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Duration of lead time in screening for gastric cancer

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ABSTRACT

Objective: Estimates of lead time (LT), i.e., from detection of cancer in asymptomatic persons to manifestations of the disease, can be obtained by follow-up of populations at risk, reviews of the past histories of patients with cancer, estimates of tumor doubling time, and from the ratio between the prevalence of cancer at the first round of screening and its annual incidence on subsequent screening rounds. Aim of this study is to derive the LT of gastric cancer (GC) from published studies.

Material and Methods: An overview of longitudinal studies and screening trials of GC; search of the reference sections of the retrieved papers for additional relevant studies; and calculation of the LT derived from these studies.

Results: LT was 2.8 – 7.3 years if derived from prospective follow-up studies; 1.0 - 4.0 years if derived from retrospective reviews of the patients' histories before the clinical diagnosis of GC; 5.9 - 8.6 years if derived from tumor doubling time; and 1.8 - 4.3 years if derived from prevalence / /incidence ratios.

Conclusions: There is wide variability in estimates of the LT of GC. Since an LT exceeding 6 six years may explain the improved survival of patients with screen-detected GS, the present survey does not obviate the need for randomized clinical trials of the effect of screening on gastric cancer mortality.

Keywords: Gastric cancer, mass screening, lead time, endoscopy

INTRODUCTION

Screening for cancer assumes that its early treatment is beneficial. There are no randomized controlled trials of the effect of early detection and treatment of gastric cancer (GC) on mortality. In Korea, a comparison between patients with GC, who participated in a national GC screening program at least once, with those who did not, indicated that screening increased 5-year survival from 62% to 78% and reduced mortality by 41% (**1-4**). However, these findings may have been confounded by biases, such as lead time (LT) bias, i.e., the interval from detection of GC by screening to development of symptoms. The duration of LT of cancer may be deduced from prospective or retrospective studies, doubling time (DT) of the cancer cells, and screening trials. Prospective longitudinal studies follow untreated patients with precancerous lesions or with early GC. Retrospective longitudinal studies review the symptoms of patients before the clinical diagnosis of GC. Inferences from tumor DT assume that a single cell of 10 µm develops into a tumor by a succession of divisions at a constant DT. Therefore, one may use the tumor DT to derive the duration of LT from the tumor size at its detection in asymptomatic and in symptomatic patients. Estimates based on screening trials have assessed the duration of LT from the ratio between the prevalence of cancer at the first (baseline) screening round and the annual incidence of cancer during subsequent rounds. The objective of this paper is to derive the duration of the LT of GC from published data.

Summary box:

What is already known about this subject? As known, There is no attempts to determine the lead time, i.e., the interval from detection of gastric cancer by screening to development of symptoms.

What are the new findings? The various approaches to the determination of lead time of gastric cancer yield widely variable results between 1 and 8 years (2.0 – 4.3 years excluding outliers).

How might it impact clinical practice in the foreseeable future? Since a lead-time exceeding 6 years may explain the improved survival of patients with screen-detected gastric cancer, the present survey does not obviate the need for randomized clinical trials of the effect of screening on gastric cancer mortality.

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MATERIAL and METHODS

Searched databases: Medline and Old Medline - from inception to March 2021 by combining the term (stomach neoplasms) AND all of the following: (a) (natural history); (b) (doubling time); (c) (clinical trials); (d) (mass screening); and (e) (endoscopy, gastrointestinal), and searched the reference sections of the retrieved papers for additional relevant studies. I selected studies that presented data on (a) retrospective or (b) prospective longitudinal analyses, (c) doubling time (DT) of the GC cells, and (d) screening trials, and derived from them estimates of the LT of GC.

Retrospective studies

Use of proton pump inhibitors, h2 blockers or antacids is associated with GC. Patients with GC have been reported to be 3 times more likely than their controls to have used h2 blockers or antacids during the 5 years preceding diagnosis (5). There was a 4.1-fold increase in mortality rates of GC during the first-year use of proton pump inhibitors that gradually declined to that expected in the population in the fourth year of follow-up (6). The GC incidence rate ratios of users vs non-users of h2 blockers were 2.6 in the first year, 0.7 in the second to fourth year (7). Similarly, the incidence ratios of users vs non-users of proton pump inhibitors were 12.8 during the first year, 2.2 in years 1-3, and 1.1 in years 3-5 (8).

