

Advanced Detection of Recent Changing Trends in Gastric Cancer Survival: Up-to-date Comparison by Period Analysis

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Objective: To establish a comprehensive cancer treatment and prevention policy, data collection should be performed in a timely manner, and survival analysis needs to reflect changes in treatment strategy. Therefore, we introduced the concept of period analysis for gastric cancer, the most prevalent cancer in Korea. We estimated 5- and 10-year survival trend of gastric cancer, based on data from the Yonsei Cancer Center Tumor Registry between 1990 and 2004.

Methods: We compared the differences in survival between cohort, complete and period analyses for two different periods, 1995–99 and 2000–04.

Results: A total of 11 724 cases were included. The median age of cancer diagnosis gradually increased over time, and more patients were diagnosed with Stage I disease in recent years. In the basic comparison of three estimated analytic methods (cohort, complete and period), period analysis (45.8%) was most similar to the actual 5-year observed survival rate (48.5%), when compared with cohort (43.6%) and complete (44.8%) analyses. When we compared survival between different 10-year periods (1990–99 and 1995–2004), period analysis demonstrated a greater difference than complete analysis (9.0 versus 3.9%). Subgroup analysis indicated that the survival improvement was determined by period analysis, and it was more pronounced for the age group <74 years and in Stages III–IV patients.

Conclusions: We observed that period analysis demonstrates the most similar results to the actual observed survival and is, therefore, a useful method to derive precise cancer survival in gastric cancer. This information is useful to understand survival differences that are influenced by changing treatment strategy.

Key words: gastric cancer – tumor registry – survival analysis – period analysis

INTRODUCTION

Gastric cancer is the second most common cause of cancer-related death worldwide (1). In particular, it is the most commonly diagnosed malignancy in East Asia and South America (2). Over several decades, the survival outcome has improved from 6–9 months to 10–12 months (3–5). Early screening, newly developed novel chemotherapeutic agents and improved supportive care have all played an important

role in this improvement of survival outcome. In addition to these medical developments, accurate and comprehensive epidemiologic information is necessary for further clinical benefits and cancer prevention. Among this information, precise survival outcome is one of the most basic and essential statistics. For this analysis, data collection should be performed in a timely manner, and survival analysis needs to reflect changing trends. Several conventional methodologies have been tested to achieve these aims.

As one of the conventional analysis methods, the cohort method denotes estimated cumulative survival only for entirely followed patients; therefore, because patients who are recently recruited or who drop-out from the study can be censored and ignored in cohort analysis, this method results in statistical inaccuracy. Specifically, it is less effective at reflecting recent advances. To include survival experience until the closing date of the follow-up, the Kaplan–Meier method, also called complete analysis, is currently widely used. Because it includes early survival experience of recently recruited patients, this method is more compensatory than cohort analysis. However, complete analysis more dominantly estimates the longer-followed patients; therefore, it is still not sufficient to reflect recent advances and trends. Hence, new methods that reflect recent trends and improvement are needed for precise survival analysis.

Period analysis was first introduced in 1996 by Brenner and Gefeller and has been shown to provide more up-to-date estimates than other traditional methods (3,4). Therefore, in this gastric cancer study, we introduced the up-to-date estimate of period analysis and compared this estimate with traditional methods. At the same time, we tried to depict the changing trend of clinical features of gastric cancer in Korea.

PATIENTS AND METHODS

STUDY POPULATION

Our analysis is based on data from the Yonsei Cancer Center Registry, an approximately 2000-bed major tertiary hospital in Korea. Patients who were diagnosed with carcinoma *in situ* or carcinoma were included, together with those having brain and central nervous system tumors. Our cancer registry receives all accrual records when cancer is diagnosed in both outpatient and inpatient clinics. At the time of this analysis, our database included all cancer patients diagnosed since 1980. Among the various cancer types, our study population was gastric cancer patients aged 15 years or older with a first diagnosis between 1990 and 2004. Stage was not recorded until 1995; therefore, stage analysis was performed only for patients diagnosed after 1996. Stage registration was recorded as initial stage at diagnosis with the American Joint Committee on Cancer (AJCC) staging system.

