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Original articles

Analysis of published studies on the detection of extrathoracic metastases in patients presumed to have operable non-small cell lung cancer

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Abstract

Background **– A study was undertaken to determine the proportion of patients with potentially operable non-small cell lung cancer that could be spared thoracotomy by a systematic search for extrathoracic metastases.**

Methods **– An English language literature search was carried out using MEDLINE (1966–91) and bibliographic reviews of textbooks, review articles, and key articles. Studies were included in which at least 90% of the patients had histologically proven non-small cell cancer of the lung, were presumed otherwise operable, and for which the results of computed tomography of the head or abdomen, ultrasonography of the abdomen, or radionuclide imaging (scan) of bone or liver were available. Study quality and specific descriptive information concerning population, intervention, and outcome measurements were assessed.**

Results **– Of approximately 1500 citations which were screened, 100 were reviewed in detail and data abstracted from 16. The number of patients (total number, followed in square brackets by number of asymptomatic patients) shown to be inoperable directly as a result of the investigation and thus spared unnecessary thoracotomy was: computed tomography of the head: 26/785 (3·3%), 95% confidence interval (CI) 2·1% to 4·4% [14/353 (4·0%), 95% CI 2% to 6%], computed tomography of the adrenal glands: 30/632 (4·7%), 95% CI 3·0% to 6·4% [number asymptomatic indeterminate], bone scan: 45/480 (9·3%), 95% CI 6·7% to 12% [9/301 (3·0%), 95% CI 1·1% to 4·9%], liver imaging: 12/529 (2·3%), 95% CI 0·9% to 3·3% [4/268 (1·5%), 95% CI 0·1% to 3%].**

Conclusions **– A study with a large sample size and preferably incorporating thoracic computed tomography is required to narrow the confidence intervals around each test. All tests may play an important part in the preoperative evaluation of patients with non-small cell carcihoma of the lung who are presumed to be operable, including asymptomatic patients. Limitations of present data preclude definitive recommendations for asymptomatic patients.**

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The five year survival for patients with non-small cell carcinoma of the lung who are presumed operable and who undergo "curative" surgery remains less than 50%. Most deaths are due to local recurrence or disseminated disease.[1] Some authors have concluded that as many as 30% of patients who undergo resection for cure have silent metastatic disease.[2,3] The single most important factor in determining appropriate treatment and subsequent survival in patients with non-small cell carcinoma of the lung is the extent of metastasis from the primary lesion.[4–8]

Clearly, preoperative staging in its present form fails to identify a significant proportion of patients who undergo thoracotomy with no benefit. This raises the question of whether more thorough screening could prevent some inappropriate thoracotomies. Many authorities have recommended that investigation of the most likely sites of metastatic disease (bone, brain, liver, and adrenal glands) be restricted to patients with symptoms or signs which suggest metastases.[5,9–13] These recommendations are reflected in the current practice of most physicians. Others have, however, suggested that imaging of the adrenal glands,[14] head,[15,16] bones,[3] and liver,[17] or some combination[2,3,17,18] be included in the routine investigation of *all* patients with lung cancer before thoracotomy.

The uncertainty may be exacerbated by the lack of an adequate summary of the available literature. To date, no review of this area has conducted a comprehensive search of the relevant literature, used explicit criteria to select or evaluate the original reports, or attempted a quantitative summary. We have therefore conducted an overview of the English language medical literature to determine what proportion of patients with potentially operable non-small cell lung carcinoma would be likely to be spared a futile thoracotomy by imaging of the head, abdomen, and skeletal system to detect extrathoracic metastases.

Methods

SEARCH STRATEGY

Studies were identified with a computerised search of the MEDLINE and CANCERLIT databases from 1966 to November 1991. Four search strategies were used. The first search included the following MESH headings: (carcinoma, non-small cell lung; carcinoma bronchogenic) and (neoplasm metastasis; neoplasm staging). A second search was based upon the diagnostic procedures and included the following MESH headings: (carcinoma, non-small cell; carcinoma bronchogenic) and each of the following diagnostic procedures: (tomography; *x* ray; computed), (ultrasonic diagnosis) and (radionuclide imaging). A third search used the following MESH strategy: (brain, liver, bone, adrenal neoplasms) and (carcinoma non-small cell; carcinoma bronchogenic). Finally, an organ-specific search involved searching (bone neoplasms; adrenal gland neoplasms; brain neoplasms; liver neoplasms) in combination with each appropriate diagnostic procedure and (metastasis). In addition, these searches were supplemented by reviewing the references that appeared in all relevant articles retrieved, and in current oncology and respiratory textbooks.

