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Epidemiology and survival analysis according to the histologic subtype of pancreatic cancer: a population-based cohort study

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Purpose: This study investigated epidemiologic features of patients with pancreatic cancer in Korea, according to the histologic subtypes.
Methods: The Korea Central Cancer Registry data on patients with pancreatic cancer from 1999 to 2019 were reviewed. The 101,446 patients with pancreatic cancer (C25 based on the International Classification of Diseases, 10th revision) were allocated according to the following morphological codes: A, endocrine; B, carcinoma excluding cystic and mucinous; C, cystic or mucinous; D, acinar cell; and E, sarcoma and soft tissue tumor.
Results: The distribution of each pancreatic cancer subtype group in Korea from 1999 to 2019 was as follows: A, n = 3,101 (3.1%); B, n = 95,051 (93.7%); C, n = 2,856 (2.8%); D, n = 299 (0.3%); and E, n = 139 (0.1%). In group B, 49.2% of patients were aged >70 years, and half of them did not receive treatment within 4 months of diagnosis. In addition, only 30.9% of the patients were in the localized and regional stage in which surgical treatment was possible. Pancreatic cancer occurred more frequently in females than in males only in group C. Between 1999 and 2019, the average annual percentage changes in the age-specific incidence rates were positive in groups A (13.9%, $P < 0.001$), B (1.0%, $P < 0.001$), and C (6.5%, $P = 0.025$). Significant improvements in 5-year survival rates over time were observed in subtypes A, B, and C.
Conclusion: The subgroups of pancreatic cancer show different epidemiologic features, including incidences, treatment rates, and prognoses.
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Key Words: Epidemiology, Neoplasms by histologic type, Pancreatic neoplasms, Survival rate, Therapeutics

INTRODUCTION

Pancreatic cancer is one of the most malignant diseases and its prognosis is dismal [1,2]. In contrast to the steady improvement in survival for most cancers, advances have been slow for pancreatic cancers, for which the 5-year relative survival rates are currently 9% in the United States and 13.9% in Korea [3,4]. Globally, pancreatic cancer remains the seventh leading

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cause of cancer deaths, with limited improvements in prognosis despite advances in diagnostic and treatment modalities [5]. This low survival rate is partly due to the aggressive biologic characteristics and high rate of an advanced stage at the time of diagnosis of pancreatic cancer. In addition, the rate of no active treatment for pancreatic cancer is high despite the worldwide adoption of guidelines for pancreatic cancer diagnosis and treatment, including the National Comprehensive Cancer Network, American Society of Clinical Oncology, and European Society for Medical Oncology [6-8]. The annual cancer statistics from the Korea Central Cancer Registry (KCCR) have shown the incidence and mortality rates of pancreatic cancer in Korea. The incidence and mortality of pancreatic cancer had increased gradually from 1997 and 2002, respectively, when these data started to be collected and available for use [9]. In the recent epidemiologic reports for cancer statistics, pancreatic cancer was the eighth (3.2% of all new cancers) most common cancer and ranked fifth in the most common causes of cancer-related death in Korea [4]. However, they could not show the epidemiologic features of individual histologic subgroups of pancreatic cancer. In addition, clinical studies based on data from individual hospitals have limitations in holistic assessment of the national trend of cancer incidence and prognosis due to the limitations of accessible data range and size. Therefore, this study aimed to investigate the epidemiologic features, survival, and trends in the initial treatment of patients with pancreatic cancer in Korea, according to the histologic subtypes of pancreatic cancer.

METHODS

Ethical statement

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in the prior approval obtained from the Institutional Review Board of National Cancer Center in Goyang, Korea (No. NCC2021-0112). Written informed consent from the participants was waived because of the retrospective design of the study.

Data collection

In 1980, the Korean Ministry of Health and Welfare developed the KCCR, a nationwide, hospital-based cancer registry. Since 1999, the KCCR has collected cancer incidence data nationwide by integrating a national hospital-based KCCR database with data from regional cancer registries. The KCCR built the Korea National Cancer Incidence Database, which has collected data from hospitals, 11 population-based registries, and additional medical record reviews since 2005. In addition, they have provided nationwide cancer incidence, survival, and prevalence statistics annually [10]. This database contains age; sex; region; diagnosis; date; primary cancer site; histologic type; most valid diagnostic method; summary stage of the Surveillance, Epidemiology, and End Results (SEER, since 2006); and first treatment course within 4 months after diagnosis [11]. In this study, the KCCR data of patients with pancreatic cancer in Korea from 1999 to 2019 were retrospectively reviewed. The 101,446 patients with pancreatic cancer coded as C25 based on the International Classification of Diseases, 10th revision [12] were allocated to 5 subgroups according to morphologic codes by referencing previous literature: A, endocrine (n = 3,101; 8150–8157, 8240–8246, 8248–8249, 8002, 8040–8045, and 8013); B, carcinoma excluding cystic (n = 95,051; 8000–8004, 8010–8011, 8020–8039, 8230–8231, 8140–8149, 8490, 8500–8503, 8560–8570, 8571–8576, 8680, and 8980); C, cystic or mucinous (n = 2,856; 8050-8260, 8440–8479, 8480–8482, and 8504); D, acinar cell (n = 299; 8550–8551); and E, sarcoma and soft tissue tumor (n = 139; 86803, 87003, 88003–88063, 88113, 88153, 88303, 88503, 88523, 88543, 88583, 88903, 88913, 89003, 89363, 89803, 91203, 91503, 92403, 95403, and 95813) [4,13,14]. The first course of treatment (FT) was defined as the cancer-directed treatment administered within 4 months after cancer diagnosis according to the SEER program. We divided the FT into 3 groups: surgical FT (surgery with or without chemotherapy or radiotherapy or both), nonsurgical FT (chemotherapy, radiotherapy, and chemotherapy with radiotherapy), and no active treatment (NT).

Statistical analysis

The rates were expressed as crude rates (CRs), age-specific incidence rates (ASIRs), or age-standardized rates (ASRs) per 100,000 individuals. The CR was calculated as the total number of incidence cases divided by the midyear population of the specified years. The ASIR was calculated as the CR for a specified age group, in which the numerator and denominator were referred to the same age group. For the statistical analysis, age was stratified into 6 groups: <40, 40–49, 50–59, 60–69, 70–79, and ≥80 years. The ASRs were standardized using Segi's world standard population and expressed per 100,000 persons [15].

Trends in the ASRs were estimated using joinpoint regression, with a maximum number of 4 joinpoints. The results are summarized as annual percentage changes (APCs) with the best model fit, based on a linear model for the natural log-transformed ASRs.

The APC of the ASRs is calculated as follows:

$$APC = \frac{R_{y+1} - R_y}{R_y} \times 100 = (e^{b1} - 1) \times 100,$$

where $\log(R_y) = b_0 + b_{1y}$, $\log(R_y)$ is the natural log-transformed ASR [16], y = year, b_0 = intercept, and b_1 = slope.