Patient follow-up was efficiently performed using a personal identification number. The cases were matched twice per year with the list of deaths. These data were also matched with the national population registries for a second check. Because a computerized matching system was used, only a small number of deaths were missed in our registry. All patients in this analysis were followed until 31 December 2004.

STATISTICAL ANALYSIS

In this study, we comparatively assessed cohort, complete and period analyses. The description of each method is

illustrated in Fig. 1. First, we set standard 5-year survival as the observed analysis, defined as patients diagnosed between 1995 and 1999 and followed for 5 years. After that, we compared the observed survival with three estimated analyses (cohort, complete and period). For the estimated 5-year survival analyses, all the patients were recruited between 1990 and 1999. For cohort analysis, the 5-year survival was estimated with the patients recruited in 1990–94, and all patients had a complete 5-year follow-up by the end of 1999. For complete analysis, all patients recruited between 1990 and 1999 were included and were observed for a maximum 5 years. Because of these inclusions, complete analysis would be a more precise and up-to-date analysis than cohort analysis. However, some patients recruited during 1995–99 would not have completed 5-year follow-up; therefore, the complete analysis is defined as ‘right censored’ observations.

Like complete analysis, period analysis was obtained from patients recruited between 1990 and 1999. In contrast to complete analysis, period analysis was restricted to patients and events during a more recent period between 1995 and 1999. As well as ‘right censoring’ in the complete analysis, this was performed by left truncation of survival experience between 1991 and 1994 (5,6). Therefore, when compared with other traditional analyses (cohort and complete), period estimates reflect the survival experience during a more recent period.

To verify these results over extended time, we also used a 10-year time window (1990–99 and 1995–2004). Due to the definition of cohort analysis, 10-year survival was only available for complete and period analyses. Similar to the 5-year survival analysis, 10-year complete analysis included patients recruited between 1990 and 1999 with a maximum 10 years of follow-up. In addition, 10-year complete survival was also analyzed for patients recruited between 1995 and 2004. However, extension of time windows is somewhat difficult for recent cancer registries because extension requires additional inclusion of patients diagnosed a long time ago. Therefore, we used abbreviated-period modeling which needs a minimum number of 1-year cohorts for analysis, as shown in a previous study (7). Instead of conventional period analysis, which uses a full 5- or 10-year period, this modified period analysis uses the single most recent year. Therefore, for the period analysis, we estimated the abbreviated period between the most recent single year 1999 (1990–99) and 2004 (1995–2004) for 10-year survival (dotted box in Fig. 1).

RESULTS

DEMOGRAPHICS

A total of 11 724 cases were included in this analysis. Between 1990 and 2004, approximately two-thirds of patients were male, with a constant male/female ratio (7917 male and 3807 female). Figure 2 depicts the changes in age

Analysis	Years of recruitment	Calendar year of follow-up														
		1991	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Observed	1990						1	1/2	2/3	3/4	4/5	5				
	1991							1	1/2	2/3	3/4	4/5	5			
	1992								1	1/2	2/3	3/4	4/5	5		
	1993									1	1/2	2/3	3/4	4/5	5	
	1994										1	1/2	2/3	3/4	4/5	5
Cohort	1990	1	1/2	2/3	3/4	4/5	5									
	1991		1	1/2	2/3	3/4	4/5	5								
	1992			1	1/2	2/3	3/4	4/5	5							
	1993				1	1/2	2/3	3/4	4/5	5						
	1994					1	1/2	2/3	3/4	4/5	5					
Complete	1990	1	1/2	2/3	3/4	4/5	5									
	1991		1	1/2	2/3	3/4	4/5	5								
	1992			1	1/2	2/3	3/4	4/5	5							
	1993				1	1/2	2/3	3/4	4/5	5						
	1994					1	1/2	2/3	3/4	4/5	5					
	1995						1	1/2	2/3	3/4	4/5	5				
	1996							1	1/2	2/3	3/4	4/5	5			
	1997								1	1/2	2/3	3/4	4/5	5		
	1998									1	1/2	2/3	3/4	4/5	5	
	1999										1	1/2	2/3	3/4	4/5	5
Period	1990	-	-	-	-	-	5									
	1991		-	-	-	-	4/5	5								
	1992			-	-	-	3/4	4/5	5							
	1993				-	-	2/3	3/4	4/5	5						
	1994					-	1/2	2/3	3/4	4/5	5					
	1995						1	1/2	2/3	3/4	4/5	5				
	1996							1	1/2	2/3	3/4	4/5	5			
	1997								1	1/2	2/3	3/4	4/5	5		
	1998									1	1/2	2/3	3/4	4/5	5	
	1999										1	1/2	2/3	3/4	4/5	5

