Influence of "diagnostic delay" upon cancer survival: an analysis of five tumour sites

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Abstract

Study objective—The aim was to assess the relationship between survival, tumour stage, and the interval from first symptom to diagnosis (SDI, or duration of symptoms).

Design—This was a retrospective follow up study of a cohort of patients registered in the tumour registry of the Hospital del Mar (Barcelona).

Setting—Hospital based tumour registry, with patients derived mainly from the City of Barcelona.

Participants—1247 cases of lung, breast, stomach, colon, or rectal cancer were analysed using survival curves and Cox proportional hazards regression. Subjects (mean age 63·6 years) were followed for a median length of 12·9 months after diagnosis. At the time of diagnosis one fourth of patients had disseminated disease.

Measurements and main results—Based on clinical records, a physician registered the onset time of the first symptom attributable to cancer (from which the SDI is computed), as well as the tumour stage at diagnosis. Other measurements followed standard tumour registry procedures. Overall, the crude mean SDI was 5·15 months (SD 8·03, median 2·03); only 24·5% of cases had an SDI less than a month. Crude mean SDIs by anatomical site were as follows: lung cancer 3·07 months; breast 7·44; stomach 5·34; colon 5·74; rectum 5·03. Tumour extension did not appear to be significantly influenced by SDI, only breast cancer showing a distinct pattern of increased extension with increasing SDI. As expected, the probability of survival decreased monotonically with increasing stage in all sites. Tumour site was also a significant predictor of survival, which at one year ranged from 93% for breast cancer to 28% for lung cancer. However, a longer SDI tended sometimes to be associated with a better chance of survival, a fact that was most apparent in colon cancer. All Cox proportional hazards models showed a consistent picture: SDI was not a significant predictor of survival (age and sex adjusted hazard ratios ranging from 0·97 to 1·01), neither was sex; age did predict survival, and so did site and stage.

Conclusions—The results provide further evidence of a very weak relationship between SDI and tumour stage at diagnosis (except for breast cancer), and between SDI and survival, thus emphasising some limitations within which early clinical detection operates. They also suggest that in addition to reflecting patient and physician behaviour, as well as the functioning of the health system, SDI may be influenced by the biological behaviour of the tumour.

Conflicting results have been found in studies analysing the influence upon cancer prognosis of the time interval between onset of symptoms and diagnosis (SDI, or duration of symptoms). Some authors show[1-6] or imply[7-9] that a relationship exists (eg, the shorter the SDI, the more localised the tumour and the longer the survival), whereas others[10-26] have found that long SDIs are not necessarily associated with more disseminated disease or with increased mortality. Indeed, for some cancers it is often accepted: (1) that they are curable if discovered early in the preclinical course, (2) that delay in diagnosis is a most significant factor in poor prognosis, and (3) that the extent of spread at the time of diagnosis and treatment is closely correlated with prognosis.[27 28]

Nevertheless, the three points need not be equally true. Furthermore, while the degree of differentiation is not always well correlated with the degree of invasiveness or the rapidity of growth,[28-30] a shorter clinical history is not uncommonly associated with poorly differentiated cancers.[13 14 28-34]

Hence, it seems crucial to note that uses of the concept of *early detection* may hide two very different phenomena: (a) a limited spread of the tumour at the time of diagnosis, and (b) a short time interval between clinical onset of disease and diagnosis. Whereas the latter cannot be assumed to guarantee finding a localised disease, biological characteristics of the tumour, host resistance, and host-tumour interaction do appear to significantly explain its growth,[29 30 35-37] and may thus be of greater prognostic importance than the length of symptomatic illness.

However, few epidemiological studies have formally analysed the influence of the duration of symptoms upon cancer survival, maybe because—as Morrison expressed it—"there is a compelling intuitive appeal to the idea that earlier treatment *must* work; it seems inconceivable that there might be no gain in finding disease early."[34]

The primary goal of the present study was to assess the relationship between SDI, tumour stage, and survival in five cancer anatomical sites: lung, breast, stomach, colon, and rectum.

