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The impact of single and multiple occurrences, as well as the sequence of occurrences, of primary gastrointestinal cancer on overall survival: a comprehensive analysis based on the surveillance, epidemiology, and end results database in the United States from 2016 to 2019

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Abstract

Introduction Gastrointestinal cancers encompass malignant tumors of multiple digestive system organs in humans. Each type of digestive system cancer also contains different histological types, each of which has a distinct prognosis. The survival time of cancer patients has significantly extended with the development of modern medicine, allowing for primary cancers occurring more than once in a lifetime.

Methods The study analyzed multiple primary gastrointestinal cancers, including esophagus, stomach, liver, gallbladder, small bowel, colon, rectum, and anus, based on the Surveillance, Epidemiology, and End Results (SEER) database from 2016 to 2019 in the United States. A total of 119,760 cases were included in this study. Each gastrointestinal cancer was analyzed separately based on the International Classification of Diseases for Oncology third edition (ICD-O-3) for the common histologic type. Meanwhile, based on the sequence of cancer occurrence in the patients, they were divided into the one primary (OP) group and the multiple primaries (MP) group. The multiple primaries group was further subdivided into the first of multiple primaries (FMP) group and the non-first of multiple primaries (NFMP) group. The Kaplan-Meier method with the log-rank test was used to analyze overall survival (OS), while the Cox regression model was used for univariate and multivariate analyses.

Results The study enrolled nine organs of the digestive system and twenty histologic types of primary gastrointestinal cancers. The characteristics of patients in different groups with various cancers, overall survival of

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these patients, and the risk factors for developing these cancers were comprehensively analyzed. The comprehensive analysis revealed the connection between the occurrence sequence of cancers and different outcomes for patients.

Conclusions Different prognoses were observed in patients with different sequences of various primary gastrointestinal cancers. Patients with high mortality cancers in the FMP group may have potential factors, such as high treatment sensitivity, that could lead to improved OS. Patients with low mortality cancers in the NFMP group could benefit from positive treatment therapies.

Keywords Primary gastrointestinal cancers, Cancer occurrence sequence, Outcomes, Prognosis, Treatment therapy

Text box 1. Contributions to the literature

1. As the number of cancer survivors continues to rise, greater attention has to be given to the subsequent occurrence of other primary cancers.
2. Medical professionals need to adopt a more macroscopic, long-term, and proactive plan for the treatment of cancer survivors who develop other primary cancers.
3. The differences in overall survival associated with varying sequences of occurrence for the same specific gastrointestinal cancer warrant further research.

Introduction

Gastrointestinal cancers are a series of common diseases that cause amount patient deaths worldwide. According to global statistics, colorectal cancer, gastric cancer, liver cancer, and pancreatic cancer have high incidence and mortality rates [1]. The digestive system originates from the endoderm and mesoderm germ layers during human development and is completed under unified regulation [2]. Therefore, there are many similarities in the histological characteristics of digestive tract organs. In addition, the cellular components of digestive organs are complex, which can lead to various malignant tumors. It is essential to conduct comprehensive research on cancers in digestive organs.

As medical standards are being raised, the diagnostic accuracy and opportunities for cancer patients to receive effective treatment are increasing. Many cancer patients have their survival time extended, but they may also face the challenge of developing multiple primary cancers throughout their lifetime. However, most studies and clinical trials focus on primary cancer patients who do not have any other cancers or are not undergoing any other cancer treatments. More observation and research on patients with a history of cancer is necessary and meaningful.

The Surveillance, Epidemiology, and End Results (SEER) database is established by the National Cancer Institute in the United States of America (USA) using real-world population public medical data. The SEER database, as part of the national cancer surveillance and prevention project in the USA, is typically used to analyze risk factors and follow-up treatment outcomes in patients with primary tumors. As the database continues to be enhanced, some extensive studies have begun to emphasize the observation of overall survival (OS) and cancer type-specific risks of secondary primary cancer in prior cancer patients [3, 4]. Research on patients with multiple primary cancers has shown that a prior history of cancer significantly affects the occurrence and survival of subsequent cancers [5, 6]. A study on childhood and adolescent cancer survivors suggested that the risk of developing other primary gastrointestinal cancers significantly increased from 1975 to 2015 compared to adults.

With advancements in medical care, the number of cancer survivors is steadily increasing. The number of cancer survivors occurring other primary cancers has also increased. These patient groups will be a key focus for future clinical strategies in cancer treatment. Our study focused on investigating the impact of the sequence in which primary gastrointestinal cancers (PGICs) occur on their prognosis. This is an area of research that has received less attention. We compared patients grouped with one primary (OP) and multiple primaries (MP) in gastrointestinal cancers. The MP group was further subdivided into first of multiple primaries (FMP) and non-first of multiple primaries (NFMP) (Table 1). This analysis contributes to predicting the prognosis of cancer survivors, establishing correct disease expectations, and guiding the implementation of more aggressive or conservative subsequent treatment strategies.

Methods

Data selection

Data was downloaded from the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/). The protocol for data selection is outlined in Fig. 1. Each digestive system cancer included in the analysis underwent subgroup analysis based on the International Classification of Disease for Oncology third edition (ICD-O-3) to determine the common histologic type. The nine sites of the digestive system and their histologic types were selected as follows: (1) Liver, including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC); (2) Gallbladder, including gallbladder adenocarcinoma (GBAC); (3) Pancreas, including pancreatic adenocarcinoma (PAC), pancreatic infiltrating duct carcinoma (PIDC), and pancreatic carcinoid tumor

Table 1 Supplementary explanation of patient groups

Groups	Description
One primary (OP)	Only one primary cancer in patients' lifetime
Multiple primaries (MP)	Multiple primary cancers in patients' lifetime
First of multiple primaries (FMP)	First primary cancer in the patients with multiple primary cancers
Non-first of multiple primaries (NFMP)	Non-first primary cancer in the patients with multiple primary cancers

