

Figure S1 Flowchart of the inclusion and exclusion criteria.

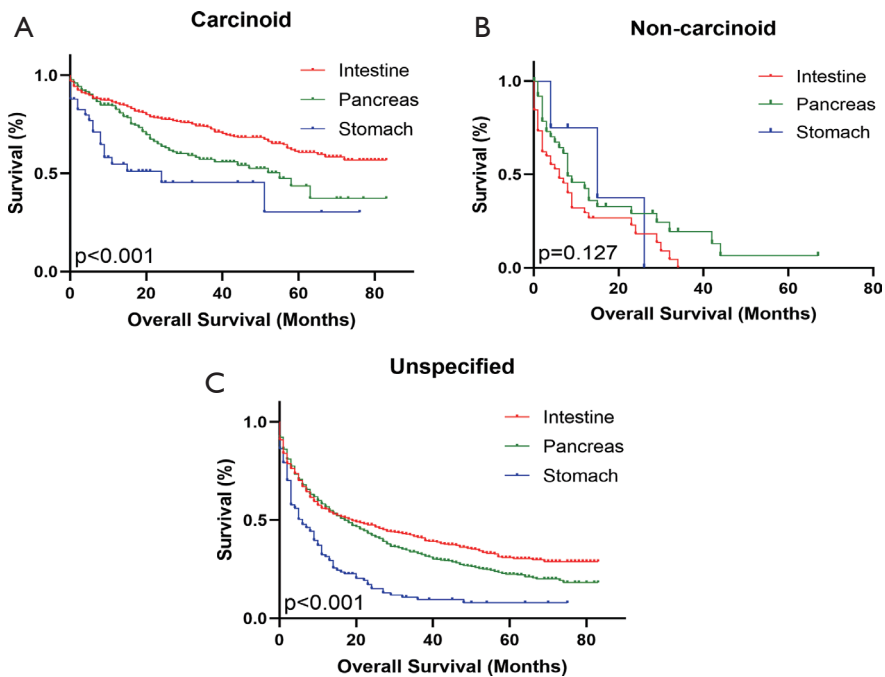


Figure S2 Kaplan-Meier survival curves depicting overall survival in patients with liver metastatic GEP-NENs according to tumor primary sites among different functional status: (A) carcinoid, (B) non-carcinoid, and (C) unspecified tumor type (includes both types). The p-values were determined by the log-rank test.

Table S1 Demographic and disease factors in all primary GEP-NEN patients with liver metastasis (all origin locations) - univariate and multivariate Cox regression results

Variables	Patients (n=3188)	Cox regression analysis			
		Univariate P value	Unadjusted HR (95% CI)	Multivariate P value	Adjusted HR (95% CI)
Gender					
Female	1444	Reference	1.151 (1.043–1.269)	Reference	1
Male	1744	0.005		0.042	1.108 (1.004–1.223)
Age, years					
Average, range	60.9 (4–97)	<0.001	1.031 (1.027–1.035)	<0.001	1.024 (1.020–1.028)
Tumor site					
Intestine	1590	Reference	1	Reference	1
Pancreas	1427	<0.001	1.447 (1.308–1.602)	0.141	0.919 (0.821–1.028)
Stomach	171	<0.001	2.563 (2.119–3.102)	0.802	1.026 (0.839–1.254)
Grade					
well	906	Reference	1	Reference	1
Moderate	394	0.011	1.337 (1.069–1.673)	0.041	1.264 (1.010–1.583)
Poor or undifferentiated	621	<0.001	7.625 (6.494–8.952)	<0.001	4.755 (3.977–5.686)
Unknown	1267	<0.001	3.544 (3.052–4.115)	<0.001	2.163 (1.837–2.547)
Functional type					
Carcinoid tumor	1125	Reference	1	Reference	1
Non-carcinoid tumor	88	<0.001	4.611 (3.541–6.003)	<0.001	2.633 (2.006–3.456)
Unspecified neuroendocrine tumor	1975	<0.001	2.703 (2.384–3.065)	<0.001	1.844 (1.613–2.108)
Surgery					
No	1959	Reference	1	Reference	1
Yes	1204	<0.001	0.290 (0.258–0.327)	<0.001	0.459 (0.398–0.530)
Unknown	25	0.185	0.709 (0.426–1.179)	0.921	1.026 (0.616–1.711)
Radiotherapy					
No	2975	Reference	1.357 (1.135–1.622)	Reference	1
Yes	213	0.001		0.428	1.078 (0.895–1.298)
Chemotherapy					
No	1888	Reference	1.472 (1.335–1.623)	Reference	1
Yes	1300	<0.001		<0.001	0.820 (0.734–0.916)
Bone metastasis					
No	2953	Reference	2.064 (1.758–2.422)	Reference	1
Yes	235	<0.001		0.007	1.261 (1.067–1.491)
Brain metastasis					
No	3163	Reference	3.183 (2.046–4.954)	Reference	1
Yes	25	<0.001		0.647	0.897 (0.564–1.428)
Lung metastasis					
No	2944	Reference	2.506 (2.147–2.926)	Reference	1
Yes	244	<0.001		<0.001	1.483 (1.260–1.745)