SELECTION CRITERIA

All citations were reviewed by one of the authors (TH) and were included if the title made reference to diagnostic procedures for metastatic neoplasms or to operability of primary lung neoplasms in adult populations. Interrater reliability was assessed by having a second author (MS) review a random sample of 70 citations.

All papers that met these initial criteria were copied and distributed to all three authors and included only if they met the following criteria.

Population

Studies were included if at least 90% of the patients in whom the results of one of the relevant tests were available had histologically proven non-small cell carcinoma of the lung which was presumed operable after history, physical examination, and chest radiography.

Intervention

Patients underwent one or more of the following procedures: (1) computed tomography (CT) of the head or abdomen, liver and/or adrenal glands; (2) ultrasonography of the abdomen; (3) radionuclide imaging of bone or liver.

Outcome measures

Both the number of patients investigated and the number shown to be inoperable were documented.

METHODOLOGICAL CRITERIA

All papers that met the relevance criteria were evaluated by two authors (TH and GG) using the following criteria:

1. Was initial investigation comprehensive (2 points if CT of chest or mediastinoscopy was conducted, 1 if it was specified that physical examination and chest radiographs were performed)?
2. Was the intervention described and reproducible (1 point for yes)?
3. Were the criteria for a positive result rigorous (1 point for biopsy or equivalent)?
4. Were cases reported consecutive cases or a random sample of consecutive cases (1 point for yes)?
5. Was the report prospective or retrospective (2 points for prospective, 1 for retrospective, 0 if undetermined)?

Throughout the process of assessing the relevance and validity of the articles, any disagreement was resolved by consensus.

Papers with scores of 5–7 were classified as grade 1, those with scores of 3 or 4 as grade 2, and those with scores of 2 or less as grade 3.

DATA ABSTRACTION

All data were abstracted in duplicate. Summaries of the data and of assessments of methodological quality were sent to the principal investigators for verification. Corrections were made on the basis of information from the authors.

STATISTICAL METHODS

Observer agreement was calculated using the kappa statistic.[19] For all proportions, 95% confidence intervals (CI) were calculated. Chi square tests (χ^2) were used to determine if proportions differed in the different studies. If the χ^2 test was positive, suggesting heterogeneity, a further analysis to determine whether the difference could be explained by variations in methodological quality was undertaken. Studies were divided into the three grades of quality and a χ^2 test was conducted to determine whether there were differences in the proportion of metastases detected within the three grades.

Results

Approximately 1500 citations were reviewed of which 100 met initial inclusion criteria. The kappa value on the random sample of 70 citations was 0·74 (95% CI 0·63 to 0·85). The kappa value for the relevance rating on the 100 papers which were retrieved was 0·72 (95% CI 0·62 to 0·82). Of the original 100 papers 16 were ultimately judged to be relevant.[15 16 20–33] Several of the more frequently cited papers[5 18] were excluded because more than 10% of the population had small cell carcinoma and the results for these patients were not separated from those of the remainder.

BRAIN

Nine papers[15 16 21 23–25 27 31 32] provided data on CT head scanning (table 1). The intervention was described and consequently reproducible in all but two of these papers.[21 32] In all but

one[15] the characteristic appearance on CT served as the basis for a diagnosis of metastatic disease. The cases were a random or consecutive sample in two,[25 27] prospective in five,[16 24 25 27 32] and retrospective in two papers.[23 31] The method was unclear in two papers.[15 21] Two papers[25 31] were classified as grade 1, two[27 32] as grade 2, and the remainder as grade 3.

