REVIEW

Second Lung Cancers in Patients After Treatment for an Initial Lung Cancer

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Background: **Prospectively and retrospectively identified patient cohorts that were successfully treated for primary lung cancer have been followed to document the rate of development of and the effectiveness of treatment of second lung cancers. This review was performed to assess rates of second lung cancer development, factors associated with the development of these cancers, and the success of their treatment.** ***Methods:*** **The MEDLINE® database was searched to identify articles published in English concerning lung cancers, second primary cancers, treatment of these cancers, and patient survival.** ***Results:*** **The risk of developing a second lung cancer in patients who survived resection of a non-small-cell lung cancer is approximately 1%–2% per patient per year. Approximately one half of the patients who develop second non-small-cell lung cancers can have these tumors resected. The median survival from diagnosis of a second lung cancer in these patients is between 1 and 2 years, with a 5-year survival of approximately 20% (range, 4%–32%). The average risk of developing a second lung cancer in patients who survived small-cell lung cancer is approximately 6% per patient per year. For patients who survived small-cell cancer, the risk increases from approximately 2% to greater than 10% per patient per year 10 years after initial treatment. Only 7% (range, 6%–12%) of patients treated for small-cell lung cancer survive 2 years or more. Survivors who continue to smoke cigarettes have an increased risk of developing a second lung cancer.** ***Conclusions:*** **In patients surviving an initial lung cancer, the cumulative risk for the development of a second primary lung cancer makes this cancer a common cause of death. The high risk of developing a second lung cancer makes patients with these cancers an important population for study of surveillance strategies and chemoprevention agents. [J Natl Cancer Inst 1998;90:1335–45]**

Patients successfully treated for both small-cell and non-small-cell lung cancers remain at risk for developing second smoking-related and other cancers *(1).* Patients with early stage non-small-cell lung cancer (stages I–IIIa) typically have been treated with surgical resection alone. We recently reviewed different cohorts of these patients *(1).* In that review, we described that the rate of developing a second lung cancer is about 1%–2%, that half the patients quit smoking cigarettes, that most have resectable early stage disease (I–II), and that their survival is similar to those patients treated for the same stage of an initial non-small-cell lung cancer. We believe it is important to perform a review of the literature following previously published guidelines and extend the information contained in the recent review. This review provides additional information about each cohort described in the previous review *(1),* and identifies additional patient cohorts. It provides information about the different histologies of the lung cancers. Furthermore, it gives an estimation in terms of percentage of lung cancers that can be safely resected and states the reasons why some lung cancers cannot be resected. The review also provides the median and 5-year survival of cohorts of patients at risk for developing second lung cancers and assesses the impact of surveillance.

In a recent review *(1),* we also have examined the outcome of patients surviving small-cell lung cancer for more than 2 years. In that review, we reported that the risk of developing a second lung cancer was 2%–14% per patient per year, and that the risk increased twofold to sevenfold at 10 years after initial diagnosis. The majority of the second lung cancers diagnosed are squamous cell carcinomas, and less than 20% can be resected. Four articles about patients with small-cell lung cancer surviving longer than 2 years have been published since our last review *(2–5).* The articles include the data reported in 1997 by Tucker et al. *(4)* from the combined retrospective analyses from 10 different institutions of 611 patients with small-cell lung cancer who had survived for 2 or more years after starting initial treatment. These analyses more than double the number of patients surviving small-cell lung cancer who go on to develop a second lung cancer. This review provides additional information about each cohort, identifies additional patient cohorts, evaluates the effects of chest irradiation and cigarette smoking, and assesses the impact of surveillance. The rates of developing second lung cancers in patients treated with surgical resection can be compared with the rates in patients treated with chemotherapy with or without chest irradiation to provide information about the potential contribution of these modalities to the development of second primary cancers.

The hypotheses generated in the retrospective studies may facilitate the interpretation of ongoing studies of chemoprevention agents for patients treated for early stage aerodigestive cancers *(6,7).* These data also may be useful for the planning of systematic collection of information in future prospective studies to confirm or refute the hypotheses generated in the retro-

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See ''Notes'' following ''References.''

spective analyses. The purpose of the review is to further define the rates of developing second lung cancers in patients treated for non-small-cell lung cancer and small-cell lung cancer, to assess the impact of cigarette smoking cessation and initial treatment variables, to report the success rates when treating these second lung cancers, to comment on surveillance strategies for following patients treated for lung cancer, and to make recommendations for future studies.