Figure 1. Differences of cohort, complete and period analyses for 5-year survival curves. Patients were recruited during 1990–99 and followed until 2004 according to the types of analysis. The numbers within cells indicate years following diagnosis.

and stage distribution. The median age for all the patients was 56.4 (range 15–94). The median age in 1990 was 54.7 years and gradually increased to 58.0 years in 2004. Among all of the patients, 4629 (39.6%) were 0–54 years old, 3795 (32.4%) were 55–64 years old, 2662 (22.7%) were 65–74 years and 628 (5.4%) were 75 years or older. As shown in Fig. 2A, the proportion of patients <54 years old and those between 55 and 64 years decreased from 45.0 to 36.2% and from 30.8 to 28.8%, respectively. Conversely, the proportion of patients between 65 and 74 years old and those older than 75 years increased from 21.4 to 28.4%, and from 2.9 to 6.6%, respectively. In terms of stage at diagnosis, 2839 (33.6%) were Stage I, 899 (10.6%) Stage II, 1653 (19.6%) Stage III, 2005 (23.7%) Stage IV and 1058 (12.5%) patients were unknown stage. The proportion of patients with Stage I disease in 1996 was 24.6% and increased ~2-fold up to 40.0% in 2004. In contrast, the proportion with Stage IV disease was 29.1% in 1996 and decreased to 22.4% in 2004 (Fig. 2B).

COMPARISON OF ANALYTIC METHODS (COHORT, COMPLETE AND PERIOD)

The results of 5-year cumulative overall survival (OS) by each method are shown in Fig. 3. The observed 5-year survival during 1995–99 was 48.5%. The estimated 5-year

survival for cohort, complete and period analyses was 43.6, 44.8 and 45.8%, respectively. The discrepancies between observed survival and estimated survival were 4.9, 3.7 and 2.7 for cohort, complete and period analyses, respectively. Therefore, the estimated period analysis demonstrated the most similar results to the observed survival.

We also assessed the 5-year survival differences among patients diagnosed during the more recent period of 1995–2004. The estimated 5-year survival analyses for this period demonstrated a similar tendency of improved accuracy with period analysis. The estimated 5-year survival for cohort, complete and period analyses during 1995–2004 were 48.5, 51.2 and 54.2%, respectively (Table 1). When we adjusted for other causes of death, defined as relative survival (RS), period analysis still yielded the highest cumulative survival estimates (59.3%, 95% confidence interval 57.7–60.8) during this period, as shown in Table 1. We also compared age or stage-specific 5-year survival rates of each analysis during the period 1995–2004. For Stages I–II patients, the three analytic methods showed almost similar survival rates. However, for patients with Stages III–IV, period analyses demonstrated better survival outcome than complete and cohort analyses. In age-specific 5-year survival analyses, for patients <74 years old, 5-year survival by period analysis also showed higher survival rates than complete analysis, and cohort analysis demonstrated the lowest survival rate.