The results are summarised in tables 1 and 5. Intracranial metastases were found in 26 of 785 asymptomatic patients (3·3%) with 95% CI 2·1% to 4·4%. Eight of the 20 patients with a positive CT scan had other evidence of disease, three of whom were asymptomatic; whether or not the CT scan would have contributed to the management of the patients would depend on the order in which the investigations were performed. In table 1 (and in tables 2–4) the final column represents the number of patients in whom a positive test result (in this case, CT of the head) constituted the sole contraindication to thoracotomy. The χ^2 test was consistent with homogeneity of study results ($\chi^2 = 7{\cdot}12$, $p = 0{\cdot}64$).

ADRENAL GLANDS

Seven papers[20–22 26 30–32] provided data on the detection of adrenal metastases. A CT scan of

Table 1 Summary of papers providing data on brain metastases

Reference no.	Author	Total no. of patients	Test	Initial examinations	No. of patients with negative initial examinations	No. of true positive scans	Asymptomatic	Symptomatic		Thoracotomies saved
								Organ	Systemic	
16	Butler	55	CT	Hx, Px	55	3	3/55	—	—	3/55
25	Mintz*	79	CT	Medical	68	8	2/47	3/13	3/8	2/68
24	Jacobs†	34	CT	Hx, Px, radiography or scan	34	2	2/34	—	—	2/34
21	Doyle	300	CT	CT thorax	150	3	?	?	?	3/150
23	Ichinose	309	CT	Tomography	224	2	0/80–93	2/2–10	—	2/103
27	Quinn	122	CT	Unknown	53	2	0/20	0/7	2/11	2/38
32	Salvatierra	146	CT	CT bronchi	102	19	1/19	—	—	1/102
15	Kormas	258	CT	Hx, Px, radiography bronchi	158	5	5/5	—	—	4/158
31	Grant	114	CT	CT thorax	77	10	1/10	—	—	1/77

— = paper does not include this group; ? = unable to extract these data from paper; Hx = history; Px = physical examination; CT = computed tomography.
* Five patients had extracranial metastases.
† Not consecutive patients.

Table 2 Summary of papers providing data on metastases of the adrenal glands

Reference no.	Author	Total no. of patients	Test	Initial examinations	No. of patients with negative initial examinations	No. of true positive scans	Thoracotomies saved
30	Whittlesey	195	CT	Unknown	180	5*	5/180
20	Chapman§	38	CT	Medical	14	2*	2/14
26	Nielsen	92	CT	Unknown	84	15†	6/84
22	Heavey	31	CT	CT thorax	25	1*	1/25
21	Doyle	300	CT	CT thorax	150	5‡	0/150
32	Salvatierra	146	CT	CT bronchi	102	11	1/102
31	Grant	114	CT	Hx, Px, CT	77	9	1/77

Hx = history; Px = physical examination; CT = computed tomography.
* All biopsy proven.
† Four biopsy proven and 9/15 had other asymptomatic metastases.
‡ None biopsy proven and all had disseminated malignancy.
§ Not consecutive patients.

Table 3 Summary of papers providing data on bone metastases

Reference no.	Author	Total no. of patients	Test	Initial examinations	No. of patients with negative initial examinations	No. of true positive scans	Asymptomatic	Symptomatic		Thoracotomies saved
								Organ	Systemic	
21	Doyle	300	Scan	CT thorax	150	6	?	?	?	6/150
29	Turner	57	Scan	Hx, Px, radiography	55	4	?	?	?	3/55
23	Ichinose	309	Scan	Tomography	224	18	1/171	15/15–23	2/2–10	16/171
27	Quinn	122	Scan	Unknown	53	10	3/20	5/20	2/13	10/53
28	Ramsdell	100	Scan	Unknown	51	1	?	?	?	0/51
32	Salvatierra	146	Scan	CT bronchi	102	19	5/19	12/29	2/19	1/102
33	Michel	110	Scan	CT	91	37	0/91	9/91		9/91

Hx = history; Px = physical examination; CT = computed tomography.
— = paper does not include this group; ? = unable to extract these data from paper.