Methods

Data from the tumour registry of the Hospital del Mar (TRHM), a 450 bed teaching hospital primarily serving a low income area in Barcelona, were used in the present study. A detailed description of TRHM[38] and other preliminary results[39] have been previously published. In summary, this is a hospital based tumour registry initiated in 1978 and currently including about 4000 neoplasms. It follows the data collection procedures established by a regional collaborative Oncology group.[40] All information is obtained from clinical records. Over 95% of tumours are microscopically confirmed, 6·8% are of unknown origin, and 5% are double neoplasms; 96·8% of cases are residents of the city of Barcelona.

Data collection, quality assurance and computerisation are all conducted on site by a research fellow under the supervision of an oncologist and an epidemiologist. The SDI is computed from the date of histological diagnosis and the first symptom attributable to cancer, as recorded in clinical notes. Stage is classified as local, regional, or disseminated; tumours with regional dissemination are those with regional nodal involvement (N+) or invasion of structures surrounding the primitive tumour. In order to achieve a minimum amount of follow up, we only selected cases registered between 1978 and 1987. Analysis was also restricted to the five most common tumours: lung, breast, colon, rectum, and stomach. Of the recorded cases, 3·2% were excluded from the analysis since the SDI was unspecified.

To assess the relationship between a categorical variable with more than two levels and a non-normally distributed quantitative variable the Kruskal-Wallis test was used. Age and sex adjusted geometric means of SDI were obtained for each site and stage by least squares linear regression of the natural logarithmic transformation of SDI to the corresponding variables.

Survival curves were estimated by the Kaplan-Meier method[41] and compared by means of a generalisation of the non-parametric Wilcoxon test to censored data for the case of variables with two categories,[42] and of a generalised Kruskal-Wallis test for comparing three or more samples.[43] Cox proportional hazards regression[44] was used to estimate the hazard rate of SDI (the hypothesised primary explanatory variable), adjusted for age, sex, and tumour site and stage (the potential confounding and effect modifying variables). Hazard ratios were used to describe the relationship between the explanatory variable and survival time. Hazard ratios are the ratios of the hazard rates for values of variables unfavourable to survival to those of variables favourable to survival; the measure can be interpreted as the approximate instantaneous relative risk associated with a particular factor, either continuous (eg, SDI, age) or categorical (eg, regional v localised tumour stage). Computations were performed by using Pecan[45] and the SAS PHGLM procedure developed by Harrell[46]; the two programs yielded identical results. Both the "Z:PH" statistic and inspection of plots of log minus log survival function against time were used to check the proportional hazards assumption.[46] The significance level was established at 0·05 and all p values are two tailed.

Results

The 1247 subjects in this study were followed for a median length of 12·9 months after diagnosis, with a mean of 23·7 months (table I). Follow up varied from a median of 36·9 months for breast cancer cases, of whom 37% died, to a median of 5·9 months for lung cancer cases, of whom 84% died. Only 67 cases (5·4%) were lost to follow up, and all but 215 patients (17·2%) were followed for two years or to death. Overall, 751 (60·2%) members of this dynamic cohort died during follow up and were thus uncensored. No anatomical site showed statistically significant differences between sexes in the proportion of uncensored cases.

Mean age was 63·6 years (SD 12·9, median 64·4). One fourth of cases had disseminated disease at the time of diagnosis. As expected, differences in stage distributions among anatomic sites were statistically significant ($\chi^2_{[12]} = 121$, p < 0·0001); lung and to a lesser extent stomach, showed more disseminated patterns.

As shown in section 2 of table I, the crude mean SDI was rather large, 5·15 months (SD 8·03, median 2 months). Only 24·5% of cases had an SDI less than a month; 75% of cases had an SDI less than 5·02 months. Interestingly, breast cancer showed the largest SDI and lung cancer the shortest interval, with colorectal and gastric cancer presenting intermediate values (p < 0·0001). Sex had barely any influence upon SDI (section 3, table I).