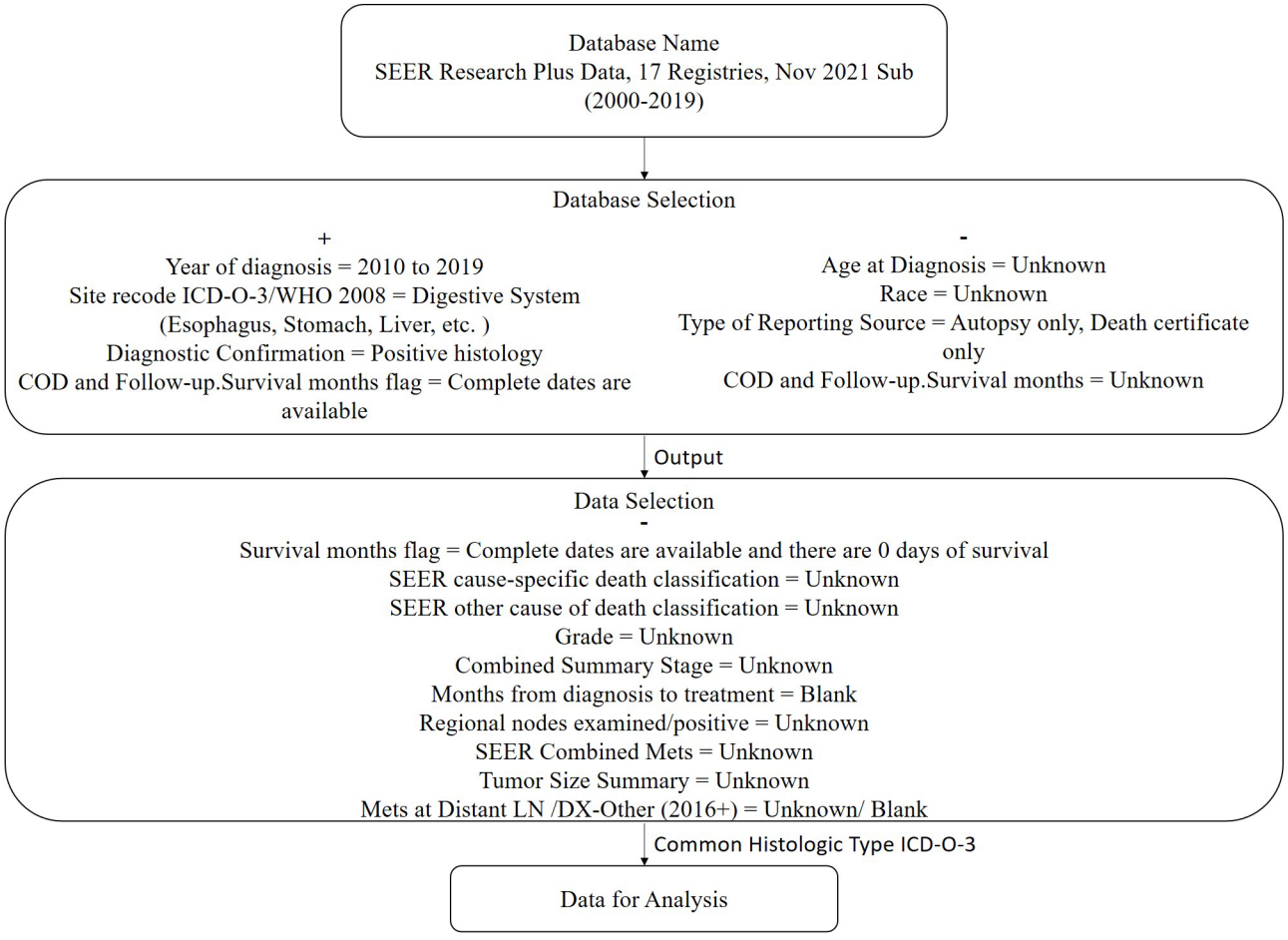


Fig. 1 The protocol for data selection based on the surveillance, epidemiology, and end results database in the United States from 2016 to 2019

(PCT); (4) Esophagus, including esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC); (5) Gaster, including gastric adenocarcinoma (GAC), gastrointestinal stromal sarcoma (GISS), and gastric carcinoid tumor (GCT); (6) Small bowel, including small bowel adenocarcinoma (SBA) and small bowel carcinoid tumor (SBCT); (7) Colon, including colon adenocarcinoma (COAD), colon papillary adenocarcinoma (COPA), and colon carcinoid tumor (COCT); (8) Rectum, including rectal adenocarcinoma (READ), rectal papillary adenocarcinoma (REPA), and rectal carcinoid tumor (RECT); (9) Anus, including anal squamous cell carcinoma (ASCC) (see Tables 2 and 3 for details).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 26. The t-test was used for continuous variables, with a comparison of two groups using the Independent-Samples T Test and a comparison of three groups using One-Way ANOVA. The Mann-Whitney U test was applied to compare skewed data. The chi-square test and Fisher's exact test were applied to analyze categorical variables. Some continuous variables were converted into categorical variables, while multiple categorical variables were transformed into binary variables. The OS was analyzed using the Kaplan-Meier method, and statistical significance was determined using the Log-rank test. The Cox regression model was used to evaluate the hazard ratio and the 95% confidence interval of risk factors.

Table 2 Cases of the analysis based on the Surveillance, Epidemiology, and end results database in the United States from 2016 to 2019

Cancer type	Total	Total Event (%)[1]	Histologic type[2]	Event (%)[3]
Liver	80 547	5343 (6.6)	hepatocellular carcinoma (HCC)	3969 (74.3)
			intrahepatic cholangiocarcinoma (ICC)	1086 (20.3)
Gallbladder	10 465	1980 (18.9)	gallbladder adenocarcinoma (GBAC)	1537 (77.6)
Pancreas	111 993	11 425 (10.2)	pancreatic adenocarcinoma (PAC)	4962 (43.4)
			pancreatic infiltrating duct carcinoma (PIDC)	3132 (27.4)
			pancreatic carcinoid tumor (PCT)	2329 (20.4)
Esophagus	37 733	6061 (16.1)	esophageal adenocarcinoma (EAC)	3856 (63.6)
			esophageal squamous cell carcinoma (ESCC)	1749 (28.9)
Gaster	62 817	9984 (15.9)	gastric adenocarcinoma (GAC)	5929 (59.4)
			gastrointestinal stromal sarcoma (GISS)	1194 (12.0)
			gastric carcinoid tumor (GCT)	849 (8.5)
Small bowel	21 188	5110 (24.1)	small bowel adenocarcinoma (SBA)	1137 (22.3)
			small bowel carcinoid tumor (SBCT)	3337 (65.3)
Colon	239 217	69 875 (29.2)	colon adenocarcinoma (COAD)	52 952 (75.8)
			colon papillary adenocarcinoma (COPA)	3450 (4.9)
			colon carcinoid tumor (COCT)	3458 (4.9)
Rectum	104 381	24 165 (23.2)	rectal adenocarcinoma (READ)	18 557 (76.8)
			rectal papillary adenocarcinoma (REPA)	1327 (5.5)
			rectal carcinoid tumor (RECT)	1954 (8.1)
Anus	17 488	3514 (20.1)	anal squamous cell carcinoma (ASCC)	2996 (85.3)
Total	685 829	137 457 (20.0)		119 760 (87.1)

[1] The numbers and proportion of patients with selected criteria

[2] Relatively common histologic type according to ICD-O-3

[3] The numbers of various histologic types and the percentage of the total events

Table 3 Abbreviations and International Classification of Diseases for Oncology third edition (ICD-O-3) of various gastrointestinal cancers

