Screening for occult lung cancer

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A pilot screening program for the early detection of lung cancer was carried out in Saskatchewan in 1968 using chest roentgenography and cytologic examination of sputum samples. The yield from 23,000 men aged 40 years and over was only 10 cases. Nine of the men had advanced disease. One had occult lung cancer. A period of 31 months elapsed between the discovery of malignant cells in this patient’s sputum and roentgenographic localization of the tumour. Following pneumonectomy he has survived with no discernible residual or metastatic tumour for 12 years. The morphologic changes in the resected lung provided a basis for discussing the preclinical phase of squamous cancer of the lung, the treatment of occult cancer and multicentric primary pulmonary tumours. The survey would have been more successful with a narrower target group and more frequent examination.


Symptomatic lung cancer is synonymous with late cancer, and the rewards of its treatment are seldom enjoyed by either the patient or the attending physician. Justification for such a statement can be found in the experience of 2000 consecutive patients with symptomatic lung cancer who were registered in the clinics of the Saskatchewan Cancer Foundation in the 10-year period 1967 through 1976. Their median survival time was 5 (mean 4) months after diagnosis, and their 5-year survival rate was 9.1%. These data fit comfortably into the dismal context of an almost fourfold increase in the incidence of the disease in men between 1950 and 1979, from 13.7 to 53.4 per 100,000, and an increase in age-standardized mortality (67.2%) that is the greatest for cancer of any site in Canadian males.

The Cooperative Early Lung Cancer Group predicted that a population of men over 45 years old who smoked 20 cigarettes per day would yield three or four individuals with lung cancer per 1000 man-years of observation. This yield was considered sufficient to justify the establishment of screening programs.

The results of these programs have been described as ranging from moderately encouraging to very discouraging. The conclusion drawn from the Philadelphia project was that with chest roentgenography alone done twice annually, “early” detection was not early in the biologic sense. Cytologic examination of sputum was added to roentgenography with advantage in the New York and Mayo Clinic lung cancer detection programs. The high yield of stage I cancers in each study was encouraging, being 40% and 48% respectively. The combination of these yields with the expected 90% 5-year survival rate among patients with stage I disease enabled these screening programs to attain most of their objectives. The impact of screening programs on the overall rate of death from lung cancer, however, has yet to be demonstrated.

In 1968 a pilot lung cancer detection project was established by the Saskatchewan Cancer Foundation at a cost of about $68,000. Most of the objectives were similar to those of the Cooperative Early Lung Cancer Group, but an additional intention was to test the feasibility of conducting such a survey on an entire population. Men aged 40 years and over were the target; the screening was done by a combination of chest roentgenography and cytologic analysis of sputum samples.

Methods

The survey was easily organized through the cooperation of both the Saskatchewan Anti-tuberculosis League and the provincial cytology laboratory. Six university students trained in the preparation of sputum smears accompanied members of the Anti-tuberculosis League on its annual itinerant survey. Over a period of 4 months they visited 70 communities ranging in popula-
tion from a few hundred people to approximately 130,000 (the provincial capital). All men aged 40 years and over in each area were invited to take part. Participation in the survey required them to make two visits to the travelling laboratory.

On the first visit each individual was given a tuberculin skin test by the League staff and was instructed on how to produce an appropriate deep-cough morning sputum specimen. At this visit he was given a small plastic sputum cup and a questionnaire pertaining to smoking habits, certain occupational hazards and relevant symptoms. On the second visit, 48 hours later, his tuberculin skin reaction was assessed, a chest roentgenogram was made, and his sputum specimen and completed questionnaire were collected. The sputum smears were prepared, fixed with ethyl alcohol, air-dried, and then packed and forwarded to the central cytology laboratory for staining and examination. The survey was attended by almost 23,000 men, of whom approximately 16,000 provided sputum specimens suitable for cytologic assessment.