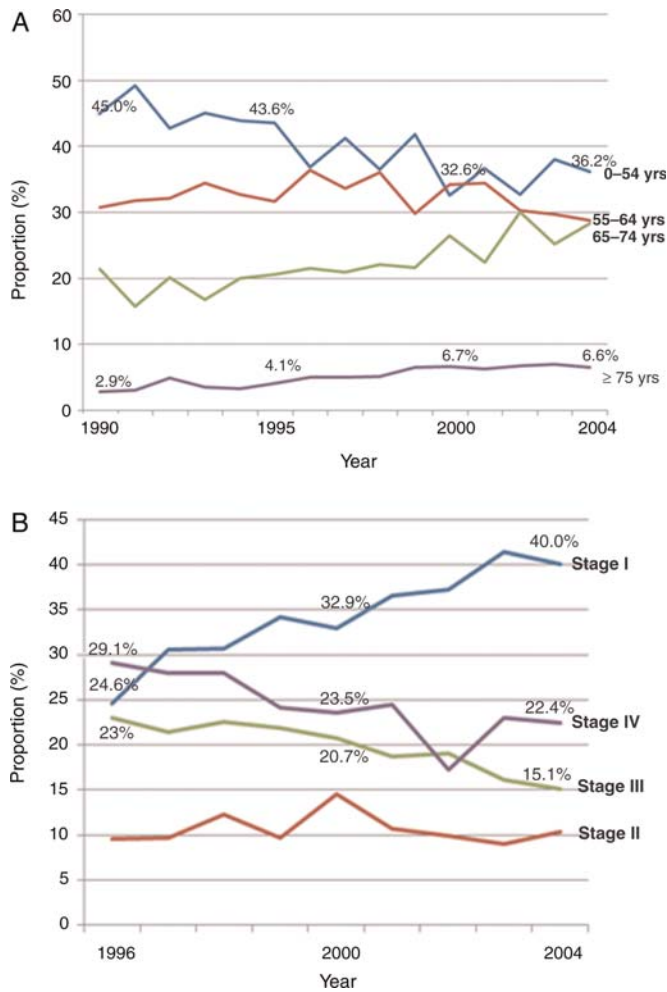


Figure 2. Changes in age (A) and stage (B) distribution.

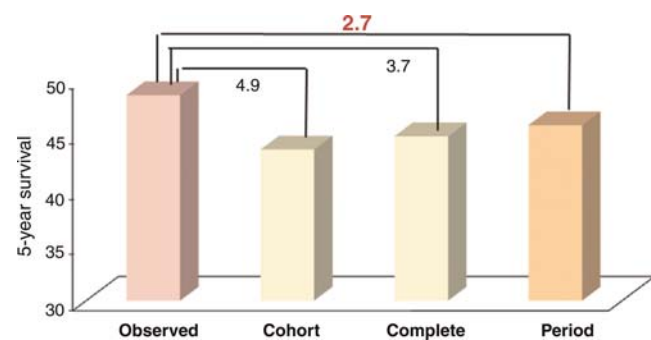


Figure 3. Comparisons of 5-year cumulative survival estimates by type of analyses during period 1990–99.

However, for patients 75 years or older, the three methods showed similar results. In addition, in gender-specific 5-year survival, period analysis also showed higher survival rates than complete analysis, and cohort analysis demonstrated the lowest survival rate.

In addition, as shown in Fig. 4, the discrepancies in RS between each analysis showed the same tendency over time.

Table 1. Comparisons of 5-year cumulative survival estimates by type of analyses during 1995–2004

Follow up year	Cohort	Complete	Period
5-year OS	48.5	51.2	54.2
5-year RS (95% CI)	53.2 (51.5–55.0)	56.1 (54.7–57.4)	59.3 (57.7–60.8)
Stage			
I (n = 2839, 33.6%)	92.9	92.5	92.6
II (n = 899, 10.6%)	72.4	72.4	73.8
III (n = 1653, 19.6%)	44.3	44.9	45.9
IV (n = 2005, 23.7%)	5.0	5.3	5.5
Age			
0–54 (n = 4629, 39.6%)	52.7	55.9	59.5
55–64 (n = 3795, 32.4%)	50.7	54	58.1
65–74 (n = 2662, 22.7%)	41.8	44.6	47.4
≥ 75 (n = 628, 5.4%)	29.8	30.6	30
Gender			
Male	42.9	44	44.7
Female	45.1	46.6	48

OS, overall survival; RS, relative survival; CI, confidence interval.

The difference between these three analyses, observed from the first year, became more prominent over time up to 3 years, and then continued until the 5-year follow-up visit. Thus, cohort, complete and period analyses demonstrated 75.9, 78.3 and 80.5% for 1-year RS rates and 58.3, 61.4 and 64.4% for 3-year survival rates, respectively.