The weighted average of APCs was the average APC (AAPC) with 95% confidence intervals for the entire period of interest [17].

The survival rate of patients with cancer diagnosed between 1999 and 2019 was calculated based on the results of follow-up until December 31, 2020. The 5-year relative survival rate was defined as the ratio of the observed survival of patients with cancer to the expected survival in the general population, adjusting for the effects of other causes of death using the standard population life table provided by Statistics Korea [18]. The relative survival rates were estimated using the Ederer II method with minor modifications based on an algorithm in SAS provided by Paul Dickman [16].

SEER*Stat, Joinpoint 4.7.0.0 (National Cancer Institute), and SAS software ver. 9.4 (SAS Institute) were used for statistical analyses. All statistical tests were 2-tailed, and the results were considered statistically significant at the P-values of <0.05.

RESULTS

Demographics

The distribution of each pancreatic cancer subtype group in Korea from 1999 to 2019 was as follows: A, n = 3,101 (3.1%); B, n = 95,051 (93.7%); C, n = 2,856 (2.8%); D, n = 299 (0.3%); and E, n = 139 (0.1%). As a result of analyzing the age of common incidence by subtype of pancreatic cancer, groups A and D were the most common in their 50s and 60s, whereas groups B and C were the most common in their 60s and 70s. In particular, group B nearly showed half of the cases in their 70s and older. In addition, the rate of NT within 4 months after diagnosis (52.5%) was higher than that in other subgroups. In contrast, the rate of localized SEER stage (7.1%) was lowest in group B. Except for group C, pancreatic cancer occurred more frequently in males than in females (Table 1).

Annual percentage change in the age-specific incidence rates of patients with pancreatic cancer

Between 1999 and 2019, the AAPCs in the ASIRs of patients with pancreatic cancer significantly increased (1.6%, $P < 0.001$), especially in females (2.5%, $P < 0.001$). In the subgroup analysis, the AAPCs in the ASIRs were positive in groups A (13.9%, $P < 0.001$), B (1.0%, $P < 0.001$), and C (6.5%, $P = 0.025$) during the same period (Table 2). The AAPCs in the ASIRs in males were significant in groups A (12.6%, $P < 0.001$,) B (0.2%, $P = 0.021$), C (3.4%, $P < 0.001$), and D (3.9%, $P = 0.013$) during the same period (Supplementary Table 1). In females, the AAPCs in the ASIRs showed significance in groups A (14.5%, $P < 0.001$), B (1.8%, $P < 0.001$), and C (8.5%, $P < 0.001$) (Supplementary Table 2).

Age-specific incidence rates according to the period

The ASIRs of patients with pancreatic cancer showed an

Table 1. Demographic and clinical characteristics of patients in subtypes of pancreatic cancer

Characteristic	Group A	Group B	Group C	Group D	Group E
No. of patients	3,101	95,051	2,856	299	139
Age (yr)					
0–39	354 (11.4)	1,170 (1.2)	398 (13.9)	22 (7.4)	15 (10.8)
40–49	516 (16.6)	5,311 (5.6)	281 (9.8)	42 (14.0)	22 (15.8)
50–59	878 (28.3)	15,393 (16.2)	494 (17.3)	77 (25.8)	28 (20.1)
60–69	811 (26.2)	26,469 (27.8)	816 (28.6)	97 (32.4)	30 (21.6)
70–79	467 (15.1)	30,501 (32.1)	707 (24.8)	48 (16.1)	36 (25.9)
≥80	75 (2.4)	16,207 (17.1)	160 (5.6)	13 (4.3)	8 (5.8)
Sex					
Male	1,588 (51.2)	51,737 (54.4)	1,379 (48.3)	203 (67.9)	74 (53.2)
Female	1,513 (48.8)	43,314 (45.6)	1,477 (51.7)	96 (32.1)	65 (46.8)
First course of treatment					
Any surgery	1,909 (61.6)	18,304 (19.3)	2,046 (71.6)	165 (55.2)	75 (54.0)
Chemo, RT, Chemo + RT	526 (17.0)	26,816 (28.2)	359 (12.6)	82 (27.4)	25 (18.0)
No active treatment	666 (21.5)	49,931 (52.5)	451 (15.8)	52 (17.4)	39 (28.1)
SEER stage (2006–2019)					
Localized	1,377 (44.4)	6,785 (7.1)	858 (30.0)	48 (16.1)	17 (12.2)
Regional	536 (17.3)	22,655 (23.8)	850 (29.8)	84 (28.1)	34 (24.5)
Distant	801 (25.8)	33,080 (34.8)	472 (16.5)	99 (33.1)	49 (35.3)
Unstaged	202 (6.5)	11,721 (12.3)	199 (7.0)	19 (6.4)	8 (5.8)

Values are presented as number only or number (%).
Group A, endocrine; Group B, carcinoma excluding cystic and mucinous; Group C, cystic or mucinous; Group D, acinar cell; Group E, sarcoma and soft tissue tumor.
Chemo, chemotherapy; RT, radiation therapy; SEER, Surveillance, Epidemiology, and End Results.