Tumour extension at diagnosis did not appear to be significantly influenced by the duration of symptoms (section 4, table I). Only breast cancer showed a distinct pattern of increased extension with increasing SDI; the differences in SDI between the local and regional stages (p = 0·036), and between the local and disseminated stages

Table I   Characteristics of cases, and interval from first symptom to diagnosis (SDI), by primary tumour site.

| Variable	Breast	Stomach	Rectum	Colon	Lung	Total
1 No of cases	335	174	132	196	410	1247
Follow up (median)[a]	36·9	9·0	11·1	17·9	5·9	12·9
Uncensored (%)	37·0	64·4	55·3	50·0	83·9	60·2
Sex (% females)	100	41·3	43·2	47·9	8·5	47·6
Age (mean, years)	57·9	67·3	69·9	64·5	64·4	63·6
Stage (%)						
Local	38·5	23·6	40·1	39·3	18·8	30·2
Regional	43·0	39·1	33·3	39·3	34·9	38·2
Disseminated	13·1	24·7	19·7	18·9	40·7	25·4
Unspecified	5·4	12·6	6·8	2·5	5·6	6·2
2 Crude SDI[a]						
Mean	7·44	5·34	5·74	5·03	3.07	5·15
SD	11·19	7·80	8·47	6·84	3·75	8·03
Median	3·02	2·98	2·98	2·97	2·00	2·03
% ⩾5 months	35·8	28·7	32·6	30·1	16·1	27·1
Q3–Q1[b]	7·97	4·92	4·98	5·04	3·93	4·00
3 Age adjusted SDI by sex (geometric mean)[a]						
Females	3·08	2·59	3·01	2·62	1·99	2·62
Males	—	2·83	3·02	2·36	1·87	2·57
4 Age and sex adjusted SDI by stage (geometric mean)[a]						
Local	2·54	2·36	2·77	2·43	1·72	2·31
Regional	3·39	3·08	3·66	2·41	2·01	2·82
Disseminated	4·24	2·89	2·46	2·86	1·92	2·76
Unspecified	2·03	2·51	3·09	1·70	2·68	2·51
Total	3·04	2·73	3·02	2·48	1·89	2·51

[a] In months.
[b] Q3–Q1 = the difference between the upper quartile (or 75th percentile) and the lower quartile (or 25th percentile).

(p = 0·01) reached statistical significance. No other site showed statistically significant differences among stages. The overall age and sex adjusted SDI for lung cancer is significantly lower than the corresponding value in each of the four other anatomical sites (p < 0·01 in all cases).

As can be seen in table II, the probability of survival at one and at five years decreased monotonically with increasing stage in all sites. As expected, tumour site was also a significant predictor of survival, which at one year ranged from 93% for breast cancer to 28% for lung cancer.

Cases were next divided in every site/stage subgroup according to whether their SDI was above or below the site median SDI (previously shown in table I), and their median survival was computed (table II); obviously, when over 50% of cases in a subgroup were alive the latter could not be estimated. For example, 50% of cases with local stomach cancer whose SDI was below 2·98 months (the group median SDI) survived ⩾29 months; but those whose SDI was above the group median SDI survived ⩾62 months. Surprisingly a longer SDI tended sometimes to be associated with a better chance of survival. This was most apparent in colon cancer, where all subgroups above the median SDI yielded longer survival times than their counterparts below the median SDI. The phenomenon was also observed in localised breast cancer, localised and regional gastric cancer, regional and disseminated rectal cancer, as well as in disseminated lung cancer. While some of the differences in survival were minor and most could be due to chance, the lack of a consistent, positive relationship between
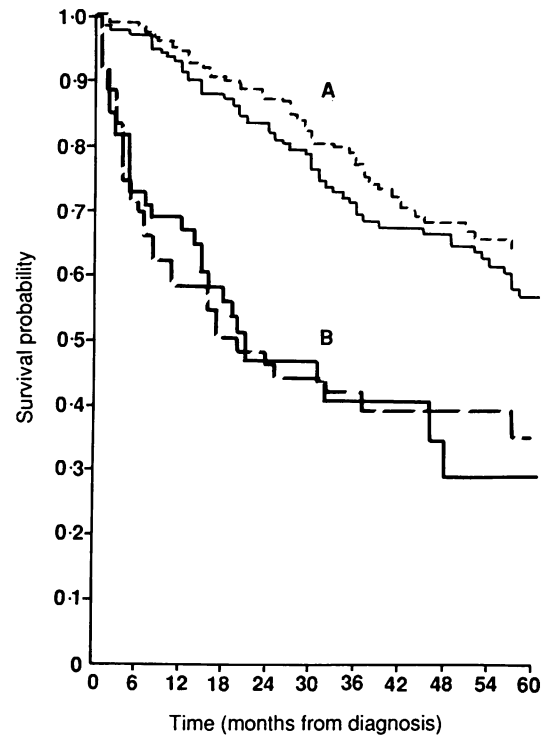
Survival distributions of cases below (interrupted line) and above (continuous line) the group median SDI for breast cancer (A) and rectal (B) cancer.