Table 4 Summary of papers providing data on liver metastases

Reference no.	Author	Total no. of patients	Test	Initial examinations	No. of patients with negative initial examinations	No. of true positive scans	Asymptomatic	Symptomatic		Thoracotomies saved
								Organ	Systemic	
23	Ichinose	309	CT	Tomography	224	1	0/87–95	1/1–9	—	1/100
23	Ichinose	309	Scan	Tomography	224	1	0/85–92	1/1–9	—	1/92
27	Quinn	122	Scan	Unknown	53	0	0/20	0/17	0/16	0/53
28	Ramsdell	100	Scan	Unknown	51	2	0/43	2/8	—	2/51
29	Turner	57	Scan	Hx, Px, radiography	54	2	?	?	?	1/54
32	Salvatierra	146	CT	CT bronchi	102	18	4/18	?	8/18	4/102
31	Grant	114	CT	Hx, Px, CT	77	9	?	?	?	1/77

Hx = history; Px = physical examination; CT = computed tomography.
— = paper does not include this group; ? = unable to extract these data from paper.

the abdomen was described and reproducible in five of the papers.[20 22 30–32] Histological confirmation of adrenal lesions was documented in all but one.[21] Cases were a random sample of consecutive cases in one paper,[30] prospective in three,[20 30 32] and retrospective in three.[22 26 31] Four of the papers were ranked as grade 1,[20 22 30 31] two as grade 2,[26 32] and the remaining paper was grade 3.

It was not possible to conclude how many of the 632 patients had organ-specific or systemic symptoms. However, 16 of the 632 patients presented with adrenal metastases as the primary contraindication to thoracotomy (tables 2 and 5). The χ^2 analysis for trend suggested heterogeneity of study results ($\chi^2 = 18{\cdot}73$, $p = 0{\cdot}004$). This heterogeneity could in part be explained by differences in methodological quality ($\chi^2 = 8{\cdot}56$, $p = 0{\cdot}014$). Higher quality studies had a greater yield. Grade 1 studies showed that 3·0% of patients would have been saved thoracotomy, while grade 2 and grade 3 studies identified 2·5% and 0·8%, respectively.

BONE

Seven papers presented data on the use of isotopic bone scanning.[21 23 27–29 32 33] The technique used for bone scans was described and reproducible in six of the seven papers.[23 27–29 32 33] An attempt to apply a "gold standard" in order to assure a true positive result was described in four papers.[23 27 28 33] In five papers all cases were studied prospectively,[27–29 32 33] one study was retrospective,[23] and the method was unclear in one paper.[21] One paper was ranked as grade 1,[29] two papers as grade 2,[21 29 33] and the remainder as grade 3. The results in tables 3 and 5 show that 45 of 480 patients were spared thoracotomy as a result of bone scans. Of these 45, at least nine patients were asymptomatic and six had systemic symptoms. In the remaining patients the presence or absence of symptoms was not specified (tables 3 and 5). The χ^2 test suggested heterogeneity of study results ($\chi^2 = 25{\cdot}42$, $p = 0{\cdot}006$). This heterogeneity could not be explained by differences in methodological quality ($\chi^2 = 0{\cdot}14$, $p = 0{\cdot}71$).

LIVER

Data regarding metastases to the liver using radionuclide scanning came from six papers;[23 27–29 31 32] one paper presented data from ultrasonography,[32] and one from CT.[23] The intervention used was described and reproducible in all papers. Rigorous criteria for positive results were outlined in four papers[23 27 28 32] and a prospective and random sample of consecutive cases was reported in four.[27–29 32] One paper was ranked as grade 1,[29] four as grade 2,[27 28 31 32] and the remainder as grade 3. The number of patients found to have metastatic disease was one of 15, six of 130, and four of 250 using, respectively, ultrasonography, CT scanning, and radionuclide scanning. Four of the 11 patients with liver metastases had organ-specific symptoms. Eight of 18 patients had systemic symptoms. Symptomatic status in the remaining patients was not ascertainable (tables 4 and 5). The χ^2 test suggested homogeneity of study results ($\chi^2 = 5{\cdot}06$, $p = 0{\cdot}65$).