This association may suggest a cause-effect relation between the use of h2 blockers or proton pump inhibitors and GC (9). However, the decline in the risk of GC with years of exposure to acid-suppressive drugs implies reverse causation, i.e., acid-suppressive drugs delay the diagnosis of GC (10). This second possibility implies an LT between dyspepsia and clinically overt GC of 1 - 4 years.

Follow-up studies

Pre-cancerous lesions

Gastric cancer is classified as cardia versus non-cardia, and intestinal - versus diffuse-type. Intestinal-type non-cardia GC develops from normal mucosa to chronic atrophic gastritis to gastric intestinal metaplasia, dysplasia, and malignancy. No precursor lesions have been identified for diffuse-type GC (11). A 2020 systematic review of the literature indicated that the prevalence of gastric intestinal metaplasia was 3.4% in Northern Europe, 4.8% in the US, 21.0% in Eastern Asia, and 23.9% in South America (12). In Holland, GC was diagnosed during a 10-year follow-up in 0.8% of patients with atrophic gastritis; 1.8% of patients with intestinal metaplasia; 3.9% of patients with mild to moderate dysplasia; and 32.7% of patients with severe dysplasia (13).

Estimates of the time interval between detection of precancerous lesions and GC have yielded an unexplained variability. In Holland, this interval was 1.6 years (SD 3.2) in patients with atrophic gastritis, 0.90 years (SD 3.4) for patients with intestinal metaplasia, 0.45 years (SD 3.1) in patients with mild-to-moderate dysplasia, and 0.13 years (SD 2.7) in patients with severe dysplasia (13). On the other hand, in the USA, the median time for intestinal metaplasia to progress to GC was 6.1 (14) and 5.0 (15) years.

Since these estimates are restricted by the duration of follow-up, they should be considered as low-bound; and since the end-point of follow-up studies of precancerous lesions was asymptomatic GC, they do not apply to the LT between screen-detected to clinically detected GC.

Progression of Gastric Cancer

Of all GC cases, the proportion of early cancers was 35.7% in symptomatic patients and 78.1% in those detected by screening of asymptomatic persons (16). Therefore, the findings of follow-up studies of the progression of early to advanced GC in untreated patients may approximate the LT between GC detected in asymptomatic persons and symptomatic patients.

Such follow-up studies have indicated that the period for GC in situ to progress to an advanced stage was 4 - 5 years in Chinese patients (17); that in Japanese patients, 50% remained in the early stage after 44 months follow-up, and about none after 100 months or 8.3 years (18); and that in Korean patients the time interval was 34.1 months from T1 ("early GC", tumor invades lamina propria or submucosa) to T2 (tumor invades muscularis propria or the sub-serosa); 9 months from T2 to T3 (penetrating serosa), and 3.8 months from T3 to T4 (invading adjacent organs) (19). Therefore, follow-up studies of the progression of early to advanced GC in untreated patients suggest an LT of 2.8 to 8.3 years.

Doubling Time

Follow-up for 25 years of untreated Japanese patients in whom the size of the tumors was measured by endoscopic ultrasound-guided fine-needle aspiration on at least two occasions indicated a doubling time of 17.2 months (20). More recent observations during a mean 35.1 ± 34.4 months follow-up of untreated Korean patients indicated that the doubling times shortened as the stages advanced from 11.8 months for T1 ("early GC", tumor invaded lamina propria or submucosa), 9.8 months for T2 (tumor invaded muscularis propria or the sub-serosa), 6.5 months for T3 (penetrating serosa), and 6.2 months for T4 (invading adjacent organs) (19). Both assessments of doubling time did not provide a detailed description of the way tumor volumes were derived from radiology (19) or endoscopic ultrasound (20) findings.

The tumor size in GC patients who underwent gastrectomy ranged between 0.2 and 24 cm (mean 5.4 cm, median 4.3 cm, mode 3 cm) (21), with a 90th percentile value of tumor size in advanced GC being 10 cm (22). Assuming that the tumor size in cm is a proxy for tumor volume, then it would take six divisions from 0.2 to 10 cm, or about 5.9 – 8.6 years.