Abbreviations	ICD-O-3*
ASCC: anal squamous cell carcinoma	C210-C212, C218 807
COAD: colon adenocarcinoma	C180, C182-C189 814
COCT: colon carcinoid tumor	C180, C182-C189 824
COPA: colon papillary adenocarcinoma	C180, C182-C189 826
EAC: esophageal adenocarcinoma	C150-C155, C158-C159 814
ESCC: esophageal squamous cell carcinoma	C150-C155, C158-C159 807
GAC: gastric adenocarcinoma	C160-C166, C168-C169 814
GBAC: gallbladder adenocarcinoma	C239 814
GCT: gastric carcinoid tumor	C160-C166, C168-C169 824
GISS: gastrointestinal stromal sarcoma	C160-C166, C168-C169 893
HCC: hepatocellular carcinoma	C220 817
ICC: intrahepatic cholangiocarcinoma	C221 816
PAC: pancreatic adenocarcinoma	C250-C254, C257-C259 814
PCT: pancreatic carcinoid tumor	C250-C254, C257-C259 824
PIDC: pancreatic infiltrating duct carcinoma	C250-C254, C257-C259 850
READ: rectal adenocarcinoma	C199, C209 814
RECT: rectal carcinoid tumor	C199, C209 824
REPA: rectal papillary adenocarcinoma	C199, C209 826
SBA: small bowel adenocarcinoma	C170-C173, C178-C179 814
SBCT: small bowel carcinoid tumor	C170-C173, C178-C179 824

*Available in the ICD-O-3 SEER Site/Histology Validation Lists (https://seer.cancer.gov/icd-o-3/)

The p-value less than 0.050 was considered statistically significant.

Results

Patient characteristics

This retrospective study collected a total of 685,829 cases from the SEER database, spanning from 2010 to 2019. The raw data downloaded from the SEER database spans a period of ten years, from 2010 to 2019. Due to the registration of data regarding whether patients have distant metastases (including those in organs and lymph nodes) beginning in 2016, the patients analyzed in this article are from the years 2016 to 2019. Due to the sensitive personal information of the patients involved, the SEER database does not provide specific dates, only monthly information. The diagnosis period is from January 1, 2016, to December 31, 2019, and the follow-up period ends on December 31, 2019. The latest data can be accessed by applying on the official SEER website (https://seer.cancer.gov/). After the removal of incomplete or non-compliant data, Table 1 shows a total of 119,760 cases of gastrointestinal cancers and subgroups included in this study, based on the data selection criteria outlined in Fig. 1. Patients were divided into the OP group and the MP group. The MP group was further subdivided into the FMP group and the NFMP group based on the sequence of occurrence of the patient's cancer. The summary of the

baseline comparison of patient characteristics in each group was presented in Fig. 2 (refer to Supplementary Table 1 for details).

Outcomes

The primary outcome was the OS of the patients. The first type of OS comparison was between the OP and MP groups for each histological type of gastrointestinal cancer. The further subgroup analysis of OS was conducted between the OP, FMP, and NFMP groups, with the latter two groups being separated from the MP group (Fig. 3).

Analysis of gastrointestinal cancers at various primary sites

Liver

This study included the first and second common primary liver cancers, HCC and ICC, respectively (Table 2). Patients in the OP group were generally younger than those in the MP group, while early-stage patients in the MP group were more than those in the OP group. The treatment strategies in the OP, FMP, and NFMP groups differed, but the overall systemic therapy ratio was not statistically significant. There were statistical differences in cancer metastasis and months from diagnosis to treatment (MFDTT) between the OP, FMP, and NFMP groups (Fig. 2, Supplementary Table 1.1). The OS comparison between the OP group and the MP group was statistically significant in ICC but not in HCC. The MP group was divided into the FMP and the NFMP groups for further subgroup analysis of OS. Patients with HCC in the FMP group had better OS than those in the OP group, and patients with ICC either in the FMP group or the NFMP group had better OS (Fig. 3). After conducting univariate and multivariate analyses, we found that patients in the FMP group could serve as an independent lower risk factor for OS in patients with HCC or ICC (Figs. 4 and 5, Supplementary Table 2.1).

Gallbladder

GBAC was the most common subtype of gallbladder cancer, accounting for approximately 80% of gallbladder cancer cases eligible for this study (Table 2). Patients with GBAC in the MP group, including the FMP and NFMP group, were receiving more passive treatments, such as fewer surgical procedures of other regional/distant sites (Surg Oth Reg/Dis), chemotherapy, and systemic treatments (Fig. 2, Supplementary Table 1.2). This therapy strategy might be related to poor OS in the GBAC patients, with no statistically significant difference between the OP and MP groups (Fig. 3). The univariate and multivariate analyses conducted with the Cox regression model demonstrated that age, p-Grade (pathological-Grade), stage, and positive metastases were independent risk factors for OS (Figs. 4 and 5, Supplementary Table 2.2).

Pancreas

The main histologic types of pancreatic cancers were PAC, PIDC, and PCT, with approximately 43%, 27%, and 20% of the selected cases (Table 2). Patients with PAC in the MP group had better tumor related characteristics, such as a lower proportion of advanced stage tumors, a higher proportion of regional lymph node surgery (RLN-Sur) with lower positive RLN, receiving a higher proportion of systemic therapy, and fewer metastases. Thus, the

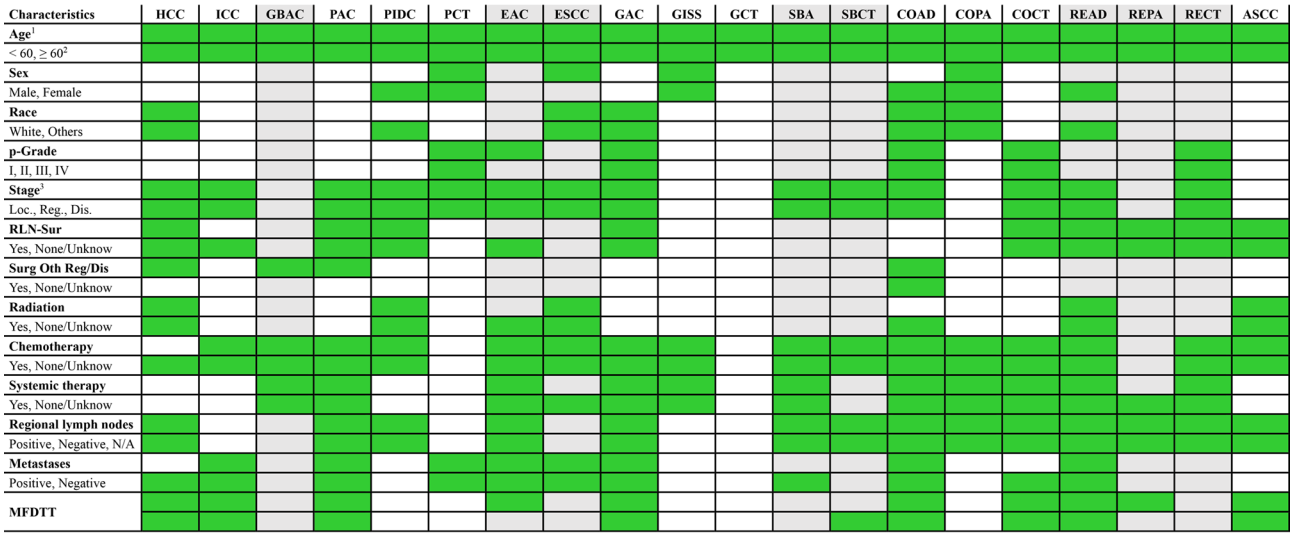


Fig. 2 Characteristics of patients with various primary gastrointestinal cancers in the United States from 2016 to 2019. [1] The bold characteristics correspond to the comparison between the OP and MP groups. [2] The non-bold characteristics correspond to the comparison between the OP, FMP, and NFMP groups. [3] Combined summary stage based on the SEER database, including localized, regional, and distant. (https://seer.cancer.gov/seerstat/variables/seer/lrd-stage/). *Variables highlighted in green are statistically significant