Table 2. Annual incidence of pancreatic cancer

Year	Both sexes																	
	Group A			Group B			Group C			Group D			Group E			Total		
	No. of cases (%)	CR	ASR	No. of cases (%)	CR	ASR	No. of cases (%)	CR	ASR	No. of cases (%)	CR	ASR	No. of cases (%)	CR	ASR	No. of cases (%)	CR	ASR
1999	22 (0.7)	0.05	0.04	2,522 (2.7)	5.35	5.41	52 (1.8)	0.11	0.11	8 (2.7)	0.02	0.02	4 (2.9)	0.01	0.01	2,608 (2.6)	5.53	5.59
2000	19 (0.6)	0.04	0.04	2,631 (2.8)	5.53	5.40	53 (1.9)	0.11	0.11	3 (1.0)	0.01	0.01	4 (2.9)	0.01	0.01	2,710 (2.7)	5.70	5.56
2001	19 (0.6)	0.04	0.03	2,705 (2.8)	5.65	5.38	49 (1.7)	0.10	0.09	5 (1.7)	0.01	0.01	6 (4.3)	0.01	0.01	2,784 (2.7)	5.81	5.52
2002	26 (0.8)	0.05	0.05	2,972 (3.1)	6.18	5.63	60 (2.1)	0.12	0.11	4 (1.3)	0.01	0.01	3 (2.2)	0.01	0.01	3,065 (3.0)	6.37	5.80
2003	27 (0.9)	0.06	0.05	3,102 (3.3)	6.42	5.64	78 (2.7)	0.16	0.14	15 (5.0)	0.03	0.03	1 (0.7)	0.00	0.00	3,223 (3.2)	6.67	5.87
2004	31 (1.0)	0.06	0.06	3,266 (3.4)	6.74	5.74	98 (3.4)	0.20	0.18	6 (2.0)	0.01	0.01	6 (4.3)	0.01	0.01	3,407 (3.4)	7.03	5.99
2005	41 (1.3)	0.08	0.07	3,612 (3.8)	7.42	6.04	87 (3.0)	0.18	0.15	8 (2.7)	0.02	0.01	7 (5.0)	0.01	0.01	3,755 (3.7)	7.71	6.28
2006	42 (1.4)	0.09	0.07	3,653 (3.8)	7.47	5.93	90 (3.2)	0.18	0.15	16 (5.4)	0.03	0.03	1 (0.7)	0.00	0.00	3,802 (3.7)	7.78	6.17
2007	47 (1.5)	0.10	0.08	3,900 (4.1)	7.94	6.02	111 (3.9)	0.23	0.17	16 (5.4)	0.03	0.03	7 (5.0)	0.01	0.01	4,081 (4.0)	8.31	6.31
2008	56 (1.8)	0.11	0.09	4,182 (4.4)	8.46	6.13	119 (4.2)	0.24	0.18	17 (5.7)	0.03	0.03	3 (2.2)	0.01	0.01	4,377 (4.3)	8.86	6.43
2009	64 (2.1)	0.13	0.10	4,290 (4.5)	8.64	6.02	132 (4.6)	0.27	0.19	11 (3.7)	0.02	0.02	4 (2.9)	0.01	0.01	4,501 (4.4)	9.06	6.33
2010	90 (2.9)	0.18	0.13	4,506 (4.7)	9.03	6.06	132 (4.6)	0.26	0.19	19 (6.4)	0.04	0.03	11 (7.9)	0.02	0.02	4,758 (4.7)	9.54	6.43
2011	176 (5.7)	0.35	0.25	4,827 (5.1)	9.63	6.23	152 (5.3)	0.30	0.22	12 (4.0)	0.02	0.02	6 (4.3)	0.01	0.01	5,173 (5.1)	10.32	6.72
2012	229 (7.4)	0.45	0.31	5,089 (5.4)	10.11	6.30	165 (5.8)	0.33	0.23	13 (4.3)	0.03	0.02	10 (7.2)	0.02	0.01	5,506 (5.4)	10.94	6.87
2013	244 (7.9)	0.48	0.33	5,166 (5.4)	10.22	6.09	144 (5.0)	0.28	0.20	21 (7.0)	0.04	0.03	11 (7.9)	0.02	0.01	5,586 (5.5)	11.05	6.65
2014	255 (8.2)	0.50	0.34	5,627 (5.9)	11.08	6.31	146 (5.1)	0.29	0.19	12 (4.0)	0.02	0.01	6 (4.3)	0.01	0.01	6,046 (6.0)	11.91	6.86
2015	265 (8.5)	0.52	0.35	5,960 (6.3)	11.70	6.46	161 (5.6)	0.32	0.21	14 (4.7)	0.03	0.02	10 (7.2)	0.02	0.01	6,410 (6.3)	12.58	7.05
2016	328 (10.6)	0.64	0.41	6,166 (6.5)	12.06	6.38	224 (7.8)	0.44	0.29	17 (5.7)	0.03	0.02	16 (11.5)	0.03	0.02	6,751 (6.7)	13.21	7.11
2017	342 (11.0)	0.67	0.41	6,500 (6.8)	12.69	6.43	268 (9.4)	0.52	0.37	18 (6.0)	0.04	0.02	6 (4.3)	0.01	0.01	7,134 (7.0)	13.93	7.24
2018	382 (12.3)	0.74	0.44	6,998 (7.4)	13.64	6.65	258 (9.0)	0.50	0.36	28 (9.4)	0.05	0.03	7 (5.0)	0.01	0.01	7,673 (7.6)	14.96	7.49
2019	396 (12.8)	0.77	0.47	7,377 (7.8)	14.37	6.74	277 (9.7)	0.54	0.36	36 (12.0)	0.07	0.04	10 (7.2)	0.02	0.01	8,096 (8.0)	15.77	7.62
AAPC, 1999–2019 (%)	13.9*			1.0*			6.5*			2.6			-			1.6*		
P-value	<0.001			<0.001			0.025			0.076			-			<0.001		

Group A, endocrine; Group B, carcinoma excluding cystic and mucinous; Group C, cystic or mucinous; Group D, acinar cell; Group E, sarcoma and soft tissue tumor.
CR, crude rate; ASR, age-standardized rate; AAPC, average annual percentage change.
*$P < 0.05$.

increasing tendency as the age of patients increased and the time of diagnosis approached the present. The ASIRs of groups A and C showed increasing trends from 1999–2005 to 2013–2019 in all age groups. However, in group B, the ASIRs in patients aged ≥50 years showed an increasing trend. Nonspecific changes in the ASIRs according to periods were observed in groups D and E (Fig. 1).

