



ELSEVIER

Journal of Clinical Epidemiology 56 (2003) 815–819

**Journal of  
Clinical  
Epidemiology**

## Semiology, proteomics, and the early detection of symptomatic cancer

Miquel Porta<sup>a,b,c,\*</sup>, Esteve Fernandez<sup>d,e</sup>, Joan Alguacil<sup>a,f</sup>

<sup>a</sup>*Institut Municipal d'Investigació Mèdica, Carrer del Dr. Aiguader 80, Barcelona E-08003, Spain*

<sup>b</sup>*Universitat Autònoma de Barcelona, Barcelona, Spain*

<sup>c</sup>*School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

<sup>d</sup>*Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona E-08907, Spain*

<sup>e</sup>*Universitat de Barcelona, Barcelona, Spain*

<sup>f</sup>*Division of Cancer Epidemiology & Genetics, National Cancer Institute, Bethesda, MD 20892, USA*

Accepted 19 June 2002

### Abstract

“Diagnostic delay,” the duration of symptoms or the symptom to diagnosis interval (SDI), are highly complex variables that reflect the behavior of the patient and the attending physician, tumor biology and host–tumor interactions, the functioning of the health care system, and sociocultural norms. In addition to tumor stage, other variables mediate the relationship between duration of symptoms and survival; clinical and epidemiologic procedures to measure them must be improved. Largely at odds with clinical and common wisdom, decades of research have shown that often SDI is not associated with tumor stage and/or with survival from cancer. It would be relevant to increase evidence in support of the notion that, for each type of tumor, there is a positive relationship between the length of the presymptomatic and the symptomatic phases. SDI could then be used to classify tumors according to their likelihood of being detected early when still asymptomatic. Also, tumors could be classified according to the ratio of the median SDI to the median survival (SDI to survival ratio, SSR), which may estimate the relative likelihood for clinical lead-time bias. If adhering to rigorous methodologic standards, proteomic analyses of early-stage cancers might provide new insights into changes that occur in early phases of tumorigenesis. More real examples are needed of uses of pathologic and genomic data to study mechanisms through which SDI influences—or fails to influence—prognosis. The degree of correlation between proteomic patterns and classic semiology constitutes an area of interest in itself; their respective correlations with cancer prognosis should be assessed in properly designed epidemiologic studies. © 2003 Elsevier Inc. All rights reserved.

*Keywords:* Lung cancer; Diagnosis; Treatment; Survival; Delay; Symptoms; Signs; Semiology; Proteomics; Genomics

### 1. Introduction

The main results of the study on “diagnostic delay” in 378 patients with lung cancer that is published in this issue [1] can be summarized as follows: “diagnostic delay” was not associated with tumor stage at diagnosis and, while stage did influence survival, “delay” did not.

“Diagnostic delay,” the duration of symptoms or the symptom to diagnosis interval (SDI), have been empirically studied in oncology and cancer epidemiology at least since the early years of the 20th century (references can be found in earlier work of us [2–7]). Subsequently, fairly sophisticated studies have been conducted, including prototypic Feinstein research at his best [8–17]. Today, problems surrounding a late diagnosis of cancer remain important from all perspectives: clinical, public health, and the social perspective at large. Yet, it is unclear whether research in this area has

reached the top of the mountain or just a plateau: is conceptual, methodologic, and practical progress possible? Will it still be feasible to unveil new paths of knowledge and action?

It is conventional wisdom that the earlier cancer patients are diagnosed and treated, the better their survival. This is often true for certain tumors, such as uterine, cervix, and breast cancer; in them, SDI is often inversely associated with survival, SDI is positively associated with tumor stage at diagnosis, and stage is the main factor mediating the effect of SDI upon survival. In some studies SDI has been found to retain some additional influence upon survival, beyond that exerted through stage; however, further evidence is still needed to clarify two aspects of this association: first, whether part of it may be due to errors of measurement; and second, more importantly, the possible mechanisms of influence other than those directly associated with stage [2–7].