SDI and survival is unmistakable. Purely to illustrate this point, fig 1 depicts the survival distributions of breast and rectal cancer cases above and below each site group median SDI.

Results of Cox proportional hazards analysis appear in table III. All models show a consistent picture: SDI was not a significant predictor of survival (age and sex adjusted hazard ratios ranging from 0·97 to 1·01), neither was sex; age did predict survival, and so did site and stage.

We finally analysed the relationship between SDI and survival in the four site/stage subgroups with over 100 cases. The corresponding age and sex adjusted SDI hazard ratios were as follows: lung, regional, 0·99; lung, disseminated, 1·01; breast, local, 0·97; and breast, regional, 1·00 (p > 0·45 in all cases). Hence, even within specific tumour stages, SDI did not appear related to survival time.

Discussion

The findings provide further evidence of a lack of a consistent relationship between SDI and survival, and of a very weak relationship between SDI and tumour stage at diagnosis.[10-26] Specifically, in the population served by our hospital, tumour extension at the time of diagnosis did not appear to be significantly influenced by SDI or duration of symptoms (with the exception of breast cancer). No excess risk of mortality associated with longer SDI was observed either: age and sex adjusted hazard ratios were always close to unity. Among the variables analysed, only age, tumour site, and extension were meaningfully related to survival time.

Differences in SDI among tumour sites were quite remarkable, particularly between breast and

Table II Proportion of uncensored (dead) cases, probability of survival at one and at five years, and 50% percentile survival for cases with interval from first symptom to diagnosis (SDI) below and above the site group median SDI.

Site/stage	Uncensored (%)	P_1	P_5	SDI <median survival[a] (n)	SDI ⩾median survival[a] (n)	p value[b]
Breast						
Local	22·5	0·975	0·760	84 (72)	nr (57)	0·107
Regional	40·3	0·932	0·551	65 (64)	65 (80)	0·699
Disseminated	70·5	0·779	0·256	36 (16)	19 (28)	0·063
Total	37·0	0·928	0·600	72 (152)	77 (165)	0·372
Stomach						
Local	41·5	0·790	0·418	29 (24)	62 (17)	0·356
Regional	64·7	0·557	0·197	11 (28)	17 (40)	0·982
Disseminated	83·7	0·367	0·046	9 (21)	4 (22)	0·249
Total	64·4	0·563	0·207	18 (73)	14 (79)	0·509
Rectum						
Local	37·7	0·709	0·491	nr (28)	29 (25)	0·669
Regional	63·6	0·603	0·266	15 (16)	19 (28)	0·968
Disseminated	73·1	0·502	0·164	5 (16)	16 (10)	0·166
Total	55·3	0·626	0·322	18 (60)	21 (63)	0·756
Colon						
Local	25·9	0·907	0·583	57 (34)	nr (43)	0·350
Regional	57·1	0·767	0·270	16 (44)	22 (33)	0·243
Disseminated	78·4	0·451	0·116	9 (17)	10 (20)	0·777
Total	50·0	0·762	0·364	28 (95)	34 (96)	0·172
Lung						
Local	64·9	0·512	0·238	14 (40)	12 (37)	0·780
Regional	86·7	0·279	0·043	6 (63)	6 (80)	0·507
Disseminated	89·2	0·164	0·000	4 (71)	5 (96)	0·694
Total	83·9	0·278	0·067	6 (174)	6 (213)	0·282
Total						
Local	36·1	0·809	0·554	57 (197)	nr (180)	0·006
Regional	62·6	0·625	0·280	16 (213)	21 (263)	0·429
Disseminated	83·3	0·340	0·070	6 (155)	7 (162)	0·484
Total	60·2	0·605	0·307	17 (565)	21 (605)	0·130

P_1 = probability of survival at one year.
P_5 = probability of survival at five years.
[a] survival of 50% percentile of subgroup cases (median survival, in months); cases with unspecified extensions are excluded.
[b] Two tailed probability for the difference in survival distributions between subjects with SDI below and above the group median SDI.
nr = Median survival not yet reached (over 50% of cases were alive).

lung neoplasms. This finding seems coherent with the notion that SDI may partially be influenced by the biological behaviour of the tumour.[39] [47] Clinical ("auxometric") measures of tumour growth[48–51] may, in this respect, be of relevance.