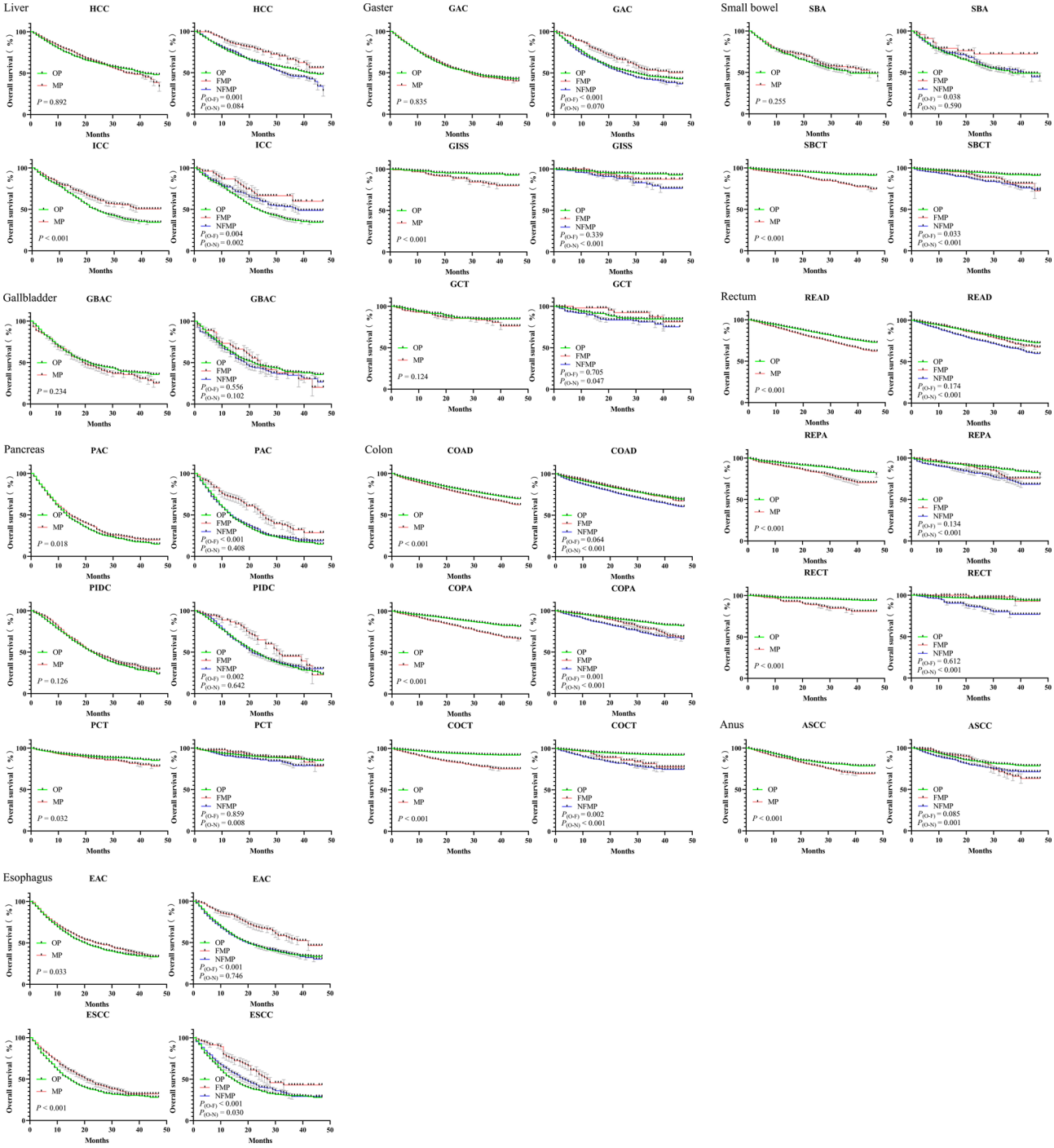


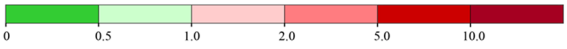
Fig. 3 Overall survival of patients with various primary gastrointestinal cancers in the United States from 2016 to 2019

patients with PAC in the MP group, particularly in the FMP group, had a better OS than those in the OP group (Fig. 3).

Similar characteristics appeared in the PIDC patients with a lower proportion of advanced stage tumors, a higher proportion of RLN-Sur with lower positive RLN (Fig. 2, Supplementary Table 1.3). The OS of patients PIDC in the FMP group was better than those in the OP group. The PCT cases in this study showed that the OP group had more low-grade patients, but a higher proportion of patients with advanced stage and metastases than the MP group. However, the patients with PCT in the OP group presented higher OS than those in the MP group, and the NFMP group particularly (Fig. 3).

Combined with the results of the univariate and multivariate analyses, we found that age, p-Grade, stage,

Variables	HCC	ICC	GBAC	PAC	PIDC	PCT	EAC	ESCC	GAC	GISS	GCT	SBA	SBCT	COAD	COPA	COCT	READ	REPA	RECT	ASCC
Age (< 60 vs. ≥ 60)	1.231		1.303	1.157	1.155	1.978				3.195	1.670	1.453	3.581	2.027	2.408	6.668	1.980	2.369	2.212	1.376
Sex (Male vs. Female)	0.880	0.739		0.902		0.685		0.792			0.503					0.732	0.921	0.726	0.478	0.668
Race (White vs. Others)									0.839					0.914			1.178		0.637	1.420
p-Grade (I/II vs. III/IV)	1.600	1.568	1.980	1.761	1.523	9.348	1.754	1.260	1.591	2.120	11.758	1.778	4.635	1.942	1.840	11.464	2.083		44.857	
Stage (Loc. vs. Reg./Dis.)	3.340	3.054	4.105	1.588	2.259	4.418	3.056	2.079	3.248	3.517	6.590	2.767	0.738	2.667	2.435	5.552	2.159	2.150	25.961	2.734
Metastases (No vs. Yes)	4.740	2.884	3.201	2.603	2.707	7.047	3.485	2.631	3.808	6.101	9.694	3.067		4.273	6.452	11.605	4.296	6.140	23.563	5.354
OP vs. FMP	0.629	0.485		0.564	0.619		0.517	0.527	0.667			0.535	1.604		1.523	2.188				
OP vs. NFNP		0.717				1.464		0.846		2.803	1.519		2.412	1.395	2.018	3.326	1.630	1.943	4.202	1.434

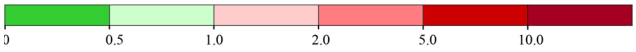


The hazard ratio of variables affecting overall survival in univariate analysis.