SUMMARY OF RESULTS

For any individual test, calculation of the number of patients spared thoracotomy without cure is complicated by the fact that more than one test can be positive. In such instances, does one attribute an avoided thoracotomy to both tests? We have dealt with this problem in table 5 in which the data are summarised. The maximum yield represents the number of patients apparently free of disease after initial investigation in whom the test showed a true positive result, irrespective of the results of other investigations for extrathoracic metastases. This number represents the yield one would find if the test under consideration was performed first in an investigation for extrathoracic metastases. The minimum yield represents the number of patients in which the test under consideration was the only positive investigation. The final column reports the yield in the most controversial group – namely, those without symptoms.

The row labelled "Total" below each organ system represents the yields when analysis is

Table 5 Summary of findings from imaging studies of liver, bone, adrenal glands, and brain

Organ	*Maximum yield*		*Minimum yield*		*Metastatic disease in asymptomatic patients*	*% (95% CI) metastatic disease in asymptomatic patients*
	No. with metastatic disease	*% (95% CI) with metastatic disease*	*No. with metastatic disease*	*% (95% CI) with metastatic disease*		
Brain						
Total	26/785	3·3% (2·1% to 4·4%)	21/785	2·6% (1·5% to 3·7%)	14/353	4·0% (2·0% to 6·0%)
Clinic*	21/460	4·6% (2·7% to 6·5%)			12/324	3·7% (1·7% to 5·7%)
CT†	5/325	1·5% (0·13% to 2·7%)			2/29	0% (0% to 15·8%)
Adrenal						
Total	30/632	4·7% (3·0% to 6·4%)	16/632	2·5% (1·3% to 3·7%)	—	—
Clinic	27/278	9·7% (6·2% to 13%)				
CT	3/354	0·84% (0% to 4·4%)				
Bone						
Total	45/480	9·3% (6·7% to 12%)	43/723	6·0% (4·3% to 7·7%)	9/301	3·0% (1·1% to 4·9%)
Clinic	29/137	21% (14% to 28%)			4/200	2·0% (0·3% to 3·7%)
CT	16/343	4·6% (0% to 17%)			5/101	4·9% (0% to 11·6%)
Liver						
Total	12/529	2·3% (0·9% to 3·3%)	10/579	1·9% (0·8% to 3·0%)	4/268	1·5% (0·1% to 3·0%)
Clinic	7/350	2·0% (0·7% to 5·3%)			0/166	0% (0% to 2·0%)
CT	5/179	2·7% (0% to 20%)			4/102	3·9% (0% to 9%)

CI = 95% confidence interval; CT = computed tomography.
* Based on studies in which patients were presumed operable without CT of thorax.
† Based on studies in which patients were presumed operable after CT of thorax.

based on all studies. The row labelled "Clinic" represents the yields when analysis was based upon studies in which patients were presumed operable after preoperative examination which did not include a CT scan of the thorax. The row labelled "CT" below each organ system represents the yields when analysis was limited to studies that included only patients who were presumed resectable after having a CT scan of the thorax for metastases to the brain,[21 31 32] adrenal glands,[21 31 32] bone,[21 32 33] and liver.[31 32]

COMPLICATIONS OF INVESTIGATIONS

In determining the efficacy of the investigations, harmful side effects or complications must be assessed. Of the 14 papers reviewed, only Turner and Haggith[29] reported that no invasive procedures resulted from false positive results. None of the remaining papers made reference to procedures that may have resulted from any of the 28 false positive bone scans, 16 false positive liver scans, one false positive abdominal ultrasonographic scan, one false positive brain CT scan, two false positive adrenal CT scans, and the 41 false positive bone scans.[22-24 27 28] Furthermore, there was no mention of reactions to contrast materials or complications as a result of invasive procedures.

Discussion

The limitations of this overview include the fact that no attempt was made to identify unpublished literature or non-English language papers, nor were those assessing the relevance or methodological quality of the articles or abstracting the data blinded to the setting of the trial or the results. Most of the methodological criteria for conducting a scientific overview were, however, satisfied.[34 35]

To determine whether imaging procedures should be undertaken, a precise estimate of the number of patients with metastatic disease spared thoracotomy in each relevant subgroup is required. Additional important information should include the complications of the imaging procedures themselves and any invasive procedures that resulted, the resulting delay in surgery, and the economic consequences (including resources expended through additional imaging and saved through avoiding thoracotomies without cure).