For other cancers (lung, pancreas) the effect upon prognosis of early clinical detection has often been found to be weak or null, although results depend on the clinical and

\* Corresponding author. Tel.: +34-93-221-1009; fax: +34-93-221-3237.  
E-mail address: mporta@imim.es (M. Porta).

sociocultural context, as well as on whether the study outcome is tumor stage at diagnosis or survival itself [5,7].

Still for some other tumors (e.g., gastrointestinal), counterintuitive results are common: patients with a *longer* duration of symptoms have been seen to have *higher* survival rates, while symptom duration was unrelated to survival in other studies. In digestive cancers, SDI does not seem to help to estimate prognosis beyond the contribution of classical clinical variables such as patient's age, tumor site, and particularly, tumor stage at diagnosis [2–4].

Many health care systems face significant pressures to improve the quality of cancer care, and specifically to decrease diagnostic and treatment waiting lists [3,18,19]. Although from an individual perspective it is almost always desirable to lessen therapeutic delays, immediate access to diagnosis and treatment for everyone in whom cancer is suspected and confirmed is often an unrealistic target in wide populations. It may therefore be useful to determine which factors are most closely associated with SDI, the relationship that this interval bears with tumor stage at diagnosis, and which interval values most strongly influence survival. Perhaps if a specific duration of symptoms had more of an influence, the public could be encouraged to present before a given time, and health care efforts could be concentrated on those critical periods; or perhaps time standards could be proposed. Alternatively, if the duration of symptoms has little prognostic impact, we may continue to rely on classic prognostic indicators, and efforts could concentrate on generalizing a timely access to treatments of the highest quality [2,3].

Thus, largely at odds with clinical and common wisdom, for decades a common finding has been that SDI was not associated with tumor stage and/or with survival from cancer. To what extent can such findings be due to weaknesses in the methodology of studies? What are the most important methodologic challenges in studying the relation between SDI and the ensuing clinical course? Can we envisage new study designs and measurement options? What are the most important pitfalls, and how can these be avoided or handled?

Prominent among the strengths of the study [1] stands, in our view, a wise, robust, and straightforward statistical analysis, as well as a balanced and succinct presentation of results (e.g., the stratification by stage summarized in Table 2). The specification of variables, the choice of statistical tests, and the overall presentation of results is rather fine, with simple and balanced tables and figures. One methodologic limitation might lie in the measurement of the date of the first symptom attributable to the cancer—a pervasive problem in this area of research. A large number of studies on SDI have been based on medical records. But it seems as if in daily cancer clinical care the collection of dates of symptom onset needs only to be approximate, while pathologic and staging information are more relevant for decision making at the time of diagnosis [20]. Thus, the accuracy of data on such dates is limited in clinical records [21]. Other

studies on SDI have used *ad hoc* questionnaires and standardized interviews; however, there may be ample room to develop better instruments to measure the cluster of initial symptoms, their dates, severity, and related characteristics. These efforts could benefit from theoretic, methodologic, and technical developments made during the last decades in the clinical social sciences [3–7]. They could also use advances made in outcomes research [22].

Medical records can still be useful to extract information on other variables, such as pathologic (“anatomopathologic”) diagnoses, route of hospital admission (e.g., urgent or elective) or the clinical status of the patient (at admission, at the time of interview). Records may also be used to gather information on surgical procedures, characteristics of attending surgeon or physician, and early outcomes (e.g., intraoperative mortality, complications within the first 48–72 hours after surgery). Cases with an abrupt presentation (e.g., an intestinal occlusion) may have a short SDI and a short survival. They may be cared for by the more experienced physicians [3].

The identification and selection of patients is also a delicate task in this research area as in so many others. It is seldom possible to detect, include, interview, and follow up all patients newly diagnosed with cancer in a well-defined geographic or clinical setting because, often, at least some will be too ill to participate, or will decline to do so.