Prevalence / Annual Incidence Ratios

When applied for the first time, screening detects cancers at the lead time of the disease. The number of these prevalence cases equals the annual incidence of the disease in the same population multiplied by the lead time in years, and therefore, its duration may be derived from the prevalence/incidence ratios (23). The prevalence/incidence ratios of GCs detected by mass screening (Table 1) suggest a lead time of 3.4 (24), 1.9 (25) and 4.3 (26) years in Japan, 1.9 - 2.3 years in Russia (27), and 1.8 – 4.0 years in Korea (28, 29).

Table 1: Estimated duration of the lead time from pre-symptomatic to symptomatic disease derived from trials of screening for gastric cancer by endoscopy (e) or radiography (r)

Trial and authors	Study population, prevalence (n)	Prevalence of gastric cancer per 1000 at T_0, (a)	Average duration of screening (years)	Study population, incidence (n)	Average annual incidence of confirmed screen-detected and interval gastric cancers per 1000 during screening		Time from pre-symptomatic to symptomatic gastric cancer (years)
					Screen- detected (b)	Interval (c)	a / (b + c)
Screening for gastric cancer by radiography							
Shiratori et al 1985 [24]	20,692	1.7	6	18,558	0.5		3.4
Portnoi et al 1999 [27]	30,714	1.2	15		0.6		2.0
Hamashima et al 2013 [25]	5,410	5.1	5	11,417	2.0	0.3	2.2
Kim et al 2018 [29]	2,758	19	11	2,015	8.9		2.1
Screening for gastric cancer by endoscopy							
Matsumoto et al 2007[26]	3,200	1.3	13	3,200	0.3		4.3
Hamashima et al 2013 [25]	7,388	9.1	5	18,021	4.8	0.1	1.9
Bae et al 2015 [28]	293,520	0.092	2.2	91,850	0.05		1.8
Kim et al 2018 [29]	6,553	29	11	4,356	7.3		4.0

Table 2: Estimated duration (years) of the progression along the natural history of gastric cancer by methods of study

Estimates derived from	Time in years			
	From precancerous lesion to early gastric cancer	From dyspepsia to symptomatic gastric cancer	From early to advanced gastric cancer	From pre-symptomatic to symptomatic gastric cancer
Prospective studies of precancerous lesions				
Atrophic gastritis, Intestinal metaplasia, Mild-to-moderate dysplasia	1.6 [13] 0.9 [13] – 6.1[14,15] 0.5 [13] – 2.6 [14]			
Severe dysplasia	0.1 [13]			
Retrospective studies		1.0 – 4.0 [5-8]		
Prospective studies of early gastric cancer			2.8 – 8.3 [17-19]	
Tumor doubling time			5.9 - 8.6 [20-22]	
Prevalence/incidence ratios screening by upper gastrointestinal x-rays				2.0 – 3.4 [24-25,29]
Prevalence/incidence ratios screening by endoscopy				1.8 – 4.3 [25,26,28,29]

DISCUSSION

Table 2 summarizes the main findings of this survey. The approaches to estimates of the LT of GC remain a challenging exercise, as they yield widely variable results between 1 and 8 years (2.0 – 4.3 years excluding outliers). Possible causes of this variability are methodological biases or erroneous assumptions of the different approaches to the estimation of LT. First, estimates derived from screening trials may have been confounded by differences in their study populations. Second, estimates derived from tumor doubling time may have been biased by uncertainties whether it is constant or diminishing during the natural history of GC. Finally, it is uncertain whether the duration of the transition from early to advanced cancer is generalizable over LT between asymptomatic to symptomatic patients.

The main limitation of this survey is its restricted, rather than systematic, review of the literature. However, I believe that this limitation does not invalidate its main conclusion that the LT of GC may exceed 6 years. Therefore, a backward prolongation of survival may explain the improved survival of screen-detected patients with GC (**4, 30**). The present survey does not obviate the need for randomized clinical trials of the effect of screening on GC mortality.

CONCLUSION

There is wide variability in estimates of the LT of GC. Since an LT exceeding 6 years may explain the improved survival of patients with screen-detected GS, the present survey does not obviate the need for randomized clinical trials of the effect of screening on gastric cancer mortality.

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