**Materials and methods**

**Gene set enrichment analysis (GSEA)**

The input data was pre-ranked by log2-FoldChange. GSEA was carried out to determine the biological functions and pathways of genes. R package clusterProfiler (version 3.16.1) was used to perform the analysis and plot the results. The enrichment results that satisfied two conditions (p-value < 0.05 and q-value < 0.05 indicated statistical significance and were visualized by the R package enrichplot (version 1.8.1). For Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, the genes were downloaded from KEGG PATHWAY Database(https://www.genome.jp/kegg/pathway.html). For Gene Ontology (GO) analysis all the gene sets were downloaded from Gene Ontology Resource (http://geneontology.org/). Gene sets with p value <0.05 and adjusted p value <0.05 were considered statistically significant.

**Figure&Table Legends**

**Figure S1：**KEGG and GO analysis of gastric papillary adenocarcinoma. a. Heatmap of the all different expression genes obtained by comparing gastric papillary adenocarcinoma and gastric tubular adenocarcinoma; b. Top 20 KEGG pathway enrichment; c. GSEA analysis of different pathways.

图片1

**Table S1:** **Comparison of** **clinicopathologic characteristics of EPAC patients and non-EPAC patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | EPAC (N=335) | Other differentiated EGC (N=1077) | Poorly differentiated EGC (N=1101) | p Univariate analysis |
| Gender, N(%) |  |  |  | <0.001 |
| Male | 232 (69.3%) | 848 (78.7%) | 660 (59.9%) |  |
| Female | 103 (30.7%) | 229 (21.3%) | 441 (40.1%) |  |
| Age, N(%) |  |  |  | <0.001 |
| <60 years | 67 (20.0%) | 327 (30.4%) | 579 (52.6%) |  |
| ≥60 years | 268 (80.0%) | 750 (69.6%) | 522 (47.4%) |  |
| Tumor location, N(%) |  |  |  | <0.001 |
| Upper stomach | 171 (51.0%) | 491 (454.6%) | 391 (35.5%) |  |
| Lower stomach | 164 (49.0%) | 586 (54.4%) | 710 (64.5%) |  |
| Tumor size, N(%) |  |  |  | <0.001 |
| ≤2.0 cm | 184 (54.9%) | 718 (66.7%) | 681 (61.9%) |  |
| >2.0 cm | 151 (45.1%) | 359 (33.3%) | 420 (38.1%) |  |
| Ulceration, N(%) | 52 (15.5%) | 211 (19.6%) | 246 (22.3%) | 0.019 |
| Differentiation, N(%) |  |  |  | <0.001 |
| Well/moderate | 320 (95.5%) | 1077 (100.0%) | 0 (0.0%) |  |
| Poor | 15 (4.5%) | 0 (0.0%) | 1101 (100.0%) |  |
| Gross pattern, N(%) |  |  |  | <0.001 |
| 0-I+IIa | 103 (30.7%) | 178 (16.5%) | 143 (13.0%) |  |
| 0-IIb | 79 (23.6%) | 310 (28.8%) | 296 (26.9%) |  |
| 0-IIc+III | 153 (45.7%) | 589 (54.7%) | 662 (60.1%) |  |
| Invasion depth, N(%) |  |  |  | <0.001 |
| M | 96 (28.7%) | 582 (54.0%) | 485 (44.1%) |  |
| SM1 | 77 (23.0%) | 225 (20.9%) | 194 (17.6%) |  |
| SM2 | 162 (48.4%) | 270 (25.1%) | 422 (38.3%) |  |
| Necrosis, N(%) | 149 (44.5%) | 378 (35.1%) | 296 (26.9%) | <0.001 |
| Micropapillary adenocarcinoma, N(%) | 22 (6.6%) | 5 (0.5%) | 3 (0.3%) | <0.001 |