Results

Atypical cells were found in the sputum of 162 men. The appearance of these cells ranged from moderately metaplastic to severely dyskaryotic. None of these 162 men had roentgenographic evidence of pulmonary abnormality. They are presently the subject of a separate study, similar to that reported by Melamed and coworkers, in which only 1 of 23 men whose sputum samples had been found to have cells showing moderate atypia subsequently exhibited cancer cells.

Ten men were found to have lung cancer. Two had chest roentgenograms typical of lung cancer but no abnormal cells in the sputum. Seven had both roentgenographic and cytologic evidence of lung cancer. The longest survival of these patients was 42 months, and the mean was 7 months.

The other patient had occult lung cancer. He was then 54 years old and was well except that he had had dyspnea for the previous 5 years. This symptom had worsened over the last 2 years, when he had had no cough but did notice that the sputum produced by clearing his throat was blood-streaked. He had not smoked for 11 years but had used, on an average, 20 cigarettes per day for 25 years before that. At the survey his chest roentgenography was repeated and sputum samples were examined. The samples always contained malignant cells, but 31 months passed before chest roentgenography, including tomography, revealed a lesion 2.0 cm in diameter in the upper lobe of the right lung. The patient's clinical condition and symptoms had not changed during this time. Bronchoscopy and biopsy confirmed the site of the neoplasm. A right pneumonectomy was performed. The patient is still alive and well.

**FIG. 1—Poorly differentiated invasive squamous cell carcinoma of the lung (hematoxylin–eosin [H–E]; original magnification ×200).**
with no discernible residual or metastatic tumour, 12 years after surgery.

There were three separate tumour nodules in the resected lung specimen, all in the posterior segment of the upper lobe. One, 1.2 cm in diameter, was situated in the posterior segmental bronchus at the point of its bifurcation. Two other nodules, 2.4 and 1.2 cm in diameter, were situated peripherally to the first tumour and showed no direct continuity with it or with each other. The three nodules exhibited the features of poorly differentiated squamous cell carcinoma (Fig. 1). In close proximity to the tumours the small bronchi showed changes characteristic of in-situ cancer (Fig. 2). Squamous cell epithelium also showing these changes covered much of the apical and posterior segmental bronchi and the anterior segmental bronchus, including its two primary branches. One of the branches of the apical segmental bronchus was occupied by a papillary mass that had the histologic appearance of an endobronchial exophytic carcinoma. The in-situ cancer extended along the ducts of the subepithelial mucous-secreting glands of all three segmental bronchi. In one area of the posterior segmental bronchus a focus of early invasion of the submucosa was found (Fig. 3). Similar in-situ changes were found in areas within the upper lobe bronchus, where another small focus of submucosal invasion was identified. Examination of the main bronchus revealed a few areas of squamous metaplasia and a moderate degree of dysplasia but no in-situ cancer.

Discussion

The one patient with occult cancer

This patient exhibited several features of interest concerning occult lung cancer. The long period — more than 2 1/2 years — between the discovery of tumour cells in his sputum and location of the cancer by roentgenography, for instance, does not appear to have compromised his longevity. In another series of patients with occult lung cancer, too, the time lag between cytologic diagnosis and eventual localization of the tumour had little bearing on either the survival time or the subsequent integrity of the hilar lymph nodes.18

The initial means of detecting our patient's cancer and its site and type are consistent with the observations that lesions detected by cytologic study are most frequently located in the major and segmental bronchi and that these tumours are usually epidermoid cancers.18 Taylor and associates14 suggested that lung cancer screening is promising for the detection of squamous cell cancers and some adenocarcinomas but not small- or large-cell undifferentiated tumours.

The morphologic changes identified in this man's lung are similar to those described by Carter19 and Melamed20 and their collaborators. Widespread in-situ cancer was present in the surface epithelium and also along the ducts of the subepithelial mucous-secreting glands, where there were small areas of submucous invasion.

