Time to Diagnosis of Lung Cancer

Technical and Pyschological Factors that Slow Down Diagnostic and Treatment Timelines

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It is now clearly established that prognosis of non-small cell lung cancer mainly depends on the disease stage at time of diagnosis.[1] Screening programs,[2] early detection of lung cancer, and implementation of new health systems toward shorter diagnosis timelines[3,4] are sharing in common a nearly similar end point, bringing lung cancers to curative treatment by detecting them as earlier as possible. In this issue of the *Journal of Thoracic Oncology*, Aukema et al.[3] have reported a prospective study describing feasibility of a "Fast track one-day lung schedule." This pilot study was designed in an attempt at determining in 1 day, whether suspicious abnormalities (SAs) on standard chest radiographies could be diagnosed as malignancy or not. Patients underwent both ^{18}F-fluorodeoxyglucose positron emission tomography and bronchoscopy in a single day; then, a final report of the conclusions was presented to the patient. Delays in diagnosis of lung cancer are potentially a loss of chance for curative treatment; furthermore, they increase anxiety in patients in whom the SA has been detected. This original attempt at reducing these wait times merit analysis under the dual points of methodological and psychologic aspects. In this brief editorial, we also like to put this article into perspective with other studies on diagnosis of SA that have been recently published in the *Journal of Thoracic Oncology*.[4,5]

The length of time of asymptomatic lung cancer is probably the main factor for delayed diagnosis and a loss of chance for curative treatment. Time passing from the beginning of bronchial carcinogenesis until the onset of symptoms or the serendipitous discovery of a radiographic SA is likely to be counted in years rather than in months. A recent review on natural history (i.e., patient survival in the absence of any active treatment) suggested that the estimated volume-doubling time of incidentally detected abnormalities on computed tomography scan, such as ground glass opacities, might be longer than 400 days.[6] Screening programs are designed in an attempt at reducing this preclinical period without adding morbidity to subjects presenting with benign diseases. Once symptoms have occurred, rapid diagnosis is less important in determining treatment with curative intent than detecting lung cancer during the asymptomatic period.

Time to diagnosis has been shown to vary widely, and this is a complex and multidimensional variable.[7] A long time from suspicion until diagnosis reduces the chance for a patient to undergo treatment with curative intent, particularly in the case of lung tumor with short doubling time such as small cell lung cancers. Waiting time to diagnosis is from the patient's point of view, a period of uncertainty that clearly feeds fears and anxiety. Arbitrarily, one can separate this waiting time to diagnosis in two different periods: first, from symptoms until detection of SA and second from suspicion (SA) until a complete diagnosis including histology, characteristics of the disease, and patient comorbid conditions; In other words, time from detection until treatment decision.

There are numerous factors that influence both times from symptoms until detection and from suspicion until diagnosis. During the first period, patient and physician could

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unintentionally extend the length from symptom onset until suspicion. Patients are frequently reluctant to frankly speak about respiratory symptoms when they are smokers, a behavior clearly related to the feelings of shame and guilty.[8] This behavior is a consequence of general supposition that lung cancer is a self-inflicted disease, and this is a stigma commonly felt by patients. General practitioners know that lung cancer has one of the poorer prognoses of any human malignancies and that might unintentionally limit proposals a patient presenting with symptoms adequate investigations. In addition, symptoms of lung cancer sometimes divert investigations from the thorax. This is the case of Pancoast syndrome frequently presenting as shoulder pains that could refer the patient for months to the rheumatologist.[9]

During the period lasting from suspicion (i.e., detection of a SA on chest radiography or computed tomography scan) until diagnosis, the main factors that slow down the diagnosis process are access to complex investigations and delays in consultation with medical oncologists or surgeons. In a recent retrospective review of 540 patients diagnosed with non-small cell lung cancer in different health institutions of Nova Scotia, Canada, during the year 2005, elapsed times have been measured in different care intervals.[7] As a marker of timelines in the spectrum of lung cancer management, the median waiting time from detection until adjuvant chemotherapy has been evaluated as 141 days. The most important finding of this study was that elapsed times in lung cancer care greatly varied from one case to another depending on differences in practice patterns, health center capacities, multidisciplinary approaches in decision making, and system-related variables such as time from diagnosis to medical oncologist referral or to surgeon referral. When lung cancer has been indirectly compared with breast cancer, evaluated in a separate study,[10] median waiting time from detection to surgery was 107 and 36 days, respectively. Interestingly, the range was amazingly large from 1 day to 3 years and a half for lung cancer. A possible explanation of such wide patterns of elapsed time could be due to the subset of patients who underwent a period of monitoring of SAs before surgery. One can suggest that when analyzing timelines in the lung cancer management, it is very difficult to distinguish between disease driven timelines (solitary nodule requiring monitoring before decision making and lack of specificity of some symptoms as mentioned previously) and true wait times reflective of system efficiency.

