Early Detection of Asymptomatic Pulmonary Melanoma Metastases by Routine Chest Radiographs Is Not Associated With Improved Survival

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Objective: To determine if earlier detection of pulmonary metastasis by routine chest radiography (CR) is associated with a prolonged survival.

Design: A computer-assisted search of all CR reports on patients with melanoma between 1990 and 1994 at the Massachusetts General Hospital, Boston. Positive or suspicious findings for pulmonary metastasis were further pursued through review of medical records and tumor registry files.

Setting and Patients: A hospital-based population of patients with melanoma undergoing routine CR at Massachusetts General Hospital.

Results: Overall, of 994 patients, 75 were identified as having pulmonary metastases by CR (1937 total chest radiographs). In addition, there were 63 patients with suspicious findings that were later shown to be false positive. Chest radiographs provided the initial evidence of metastases in 41 asymptomatic individuals. Thirty-four patients had known melanoma metastases to other sites at the time of the first abnormal chest radiograph. Survival after identification of pulmonary metastasis did not differ significantly between the 2 groups.

Conclusions: In this study, there was no evidence to support the notion that earlier detection of pulmonary metastasis in otherwise asymptomatic individuals confers a survival advantage in an unselected melanoma population.

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Although chest radiography (CR) is routinely used in the initial staging of patients with cutaneous melanoma and in post-melanoma surveillance, its utility and impact on survival is still uncertain. Terhune et al¹ reported that only 1 of 876 patients had a true-positive CR finding on initial staging for localized melanoma, although an additional 128 disease-free patients had abnormalities that necessitated further workup. This relatively high false-positive rate (15%) adds both a real economic cost to the health care system and a potential emotional cost to the patient.¹ The utility of CR as a component of post-melanoma surveillance has also been challenged, since several studies have found that most melanoma recurrences after local resection are detected through symptoms and/or physical findings rather than laboratory tests, such as CR.¹,² Earlier detection of resectable pulmonary disease may lead to earlier surgery and better outcome in some selected patients.²,⁶,⁸ However, these individuals represent a highly select group of patients with stage IV disease referred to surgical centers, and the impact of earlier detection by routine CR on survival of the general postmelanoma population is still unknown. The routine use of CR has not been promulgated worldwide. For instance, guidelines from the United Kingdom,⁹ the Netherlands,¹⁰ and Australia¹¹ do not consider radiological examination worthwhile in routine follow-up. Although the German Society of Dermatology recommends annual CR for patients with localized disease and biannual CR for patients with in-transit and/or regional disease,¹² Garbe et al¹² recently found that only 12 of 2396 routine chest radiographs (0.5%) obtained over a 25-month period were confirmed as true metastases.

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In the United States, although the National Comprehensive Cancer Network (http://www.nccn.org) and the American Academy of Dermatology¹³ endorse routine CR only as an option during follow-up surveillance, a recent survey of 30...
dermatologists, surgical oncologists, and medical oncologists revealed that more than 70% of physicians treating patients with melanoma ordered annual CR during the first 5 years after initial diagnosis. Thus, routine CR is still part of common practice, although there is no evidence that earlier detection of asymptomatic pulmonary metastases confers a survival advantage in the general melanoma population. To this end, we set out to determine if there is apparent survival prolongation associated with earlier detection of asymptomatic pulmonary metastasis by routine CR.

METHODS

The study was approved by the institutional review board at the Massachusetts General Hospital (MGH), Boston. Reports of diagnostic imaging studies are transferred to an indexed text-search engine that allows real-time interactive searches using Boolean operators (Folio Views; NextPage Inc, Lehi, Utah; systems integrator, Camberley Systems Inc, Needham, Mass). Patient and examination identifiers are included, and the “History,” report “Body,” and “Impression” are stored in separate fields. Reports were obtained for all CR examinations for which a history of melanoma had been provided during the years 1990 through 1994. All patients would have at least 5 years of follow-up information at the time of the search. Our clinic protocol recommends a single baseline CR for all thin (≤1.0 mm) melanomas and annual CR for melanomas 1.0 mm or thicker. Since the care of our patients is often shared with outside dermatologists and oncologists, not all patients receive an annual CR at MGH. All suspicious CR findings from an outside hospital, however, are confirmed by a radiological examination at MGH. Only chest radiographs that have been reviewed by the MGH Radiology Department were used in this study. A total of 1938 chest radiographs from 994 patients were identified.