*Variables with hazard ratios have statistical significance.

Fig. 4 Univariate analysis of variables affecting overall survival in patients with various primary gastrointestinal cancers in the United States from 2016 to 2019

HCC	ICC	GBAC	PAC	PIDC	PCT	EAC	ESCC	GAC	GISS	GCT	SBA	SBCT	COAD	COPA	COCT	READ	REPA	RECT	ASCC
1.256		1.378	1.240	1.211	1.837				3.009		1.529	3.042	2.363	2.426	3.246	2.167	2.300		1.410
	0.749						0.861									0.926	0.729		0.645
								0.879								1.170			1.302
1.387	1.343	1.632	1.528	1.480	3.998	1.464	1.162	1.315		6.720	1.482	4.355	1.551	1.529	3.836	1.778		13.463	
2.772	2.425	3.042	1.161	2.085	1.507	1.947	1.668	2.183			1.966	0.748	1.865	1.663	1.500	1.477	1.636	3.040	2.268
2.271	1.870	2.581	2.348	2.494	3.909	2.740	2.251	2.883	3.714	3.943	2.666		3.800	4.711	4.402	4.023	4.844	1.901	3.841
0.671	0.458		0.599	0.652		0.642	0.550	0.764			0.530			1.443					
		1.248				1.195		1.245	2.415	1.768		1.914	1.360	1.746	2.413	1.450	1.644	1.865	1.493



The hazard ratio of variables affecting overall survival in multivariate analysis.

*Variables with hazard ratios have statistical significance.

Fig. 5 Multivariate analysis of variables affecting overall survival in patients with various primary gastrointestinal cancers in the United States from 2016 to 2019

and positive metastases were high-risk factors for OS, whereas the FMP in patients with PAC or PIDC was a low-risk factor for OS but not with PTC (Figs. 4 and 5, Supplementary Table 2.3).

Esophagus

The two most prevalent histological types of esophageal cancer were EAC and ESCC, accounting for approximately 64% and 29% of the selected cases, respectively (Table 2). The patients EAC in the MP group exhibited a higher proportion of patients with early-stage and age (≥60), as well as lower rates of positive RLN and metastases, in comparison to the OP group. The subsequent subgroup analysis revealed that patients in the FMP group received a higher proportion of RLN-Sur, radiation therapy, and systemic therapy compared to the OP group (Fig. 2, Supplementary Table 1.4). Consequently, patients with EAC enrolled in the MP group had a superior OS compared to the OP group. The statistically significant difference was observed between the OP and FMP groups (Fig. 3).

In patients with ESCC, the proportion of female patients in the MP group was higher than that in the OP group. The MP group had a higher proportion of patients with early-stage tumors, fewer metastases, and received chemotherapy and radiation therapy (Fig. 2, Supplementary Table 1.4). In the OS analysis, we found that the OS in the MP group, whether in the FMP or NFMP group, was better than that in the OP group (Fig. 3).

There were similarities and differences in the risk factors for OS in EAC and ESCC. The age, p-Grade, stage, and positive metastases were high-risk factors, while the FMP was found to be a low-risk factor in EAC and ESCC. In patients with EAC, the NFMP was regarded as a high-risk factor in multivariate analysis but not in the univariate analysis. Gender female was considered to be an independent low-risk factor in patients with ESCC (Figs. 4 and 5, Supplementary Table 2.4).

Gaster

The study examined three histologic types of gastric cancers, including GAC, GISS, and GCT, which accounted for approximately 59%, 12%, and 9% of cases, respectively (Table 2). Patients with GAC exhibited various differences in characteristics, except for gender, Surg Oth Reg/Dis, and radiation therapy between the OP and MP groups. Patients with GISS exhibited characteristic differences in age, gender, chemotherapy, and systemic therapy. Patients with GCT exhibited only a characteristic difference in age (Fig. 2, Supplementary Table 1.5).

Significant differences in OS were observed in the comparison between the OP and FMP groups in GAC, the OP and MP groups in GISS, the OP and NMP groups

in GISS, and the OP and NFMP groups in GCT. All OP groups had better OS in the above comparison (Fig. 3).

Three types of gastric cancers possessed different independent risk factors for OS. For patients with GAC, the high-risk factors were p-Grade, stage, positive metastases, and NFMP, and the low-risk factors were female and FMP. For patients with GISS, the high-risk factors for OS were age (≥60), positive metastases, and the NFMP. Among patients with GCT, the high-risk factors were p-Grade, positive metastases, and the NFMP (Figs. 4 and 5, Supplementary Table 2.5).

Small bowel

The two most common histologic types of cancers in the small bowel were SBA and SBCT, with 1,137 cases (22%) and 3,337 cases (64%) included in this study (Table 2). Patients with SBA or SBCT in the MP group had a higher proportion of age (≥60), a higher proportion of advanced stage tumors, and a lower rate of positive RLN compare to the OP group (Fig. 2, Supplementary Table 1.6). In patients with SBA, the OS of the FMP groups was superior to that of the OP group. Regarding SBCT, the OP group demonstrated superior OS compared to the MP group (Fig. 3).

Age (≥60) and p-Grade were independent high-risk factors for OS in both SBA and SBCT. The stage and positive metastases were independent high-risk factors for OS in SBA, while the FMP was a low-risk factor. In regard to SBCT, the NFMP was a high-risk factor for OS. The advanced stage was found to be an independent low-risk factor (Figs. 4 and 5, Supplementary Table 2.6).

Colon

Approximately 76%, 5%, and 5% of the selected cases of colon cancers were classified as COAD, COPA, and COCT, respectively (Table 2). Patients with COAD in the OP group exhibited statistically different characteristics compared to the MP group including a higher proportion of patients under the age of 60, a higher proportion of low-grade and early-stage patients, a shorter MFDTT, and receiving more positive treatments. Nevertheless, the positive rates of RLN and metastases in the OP group were higher than those in the MP group (Table 4). The characteristic differences between the OP group and the MP group in patients with COPA were age, gender, race, p-Grade, stage, chemotherapy, systemic therapy, and positive rates of RLN. In regard to COCT, there were several characteristic differences between the OP and MP groups, except for gender, race, Surg Oth Reg/Dis, and radiation therapy (Fig. 2, Supplementary Table 1.7).