Male-to-female ratio according to the period

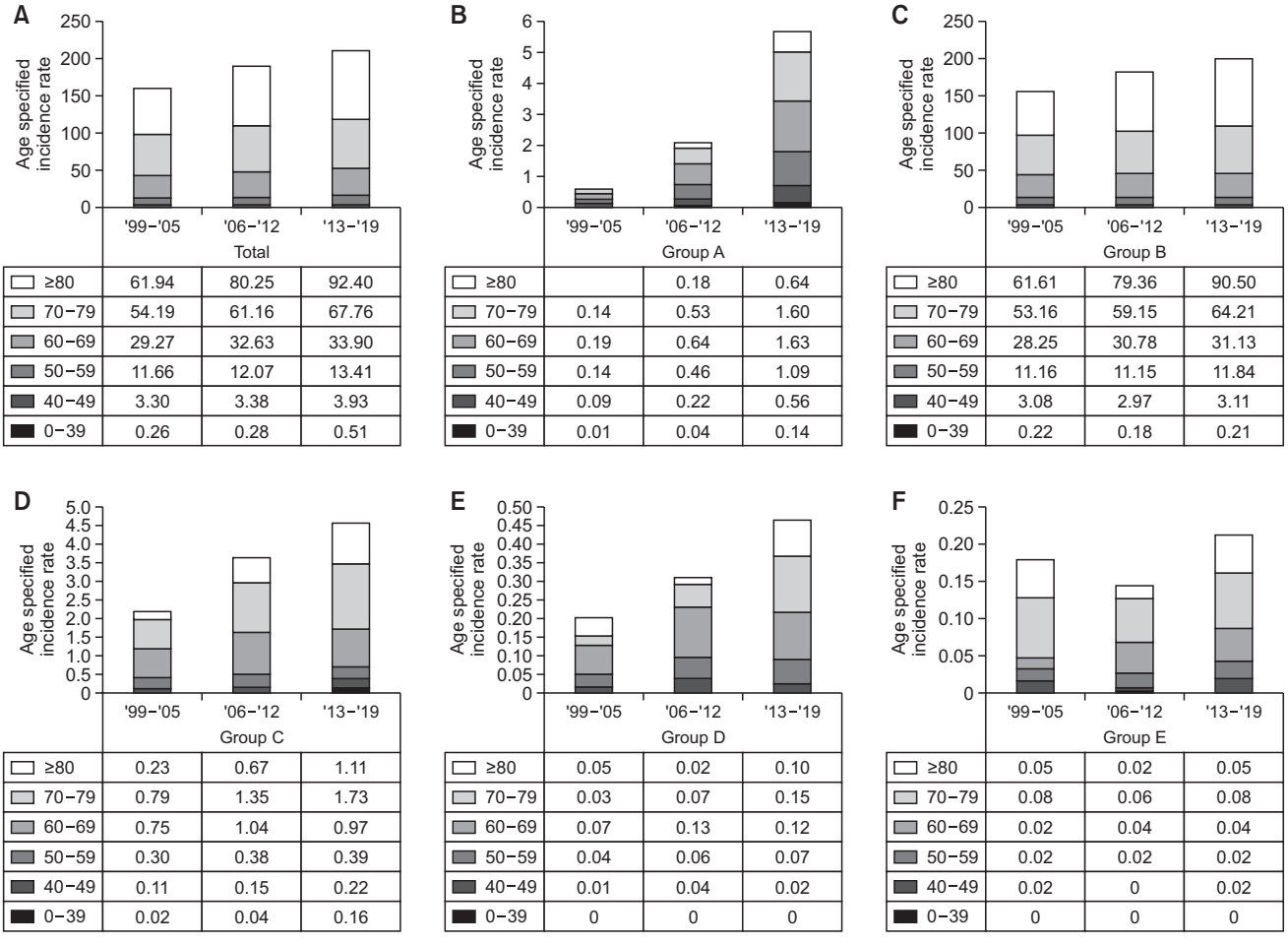
The male-to-female ratio of the ASIR decreased from 1999–2005 (1.81) to 2006–2012 (1.64) and 2013–2019 (1.41). In the subgroup analysis, only groups A (from 1.38 to 1.14 and 1.05) and B (from 1.84 to 1.67 and 1.46) showed a similarly decreasing trend of the male-to-female ratio of the ASR. All pancreatic cancer subgroups were shown to have higher ASIRs in males than in females from 1999 to 2019. Especially, the male-to-female ratio in group C reversed from 2013 to 2019 (from 1.12 and 1.27 to 0.70). Conversely, the male-to-female ratio of the ASIRs in groups D (from 1.95 to 2.42) and E (from 1.15 to 1.24) increased in 2013–2019 compared with that in 1999–2005 (Fig. 2).

Incidence in the histologic subgroups of pancreatic cancer

In a subgroup analysis, from 2006–2012 to 2013–2019, the numbers of cases and proportions of groups A (from 222 and 6.6% to 1,555 and 20.2%) and C (from 302 and 9.0% to 556 and 9.7%) in overall pancreatic cancer increased. In particular, the number of patients with localized stage cancer significantly increased in group A. Group B also showed an increased number of cases. However, the proportion of group B among overall pancreatic cancer decreased in all SEER stages. Although the number of cases increased in groups D and E, the relative proportions of these groups in overall pancreatic cancer remained similar (Table 3).

Survival according to the period

The overall 5-year survival rate of patients with pancreatic



Total	'99–'05	'06–'12	'13–'19
≥80	61.94	80.25	92.40
70–79	54.19	61.16	67.76
60–69	29.27	32.63	33.90
50–59	11.66	12.07	13.41
40–49	3.30	3.38	3.93
0–39	0.26	0.28	0.51

Group A	'99–'05	'06–'12	'13–'19
≥80		0.18	0.64
70–79	0.14	0.53	1.60
60–69	0.19	0.64	1.63
50–59	0.14	0.46	1.09
40–49	0.09	0.22	0.56
0–39	0.01	0.04	0.14

Group B	'99–'05	'06–'12	'13–'19
≥80	61.61	79.36	90.50
70–79	53.16	59.15	64.21
60–69	28.25	30.78	31.13
50–59	11.16	11.15	11.84
40–49	3.08	2.97	3.11
0–39	0.22	0.18	0.21

Group C	'99–'05	'06–'12	'13–'19
≥80	0.23	0.67	1.11
70–79	0.79	1.35	1.73
60–69	0.75	1.04	0.97
50–59	0.30	0.38	0.39
40–49	0.11	0.15	0.22
0–39	0.02	0.04	0.16

Group D	'99–'05	'06–'12	'13–'19
≥80	0.05	0.02	0.10
70–79	0.03	0.07	0.15
60–69	0.07	0.13	0.12
50–59	0.04	0.06	0.07
40–49	0.01	0.04	0.02
0–39	0	0	0

Group E	'99–'05	'06–'12	'13–'19
≥80	0.05	0.02	0.05
70–79	0.08	0.06	0.08
60–69	0.02	0.04	0.04
50–59	0.02	0.02	0.02
40–49	0.02	0	0.02
0–39	0	0	0

Fig. 1. Age-specific incidence rates in patients with pancreatic cancer according to the period. (A) Total, overall pancreatic cancer. (B) Group A, endocrine. (C) Group B, carcinoma excluding cystic and mucinous. (D) Group C, cystic or mucinous. (E) Group D, acinar cell. (F) Group E, sarcoma and soft tissue tumor.

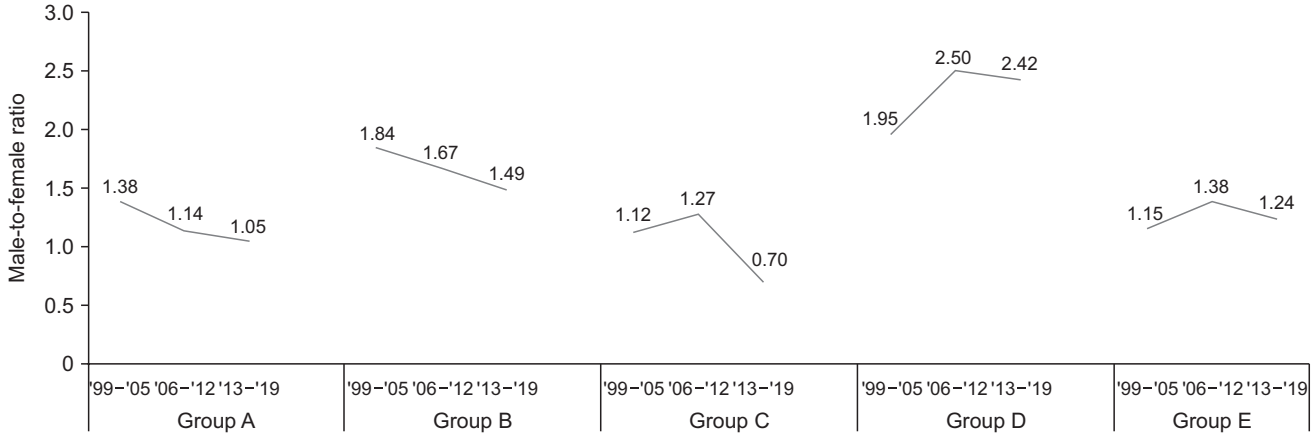


Fig. 2. Male-to-female ratio in the age-standardized incidence rate of pancreatic cancer according to the period.