All CR reports were reviewed, and the findings were classified as “negative,” “positive,” or “questionable.” Reports with findings of masses, nodules, ill-defined opacities, hilar changes, or pleural changes were considered “positive.” Reports with “uncertain findings” and findings from follow-up tests requested by the radiologist were considered “questionable.” For each patient with a “positive” or “questionable” CR report (n=155) on the initial CR within the study period, we established the diagnosis and eventual outcome of the patient based on a manual search of hospital medical records, clinic medical records, the MGH tumor registry, and the Massachusetts State Death Registry. A database was created using Microsoft Access (Microsoft Inc, Redmond, Wash) to organize, combine, and assess information gained from record review.

Based on findings from medical record review, the 155 results that were “positive” or “questionable” were further categorized into 1 of the 5 following groups (Figure 1):

1. “Converted stage IV (C-IV)” included those patients (with localized or regional disease) who previously had no history of visceral metastasis and were found to have pulmonary metastasis (stage IV disease) based on CR findings. All patients in this category had documented follow-up study results that confirmed that the finding on CR was a metastatic melanoma.

2. “Known stage IV (K-IV)” included those individuals who had a prior history of stage IV disease at a nonpulmonary site before their first CR in this study.

3. “False positives” included those who had questionable findings that were later shown not to represent pulmonary metastasis by additional noninvasive tests, which included repeated CR, computed tomography, magnetic resonance imaging, bone scans, ultrasound examinations, or subsequent CR or biopsy.

4. “Occult positives” were those persons whose positive findings ultimately proved to be related to a cancer other than melanoma. In addition, since the pattern of metastases and follow-up regimen is different for mucosal and ocular melanomas, we excluded these patients (n=6) from our analysis as well.

5. “Nonevaluable” patients were lost to follow-up despite all attempts to identify an outcome.

All C-IV and K-IV patients were assessed for treatment of metastatic disease and survival. Kaplan-Meier analysis was used to estimate the rate of survival among K-IV and C-IV patients, and the log-rank test was used to calculate the P values between these 2 groups.

RESULTS

Of the 1938 chest radiographs from 994 patients with melanoma obtained over the 5-year period (1990-1994), 1783 (92.0%) were normal and 155 (8.6%) were positive or questionable (Figure 1). On further analysis, of these 155 chest

Figure 1. Breakdown of chest radiography results.
radiographs, 63 were eventually found to be false positive (false-positive rate: 63/[1783+63] or 3.4%). Of the remaining 92 suspicious chest radiographs, 75 represented true pulmonary metastases on follow-up and additional investigations. Each of the 75 chest radiographs were from separate individuals; 34 individuals had CR findings suggestive of pulmonary metastasis in the context of known distant disease (K-IV), while 41 (4% of all patients) demonstrated their stage IV disease through CR findings (C-IV). There were 7 chest radiographs that were later found to represent cancers in the lung other than melanoma (1 squamous cell carcinoma of the lung, 5 adenocarcinomas of the lung, and 1 metastatic breast cancer), and 6 suspicious chest radiographs were from persons with uveal or mucosal melanoma and were excluded from the study. Four chest radiographs were from patients who had no further contact with MGH and thus whose outcome could not be determined.

For the 34 K-IV patients with known metastatic disease, 6 patients did not receive further treatment at MGH and records of subsequent events were unavailable. Of the remaining 28 patients who received further treatment, 13 had surgical resection of their pulmonary disease in addition to other systemic treatments. All 28 patients who had known treatments and 4 of 6 patients who had unknown treatments eventually died; the status of the remaining 2 patients with stage IV disease is unknown.