METHODS

We have attempted to follow the published guidelines for a review of the medical literature *(8–10).* The medical literature was searched in Medline from 1990 through 1997 using the MESH terms lung neoplasm, carcinoma, small cell, carcinoma non-small-cell, second malignancy, and survivors. The studies included in this review were both prospective and retrospective in design, and are published in peer-reviewed journals. The tables of contents and abstracts in journals that provided studies fitting our criteria were hand searched from January 1997 through July 1997 to ensure that no recent articles were missed. The references from the selected articles were reviewed to identify other pertinent articles. The titles and abstracts of the articles were searched for information on the development and secondary treatment of second primary (metachronous) lung cancers in patients treated for an initial lung cancer. Sixty-six articles were identified. Eight experts in the field who had performed these studies were contacted to help identify additional articles and to provide missing information. All eight experts returned comments and/or suggestions and are acknowledged at the end of the manuscript. The published studies were examined for information on the rates of developing second tumors. The rate of secondary lung cancer development was calculated as the ratio of second primary cases over 100 patient-years of follow-up *(11,12).* The cumulative risk of developing a second cancer was determined using the Kaplan–Meier method *(4,13).* The numbers and characteristics of patients, the dates of the studies, the institutional settings, the impact of chest irradiation, the impact of chemotherapy, and cigarette smoking on the rates of developing these second cancers were collected. Information collected at the time of developing a second cancer included patient characteristics, diagnostic tests, histology and anatomic localization of the first and second cancers, secondary treatment, and the success of secondary treatment of patients developing metachronous cancers. The information on success of patients treated for cancer needed to define the number of patients followed, the number developing a second primary lung cancer, the number of patients treated, the method of secondary treatment, and the duration of follow-up after the treatment of the second lung cancer. All of the studies did not include all of this information, so the data were collected from articles containing heterogeneous information.

RESULTS

Patients With Non-Small-Cell Lung Cancer

The risk of a second lung cancer after an initial non-small-cell lung cancer. For more than 20 years, investigators have reported the rates of developing second primary cancers in patient cohorts followed after their initial resection for early stage lung cancer. The criteria for a second primary lung cancer provided by Martini and Melamed in 1975 *(14)* have been used in nearly all the studies shown here (Table 1). Five studies provided information on the development of second primary cancers other than lung cancer, but they did not provide adequate follow-up information to determine relative risk or percent risk per patient per year *(12,13,15–17).* Therefore, the useful information on cancers other than second primary lung cancers is very limited, and this review will only cover the development of second primary lung cancers.

We have focused on studies that have identified all of the second lung cancers in the patients followed at their institution(s) rather than simply those who have undergone resection. Authors have identified and followed a median of 595 patients (range, 127–1980) treated for their initial non-small-cell lung cancer in retrospective and prospective studies in single institutions, cooperative groups, and patient registries (Table 2). Only three of the studies have followed fewer than 300 patients with resected non-small-cell lung cancer. Therefore, these studies represent relatively large numbers of patients. Most studies included in Table 2 have been performed at single institutions (10 of 14), while a minority is from cooperative groups (three), and from a patient registry (one). The patients have had their initial treatment for non-small-cell lung cancer over a median of 10 years (range, 3–28 years). Although these patients have been followed from the 1940s through the 1990s, 11 of the 14 reports have been published in the last 5 years. This time span includes the introduction of imaging techniques (computerized tomography of the chest and fiberoptic bronchoscopy) that are more sensitive for identifying newly developing metachronous lung cancers.

The patient cohorts listed in Table 2 vary in their size and in the number of patients with second lung cancers. There is a median of 29 second lung cancers (range, five to 51) identified in these patient cohorts. The numbers listed in Table 2 are the number of second primary lung cancers developing after the initial lung cancer rather than the number of patients. Seventy percent of these metachronous cancers have the same histology as the initial lung cancer, and 55% are in the opposite lung from the initial lung cancer *(11,17–26).* The great differences in duration of follow-up (4–28 years) have prompted us to list the percentage of patients per year developing second primary lung cancers rather than the percentage of patients developing non-small-cell lung cancer in the total cohort of patients. This controls for the duration of follow-up between the series. Nine of the 10 studies of patients with resected non-small-cell lung cancer reported a rate of developing second primary lung cancers at 1% or 2% per patient per year *(12,15,26–30).* The rates of developing a second primary lung cancer shown in Table 2 have been rounded off to the nearest percent. A single prospective study