## 2. Tumor stage, the core mediating factor of the effect of SDI upon survival

Tumor stage at diagnosis is a fundamental variable in studies on SDI. It is also an excellent example of the need to use highly accurate clinical information: factors as the patient's age, education, or type of insurance may affect both the accuracy of staging and survival itself. Thus, attention should be devoted to the possibility that differential misclassification of stage may bias results—another topic dear to clinical epidemiologists [8–16,23–25]. Tumor stage at diagnosis is often *the* main intervening variable: most of the effect of SDI upon survival—if not all—is mediated or channeled through stage. It is thus important not to overadjust by stage; rather, stratification by stage may be warranted to clarify the effect—or lack thereof—of SDI upon survival. It also remains important to identify biologic, clinical, sociocultural, and health care-related predictors of stage, and to compare their relative influence with that of SDI.

## 3. Any relations between the asymptomatic and the symptomatic phases?

Results of the study that we comment on [1] contribute to the debate on the promises and limitations of early clinical detection of symptomatic cancer. Are they also relevant beyond that? For instance, does the study bear upon current debates on screening of asymptomatic populations? In

the methodologic arena, can SDI and active screening be related and weighed? Conceptually, the initial, broad answer is “yes” to both questions. However, empirical, direct comparisons of the range of clinical impacts that asymptomatic and symptomatic detection may have are scant. A main conceptual similarity is that the two sorts of studies address a coin with two sides: early/late detection of disease. A main difference is—by definition—that screening can count on, take advantage of and, hence assess, the impact of the presymptomatic phase, while SDI encompasses a later phase—that which starts once symptoms emerge.

In cancer, the *length* of the symptomatic phase is commonly thought to be shorter than the length of the presymptomatic phase. It is a challenge to test whether this assumption holds for all types of cancer and for all cases within a given morphology or site. Undeniably, some tumors are more aggressive and hostile, while others are more indolent. However, there seems to be little empirical evidence on the following question: within a given type of tumor, is there a direct, positive relationship between the clinical *aggressiveness* of the presymptomatic and the symptomatic phases? Common clinical sense would suggest that yes, there is—that is, that a short, clinically aggressive SDI will often have been preceded by a short presymptomatic phase. If this notion could be well characterized in large numbers of patients and in different settings, for a variety of tumors types, then SDI could be used to classify tumors according to their likelihood of being detected early—either when still asymptomatic, when already symptomatic, or in both instances. We know of no such classification based on the type of evidence that we mentioned. Nevertheless, the ratio of the median SDI to the median survival (SDI to survival ratio, SSR) has been proposed as an estimate of the relative likelihood for clinical lead-time bias [6,26]. SSR may be expected to be highest, for instance, for lung and pancreatic cancers, two sites with poor prognosis, and lowest for breast and urinary bladder cancer, two sites with more favorable course [6]. A low SSR reflects that an SDI of a given magnitude represents a lower fraction of the time from first symptom to death or to censoring in breast and bladder cancers than in lung and pancreas cancers. Thus, the opportunity for a decrease in SDI to appear spuriously associated to increased survival would be lower in the former two sites than in the latter two. This sort of conceptual and methodologic developments could help clarify links between SDI and active screening.

Molecular pathologic information (such as DNA content or oncogene expression) can help explain biologic aggressiveness of a tumor. Hence, theoretically, pathologic information might be used to assess the apparent paradox—quite frequent—that patients with shorter SDI have a shorter survival. However, molecular correlates of SDI are scant; it is unknown whether this reflects a lesser role of biologic variables vis-à-vis health care-related and social factors. It would, hence, be interesting to have more real examples of application of pathologic and genetic data to research on

the mechanisms through which SDI influences—or fails to influence—prognosis.

#### 4. The classic diagnostic role of semiology vs. the potential role of proteomics

When we look at relatively large groups of patients with cancer it is easy to realize how often “cancer symptoms” are unspecific; and when the same signs and symptoms are quantitatively studied in cohorts of patients attending primary care centers it is even clearer that such symptoms have a low positive predictive value for cancer [18,27–29]. Furthermore, assessing symptom onset is difficult, time consuming, and not highly valued in these technology-leaning times [17,30].