The OS analysis of patients with these three types of colon cancers demonstrated that patients in the OP group obtained superior OS than those in the MP group, regardless of whether they were in the FMP or NFMP group (Fig. 3). Age (≥60), low p-Grade, advanced stage, and positive metastases were independent high-risk factors for OS in patients with COAD, COPA, or COCT. The FMP was an independent high-risk factor for OS in patients with COPA. Whereas the NFMP was an independent high-risk factor for OS in patients with COAD, COPA, or COCT (Tables 5 and 6; Figs. 4 and 5, Supplementary Table 2.7).

Rectum

The three types of rectal cancers enrolled in the study were READ, REPA, RECT, with approximately 77%, 6%, and 8% of the selected cases (Table 2). Patients with READ had various statistically different characteristics between the OP and MP groups, except for gender, race, and p-Grade. Patients with READ in the OP group, in comparison to the MP group, had a lower proportion of patients over the age of 60 and several tumor-related characteristics including a higher proportion of low-grade patients, a higher proportion of positive RLN and metastases, and a higher proportion of patients receiving positive treatments with shorter MFDTT. Similar characteristic differences were observed in patients with RECT, excluding metastases, MFDTT, and radiation therapy. Patients with REPA in the OP group had a higher proportion of RLN-Sur with a lower positive rate of RLN compared to those in the MP group (Fig. 2, Supplementary Table 1.8).

According to OS analyses for patients with READ, REPA, or RECT, patients in the OP group exhibited superior OS than those in the MP group. Further subgroup analysis revealed statistical differences in OS between the OP group and the NFMP group in READ, REPA, and RECT (Fig. 3). The univariate and multivariate analyses demonstrated that age (≥60), non-white race, low p-Grade, advanced stage, positive metastases, and the NFMP were independent high-risk factors, while gender female was an independent low-risk factor for OS in patients with READ. In patients with REPA, we found that independent high-risk factors were age (≥60), advanced stage, positive metastases, and the NFMP, while independent low-risk factor was gender female. In regard to RECT, the independent high-risk factors for OS were low p-Grade, advanced stage, positive metastases, and the NFMP (Figs. 4 and 5, Supplementary Table 2.8).

Anus

The most common type of anal cancer that occurs in the anus is squamous cell carcinoma. The study comprised 2,999 cases of ASCC, which accounted for 85% of the total cases of anal cancer (Table 2). Patients in the OP group received a lower ratio of RLN-Sur, had a lower rate of positive RLN, and received positive treatment such as radiation therapy and chemotherapy compared to the

Table 4 Characteristics of patients with colon adenocarcinoma (COAD) in various patient groups in the United States from 2016 to 2019

Characteristics	COAD			
	OP	MP		*P*
		FMP	NFMP	
Age	12 698, 26 354	2126, 11 774		0.000
< 60, ≥ 60		823, 2639	1303, 9135	0.000
Sex	19 594, 19 458	6991, 6909		0.807
Male, Female		1856, 1606	5135, 5303	0.000
Race	29 754, 9298	11,424, 2476		0.000
White, Others		2738, 724	8686, 1752	0.000
p-Grade	3702,	1408, 9949, 2283, 260		0.000
I, II III, IV	28 717, 5987, 646	324, 2557, 517, 64	1084, 7392, 1766, 196	0.000
Stage	13 444, 19 264, 6344	5599, 6666, 1635		0.000
Loc., Reg., Dis.		1272, 1768, 422	4327, 4898, 1213	0.000
RLN-Sur	36 856, 2196	13 159, 741		0.196
Yes, None/Unknow		3291, 171	9868, 570	0.221
Surg Oth Reg/Dis	2665, 36 387	846, 13 054		0.003
Yes, None/Unknow		258, 3204	588, 9850	0.000
Radiation	558,	188, 13 712		0.512
Yes, None/Unknow	38 454	62, 3400	126, 10 312	0.033
Chemotherapy	15 767, 23 285	4226, 9674		0.000
Yes, None/Unknow		1297, 2165	2929, 7509	0.000
Systemic therapy	14 880, 24 172	4011, 9889		0.000
Yes, None/Unknow		1243, 2219	2768, 7670	0.000
Regional lymph nodes	15 948, 21 394, 1710	4860, 8461, 579		0.000
Positive, Negative, N/A		1276, 2054, 132	3584, 6407, 447	0.000
Metastases	5907,	1493, 12 407		0.000
Positive, Negative	33 145	386, 3076	1107, 9331	0.000
MFDTT	0.67 ± 1.03	0.77 ± 1.14		0.000
		0.79 ± 1.14	0.76 ± 1.15	0.000
Total	39 052	13 900		52 952
		3462	10 438	

Table 5 The univariate analysis of variables affecting overall survival in patients with colon adenocarcinoma (COAD) in the United States from 2016 to 2019

Variables	COAD		
	P	HR	95%CI
Age (< 60 vs. ≥ 60)	0.000	2.027	1.924–2.135
Sex (Male vs. Female)	0.751	0.994	0.956–1.033
Race (White vs. Others)	0.000	0.914	0.871–0.959
p-Grade (I/II vs. III/IV)	0.000	1.942	1.859–2.029
Stage (Loc. vs. Reg./Dis.)	0.000	2.667	2.534–2.808
Metastases (No vs. Yes)	0.000	4.273	4.101–4.453
OP vs. FMP	0.070	0.928	0.856–1.006
vs. NFNP	0.000	1.395	1.332–1.460

Table 6 The multivariate analysis of variables affecting overall survival in patients with colon adenocarcinoma (COAD) in the United States from 2016 to 2019

Variables	COAD		
	P	HR	95%CI
Age (< 60 vs. ≥ 60)	0.000	2.363	2.241–2.492
Sex (Male vs. Female)			
Race (White vs. Others)	0.065	0.955	0.910–1.003
p-Grade (I/II vs. III/IV)	0.000	1.551	1.484–1.622
Stage (Loc. vs. Reg./Dis.)	0.000	1.865	1.765–1.970
Metastases (No vs. Yes)	0.000	3.800	3.636–3.972
OP vs. FMP	0.228	0.952	0.878–1.032
vs. NFNP	0.000	1.360	1.298–1.425

MP group (Fig. 2, Supplementary Table 1.9). Hence, the OS of the OP group was significantly superior to that of the MP group. A subsequent subgroup analysis revealed a statistical difference in OS between the OP group and the NFMP group (Fig. 3). Gender was an independent risk factor for OS in ASCC, with females at low risk. Age (≥60), non-white race, advanced stage, positive metastases, and the NFMP were identified as high-risk factors for OS in patients with ASCC (Figs. 4 and 5, Supplementary Table 2.9).