Table 1. Definitions of second primary lung cancers

Initial non-small-cell lung cancer *(14)*
Metachronous tumors
- A. Histology different
- B. Histology the same, if:
  - 1) Free interval between cancers at least 2 years or
  - 2) Origin from carcinoma *in situ*
  - 3) Second cancer in different lobe or lung, but:
    - *(a)* No carcinoma in lymphatics common to both
    - *(b)* No extrapulmonary metastases at time of diagnosis

Initial small-cell lung cancer *(60)*
Non-small-cell lung cancer
- A. Histology is non-small-cell lung cancer without small-cell lung cancer elements
- B. No evidence of local or distant recurrence of small-cell lung cancer
- C. The second lung cancer is identified more than 2 years after the diagnosis of the original small-cell lung cancer

Small-cell lung cancer
- A. Histology shows small-cell lung cancer in a lobe or previously described extrapulmonary site different from the lobe in which the first small-cell lung cancer first presented
- B. No evidence by chest roentgenogram, computerized tomography of chest, and fiberoptic bronchoscopy that the small-cell lung cancer has recurred in the lobe of origin
- C. The second cancer is identified more than 2 years after the diagnosis of the original small-cell lung cancer

Table 2. Rate of developing second primary lung cancers after developing an initial non-small-cell lung cancer

Authors (reference No.)	No. of patients	Source of cohort	Years of study	No. of second primary lung cancers	Rate of developing second cancer per patient per year*
Tockman et al. *(27)*	595	Cooperative group	1992–1995	13	2%
Walsh et al. *(16)*	358	Single institution	1987–1991	7	—
Van Meerbeeck et al. *(11)*	534	Hospital registry	1990–1995	23	4%
Martini et al. *(15)*	598	Single institution	1973–1985	45	1%†
Ribet and Dambron *(19)*	1980	Single institution	1971–1990	51	1%–2%†
Ginsberg and Rubenstein *(28)*	247	Cooperative group	1982–1988	5	1%
Antakli et al. *(29)*	1572	Single institution	1966–1994	39	1%
Saito et al. *(17)*	127	Single institution	1982–1990	13	2%
Verhagen et al. *(18)*	1287	Single institution	1970–1990	45	—
Pastorino et al. *(13)*	157	Single institution	1985–1989	21	1.5%–2%†
Thomas et al. *(12)*	973	Cooperative group	1977–1988	45	1%–2%
Pairolero et al. *(30)*	346	Single institution	1972–1978	35	2%
Smith et al. *(32)*	1400	Single institution	1953–1973	45	—
Razzuk et al. *(26)*	904	Single institution	1945–1972	29	1%
Total	11 078			416	1%–4%

*The dashes in the column represent data that were not present in the publication and were not obtained by correspondence with the author.

†Not specifically stated in the publication but obtained from written correspondence with the author, evaluating the actuarial curves, or estimated from median follow-up, patients at risk, and numbers of cases.

(hospital registry study) of a cohort of 534 patients shows a higher rate of 4% per patient per year *(11)*. This study does not present information on the stage of the subsequent tumors.

Four studies *(11,12,26,30)* report on the changes in the rate of development of second primary lung cancers in patients treated for non-small-cell lung cancer with the passage of time. Three such studies show an increase in the rate of developing second primary lung cancers. Two studies *(12,26)* show that patients have a rate that increases from 1% for the first 5 years after surgical resection of a lung cancer to 2% after the fifth year. The third study *(11)* reports that the rate of developing second primary lung tumors was higher after the start of the fourth year than during the first 3 years, but it did not quantify this increase. The fourth study *(30)* reports that the rate was 2.6% during the first 5 years after the initial resection but was only 1% after 6 or more years. However, the estimate of 1% per patient per year after 6 years was based on only three second primary cancers of the 35. Therefore, I believe the data on the increasing risk are more accurate than those for the decreasing risk.