Is semiology losing the battle again, this time against proteomics? A rather convoluted history of half-fulfilled promises shows the paucity of clinically meaningful procedures to detect biologic onset of cancer [31–36]. Again, we need to think—beyond individual anecdotes—of the impact of technology upon the clinical course in minimally significant numbers of patients. Nonetheless, the new wave of genomic and proteomic analyses of early-stage cancers might provide new insights into changes that occur in early phases of tumorigenesis; it is already offering new candidate biomarkers for early-stage disease [37–39]. Studies that profile proteomic patterns in body fluids should adhere to the methodologic standards that are usual in clinical epidemiology but less widely applied in basic science [40–42]. Rigorous pathophysiologic and clinical thinking should guide studies that pretend to correlate molecular abnormalities, symptoms, diagnostic performance, and clinical course—as exemplarily illustrated by *auxometric* measures of tumor growth and other works of Alvan Feinstein [8–17,43]. Whether the degree of correlation between proteomic patterns and classic semiology will be strong or weak remains to be seen (“weak” is our informed guess). Such analysis is of interest in itself. The respective relations of proteomic and semiologic patterns with cancer prognosis should be assessed in properly designed clinicoepidemiologic studies.

#### 5. Conclusions

SDI is a highly complex variable that reflects the behavior of the patient and the attending physician, tumor biology and host–tumor interactions, the functioning of the health care system, and sociocultural norms. It is, hence, plausible that the group of patients with a short SDI is comprised of a mixture of patients with more aggressive tumors and of patients with less biologically active tumors, but who seek and get care sooner. Conversely, patients whose disease takes longer to diagnose may include patients with relatively slow-growing tumors and patients with more aggressive disease but a slower access to diagnosis. The number of health

system-related and sociocultural variables mediating the relationship between symptoms and survival is bound to be high, and the procedures to measure them with clinical and epidemiologic tools must be improved.

The results of the study by Pita et al. [1] do not imply that we should not attempt to diagnose lung cancer as swiftly as possible. Even if there is no net population effect of SDI on survival, individual gains are likely in reducing complications and increasing quality of life. Although the population impact of decreasing SDI in lung cancer may turn out to be small, the health system appears to have—as a sort of cultural or social contract—an obligation to detect, diagnose, and treat symptomatic individuals promptly. The fulfillment of such obligation has traditionally relied on careful assessment of symptoms; it has had precedence over the organization of (population-based) screening programs, as well as over the responsibility to adopt the newest diagnostic technology—at present, genomics and proteomics. Policy makers must hence keep in mind that attention to symptoms and signs remains crucial to properly care for symptomatic individuals who seek—and have the right to get—a diagnosis, no matter how much technology evolves. The study [1] must not be regarded as favoring diagnostic and treatment nihilism, nor “genomic optimism,” “proteomic naïveté,” or any other variety of wishful thinking. Rather, these [1] and many other results [44–51] are a compelling reminder that achieving further progress in the early clinical detection and efficient treatment of lung cancer will remain a huge challenge in the years to come.