Discussion

The study aims to analyze the sequence and outcome of PGICs based on the SEER database, which is a real-world population database. Many previous studies based on the SEER database have revealed the relationships between population characteristics and prognoses in various cancers. It is inevitable to consider real-life factors when studying risk factors related to diseases in the real world. A study involving nine major cancers in the SEER database from January 2004 to December 2010 suggested that race and ethnicity were associated with the stage at diagnosis, treatment, and survival [7]. There are disparities in the customs and practices of diverse ethnic groups, as well as in the economic and medical conditions of their respective regions. An analysis of HCC based on the SEER database demonstrated that treatment delays were more common among Black patients and low-income communities [8]. As shown in Fig. 2 and Supplementary Table 1.1 of our study, the MFDTT of non-white patients with HCC was significantly longer than that of white patients with HCC. A study on gastric cancer revealed that race was associated with significant differences in anatomic subsite, subsite-specific distribution of risk factors (such as Helicobacter pylori), and occurrence sites of tumors [9]. The disparities in OS across races were not only related to racial differences, but also to variations in the treatment of comorbidities and diseases [10].

It is acknowledged that treatment therapy is a significant factor affecting the prognosis of cancer. Previous studies have suggested that, in addition to surgery as a primary treatment, the application and sequence of radiotherapy and chemotherapy are independent risk factors for OS [11, 12]. Radiotherapy used before surgery was found to be beneficial for patients with locally advanced esophageal cancer and obtained a better OS in patients with stage-III ESCC compared to radiotherapy administered after surgery [13, 14]. Furthermore, radiotherapy has been reported to have the impact of reducing rectal cancer recurrence and second primary cancers by using radiation therapy before surgery [15]. Meanwhile, many researchers have realized that the sequence of treatments, such as surgery, radiotherapy, and chemotherapy, is closely related to the prognosis of primary and metastatic cancers [16, 17].

Cancer survivors have increased with the advancement of modern medical technology, which means that more patients may experience multiple primary cancers during their lifetimes. Major studies based on the SEER database of cancer survivors have been conducted and are concerned [3, 4, 6, 18]. Human systems are composed of multiple organs, which are closely related during embryonic development. Organs of the same system exhibit both histological differences and similarities. A study on renal cancer suggested that first primary renal cell carcinoma could potentially affect the pathogenesis and clinical features of second primary glioblastoma [19]. There were indeed differences in prognosis among one primary only or first primary of multiple primaries and second primary or subsequent primary tumor in patients with malignant gliomas [20]. Another study on liver cancer showed that patients with the first primary HCC were still at a high risk of developing second primary malignancies [5].

Our study demonstrated the characteristics and outcomes of patients with various PGICs in different sequences of cancer occurrence. These differences between different groups include age, stage, p-Grade, treatment therapies, metastases, and MFDTT. It was reasonable that patients in the MP group were older than those in the OP group. Age over 60 was identified as an independent high-risk factor for most cancers in the study, with the exception of ICC, EAC, ESCC, GAC, GCT, and RECT (Figs. 4 and 5). The differences of other characteristics were influenced by numerous real-world factors, including the habits and customs of diverse populations, the economic and medical levels of the regions, and the treatment intentions of various patient groups. Hence, our retrospective study focused on the influence of the sequence of patients with PGICs.

Our study found that patients in the FMP group or the NFMP group could serve as risk factors for OS in comparison to the OP group. FMP served as an independent low-risk factor for OS in patients with several PGICs, including HCC, ICC, PAC, PIDC, EAC, ESCC, GAC, and SBA. NFMP served as a high-risk factor for OS in patients with most of cancers in the study, with the exception of HCC, ICC, PAC, PIDC, PCT, ESCC, and SBA. Combined with the OS of these gastrointestinal cancers in Fig. 3, patients with high mortality cancers in the FMP group seem to have superior OS to those in the OP group. However, patients in the FMP group were cancer survivors who might survive for relatively long time until other primary cancers occur. Further study ought to focus on the factors that contribute to the prolonged survival of these patients. Whether in certain patients with high-risk genes for cancers who also have significant treatment sensitivity, including surgical treatment, chemotherapy, radiation therapy, and other systemic treatments. Furthermore, patients with high-mortality cancers like ICC and ESCC in the NFMP group also have better OS than those in the OP group. It is noted that the time of OS in the NFMP group counted from diagnosis of the cancer and not related to previous cancers.

As for PGICs with good OS shown in Fig. 3, the OP group exhibited better OS than the NFMP group in patients with GISS, SBCT, COAD, COPA, COCT, READ, REPA, RECT, or ASCC. The outcomes might be correlated with positive treatment therapies and desire in

patients with the initial diagnosis of cancer. At the same time, medical staff should realize that positive treatment therapies are beneficial for patients with multiple PGICs. Multiple factors may contribute to varying prognoses for patients in the NFMP group, including, but not limited to: (1) Received anticancer therapy, general condition and tolerance are poor. (2) Patients ' psychological burden, economic ability, and other practical reasons affect follow-up treatment. (3) Medical personnel adopt a relatively conservative treatment approach based on experiences. (4) The patient's tolerance to anticancer therapy leads to poor efficacy. (5) Patients are sensitive to anticancer treatment and are able to survive the course of cancer with poor prognosis until they develop other primary cancer again.

With advancements in modern medical treatments, the number of cancer survivors is gradually increasing. In addition to the disease itself and the anticancer treatments, treatment compliance is also a crucial factor that influences patient prognosis. This issue involves numerous practical factors, including individual economic situation, transportation availability, regional healthcare standards, and medical insurance, among others. Therefore, in subsequent real-world population studies, subgroup analyses should consider not only factors such as race, gender, and age but also the baseline characteristics of patients that affect treatment compliance. Another interesting point is that in specific cancer types with poor prognoses, such as ICC, PAC, EAC, ESCC, patients in the MP group have better OS than those in the OP group. We believe that the possible factors include, but are not limited to: (1) The patient has a positive response to anticancer treatments; (2) The patient demonstrates good treatment compliance; (3) Medical personnel adopt a proactive treatment philosophy. The above factors warrant further detailed research to improve the OS of cancer patients with poor prognoses.

When a patient develops other PGICs from only one PGIC, the survival time of the first PGIC is classified as the FMP in the MP, not in the OP. The survival time for other PGICs is calculated from the date of diagnosis and classified as the NFMP. In the SEER database, a few patients may be classified in both the FMP and NFMP groups simultaneously. Based on the "survival months" collected from the database, we found that the survival time of the FMP group includes that of the NFMP group. Previous studies have often focused on primary and secondary cancers. This study aims to conduct a preliminary analysis and comparison of patients with a primary cancer and those with multiple cancers (two or more primary cancers) in the digestive tract. The survival curves of the FMP group and the NFMP group differed from those of the OP group across various specific cancers (Fig. 3). This was determined by comparing the OP group with the MP group, the OP group with the FMP group, and the OP group with the NFMP group. Although there is an overlap in survival times between the FMP and NFMP groups, we believe that distinguishing between patients in the FMP and NFMP groups is essential for future prospective studies.