**Table S2:** **Univariate and multivariate analysis of clinicopathologic characteristics of EGC patients with and without LNM**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | LNM (N=364) | Non-LNM (N=2149) | p Univariate analysis | p Multivariate analysis | Odds ratio (95% CI) |
| EPAC | 62 (18.5%) | 273 (81.5%) | 0.025 | 0.004 | 1.8 (1.2-2.7) |
| Gender, N(%) |  |  | <0.001 | 0.002 |  |
| Male | 216 (12.4%) | 1524 (87.6%) |  |  | 1 (reference) |
| Female | 148 (19.1%) | 625 (80.9%) |  |  | 1.5 (1.2-2.0) |
| Age, N(%) |  |  | 0.005 | 0.100 |  |
| <60 years | 165 (17.0%) | 808 (83.0%) |  |  |  |
| ≥60 years | 199 (12.9%) | 1341 (87.1%) |  |  |  |
| Tumor location, N(%) |  |  | <0.001 | 0.003 |  |
| Upper stomach | 114 (10.8%) | 939 (89.2%) |  |  | 1 (reference) |
| Lower stomach | 250 (17.1%) | 1210 (82.9%) |  |  | 1.5 (1.2-2.0) |
| Tumor size, N(%) |  |  | <0.001 | 0.001 |  |
| ≤2.0 cm | 171 (10.8%) | 1412 (89.2%) |  |  | 1 (reference) |
| >2.0 cm | 193 (20.8%) | 737 (79.2%) |  |  | 1.5 (1.2-2.0) |
| Ulceration, N(%) | 104 (20.4%) | 405 (79.6%) | <0.001 | 0.164 | 1.3 (0.9-1.7) |
| Differentiation, N(%) |  |  | <0.001 | <0.001 |  |
| Well/moderate | 127 (34.9%) | 1270 (59.1%) |  |  | 1 (reference) |
| Poor | 237 (65.1%) | 879 (40.9%) |  |  | 2.8 (2.0-3.8) |
| Gross pattern, N(%) |  |  | 0.001 |  |  |
| 0-I+IIa | 63 (14.9%) | 361 (85.1%) |  |  | 1 (reference) |
| 0-IIb | 52 (7.6%) | 633 (92.4%) |  | 0.021 | 0.6 (0.4-0.9) |
| 0-IIc+III | 249 (17.7%) | 1155 (82.3%) |  | 0.630 | 1.1 (0.8-1.6) |
| Invasion depth, N(%) |  |  | <0.001 |  |  |
| M | 71 (6.1%) | 1092 (93.9%) |  |  | 1 (reference) |
| SM1 | 71 (14.3%) | 425 (85.7%) |  | 0.002 | 1.8 (1.2-2.6) |
| SM2 | 222 (26.0%) | 632 (74.0%) |  | <0.001 | 2.3 (1.6-3.2) |
| Necrosis, N(%) | 152 (18.5%) | 671 (81.5%) | <0.001 | 0.007 | 1.4 (1.1-1.9) |
| Micropapillary adenocarcinoma, N(%) | 11 (36.7%) | 19 (63.3%) | 0.001 | 0.476 |  |
| LVI, N(%) | 168 (48.6%) | 178 (51.4%) | <0.001 | <0.001 | 5.6 (4.1-7.5) |
| Perineural invasion, N(%) | 47 (40.2%) | 70 (59.8%) | <0.001 | 0.307 |  |
| Upper stomach: cardia, body and fundus, Lower stomach: angle, antrum, and pylorus, M:confined to mucosa, SM1: <500 micron from the muscularis mucosae, SM2: confined to the submucosa, >500 micron from the muscularis mucosae. LVI: lymphovascular invasion, LNM: lymph node metastasis. | | | | | |