For the 41 C-IV patients whose chest radiographs demonstrated their visceral metastases, 3 patients were lost to follow-up and 7 patients elected not to receive any treatment. Of the remaining 31 treated patients, 10 underwent lung partial resection along with various systemic regimens. From this group of 38 patients, 37 individuals died from their disease. One patient is still alive more than 10 years after chemotherapy and thoracotomy for his pulmonary relapse. Three C-IV patients had unknown treatment regimens, and 2 of these 3 persons died from metastatic disease; for 1 individual, no further information on treatment or life status was found.

**Figure 2** shows the Kaplan-Meier survival curves for C-IV and K-IV patients. There was no statistically significant difference (P=.68, log-rank test) in survival between asymptomatic patients whose chest radiograph was the first indication of stage IV disease and patients whose chest radiograph revealed pulmonary pathologic condition in addition to other known metastatic disease.

**COMMENT**

Although several studies have documented a low detection rate of pulmonary metastases by CR in otherwise asymptomatic patients with melanoma, the practice of routine surveillance CR still persists. Because the lungs represent a common site of metastasis for cutaneous melanoma, there is a rational, rather than evidence-based, argument that early detection of pulmonary disease may enhance survival through earlier chemotherapeutic or surgical intervention. The utility of CR in detecting asymptomatic lung recurrences depends on the overall probability of first recurrence, the percentage of systemic recurrences, and the sensitivity and specificity of the procedure. The impact of CR on survival, however, depends largely on effective treatments for pulmonary disease.

Over a 5-year period, approximately 8% of our study patients exhibited CR findings that represented metastatic melanoma. For 41 individuals (4% of patients), routine CR represented the first indication of stage IV dis-
ease in an otherwise asymptomatic individual. This rate is similar to rates reported in the literature. In 34 cases, CR identified additional metastatic deposits in patients already known to harbor distant disease. Of the 155 positive/questionable radiographic findings, 63 (41%), eventually proved to be false positive (overall false-positive rate, 3.5%), although 7 additional unrelated pulmonary malignancies were diagnosed in the process. The high proportion of false positives may reflect, in part, an unusually high index of suspicion among radiologists, since a clinical history of melanoma was provided for all the retrieved requisitions. Moreover, our ascertainment may have enhanced sensitivity but diminished specificity because we included all chest radiographs with any suspicious radiographic finding in the positive/questionable group that was further evaluated.

Several studies suggest that earlier detection of limited lung metastases along with aggressive surgical intervention may lead to an improved outcome for patients with stage IV disease. However, these studies were based on a select group of patients with resectable pulmonary disease. In one large series from the John Wayne Cancer Institute, Santa Monica, Calif, only 10% of all patients with metastatic melanoma involving the lung or thorax were eligible for surgical treatment. We studied a general melanoma population and did not observe a survival advantage for asymptomatic patients whose pulmonary relapse was initially detected by routine CR. Our data suggest that, for most patients with melanoma, treatment of those with pulmonary metastases even at the earliest possible time of detection does not significantly contribute to overall survival. Since the patients with stage IV disease were treated with a broad range of surgical and systemic approaches, we did not attempt to further stratify these patients into treatment groups and assess outcome.

It is also possible that the observed benefit of aggressive surgical resection reported in the literature is related to a more indolent tumor or a more aggressive immune response. It is thus interesting to note that the 1 patient who had an ostensible cure of his stage IV disease (ie, response. It is thus interesting to note that the 1 patient whose pulmonary relapse was initially detected by routine CR. Our data suggest that, for most patients with melanoma, treatment of those with pulmonary metastases even at the earliest possible time of detection does not significantly contribute to overall survival. Since the patients with stage IV disease were treated with a broad range of surgical and systemic approaches, we did not attempt to further stratify these patients into treatment groups and assess outcome.

In summary, this study further challenges the use of CR in routine postmelanoma surveillance, since survival does not appear to be affected. Many studies have already documented the questionable utility of large-scale CR screening, since most melanoma metastases are detected by simple history and physical examination and not by laboratory tests. The most definitive study, however, would be a multicenter prospective randomized trial of patients with high-risk melanoma assigned to imaging vs nonimaging arms. However, until more effective treatments are developed, earlier identification of pulmonary relapse can potentially benefit only a small, select group of patients with surgically resectable stage IV disease.

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REFERENCES