To the best of our knowledge, this is the first comprehensive analysis focusing on the sequences and outcomes of PGICs. There are still certain aspects that require enhancement in further research. The study retrospectively collected numerous cases but lacked prospective cases. More precise subgroup analysis is needed for occurrence sequences of different cancers due to the inherent differences between the OP group and the MP group. Based on the comprehensive analysis of this study, further prospective studies could be conducted to focus on the influence of cancer occurrence sequences, treatment selection for specific patients, and treatment sensitivity in patients with multiple cancers.

Conclusion

Our study demonstrated that malignant tumors in the same site of the digestive system, but with diverse histologic types, present different prognoses. This phenomenon was also observed in patients with different sequences of PGICs. Patients with high mortality cancers in the FMP group may have potential factors, such as high treatment sensitivity, that could lead to improved OS. Patients with low mortality cancers in the NFMP group could benefit from positive treatment therapies. The sequence of cancer occurrences, subsequent detections, and establishing correct expectations for cancer treatment require greater concentration and research due to the rising number of cancer survivors. Further research, especially prospective studies, is meaningful in uncovering the potential factors that can contribute to the survival of cancer patients.

Abbreviations

CI	Confidence interval
Dis.	Distant
Fig.	Figure
FMP	First of multiple primaries
ICO-D-3	International classification of diseases for oncology third edition
Loc.	Localized
MFDTT	Months from diagnosis to treatment
MP	Multiple primaries
NFMP	Non-first of multiple primaries
OP	One primary
PGICs	Primary gastrointestinal cancers
p-Grade	Pathological Grade
Reg.	Regional
RLN	Regional lymph node
RLN-Sur	Regional lymph node surgery
Surg Oth Reg/Dis	Surgical procedure of other regional/distant sites

Supplementary Information

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Supplementary Material 1

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Author contributions
The contribution of ZH include conceptualization, data curation, formal analysis, methodology, investigation, software, writing–original draft, writing–review and editing. The contribution of DT include resources, conceptualization, formal analysis, supervision, writing–review and editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Competing interests
The authors declare no competing interests.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and Mortality Worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Zorn AM. Development of the digestive system. Semin Cell Dev Biol. 2017;66:1–2.
3. Sung H, Hyun N, Leach CR, Yabroff KR, Jemal A. Association of First Primary Cancer with risk of subsequent primary Cancer among survivors of adult-onset cancers in the United States. JAMA. 2020;324(24):2521–35.
4. Murphy CC, Gerber DE, Pruitt SL. Prevalence of prior Cancer among persons newly diagnosed with Cancer: an initial report from the Surveillance, Epidemiology, and end results program. JAMA Oncol. 2018;4(6):832–6.
5. Kong J, Yu G, Si W, Li G, Chai J, Liu Y, Liu J. Second primary malignancies in patients with Hepatocellular Carcinoma: a Population-based analysis. Front Oncol. 2021;11:713637.
6. Zhou H, Huang Y, Qiu Z, Zhao H, Fang W, Yang Y, Zhao Y, Hou X, Ma Y, Hong S, et al. Impact of prior cancer history on the overall survival of patients newly diagnosed with cancer: a pan-cancer analysis of the SEER database. Int J Cancer. 2018;143(7):1569–77.
7. Zhang C, Zhang C, Wang Q, Li Z, Lin J, Wang H. Differences in stage of Cancer at diagnosis, treatment, and survival by race and ethnicity among leading Cancer types. JAMA Netw Open. 2020;3(4):e202950.
8. Wagle NS, Park S, Washburn D, Ohsfeldt RL, Rich NE, Singal AG, Kum HC. Racial, ethnic, and socioeconomic disparities in treatment Delay among patients with Hepatocellular Carcinoma in the United States. Clin Gastroenterol Hepatol. 2023;21(5):1281–e12921210.
9. Gupta S, Tao L, Murphy JD, Camargo MC, Oren E, Valasek MA, Gomez SL, Martinez ME. Race/Ethnicity-, socioeconomic Status-, and anatomic subsite-specific risks for gastric Cancer. Gastroenterology. 2019;156(1):59–e6254.
10. Soneji S, Tanner NT, Silvestri GA, Lathan CS, Black W. Racial and ethnic disparities in early-stage Lung Cancer Survival. Chest. 2017;152(3):587–97.
11. López Alfonso JC, Poleszczuk J, Walker R, Kim S, Pilon-Thomas S, Conejo-Garcia JJ, Soliman H, Czerniecki B, Harrison LB, Enderling H. Immunologic consequences of sequencing Cancer radiotherapy and surgery. JCO Clin cancer Inf. 2019;3:1–16.
12. Scampa M, Kalbermatten DF, Oranges CM. Squamous cell carcinoma of the Vulva: a survival and epidemiologic study with focus on surgery and Radiotherapy. J Clin Med 2022, 11(4).
13. Yu J, Ouyang W, Li Y, Hu J, Xu Y, Wei Y, Liao Z, Liu Y, Zhang J, Xie C. Value of radiotherapy in addition to esophagectomy for stage II and III thoracic esophageal squamous cell carcinoma: analysis of surveillance, epidemiology, and end results database. Cancer Med. 2019;8(1):21–7.
14. Wojcieszynski AP, Berman AT, Wan F, Plastaras JP, Metz JM, Mitra N, Apisarnthanarax S. The impact of radiation therapy sequencing on survival and cardiopulmonary mortality in the combined modality treatment of patients with esophageal cancer. Cancer. 2013;119(11):1976–84.
15. Smith-Gagen J, Goodwin GA 3rd, Tay J. Multiple primary tumors following stage II and III rectal cancer in patients receiving radiotherapy, 1998–2010. J Cancer Res Clin Oncol. 2014;140(6):949–55.
16. Shridhar R, Almhanna K, Hoffe SE, Fulp W, Weber J, Chuong MD, Meredith KL. Increased survival associated with surgery and radiation therapy in metastatic gastric cancer: a Surveillance, Epidemiology, and end results database analysis. Cancer. 2013;119(9):1636–42.
17. Rocque GB, Kandhare PG, Williams CP, Nakhmani A, Kenzik KM. Visualization of Sequential Treatments in Metastatic Breast Cancer. 2018.
18. Anderson C, Mayer DK, Nichols HB. Trends in the proportion of second or later primaries among all newly diagnosed malignant cancers. Cancer. 2021;127(15):2736–42.
19. Zhang GT, Liu Q, Zuo FX, Liu HJ, Wang SQ, Yuan Q, Liu AS, Hu K, Meng XL, Wang WJ, et al. Clinical and genomic features in patients with second primary glioblastoma following first primary renal cell carcinoma. BMC Cancer. 2023;23(1):104.
20. Nguyen HS, Doan NB, Gelsomino M, Shabani S, Awad AJ, Kaushal M, Mortazavi MM. Management and survival trends for adult patients with malignant gliomas in the setting of multiple primary tumors: a population based analysis. J Neurooncol. 2019;141(1):213–21.

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