**Table S3:** **The clinicopathologic characteristics of EPAC patients in the internal validation set.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patients no. | Gender | Age (Years) | Tumor location | Tumor size (cm) | Ulceration | Differentiation | Gross pattern | Invasion depth | Micropapillary adenocarcinoma | LVI | Perineural invasion | LNM | Score# | Category\* |
| 1 | male | 67 | Cardia | 0.9 | No | Well/moderate | 0-I | M | No | No | No | No | 0 | Low |
| 2 | male | 78 | [Corpus](../../../../Program%20Files%20(x86)/Youdao/Dict/7.5.2.0/resultui/dict/javascript:;" \o "../../../../Program Files (x86)/Youdao/Dict/7.5.2.0/resultui/dict/javascript:;) | 2 | No | Well/moderate | 0-IIc | M | No | No | No | Yes | 4 | Intermediate |
| 3 | male | 72 | Cardia | 1.5 | Yes | Well/moderate | III | SM1/SM2 | No | No | No | No | 4 | Intermediate |
| 4 | male | 64 | [Corpus](../../../../Program%20Files%20(x86)/Youdao/Dict/7.5.2.0/resultui/dict/javascript:;" \o "../../../../Program Files (x86)/Youdao/Dict/7.5.2.0/resultui/dict/javascript:;) | 1.5 | Yes | Well/moderate | III | SM1/SM2 | No | No | No | No | 4 | Intermediate |
| 5 | male | 75 | Cardia | 1.5 | No | Well/moderate | 0-IIa | SM1/SM2 | No | No | No | No | 4 | Intermediate |
| 6 | female | 62 | Cardia | 2.5 | No | Well/moderate | 0-IIc | SM1/SM2 | No | No | No | No | 5 | Intermediate |
| 7 | male | 66 | Antrum | 2.5 | No | Well/moderate | 0-I | SM1/SM2 | No | No | No | No | 6 | Intermediate |
| 8 | female | 67 | Antrum | 3 | No | Well/moderate | 0-I | SM1/SM2 | No | No | No | No | 6 | Intermediate |
| 9 | male | 65 | Angle | 2.5 | Yes | Well/moderate | III | SM1/SM2 | No | No | No | No | 6 | Intermediate |
| 10 | male | 67 | Cardia | 2.8 | No | Well/moderate | 0-I | SM1/SM2 | No | Yes | No | No | 8 | High |
| 11 | female | 68 | Cardia | 2.5 | No | Well/moderate | 0-I | SM1/SM2 | No | Yes | No | No | 8 | High |
| 12 | male | 68 | Cardia | 4.5 | Yes | Well/moderate | III | SM1/SM2 | Yes | Yes | No | Yes | 8 | High |
| 13 | male | 68 | [Corpus](../../../../Program%20Files%20(x86)/Youdao/Dict/7.5.2.0/resultui/dict/javascript:;" \o "../../../../Program Files (x86)/Youdao/Dict/7.5.2.0/resultui/dict/javascript:;) | 2.4 | No | Well/moderate | 0-IIc | SM1/SM2 | No | Yes | No | Yes | 8 | High |
| 14 | male | 54 | [Corpus](../../../../Program%20Files%20(x86)/Youdao/Dict/7.5.2.0/resultui/dict/javascript:;" \o "../../../../Program Files (x86)/Youdao/Dict/7.5.2.0/resultui/dict/javascript:;) | 2.5 | Yes | Well/moderate | III | SM1/SM2 | No | Yes | No | Yes | 8 | High |
| 15 | male | 54 | Cardia | 2 | Yes | Poor | III | SM1/SM2 | No | Yes | Yes | Yes | 8 | High |
| 16 | female | 60 | [Corpus](../../../../Program%20Files%20(x86)/Youdao/Dict/7.5.2.0/resultui/dict/javascript:;" \o "../../../../Program Files (x86)/Youdao/Dict/7.5.2.0/resultui/dict/javascript:;) | 5 | No | Poor | 0-IIa | SM1/SM2 | No | Yes | No | Yes | 8 | High |
| 17 | male | 59 | Antrum | 7.2 | Yes | Poor | III | SM1/SM2 | Yes | Yes | Yes | Yes | 9 | High |
| 18 | male | 64 | Angle | 5.5 | Yes | Poor | III | SM1/SM2 | Yes | Yes | No | Yes | 9 | High |
| #1 point each for Angle/Antrum/Pylorus, tumor size >2.0 cm, 3 points for LVI, 4 points for SM1/SM2; \*0-2 points for Low, 3-6 points for Intermediate and 7-9 points for High risk; LNM: lymph node metastasis, M:confined to mucosa, SM1: <500 micron from the muscularis mucosae, SM2: confined to the e submucosa, >500 micron from thmuscularis mucosae. | | | | | | | | | | | | | | |