Our overview reveals that, despite the large amount of literature in this area, most studies suffer from severe methodological limitations. Our approach to obtaining the best available answers to the questions we posed was to combine data from different studies. In cases where the results of the studies are very different (suggesting important differences in the population studied, the way the tests were conducted, or the results followed up) this approach could be questioned. For brain and liver scanning similar results were obtained and formal tests for heterogeneity were negative. For adrenal scanning the results differed substantially and a formal test for homogeneity was significant ($p < 0.005$). In this instance, differences in results may be (at least in part) explained by the methodological quality of the investigations. Higher quality studies yielded a larger number of positive test results ($p < 0.05$). Thus, the estimates of the yield of adrenal scanning in tables 2 and 5, based on all studies, may represent underestimates of the yield of the procedure.

The other instance in which results differed substantially and the test for heterogeneity was positive ($p < 0.01$) was bone scanning. Here differences cannot be explained by methodological quality. The number of thoracotomies saved by bone scanning varied from 0 of 51[28] to 10 of 53.[27] The differences may be explained by selection of patients and criteria for a true positive bone scan. Ramsdell *et al*[28] excluded all patients with "obvious metastatic disease." Several of the patients with positive bone scanning in the study by Quinn *et al*[27] had N2 disease; it is possible that such patients may have been excluded from the study by Ramsdell *et al*. Similarly, the criterion for a true positive scan in the study by Quinn *et al* was "abnormalities that were not proved benign by additional studies." Ramsdell *et al* included three patients in whom scan results suggested metastases that were excluded by lack of progression over 12 months in one and necropsy findings in two others. It is possible that findings in such patients may have been classified as positive by Quinn *et al*. Similar factors may explain the smaller differences found in the other studies.

With respect to relevant subgroups, many studies have not separated those with organ-specific symptoms, systemic symptoms, or no symptoms when reporting the number of true positive imaging procedures. Even when subgroups were specified, detailed criteria that would allow replication of the classification of subjects were not provided. To cite a single example: would a patient with moderate but unchanging weekly headaches for the previous year be classified as having organ-specific neurological symptoms suggestive of metastatic disease to the brain? Because the number of subjects available is small, the confidence intervals around the number of thoracotomies without cure that are avoided by each test are wide.

The "CT" column in table 5 points out how the number of patients identified with metastatic disease after a CT scan of the thorax is reduced, when compared with those studies in which the initial examination was limited to history taking and physical examination, with or without radiography and plain tomography. Presumably many of the patients with occult metastatic disease in the latter group of studies also had occult mediastinal disease and would be excluded from surgery on this basis. The small number of subjects available results in large confidence intervals, particularly for asymptomatic patients, in those who underwent CT scanning. Indeed, despite the trend towards lower numbers of patients found with metastatic disease and asymptomatic disease after a CT scan of the thorax, these findings did not reach statistical significance ($\chi^2 = 5.44$,

$p=0.07$; $\chi^2=0.712$, $p=0.7$). This precludes firm conclusions being made about the number of asymptomatic patients saved a thoracotomy in this subset of studies.

Complications of testing or of invasive procedures as a result of testing were poorly documented in the available studies.

Despite the limitations of this overview, the data from the primary studies do permit certain restricted conclusions. They support the current practice of investigating a particular organ system if there are symptoms or signs suggestive of metastatic disease. For brain and bone imaging, the data suggest that investigation is appropriate for patients without organ-specific symptoms, but with systemic symptoms.

The data cannot resolve the most controversial topic – namely, the investigation of the asymptomatic patient. For each test the upper limits of the confidence intervals around the proportion of patients spared futile thoracotomy include values which would mandate investigation of all patients. However, lower limits of the confidence intervals, if representing the true proportion, would support the current practice of proceeding directly to thoracotomy in asymptomatic patients. A study with a large sample size, standardised initial examinations, preferably including thoracic CT, and documentation of the complications and economic consequences of testing is required to narrow these confidence intervals and provide information missing from current studies. Nevertheless, these data provide support for a policy of carefully considering whether in each individual case a patient with potentially operable non-small cell carcinoma of the lung should have a full investigation for metastatic disease to minimise the risk of an inappropriate thoracotomy.

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