PERIOD ANALYSES OF 5- AND 10-YEAR DURATION

To verify whether period analysis showed the same pattern over a more extended period, we also assessed 10-year survival rates with those methods. Because cohort analysis needs at least 10 years of follow-up after the last enrollment, it was not possible to obtain 10-year OS by cohort analyses. For both complete and period analyses, the 10-year survival rates were generally lower than 5-year survival rates (Table 2). In complete analysis, the 5-year and 10-year RS in 2004 was 56.1 and 42.9%, respectively. Similarly, by period analysis, the 5-year RS in 2004 was 59.3% and the 10-year RS was 48.8%.

In addition, in terms of 10-year RS changes between 1990–99 and 1995–2004, period analysis demonstrated greater differences than complete analysis (Fig. 5A). The difference in 10-year survival rate for all patients between 1990–99 and 1995–2004 was 3.9% by complete analysis, when compared with 9.0% for abbreviated period analysis. Therefore, for recent changes in difference between 2004 and 1999, 10-year period analysis demonstrated a greater difference than complete analysis.

We also performed a more detailed period analysis in terms of gender and age. The survival improvement for period analysis was two times more prominent for male patients than female patients (Fig. 5B). For the comparison of 10-year OS with respect to age category, the difference between the two analytic methods was more prominent for the age group <74 years (107–221% increment) than for those ≥75 years old (54% increment).

DISCUSSION

In this study, we precisely compared various different analytic methods using a large gastric cancer database. We identified period analysis as a useful, up-to-date and precise

method that reflects the recently improved survival. In addition, because gastric cancer is the most commonly diagnosed malignancy in Korea, this result has more power to confirm the analytic advantages.

We analyzed patients who were diagnosed between 1990 and 2004. Our hospital is a 2000-bed tertiary hospital with a long history of comprehensive cancer care, and more than 10 000 new cancer patients are registered every year. We have been using standard international classification of disease for oncology tumor classification. In addition, registration information was obtained as a standardized method with AJCC, International Federation of Gynaecology and Obstetrics (FIGO) (for cervical cancer) and DUKE staging systems. The follow-up rate of our tumor registry is >90%, with only a low number of losses. These factors make our tumor registry reliable and objective.

First of all, we depicted the changing trend of gastric cancer with respect to stage and age distribution. The proportion of patients diagnosed with Stage I increased from 24.6% in 1996 to 40.0% in 2004. Since 1996, an active health care strategy, especially for gastric, breast and cervical cancer, was applied as part of a national cancer screening program in Korea (8). Therefore, this shift to an earlier stage might be attributed to the introduction of national preventive education/programs and improvement of the screening method of esophagoduodenoscopy. In addition to the stage, age distribution also changed over this period; the proportion of patients younger than 65 years decreased, whereas the proportion of elderly patients increased. These results are similar to those of previous studies (9,10), and may reflect the life span extension in the general population. This pattern is expected to continue in the future because of widely available new screening and detection methods.

Brenner and Gefeller (6) first suggested the usefulness of the period analytic method in 1997. In their study, they

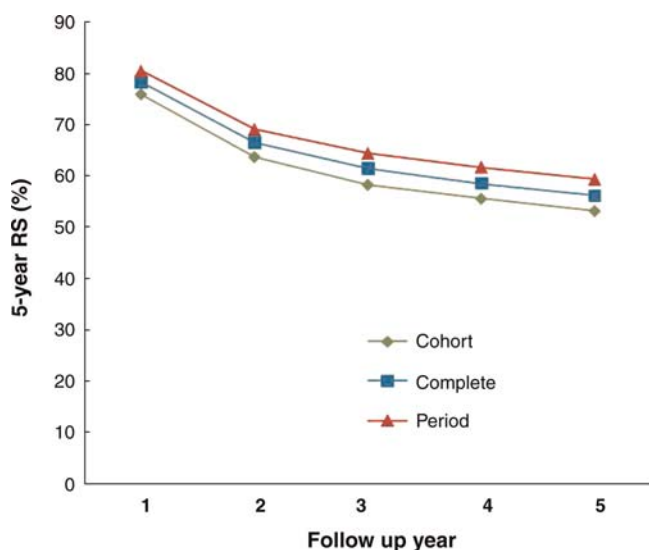


Figure 4. Five-year relative survival (RS) estimates according to follow-up period by type of analyses.