FIG. 2—In-situ cancer in small bronchus (H–E; original magnification ×320).
The invasion appeared to be of the in-situ cancer in the glandular epithelium rather than of the in-situ cancer in the surface epithelium. According to Carter and collaborators,9 this feature suggests centrifugal spread of the invasive lesion into the wall of the bronchus rather than into its lumen, and thus postponement of the signs and symptoms of bronchial obstruction.

Our knowledge of this preclinical phase is limited because the condition has been detected and treated in only a small number of patients.9-25 The duration of this phase depends on the size of the involved bronchus and on the aggressiveness or indolence of the intraepithelial spread within it. The presymptomatic phase of a rapidly developing cancer such as an oat cell carcinoma is brief, whereas that of squamous cell cancer and, possibly to a lesser extent, adenocarcinoma is long. However, relatively indolent intraepithelial spread of the neoplasm does not preclude the development of metastases before the appearance of clinical signs and symptoms.26

There was in-situ cancer proximal to the invasive lesions in our patient. This feature is common in occult squamous cell cancer of the lung, and it has given rise to speculation about what constitutes safe surgical resection. This patient's survival might have been equally long if he had had only a right upper lobectomy, instead of a pneumonectomy, even if the line of surgical resection had contained in-situ cancer.

The presence of invasive cancer at the margin of resection in a patient who has had a lobectomy is often considered to necessitate further resection either by pneumonectomy or by bronchial sleeve resection. Baker27 and Martini18 and their coworkers, however, found that patients with in-situ cancer at the margin of resection may survive for long periods. Melamed and collaborators28 recommended evaluation of the lines of resection but suggested that the presence of in-situ cancer at this site does not automatically necessitate further resection, because the residual cancer will be disrupted by the surgical procedure and the subsequent inflammatory reaction. Pneumonectomy should also be avoided because of the possibly multicentric origin of squamous cell cancer of the lung. If the initial lesion is treated by pneumonectomy, therapeutic options are limited should a second primary cancer be detected in the remaining lung. For this reason Baker and colleagues27 advocated local ablative procedures at the margin of resection if there is evidence of in-situ cancer. Cryosurgery may be applicable in such a situation.28 Patients treated in this way should be followed carefully for long periods by means of cytologic examination of their sputum.

Opinion on the frequency with which multiple primary squamous cell carcinomas of the lung occur is divided. Auerbach and coworkers,29 in a study of autopsy material, reported a 14.5% incidence. Only 1 in another series of 28 patients with in-situ and early invasive cancer, however, had multicentric tumours.25 Pearson23 and Melamed20 and their associates contended

FIG. 3—Early invasion of submucosa (H-E; original magnification ×125).
that both the invasive cancer and the adjacent in-situ malignant change are usually restricted to one area within the lung and that only rarely is the change multifocal and diffuse. Our patient had, in the bronchial system of the right upper lobe only, widespread in-situ cancer, within which were multiple centres of invasive tumour. Carter and collaborators, on the other hand, believe that multifocal in-situ or invasive cancer may be present in as many as one in four patients, either synchronously or metachronously. In a postsurgical study it was found that 6% of resected lobes and lungs contained more than one tumour mass. In the majority of these the histologic appearances were the same, so the tumours were considered to be intrapulmonary metastases rather than true multicentric primary cancers.

The survey

The Saskatchewan survey may have been optimistic in its concept, but, in retrospect, it was poorly conceived and for a variety of reasons failed to attain its objectives. Its target was too wide. To survey the entire male population over 40 years of age on just one occasion annually was really beyond the manpower and laboratory resources of the province. Then, too, a single examination was inadequate. Ideally, and especially if the disease were to be detected in the preclinical phase, each individual should have been screened three or four times each year. Moreover, because cancer cells may not exfoliate constantly, more than a single deep-cough sputum specimen should have been obtained for cytologic assessment at each examination.

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References

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