Implementation of new health systems have been designed in an attempt at decreasing the time from suspicion until diagnosis. In the November 2007 issue of the journal, the Toronto group have reported an interesting "time to treat program."[4] The tools used in this program were quite simple: (i) a referral form that was uniformly applied to a single-entry point of contact, (ii) a navigator, i.e., a person in an original clerical position able to collect referral forms, facilitating investigations and appointments with surgeon and/or medical oncologist, and (iii) a clear diagnostic algorithm. This "Time to treat" program was very efficient inasmuch as on a 430 patient population-based evaluation of pre- and post-implementation of the program, the time from suspicion until referral for treatment decision has been reduced from 128 to 20 days.

In the herein Netherlands study, 114 patients benefited from the "Fast track one-day lung schedule."[3] Among them, 96 patients were finally diagnosed with malignancies including lung cancer histology in 84. The specificity of the process was 56%, with inflammatory diseases as the main reason for false-positive diagnoses. Therefore, there might be some troubles with reporting to the patient a conclusion of malignancy, insofar as, at this step of the diagnosis process, there was still no pathologic confirmation (which could not always been given in 1 day). The authors have concluded that the "fast track one-day lung schedule" can be useful, with a high sensitivity and positive predictive value. Nevertheless, one can stress the fact that negative predictive value was 77% only. Therefore, there is another psychologic risk by reporting a diagnosis of benign disease at the end of the day and afterward having to correct this into a diagnosis of malignancy. The authors have stated that "delays in diagnosis and treatment contribute to emotional distress." It is true that waiting such a diagnosis contribute to psychologic morbidity for the patient and her (his) relatives. Nevertheless, one can suggest that bringing to him a diagnosis at the end of a day might be too fast, particularly in the case this could be a false-positive or false-negative answer. The high-sensitivity and positive predictive value (97% and 92%, respectively) might result from a selection bias; as a reference, cancer institute probably receives patients with SA (referred to the Netherlands Antioni Van Leeuwenhoek Hospital) strongly suggestive of malignancies. As a comparison, the results from the prospective cohort study nested in the NCIs Prostate Lung Colorectal Ovarian Cancer Screening Trial detected chest radiographic abnormalities in 12,314 of 77,465 asymptomatic individuals. Among these individuals, 232 (1.9%) had lung cancer. The high sensitivity, as observed in the study by Aukema et al., very likely reflects selection of symptomatic patients. In such a selected population, the prevalence of malignancy is high. Therefore, the positive predictive value in their study might have been overestimated.[3]

Whether or not reducing the elapsed time from detection to diagnosis will significantly reduce the loss of chance for a patient to be operated on remains controversial. In their study, the authors suggested that a high percentage of the accrual population of patients have been treated with curative intent. Nevertheless, almost half of the patients achieved a chemoradiotherapy program usually restricted to patients presenting with a locally advanced stage, and only 30% of the patients underwent surgery. This proportion does not seem to be clearly superior to the one usually observed with standard diagnosis procedures.[3]

In conclusion, interventions attempting to reduce the elapsed time to treatment could not control the whole timelines but only the time from detection of the SA until treatment by speeding up the diagnostic processes. We congratulate the authors in their effort at modifying variables that are specific to the health system efficiency. Nevertheless, neither psychologic variables nor disease driven timelines could be impacted by such intervention. This article by

Aukema et al. is an attempt at reducing the wait times by intervening in the system efficiency. Proof of efficacy will warrant further study in a larger population comparing this approach with more conventional ones.

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