In addition to well known limitations of hospital based tumour registries,[52] [53] the following considerations should be taken into account when interpreting the findings. Since it is not always clinically efficient to estimate the exact time of the onset of symptoms, our measure of SDI (which, as mentioned, was estimated from clinical records) was relatively crude. In fact, in a separate study currently underway, based on a structured patient interview targeting SDI phases,[54] [55] we observed slightly longer intervals than those registered based upon clinical notes. Whereas we deem it unlikely that a differential bias favouring any specific subgroup occurred in our study, we cannot rule out the possibility that non-differential measurement errors (including recall errors) might have obscured a relationship between the duration of symptoms and survival. There is no doubt that more accurate measurements of SDI phases and of tumour stage are needed; with some exceptions,[2] [56] they are more feasible in specific ad hoc studies than in tumour registry analyses.

One must also seriously consider the possibility that in the low income population here analysed

the range of SDI values was actually not wide enough for an effect upon survival to be evidenced.

We analysed a small number of factors. Indeed, we consider the duration of symptoms to be a highly complex variable reflecting patient and physician behaviour,[1–3] [8] [14] [27] [47] [57] [58] the clinical course,[1] [2] [13] [59] the functioning of the health system,[1] [6] [8] [14] [47] sociocultural values,[55] [58] [60–65] and tumour biology.[13] [14] [34] [49] Certainly, the many variables likely to mediate the SDI—prognosis relationship are not easy to measure accurately in large numbers of patients. Still, epidemiological analyses which meaningfully integrate the different clinical, biological, and psychosocial factors involved are much in need.[66]

Even though several subgroups here analysed have small numbers, the study allowed comparison of the five more frequent tumours (accounting for over half of all cancer cases) in most developed countries. While it is not implausible that differences in prognosis between SDI subgroups might be uncovered by an analysis based on a larger number of cases, we think it unlikely that their magnitude is large.

It is also worth emphasising that the primary goal of the current analysis was to assess the relationship between SDI and tumour stage, and between SDI and survival, rather than to identify a model that would fit the data.

Additionally, we suggest that interpretation of the present results may also benefit from the following conceptual considerations. Prognosis of many tumours appears to be largely influenced by factors active in the presymptomatic phases of the illness, the symptomatic phase often representing a much smaller fraction of the natural history of the malignancy.[34] [67–69] Accordingly, variations in SDI might account for only a limited portion of differences in stage at diagnosis, and of differences in survival. The group of patients presenting within a short time after onset of symptoms is likely to comprise a mixture of patients with more virulent tumours and of patients with less biologically active tumours but seeking care sooner. Conversely, patients presenting long after onset of symptoms may include patients with relatively benign tumours as well as patients with more agressive disease who greatly delay seeking care. It is the biological and clinical heterogeneity of patients with similar SDI that makes this interval somewhat misleading (though fascinating). In fact, it is possibly an error to focus exclusively on the (quantitative) time dimension: clinical (qualitative) changes experienced during tumour progression have been found to be an independent determinant of prognosis.[48–51]

In our view, a relevant question to pose is: does tumour behaviour influence patient behaviour or is it the other way round? Our hypothesis is that two simultaneous processes interact: (a) the promptness with which a person seeks medical attention and the specific medical path he or she follows influence the stage at which cancer is diagnosed, and the subsequent disease course; and (b) in turn, the biological and clinical behaviour of the tumour influence both the patient's perception, assessment, and response to symptoms, and the pathway followed among the

Table III   Cox proportional hazards survival analysis.