Table 3. Distribution of Surveillance, Epidemiology, and End Results stage of pancreatic cancer according to the period

Stage	Period	Group A	Group B	Group C	Group D	Group E	Total
Localized	'06–'12	222 (6.6)	2,820 (83.6)	302 (9.0)	22 (0.7)	7 (0.2)	3,373
	'13–'19	1,155 (20.2)	3,965 (69.4)	556 (9.7)	26 (0.5)	10 (0.2)	5,712
	'06–'19	1,377 (15.2)	6,785 (74.7)	858 (9.4)	48 (0.5)	17 (0.2)	9,085
Regional	'06–'12	147 (1.6)	8,879 (94.4)	326 (3.5)	38 (0.4)	11 (0.1)	9,401
	'13–'19	389 (2.6)	13,776 (93.3)	524 (3.6)	46 (0.3)	23 (0.2)	14,758
	'06–'19	536 (2.2)	22,655 (93.8)	850 (3.5)	84 (0.3)	34 (0.1)	24,159
Distant	'06–'12	279 (2.1)	13,065 (96.1)	199 (1.5)	36 (0.3)	20 (0.1)	13,599
	'13–'19	522 (2.5)	20,015 (95.8)	273 (1.3)	63 (0.3)	29 (0.1)	20,902
	'06–'19	801 (2.3)	33,080 (95.9)	472 (1.4)	99 (0.3)	49 (0.1)	34,501
Unknown	'06–'12	56 (1.0)	5,683 (97.6)	74 (1.3)	8 (0.1)	4 (0.1)	5,825
	'13–'19	146 (2.3)	6,038 (95.5)	125 (2.0)	11 (0.2)	4 (0.1)	6,324
	'06–'19	202 (1.7)	11,721 (96.5)	199 (1.6)	19 (0.2)	8 (0.1)	12,149
Total	'06–'12	704 (2.2)	30,447 (94.6)	901 (2.8)	104 (0.3)	42 (0.1)	32,198
	'13–'19	2,212 (4.6)	43,794 (91.8)	1,478 (3.1)	146 (0.3)	66 (0.1)	47,696
	'06–'19	2,916 (3.6)	74,241 (92.9)	2,379 (3.0)	250 (0.3)	108 (0.1)	79,894

Group A, endocrine; Group B, carcinoma excluding cystic and mucinous; Group C, cystic or mucinous; Group D, acinar cell; Group E, sarcoma and soft tissue tumor

cancer was significantly higher in 2013–2019 than in 2006–2012 and 1999–2005 (13.2%, 9.2%, and 8.5%, respectively; $P < 0.001$). In the subgroup analysis, groups A (75.3%, 59.7%, and 52.3%, respectively; $P < 0.001$), B (8.5%, 6.8%, and 7.1%, respectively; $P < 0.001$), and C (58.1%, 47.9%, and 41.3%, respectively; $P < 0.001$) showed a higher 5-year survival rate in the recent period (2013–2019) than in the previous periods. However, groups D (22.1%, 20.9%, and 34.9%, respectively; $P = 0.460$) and E (31.5%, 18.2%, and 30.7%, respectively; $P = 0.663$) showed no significant change in the 5-year survival rate (Fig. 3).

Survival according to the age group

The 5-year survival rate significantly decreased as the patients aged (from 46.1% in patients aged <40 years to 4.1% in those aged ≥80 years, $P < 0.001$). Similar trends of decreasing survival rates in elderly patients were observed in groups A (78.9% and 28.3% in patients aged <40 and ≥80 years, respectively; $P < 0.001$), B (21.3% and 3.8% in patients aged <40 and ≥80 years, respectively; $P < 0.001$), C (91.8% and 30.7% in patients aged <40 and ≥80 years, respectively; $P < 0.001$), and D (42.9% and 0% in patients aged <40 and ≥80 years, respectively; $P = 0.002$). In group E, the 5-year survival rate did not show a relationship with aging of patients and was highest in their 50s (48.1%) and lowest in their 70s (14.2%) (Fig. 4).

Survival according to the SEER stage

The 5-year survival rate increased from 2006–2012 to 2013–2019 in all SEER stages of pancreatic cancer. In the subgroup analysis, groups B (from 15.3% to 21.6%, $P < 0.001$) and C (from 79.1% to 86.2%, $P = 0.006$) showed significant improvement in the 5-year survival rate in patients with localized stage. In groups A (from 68.6% to 77.6%, $P = 0.049$), B (from 10% to