Table 2. Comparisons of 10-year survival outcomes between complete and period analyses

	Complete			Period			Change difference (period-complete, % unit)
	1999	2004	Change (1999 versus 2004)	1999	2004	Change (1999 versus 2004)	
10-year RS	39	42.9	3.9	39.8	48.8	9	5.1 (131)
Gender							
Male	38.4	41.2	2.8	38.9	46.9	8.0	5.2 (186)
Female	40.3	46.4	6.1	41.5	51.5	10.0	3.9 (64)
Age							
0–54	44.0	51.0	7.0	44.9	59.4	14.5	7.5 (107)
55–64	39.7	45.8	6.1	40.9	53.4	12.5	6.4 (105)
65–74	32.6	34.0	1.4	33.5	38.0	4.5	3.1 (221)
≥75	3.8	8.8	5.0	0.0	7.7	7.7	2.7 (54)

10-year RS: 1999–2004.

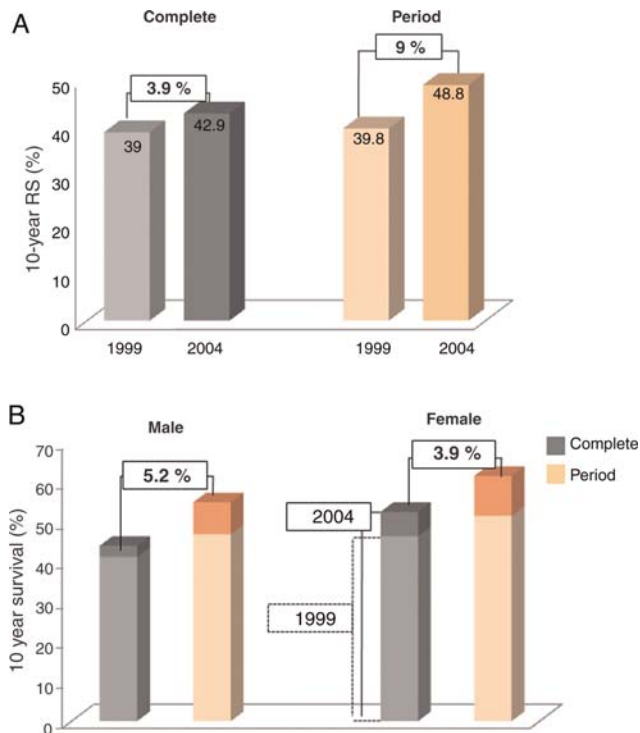


Figure 5. Comparisons of 10-year survival outcomes between complete and period analyses (A) and gender differences (B).

assessed the 5-year cumulative survival of testicular cancer patients who were diagnosed in 1978–87, with a particular focus on patients diagnosed in 1978, when new therapeutic regimens for testicular cancer became available. The study showed that period analysis yields higher survival estimates than the other types of analysis and reflects recent therapeutic improvements. Subsequently, several studies in different geographic areas have demonstrated similar results for various cancer types (11–14). As in these previous studies, we also compared 5-year survival of gastric cancer patients with cohort, complete and period analyses. Among these three estimates, period analysis showed the most similar results to the actual observed survival, and this finding implies that period analysis achieves the most up-to-date estimates. With period analysis, information from the most recent period of interest is included, and survival from the other duration is discarded. As a result, period analysis provides long-term survival estimates with consideration of more recently diagnosed and treated patients. In our comparison, period analysis best reflected trends over time and also implied that gastric cancer survival outcome has further improved in recent years. Therefore, our study indicates that period analysis may be the most useful to estimate recent trends of cancer survival, as shown in previous studies (3,7).