## References

- [1] Pita-Fernández S, Montero-Martinez C, Pértega-Díaz S, Vereza-Hernando H. Relationship between delayed diagnosis and the degree of invasion and survival in lung cancer. *J Clin Epidemiol* 2003; 56:820–5.
- [2] Fernandez E, Porta M, Malats N, Belloc J, Gallén M. Symptom to diagnosis interval and survival in cancers of the digestive tract. *Dig Dis Sci* 2002;47:2434–40.
- [3] Porta M, Fernandez E, Belloc J, Malats N, Gallén M, Alonso J. Emergency admission for cancer: a matter of survival? *Br J Cancer* 1998;77:477–84.
- [4] Porta M, Gallén M, Belloc J, Malats N. Predictors of the interval between onset of symptoms and first medical visit in patients with digestive tract cancer. *Int J Oncol* 1996;8:941–9.
- [5] Gómez G, Porta M, Grifol E, et al. Modelling breast cancer survival and the symptom-to-treatment interval. *J Epidemiol Biostat* 1996; 1:175–82.
- [6] Maguire A, Porta M, Malats N, Gallén M, Piñol JL, Fernandez E for the ISDS II Project Investigators. Cancer survival and the duration of symptoms. An analysis of possible forms of the risk function. *Eur J Cancer* 1994;30A:785–92.
- [7] Porta M, Gallén M, Malats N, Planas J. The influence of “diagnostic delay” upon cancer survival. An analysis of five tumour sites. *J Epidemiol Commun Health* 1991;45:225–30.
- [8] Feinstein AR. Symptoms as an index of biological behaviour and prognosis in human cancer. *Nature* 1966;209:241–5.
- [9] Charlson ME, Feinstein AR. The auxometric dimension. A new method for using rate of growth in prognostic staging of breast cancer. *JAMA* 1974;228:180–5.
- [10] Feinstein AR, Schimpff CR, Andrews JF Jr, Wells CK. Cancer of the larynx: a new staging system and a re-appraisal of prognosis and treatment. *J Chron Dis* 1977;30:277–305.
- [11] Charlson ME, Feinstein AR. A new clinical index of growth rate in the staging of breast cancer. *Am J Med* 1980;69:527–36.
- [12] Feinstein AR, Wells CK. Lung cancer staging. A critical evaluation. *Clin Chest Med* 1982;3:291–305.
- [13] Wells CK, Stoller JK, Feinstein AR, Horwitz RI. Comorbid and clinical determinants of prognosis in endometrial cancer. *Arch Intern Med* 1984;144:2004–9.
- [14] Charlson ME, Feinstein AR. Rate of disease progression in breast cancer: a clinical estimate of prognosis within nodal and anatomic stages. *J Natl Cancer Inst* 1984;72:225–31.
- [15] Piccirillo JF, Feinstein AR. Clinical symptoms and comorbidity: significance for the prognostic classification of cancer. *Cancer* 1996; 77:834–42.
- [16] Yueh B, Feinstein AR, Weaver EM, Sasaki CT, Concato J. Prognostic staging system for recurrent, persistent, and second primary cancers of the oral cavity and oropharynx. *Arch Otolaryngol Head Neck Surg* 1998;124:975–81.
- [17] Feinstein AR. Is “quality of care” being mislabeled or mismeasured? *Am J Med* 2002;112:472–8.
- [18] Pope C. Waiting times for outpatient appointments. *BMJ* 1993; 306:408–9.
- [19] Joint Council for Clinical Oncology. Reducing delays in cancer treatment. Some targets. London: Royal College of Physicians and Royal College of Radiologists; 1993.
- [20] Segnan N, Bugiani M, Ronco G, et al. The differential diagnosis of primary lung cancer: inter-observer agreement and contribution of specific diagnostic procedures. *J Clin Epidemiol* 1992;45:827–33.
- [21] Malats N, Belloc J, Gallén M, Porta M. Disagreement between hospital medical records and a structured patient interview on the type and date of the first symptom in cancers of the digestive tract. *Rev Epidemiol Sante Publique* 1995;43:533–40.
- [22] McDowell I, Newell C, editors. Measuring health. A guide to rating scales and questionnaires. New York: Oxford University Press; 1996.
- [23] Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985; 312:1604–8.
- [24] Porta M, Marrugat J, Pérez G. Trends in cardiovascular mortality and the quality of vital statistics. *J Clin Epidemiol* 1997;50:221–2.
- [25] Greenberg ER, Baron JA, Dain BJ, Freeman DH Jr, Yates JW, Korson R. Cancer staging may have different meanings in academic and community hospitals. *J Clin Epidemiol* 1991;44:505–12.
- [26] Porta M, Piñol JL, Maguire A, et al. Intertalacines entre el intervalo síntoma-diagnóstico y la supervivencia: ¿es posible obtener un estimador de la oportunidad relativa del sesgo del Adelanto del diagnóstico clínico? *Gac Sanit* 1994;8:68–9.
- [27] MacArthur C, Smith A. Factors associated with speed of diagnosis, referral, and treatment in colorectal cancer. *J Epidemiol Commun Health* 1984;38:122–6.
- [28] Curless R, French JM, Williams GV, James OFW. Colorectal carcinoma: do elderly patients present differently? *Age Ageing* 1994; 23:102–7.
- [29] Swenson KK, Rose MA, Ritz L, Murray CL, Adlis SA. Recognition and evaluation of oncology-related symptoms in the emergency department. *Ann Emerg Med* 1995;26:12–7.
- [30] Porta M, Malats N, Belloc J, Gallén M, Fernandez E. Do we believe what patients say about their neoplastic symptoms? An analysis of factors that influence the interviewer’s judgement. *Eur J Epidemiol* 1996;12:553–62.
- [31] Fletcher RH. CEA monitoring after surgery for colorectal cancer. When is the evidence sufficient? *JAMA* 1993;270:987–8.
- [32] Delaloye AB, Delaloye B. Radiolabelled monoclonal antibodies in tumor imaging and therapy: out of fashion? *Eur J Nucl Med* 1995; 22:571–80.