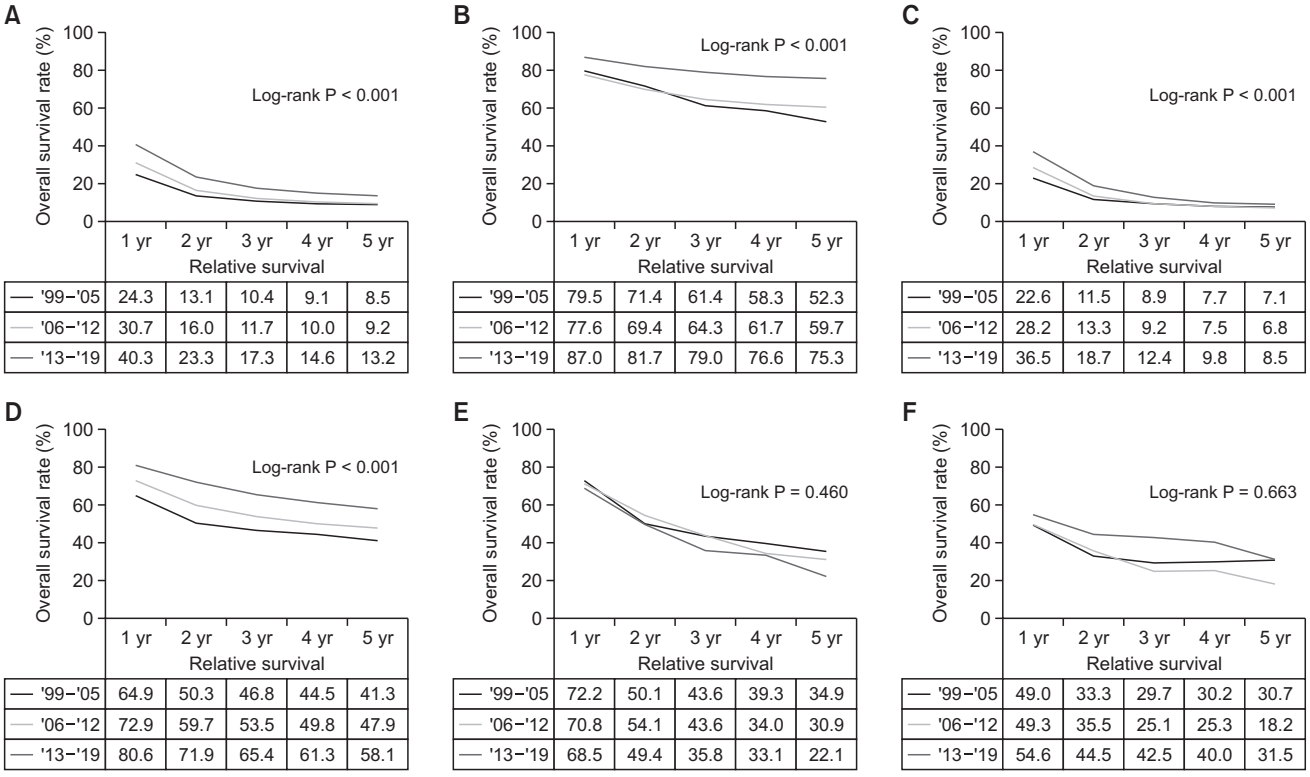


Fig. 3. Overall survival rates in patients with pancreatic cancer according to the period. (A) Total, overall pancreatic cancer. (B) Group A, endocrine. (C) Group B, carcinoma excluding cystic and mucinous. (D) Group C, cystic or mucinous. (E) Group D, acinar cell. (F) Group E, sarcoma and soft tissue tumor.

14.2%, P < 0.001), and C (from 4.5% to 53.2%, P = 0.004), the 5-year survival rate in patients with regional stage significantly improved. The 5-year survival rate in patients with distant metastasis improved only in groups B (from 1.5% to 1.6%, P < 0.001) and E (from 0% to 17.7%, P = 0.047). In addition, the 5-year survival rate was lowest in all stages of group B among overall pancreatic cancer. In contrast, groups A and C showed relatively favorable prognoses. In contrast to the improvement of survival rate in all stages in group B, groups A and C showed improvement of survival rate only in the locoregional SEER stage. Groups D and E showed no significant change in the 5-year survival rate (Fig. 5).

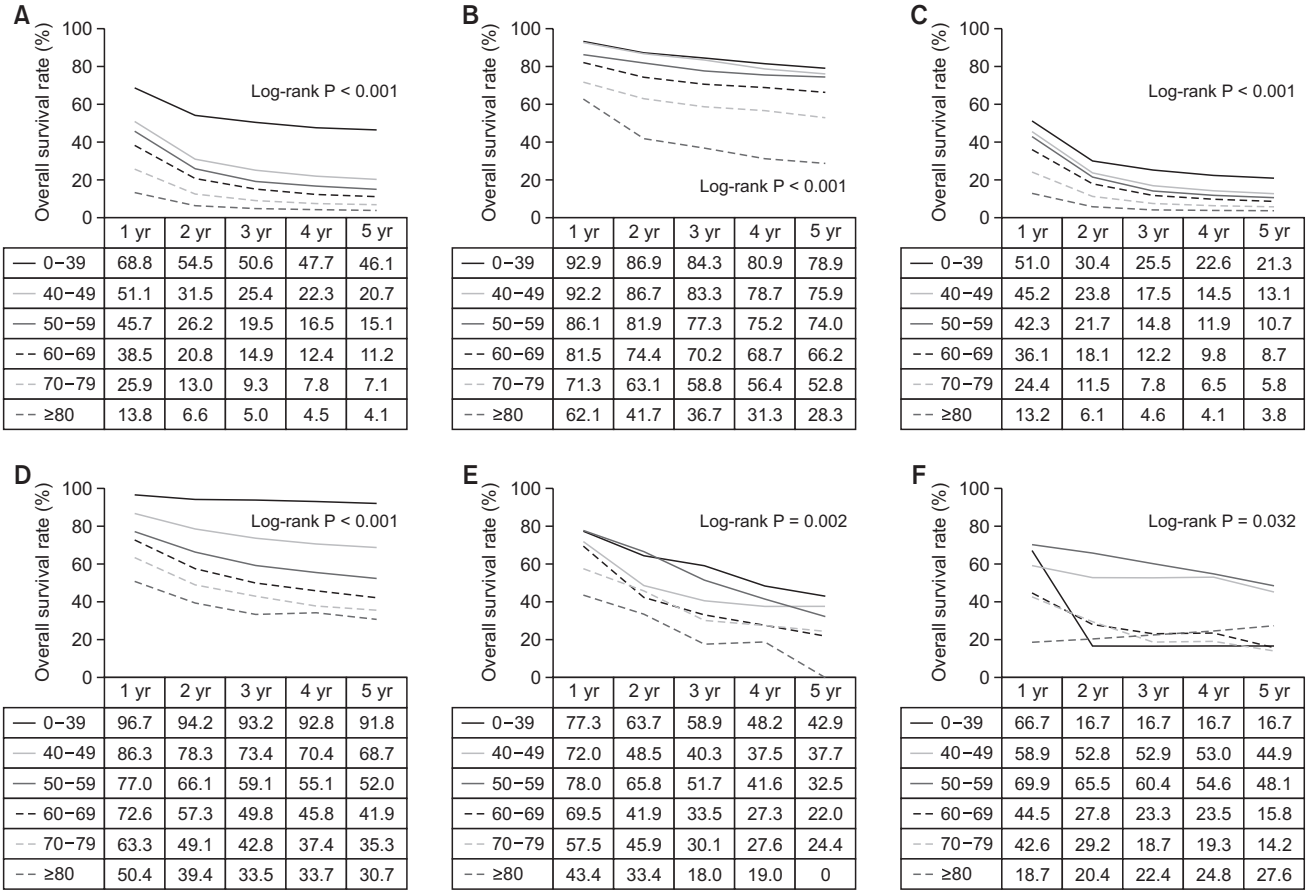
Survival according to the SEER stage with the first course of treatment

Surgical FT showed a significantly higher survival rate than other treatment modalities in all SEER stages of pancreatic cancer. The survival rate of overall pancreatic cancer according to surgical or nonsurgical FT in the same SEER stages of all subgroups in 2013–2019 significantly improved compared with that in 2006–2012. In the subgroup analysis, the survival rates in patients who received surgical or nonsurgical FT for localized or regional stages showed improvement in 2013–2019 compared with those in 2006–2012, except for the regional stage in group D. Groups A and C showed relatively higher 5-year survival rates with improvement in the recent period than the other subgroups of pancreatic cancer in patients who received surgical FT in localized and regional stages. In contrast, group B showed a worse prognosis than other groups despite active treatment, including surgical or nonsurgical treatment for each stage (Supplementary Fig. 1).