For period analysis, one of the remaining questions is the optimal time period that best reflects tumor biology and treatment modality. The comparisons between 5- and 10-year periods further clarified the advantage of period

analysis in these gastric cancer cases. In a previous study, compared with period analysis of a 5-year time window, 10-year period analysis provided more precise and accurate survival data by reducing the standard errors of survival estimates (7), and a 10 year duration was accepted as a desirable option in gastric cancer survival analysis. Brenner and Gefeller also suggested that further benefits in cancer survival could be obtained with an extended time window. In addition, in this study, an abbreviated 10-year period analysis enabled wider period estimates without additional numbers of patients. Further studies on the optimal length of time windows in the various disease entities are needed to validate this result.

In addition to overall distribution, we also assessed the changes in survival with respect to age and stage distribution. Interestingly, survival improvement with period analysis was most prominent in patients <74-years-old, and somewhat lower in elderly patients, for both 5- and 10-year survival rates, as shown in previous studies (15–17). One of the reasons for this finding is the increased prevalence of co-morbidities that negatively affect diagnostic and therapeutic choices (18). Biologically different clinicopathological features of gastric cancer in the elderly may be another explanation. Elderly patients have been shown to have much higher rates of advanced stage and multiple gastric cancers in previous studies (9,19,20). In addition, elderly patients are less likely to receive aggressive therapies (surgical management, chemotherapy and radiotherapy) than younger patients (16,21,22), and are usually not eligible to be included in clinical trials. Therefore, considering the fact that age distribution at diagnosis has shifted to higher ages, a desirable diagnostic and therapeutic strategy is necessary for this rapidly increasing population of elderly patients, and this kind of age-specific analysis may provide useful information for further studies.

Significant survival difference between male and female has been reported in several gastrointestinal tumors. In the stomach cancer patients, age-standardized death rate for gastric cancer was worse for male patients (23). One possible explanation of survival may be explained by the different life expectancy between two groups. In the 2005 registry, males live 75.1 years, whereas females live 81.9 years. This longer life expectancy may cause longer survival of female patients. However, the other biologic factors such as sex hormone or immunologic effect should be researched with further prospective studies.

For the analysis according to the stage distribution, survival improvement of period analysis was not evident for the Stages I–II patients. However, survival rate in period analysis was definitely improved for the Stages III–IV patients. As an explanation, effective chemotherapy and supportive care have developed remarkably during this period. In addition, several novel agents, such as irinotecan, oral 5-fluorouracil and molecularly targeted agents, have demonstrated activity with tolerable toxicities (24–26). Therefore, the recent advances of chemotherapy and supportive care

may significantly influence the survival outcome of patients with an advanced stage of disease.

Despite these advantages of period analysis, there are several limitations in this report. First of all, this result was deduced from a single-center cancer registry. Because our center is a tertiary center, the majority of patients were transferred from local clinics when their disease progressed to an advanced stage, even though their initial disease status was early stage. Secondly, we only analyzed disease status and survival outcome without any detailed information about treatment, which might affect the survival outcome. Patients who received active treatment and those with only supportive care were all analyzed together. Therefore, the effect of treatment was only indirectly reflected in these results. Third, patients who may have more than two types of cancer were included repeatedly in this analysis. According to our previous research on the seven most common cancers (stomach, liver, lung, colon, cervix, breast and thyroid) between 1995 and 2004, 541 of 34 217 cases (1.6%) were duplicated due to double or triple cancer types. Fourth, for the period analysis, there is some risk of survival misprediction if the data set is from the too small or immature population, or survival has not changed a lot. Therefore, it is not feasible to apply period analysis for cases of rare tumor types. For this reason, we applied this method to gastric cancer, which is the most prevalent malignancy with sufficient numbers of patients.

In conclusion, we observed that period analysis is a very useful method to derive precise survival rates in gastric cancer. Our study also described changing trends of long-term survival for different age groups using period analyses. A combination of well-established data and the analytic methodology of period analysis provide the most up-to-date information. This reliable baseline information may help to predict and establish proper health policy in the future. To our knowledge, this is the first comprehensive evaluation with the most up-to-date survival estimates for one of the more major cancers in a highly prevalent area. Moreover, this information might be useful in order to understand the survival differences resulting from a change in treatment strategy.

Conflict of interest statement

None declared.

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