- [33] Ma PC, Blaszkwosky L, Bharti A, et al. Circulating tumor cells and serum tumor biomarkers in small cell lung cancer. *Anticancer Res* 2003;23:49–62.
- [34] Duffy MJ, van Dalen A, Haglund C, et al. Clinical utility of biochemical markers in colorectal cancer. *Eur J Cancer* 2003;39:718–27.
- [35] Frankel S, Smith GD, Donovan J, Neal D. Screening for prostate cancer. *Lancet* 2003;361:1122–8.
- [36] Mulshine JL, Henschke CI. Prospects for lung-cancer screening. *Lancet* 2000;355:592.
- [37] Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 2002;359:572–7.
- [38] Petricoin EF 3rd, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. *Nat Genet* 2002;32(Suppl):474–9.
- [39] Wulfkuhle JD, Liotta LA, Petricoin EF. Early detection: proteomic applications for the early detection of cancer. *Natl Rev Cancer* 2003;3:267–75.
- [40] Rockhill B. Proteomic patterns in serum and identification of ovarian cancer. *Lancet* 2002;360:169.
- [41] Bogardus ST Jr, Concato J, Feinstein AR. Clinical epidemiological quality in molecular genetic research: the need for methodological standards. *JAMA* 1999;281:1919–26.
- [42] Feinstein AR. Misguided efforts and future challenges for research on “diagnostic tests.” *J Epidemiol Commun Health* 2002;56:330–2.
- [43] Feinstein AR. Basic biomedical science and the destruction of the pathophysiologic bridge from bench to bedside. *Am J Med* 1999; 107:461–7.
- [44] Chute JP, Chen T, Feigal E, Simon R, Johnson BE. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. *J Clin Oncol* 1999;17:1794–801.
- [45] Breathnach OS, Freidlin B, Conley B, et al. Twenty-two years of phase III trials for patients with advanced non-small-cell lung cancer: sobering results. *J Clin Oncol* 2001;19:1734–42.
- [46] Campbell DE, Greenberg ER. Racial differences in the treatment of early-stage lung cancer. *N Engl J Med* 2000;342:517.
- [47] Cartman ML, Hatfield AC, Muers MF, Peake MD, Haward RA, Forman D. Lung cancer: district active treatment rates affect survival. *J Epidemiol Commun Health* 2002;56:424–9.
- [48] Earle CC, Venditti LN, Neumann PJ, et al. Who gets chemotherapy for metastatic lung cancer? *Chest* 2000;117:1239–46.
- [49] Greenwald HP, Polissar NL, Borgatta EF, McCorkle R, Goodman G. Social factors, treatment, and survival in early-stage non-small cell lung cancer. *Am J Public Health* 1998;88:1681–4.
- [50] Husgafvel-Pursiainen K, Kannio A, Oksa P, et al. Mutations, tissue accumulations, and serum levels of p53 in patients with occupational cancers from asbestos and silica exposure. *Environ Mol Mutagen* 1997;30:224–30.
- [51] Kogevinas M, Porta M. Socioeconomic differences in cancer survival: a review of the evidence. In: Kogevinas M, Pearce N, Susser M, Boffetta P, editors. *Social inequalities and cancer*. IARC Scientific Publications No. 138. Lyon: International Agency for Research on Cancer; 1997. p. 177–206.