Model	Regression coefficient	Standard error	Hazard ratio[a]	Hazard ratio 95% CI
1 SDI	0·00279	0·00491	1·003	0·99–1·01
2 SDI	0·00291	0·00488	1·003	0·99–1·01
Age	0·01689	0·00329	1·017*	1·01–1·02
3 SDI	0·00280	0·00490	1·003	0·99–1·01
Sex	0·04157	0·10288	1·042	0·85–1·28
4 SDI	0·00297	0·00488	1·003	0·99–1·01
Age	0·01697	0·00329	1·017*	1·01–1·02
Sex	0·06153	0·10371	1·063	0·87–1·30
5 Stage				
Regional	0·73580	0·10450	2·087*	1·70–2·56
Disseminated	1·30400	0·11070	3·684*	2·97–4·58
Unknown	0·94340	0·16370	2·569*	1·86–3·54
6 Stage				
Regional	0·75030	0·10470	2·118*	1·72–2·60
Disseminated	1·31400	0·11080	3·721*	2·99–4·62
Unknown	0·88090	0·16440	2·413*	1·75–3·33
Age	0·01760	0·00360	1·018*	1·01–1·02
Sex	0·11280	0·10400	1·119	0·91–1·37
SDI	−0·00020	0·00480	0·999	0·99–1·01
7 Site				
Colon	0·58730	0·14870	1·799*	1·34–2·41
Rectum	0·76050	0·16310	2·139*	1·55–2·95
Stomach	1·11700	0·14490	3·056*	2·30–4·06
Lung	1·83900	0·14830	6·290*	4·70–8·41
Age	0·01770	0·00330	1·018*	1·01–1·02
Sex	0·07610	0·10310	1·079	0·88–1·32
SDI	0·00330	0·00480	1·003	0·99–1·01
8 Site				
Colon	0·59160	0·14940	1·807*	1·35–2·42
Rectum	0·75760	0·16330	2·133*	1·55–2·94
Stomach	1·01700	0·14600	2·765*	2·08–3·68
Lung	1·66600	0·15100	5·291*	3·94–7·11
Age	0·01850	0·00330	1·019*	1·01–1·03
Sex	0·13410	0·10330	1·144	0·93–1·40
SDI	−0·00010	0·00480	0·999	0·99–1·01
Stage				
Regional	0·77530	0·10440	2·171*	1·77–2·66
Disseminated	1·36800	0·11040	3·927*	3·16–4·88
Unknown	0·90770	0·16400	2·479*	1·80–3·42

CI = Confidence interval; SDI = Interval from first symptom to diagnosis
[a] Ratio to hazard rates for categories of each variable. The ratio contains the hazard rate for the "unfavourable to survival" category in the numerator and the "favourable to survival" category in the denominator. Favourable or reference categories are female, local stage, and breast site.
* $p < 0.001$

several usually available within a health care system. The resulting SDI, duration of symptoms, or "progression interval"[49] (terms we deem more neutral and appropriate than diagnostic "delay") is also modified by psychosocial factors (such as patient's personality, education, income, and access to care) and by other environmental factors (eg, the prevalence of cancer influences the predictive value of clinical signs, thus determining physician's diagnostic accuracy.[70]) An elaboration of this model is beyond the scope of this paper.

Given that the rate of tumour growth is commonly related both to survival and to the likelihood of SDI reduction (slower growing tumours being more amenable to early clinical detection),[27 33 34 69] evaluators of early clinical detection programmes should consider the potential for *clinical length bias* and *clinical lead time bias* to occur. Early detection must be measured in terms of tumour stage rather than duration of symptoms.

Although the idea that many cancers are curable if discovered early in the clinical course is clinically appealing, and in spite of solid scientific evidence that high quality screening programmes improve prognosis of some cancers,[27 33 34 71] the present results show that in a particular population group observed under natural conditions, the interval from first symptom to diagnosis very weakly influences the spread of the tumour at the time of diagnosis, and does not affect survival beyond the effect of stage at diagnosis. In our view, this cannot be taken to imply that specific interventions aimed at speeding up diagnosis in individuals are ineffective. There undoubtedly is an ethical obligation to detect, diagnose, and treat promptly individuals presenting with symptoms. Furthermore, diagnostic and treatment delays caused by malfunctioning of the health system must be reduced. Yet from a public health perspective one question remains: how wide a community impact in terms of mortality reduction can a decrease in SDI have? While secondary prevention undoubtedly has a role in medical care, findings such as ours emphasise some limitations within which it operates.[71] More efforts should be devoted towards the discovery of better tools for presymptomatic detection of cancer. Primary prevention remains the outstanding top priority for cancer control.

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