DISCUSSION

The epidemiologic analysis of specific cancers should include information from all patients in the region with the same medical environment to add meaning to the results. Because of the National Health Insurance system in South Korea, which covers the entire nation, patients with cancer can easily approach the high-volume center in a homogenous manner [19]. Therefore, the data of patients with pancreatic cancer in the KCCR is an appropriate substitute for population-based data with minimal disturbance caused by geographical distribution and the wealth gap, which can affect cancer treatment and survival [20-22].

The report in 2018 about the incidence trends of pancreatic cancer in the United States showed that the incidence of overall pancreatic cancer had increased. However, the degree of



	1 yr	2 yr	3 yr	4 yr	5 yr
0–39	68.8	54.5	50.6	47.7	46.1
40–49	51.1	31.5	25.4	22.3	20.7
50–59	45.7	26.2	19.5	16.5	15.1
60–69	38.5	20.8	14.9	12.4	11.2
70–79	25.9	13.0	9.3	7.8	7.1
≥80	13.8	6.6	5.0	4.5	4.1

	1 yr	2 yr	3 yr	4 yr	5 yr
0–39	92.9	86.9	84.3	80.9	78.9
40–49	92.2	86.7	83.3	78.7	75.9
50–59	86.1	81.9	77.3	75.2	74.0
60–69	81.5	74.4	70.2	68.7	66.2
70–79	71.3	63.1	58.8	56.4	52.8
≥80	62.1	41.7	36.7	31.3	28.3

	1 yr	2 yr	3 yr	4 yr	5 yr
0–39	51.0	30.4	25.5	22.6	21.3
40–49	45.2	23.8	17.5	14.5	13.1
50–59	42.3	21.7	14.8	11.9	10.7
60–69	36.1	18.1	12.2	9.8	8.7
70–79	24.4	11.5	7.8	6.5	5.8
≥80	13.2	6.1	4.6	4.1	3.8

	1 yr	2 yr	3 yr	4 yr	5 yr
0–39	96.7	94.2	93.2	92.8	91.8
40–49	86.3	78.3	73.4	70.4	68.7
50–59	77.0	66.1	59.1	55.1	52.0
60–69	72.6	57.3	49.8	45.8	41.9
70–79	63.3	49.1	42.8	37.4	35.3
≥80	50.4	39.4	33.5	33.7	30.7

	1 yr	2 yr	3 yr	4 yr	5 yr
0–39	77.3	63.7	58.9	48.2	42.9
40–49	72.0	48.5	40.3	37.5	37.7
50–59	78.0	65.8	51.7	41.6	32.5
60–69	69.5	41.9	33.5	27.3	22.0
70–79	57.5	45.9	30.1	27.6	24.4
≥80	43.4	33.4	18.0	19.0	0

	1 yr	2 yr	3 yr	4 yr	5 yr
0–39	66.7	16.7	16.7	16.7	16.7
40–49	58.9	52.8	52.9	53.0	44.9
50–59	69.9	65.5	60.4	54.6	48.1
60–69	44.5	27.8	23.3	23.5	15.8
70–79	42.6	29.2	18.7	19.3	14.2
≥80	18.7	20.4	22.4	24.8	27.6

Fig. 4. Overall survival rates in patients with pancreatic cancer according to the age group. (A) Total, overall pancreatic cancer. (B) Group A, endocrine. (C) Group B, carcinoma excluding cystic and mucinous. (D) Group C, cystic or mucinous. (E) Group D, acinar cell. (F) Group E, sarcoma and soft tissue tumor.

increase or decrease in the incidence depends on the histologic subtype. In the report, nonsecretory endocrine cancers (>6%) showed the highest increase trend, followed by ductal adenocarcinoma (approximately 5%) and adenocarcinoma, not otherwise specified (approximately 1.4%). However, the authors reported that the incidence of mucinous adenocarcinoma and poorly specified pancreatic cancer have decreased [14]. In the present study, the overall pancreatic cancer incidence in Korea also increased. By histologic subtype, the AAPC of endocrine cancers (13.9%) between 1999 and 2019 was highest, followed by cystic, including mucinous cancers (6.5%), acinar cell cancers (2.6%), and carcinoma excluding cystic cancers (1.0%).

Overall, the gender ratio in the incidence of pancreatic cancer, which had a high incidence in men, showed a decreasing trend, and group C showed a reversal of the gender ratio. The observed trends in pancreatic cancer incidence with decreasing male predominance and increasing rate in females, highlight a shift that cannot be explained by traditional risk factors, such as smoking and drinking, which are more common in men [9,18]. It suggests the influence of other variables, such as biology, environment, and genetics, might impact the genders differently. The complexity of these trends underlines the need for interdisciplinary research to understand and address the disease, emphasizing the need for strategies for prevention, early detection, and treatment.

Although endocrine and cystic cancers accounted for small proportions of overall pancreatic cancer because of their rarity, increasing trends of these subtypes were also prevalent in previous studies [23-25]. In addition to the growing incidences, we found improved survival rates in the recent period (2012–2019) compared with the previous, especially in localized or regional SEER stages of these histologic subtypes of pancreatic cancer. These rapidly increasing incidences and improved survival trends of endocrine and cystic cancers could be attributed to either an increase in the actual cancer occurrence or increased diagnosis of premalignant lesions (e.g., mucinous cystic neoplasm, intraductal papillary mucinous neoplasm, and neuroendocrine neoplasm) and early-stage (local or regional SEER stage) disease. The fact that the survival rates in all SEER stages in group B showed significant improvement, which led to the advancement of survival rates of overall pancreatic cancer in Korea, is also a significant result in this study [26]. However, the