Table S2 Demographic and disease factors in all primary iNEN patients with liver metastasis - univariate and multivariate Cox regression results

Variables	Patients (n=1590)	Overall survival			
		Univariate P value	HR (95% CI)	Multivariate P value	HR (95% CI)
Gender					
Female	773	Reference	1		
Male	817	0.086	1.139 (0.982–1.321)		
Age, years					
Average, range	61.2, 14–95	<0.001	1.035 (1.028–1.041)	<0.001	1.033 (1.027–1.040)
Grade					
Well	597	Reference		Reference	1
Moderate	212	0.051	1.386 (0.999–1.922)	0.095	1.323 (0.953–1.838)
Poor or undifferentiated	347	<0.001	11.312 (9.049–14.141)	<0.001	4.886 (3.737–6.388)
Unknown	434	<0.001	3.663 (2.933–4.574)	<0.001	2.489 (1.955–3.169)
Functional type					
Carcinoid tumor	726	Reference	1	Reference	1
Non- carcinoid tumor	45	<0.001	6.246 (4.372–8.922)	<0.001	2.138 (1.461–3.128)
Unspecified neuroendocrine tumor	819	<0.001	2.789 (2.350–3.309)	<0.001	1.722 (1.427–2.078)
Site					
Colorectum and anus	625	Reference	1	Reference	1
Appendix	22	0.008	0.409 (0.211–0.791)	0.120	0.586 (0.299–1.150)
Small intestine	943	<0.001	0.201 (0.171–0.235)	<0.001	0.357 (0.294–0.434)
Surgery					
No	633	Reference	1	Reference	1
Yes	947	<0.001	0.307 (0.263–0.357)	<0.001	0.619 (0.519–0.738)
Unknown	10	1.000	1.000 (0.497–2.014)	0.655	1.174 (0.580–2.377)
Radiotherapy					
No	1492	Reference	1	Reference	1
Yes	98	0.002	1.531 (1.170–2.003)	0.867	1.024 (0.774–1.355)
Chemotherapy					
No	1117	Reference	1	Reference	1
Yes	473	<0.001	1.908 (1.641–2.219)	0.004	0.759 (0.630–0.915)
Bone metastasis					
No	1490	Reference	1	Reference	1
Yes	100	<0.001	2.587 (2.023–3.308)	0.717	0.953 (0.733–1.238)
Brain metastasis					
No	1579	Reference	1	Reference	1
Yes	11	0.001	3.304 (1.643–6.644)	0.691	1.160 (0.558–2.408)
Lung metastasis					
No	1477	Reference	1	Reference	1
Yes	113	<0.001	2.604 (2.065–3.285)	0.052	1.273 (0.998–1.624)

Table S3 Demographic and disease factors in all primary pNEN patients with liver metastasis - univariate and multivariate Cox regression results

