suggest that patients with HG-NEC need to be identified early and started on treatment as soon as possible.

All the patients in the study received systemic therapy, predominantly etoposide-platinum combinations. This is based on available data from NECs as well as the fact that SCLC of the lung are also commonly treated with these regimens.[4,5] The etoposide-platinum combination remains standard in HG-NECs, although there is some data for other options such as cisplatin-irinotecan (as seen in SCLCs) and early phase 2 data for carboplatin-nab-paclitaxel combination.[8,9] A small percentage of patients (~1%) received durvalumab in addition to chemotherapy and this is reflective of extrapolation of data from the use of durvalumab in SCLCs in the Caspian study as well as limited data from phase 2 studies.[10,11]

The median survivals seen in patients with HG-NEC in the current study are reassuring, approximating 15 months. The slightly higher survivals are likely due to a higher proportion of patients with localized disease in the current study (as compared with the NORDIC-NEC study), as well as improved supportive care over the periods the studies have been conducted. The differential proportion of various primary tumors may have also contributed to these differences as the NORDIC-NEC study had a high proportion of colonic NECs, and colonic NECs had inferior survivals compared with other primary sites in that study.

The factors that were noted to be prognostic in the current study were primarily resectability status at baseline and the presence of liver metastases. This highlights the importance of an MDT discussion in the management of these rare tumors and dynamic assessments for patients while being treated. Despite only 17% of patients being classified as resectable initially, 23% of patients finally underwent curative resection given response to systemic therapy. Factors traditionally associated with inferior survivals such as small cell histology and high MIB-1 index were not prognostic for outcomes in this study.[1] As expected, patients who underwent curative resection and systemic therapy had improved survival compared with the rest of the cohort. However, in the cohort of patients who did not have distant metastases at baseline, there was no statistical difference in OS between patients who underwent surgery and those who did not. This is reflective of the need for careful selection of patients undergoing surgery as well as the importance of systemic therapy in patients with HG-NEC. The high recurrence or disease progression rates even in patients with resectable HG-NEC underline the need for greater focus on evaluating the genomic features of these cancers and identifying

potential therapeutic targets as opposed to extrapolating data from the management of SCLCs and treating them with current used approaches.[12] Patients with GB primary tended to perform inferiorly compared with other sites of primary HG-NEC, though this did not attain statistical significance. GBCs are primarily aggressive cancers and NECs of the GB appears to follow a similar course as per the results of the current study.

The study, while evaluating a relatively large number of cancers of a rare nature, does have certain drawbacks. We do not have follow-up of patients planned for best supportive care alone. Data on the presence or absence of secretory symptoms as well as somatostatin receptor expression in patients with lower MIB-1 index is not available. We have not provided details of resectability criteria for patients classified as "resectable" as this was beyond the scope of the current study, though all patients were classified after an MDT discussion. The platinum agent (in combination with etoposide) administrated to patients was based on individual physician choice and preference, with no data provided on why such a decision was taken.

Conclusion

In conclusion, the current large retrospective study in patients with HG-NECs suggests that a majority of patients present with advanced disease while approximately 16% of patients are unable to undergo treatment upfront. Classification of patients into resectable, unresectable, and metastatic HG-NECs based on MDT decisions clearly defines patients with differential prognosis and survivals. The most common primary in the data set was GBC. Patients undergoing surgery and systemic therapy have improved survival compared with patients who are not candidates for surgery. Besides resectability, the presence of liver metastases predicts for inferior OS.

Conflict of Interest

None declared.

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