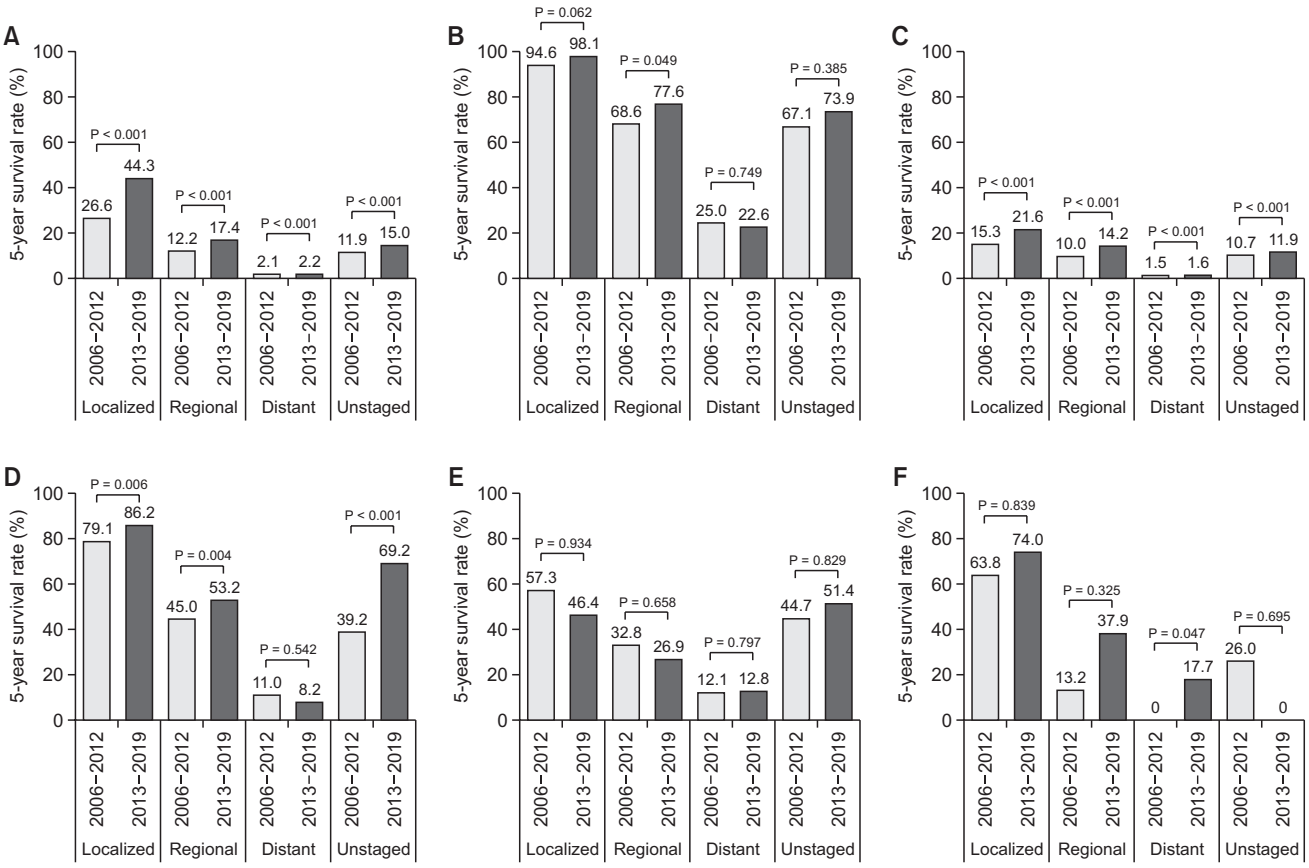


Fig. 5. Comparison of the 5-year survival rates according to the period in each Surveillance, Epidemiology, and End Results stage of pancreatic cancer. (A) Total, overall pancreatic cancer. (B) Group A, endocrine. (C) Group B, carcinoma excluding cystic and mucinous. (D) Group C, cystic or mucinous. (E) Group D, acinar cell. (F) Group E, sarcoma and soft tissue tumor.

recent 5-year survival rate of group B is still <9%, which could not reach the 5-year survival rate of overall pancreatic cancer. Therefore, the recent improvement in the 5-year survival rate of pancreatic cancer in Korea may be derived from the increasing incidence of groups A and C, which showed favorable prognoses with much higher rates of active treatments than in group B. These improvements in survival rates may be due to improved diagnostic tools, including imaging modalities, attributed to incidental detection at an early stage or early diagnosis of malignant change from benign disease during follow-up and better treatment strategies [27,28].

Our previous study showed that surgical FT increased from 2006 to 2017 (from 20.6% to 23.1%) in patients with overall exocrine pancreatic cancer in Korea from 2006 to 2017. In addition, the proportion of surgical treatment was inversely related to the patient's age (37.3% of septuagenarians and 10.9% of octogenarians or older). However, surgical treatment showed a better prognosis than other treatments or no treatment in patients with pancreatic cancer, regardless of histology groups [4]. In this study, the incidence of active cancer-directed FT after diagnosis increased in 2013–2019 compared with that in 2006–2012 in all SEER stages of group B. However, these treatment rates were still lower than those in other groups, especially the surgical treatment rate in the locoregional stage (Supplementary Table 3). The lower treatment rates in group B may be attributed to the high proportion of elderly patients with frailty, including comorbidities and poor performance status. Therefore, screening and treatment guidelines for elderly patients with pancreatic cancer should be developed, whose proportions increase as life expectancy is prolonged globally [29,30]. Although the proportion of surgical treatment in the locoregional stages of group A and localized stage of group C decreased in 2013–2019 compared with that in the previous period, the 5-year survival rates in the same stages significantly improved. These paradoxical improvements in survival may result from the favorable biologic characteristics of groups A and C in a slow pace of progression. Therefore, several patients who did not receive surgical FT may have a chance to receive active treatment after 4 months from the date of diagnosis. However, information about whether these patients received active treatment or not 4 months after diagnosis is not collected in the KCCR database. In addition, advances in treatment modalities (e.g., surgery, chemotherapy, and radiation therapy) for pancreatic cancer would have improved survival rates.

This study has some limitations. First, the cancer registry did not include information about treatment administered after the first 4 months of the diagnosis of pancreatic cancer. Therefore, the exact rates of patients receiving multimodality treatment could not be evaluated. Second, the registry could not provide sufficient information on treatment regarding the type of surgery and regimen and duration of chemotherapy or radiation therapy. Therefore, although palliative surgery was not principally classified as surgical FT, the possibility of some inclusion cannot be excluded. In addition, this study could not identify the causes for not receiving treatment within the first 4 months of diagnosis. Third, it was impossible to differentiate the American Joint Committee on Cancer (AJCC) stage or resectability based on the SEER stage, as recorded in the registry; localized and regional stages may have included resectable, borderline resectable, and locally advanced unresectable tumors. Therefore, there is a limitation in direct comparison with the results of clinical studies using the AJCC stage. Finally, there is a notable variance in incidence rates across pancreatic cancer subtypes, with groups D and E representing particularly rare forms of carcinoma. Consequently, caution is advised when interpreting statistical analysis for these groups.

In conclusion, the findings of this study could provide valuable insights into understanding reliable epidemiologic and treatment pattern differences between the histologic subtypes of pancreatic cancer. The incidence and survival rates of pancreatic cancer have increased in Korea. However, the degree of these epidemiologic changes differs among histologic subtypes. Efforts for early diagnosis and active treatment for pancreatic cancer should be continued, especially for group B, which accounts for most pancreatic cancer cases and shows a still lower survival rate than other groups. There is also a need for systematic and institutional improvement in the diagnosis and treatment of rapidly increasing groups A and C.

SUPPLEMENTARY MATERIALS

Supplementary Tables 1–3 and Supplementary Fig. 1 can be found via https://doi.org/10.4174/astr.2025.108.1.20.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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