Variables	Patients (n=1427)	Overall survival			
		Univariate P value	HR (95% CI)	Multivariate P value	HR (95% CI)
Gender					
Female	604	Reference	1		
Male	823	0.243	1.087 (0.945–1.251)		
Age, years					
Average, range	60.2 (4–97)	<0.001	1.029 (1.023–1.035)	<0.001	1.022 (1.016–1.028)
Grade					
Well	282	Reference		Reference	1
Moderate	166	0.572	1.099 (0.793–1.523)	0.986	0.997 (0.719–1.383)
Poor or undifferentiated	189	<0.001	3.881 (2.991–5.036)	<0.001	2.630 (2.010–3.441)
Unknown	790	<0.001	2.694 (2.163–3.355)	<0.001	1.631 (1.297–2.051)
Functional type					
Carcinoid tumor	358	Reference	1	Reference	1
Non- carcinoid tumor	38	<0.001	3.134 (2.064–4.760)	<0.001	2.608 (1.710–3.978)
Unspecified neuroendocrine tumor	1031	<0.001	2.183 (1.774–2.687)	<0.001	1.720 (1.392–2.126)
Surgery					
No	1182	Reference	1	Reference	
Yes	232	<0.001	0.231 (0.176–0.305)	<0.001	0.319 (0.239–0.427)
Unknown	13	0.139	0.545 (0.244–1.217)	0.602	0.807 (0.360–1.807)
Radiotherapy					
No	1331	Reference	1		
Yes	96	0.471	1.105 (0.842–1.450)		
Chemotherapy					
No	682	Reference	1		
Yes	745	0.518	1.047 (0.911–1.203)		
Bone metastasis					
No	1310	Reference	1	Reference	1
Yes	117	<0.001	1.690 (1.346–2.122)	0.018	1.329 (1.050–1.683)
Brain metastasis					
No	1418	Reference	1	Reference	1
Yes	9	<0.001	4.141 (2.057–8.338)	0.111	1.817 (0.872–3.785)
Lung metastasis					
No	1315	Reference	1	Reference	1
Yes	112	<0.001	2.661 (2.124–3.333)	<0.001	1.798 (1.421–2.273)

Table S4 Demographic and disease factors in all primary gNEN patients with liver metastasis - univariate and multivariate Cox regression results

Variables	Patients (n=171)	Overall survival			
		Univariate P value	HR (95% CI)	Multivariate P value	HR (95% CI)
Gender					
Female	67	Reference	1		
Male	104	0.167	1.291 (0.899–1.854)		
Age, years					
Average, range	64.3, 14–96	<0.001	1.025 (1.012–1.038)	0.001	1.023 (1.010–1.036)
Grade					
Well	27	Reference	1	Reference	1
Moderate	16	0.516	1.369 (0.531–3.534)	0.407	1.499 (0.576–3.907)
Poor or undifferentiated	85	<0.001	4.325 (2.278–8.209)	0.001	3.354 (1.694–6.642)
Unknown	43	0.009	2.487 (1.252–4.938)	0.089	1.863 (0.909–3.821)
Functional type					
Carcinoid tumor	41	Reference	1		
Non- carcinoid tumor	5	0.556	1.442 (0.426–4.880)		
Unspecified neuroendocrine tumor	125	0.001	2.230 (1.366–3.641)		
Surgery					
No	144	Reference	1	Reference	1
Yes	25	<0.001	0.308 (0.164–0.576)	0.013	0.419 (0.211–0.832)
Unknown	2	0.271	0.330 (0.046–2.372)	0.196	0.271 (0.037–1.962)
Radiotherapy					
No	152	Reference	1		
Yes	19	0.187	1.419 (0.843–2.387)		
Chemotherapy					
No	89	Reference	1		
Yes	82	0.461	0.876 (0.616–1.246)		
Bone metastasis					
No	153	Reference	1		
Yes	18	0.453	1.238 (0.709–2.165)		
Brain metastasis					
No	166	Reference	1		
Yes	5	0.658	1.253 (0.461–3.402)		
Lung metastasis					
No	152	Reference	1		
Yes	19	0.317	1.318 (0.767–2.262)		