This risk of second primary lung cancers translates into an important cumulative risk. Two different prospective studies of 284 patients reported the cumulative risk of a second primary lung cancer in the 1990s *(13,17)*. The cumulative risk determined by the Kaplan–Meier method censors events other than the development of second cancers, so the cumulative risk is biased upward. Nonetheless, the cumulative actuarial risk of developing a second primary lung or smoking-related cancer in these studies is similar and reaches 13%–20% at 6–8 years after resection of the initial non-small-cell lung cancer [Fig. 1, adapted from *(13)*]. These two studies followed the fewest number of patients, which may be responsible for some variation between the two different studies. The available information suggests the risk of developing second lung cancers in patients treated with surgical resection of an early stage lung cancer is 1%–2% per patient per year and appears to increase with the passage of time. An ongoing intergroup study (91025) for patients with resected stage I non-small-cell lung cancer randomly assigned patients either to placebo or *cis*-retinoic acid *(7)*. The

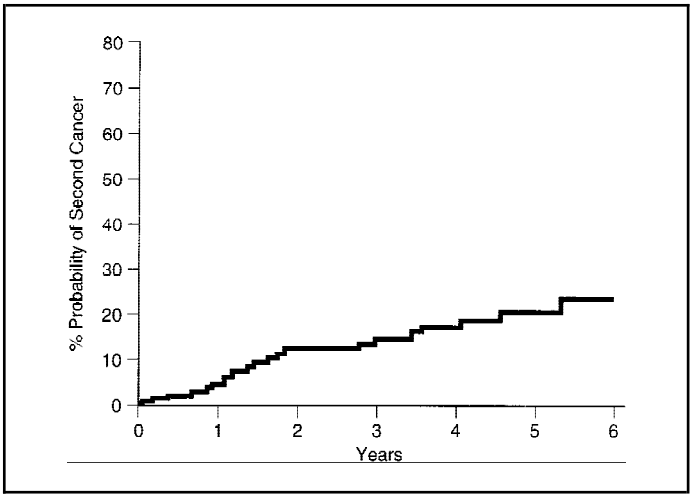

Fig. 1. Cumulative actuarial percentage of 157 patients with resected stage I non-small-cell lung cancer treated on the placebo arm who developed a smoking-related cancer (lung, head and neck, or bladder). *Adapted from Pastorino et al. (13) with permission.* The cumulative risk is determined by the Kaplan–Meier technique with events (deaths and other malignancies) other than these cancers censored.

overall rate of developing new second primary cancers is currently estimated at 2%–3% per patient per year. The treatment arms are still blinded, so the potential efficacy of *cis*-retinoic acid is thus far unknown. Therefore, the underlying rate of developing second primary cancers is undefined in the placebo group.

The impact of continued cigarette smoking and type of initial treatment administered on the rate of developing second lung cancers with the passage of time has rarely been reported in the studies of patients surviving early stage non-small-cell lung cancer. We identified seven studies that collected information on the smoking status of either the patient cohort *(13)* or those who developed second cancers *(11,18,19,22,31,32)*. Approximately one-half of the patients discontinued smoking after resection of their first or second lung cancer. The percentage of patients who

discontinued smoking after initial treatment of their first lung cancer varied widely in these studies, from 10% *(19,31)* to 80% *(13)*. None of the studies reported any data on the relative rates of developing metachronous tumors in patients who did or did not quit smoking. A case–control study showed patients who developed multiple primary lung cancers had a greater exposure to cigarette smoke than patients who developed a single lung cancer *(33)*. Confirmation that continued smoking and increased duration of follow-up are associated with increased rates of developing second lung cancers awaits further studies.

Few patients with stage III non-small-cell lung cancer can be surgically resected and achieve long-term survival *(34,35)*. The introduction of combined modality therapy (chest radiotherapy and chemotherapy) in the late 1980s and 1990s for patients with stage III non-small-cell lung cancer has resulted in a few patients achieving long-term survival (>3 years) *(36–38)*. However, there is inadequate follow-up information to assess the impact of chemotherapy and chest radiation on the development of second lung cancers in this patient group.

Secondary treatment of patients developing lung cancer after initial treatment for non-small-cell lung cancer. Eleven studies have reported the rate of successful resection of patients who develop second primary lung cancers (Table 3). Two hundred sixty-seven (54%) of 494 second primary lung cancers have been resected. The reasons for patients not undergoing resection or limited resection were provided for 130 patients in six studies. Fifty-two (40%) patients had pulmonary insufficiency, 49 (38%) had dissemination of lung cancer beyond the limits of resection, 15 (12%) had metastatic disease, 7 (5%) refused surgical resection, five (4%) had small-cell lung cancer, and two (1.6%) were of advanced age *(11,18,21,22,26,39)*. There is extensive information about the operations performed on patients undergoing surgical resection. The surgical procedures have been reported in 16 different studies for 521 patients developing a second primary lung cancer. These include a tracheal resection in 2 (<1%), pneumonectomy in seven (1%), completion pneumonectomy in 85 (16%), bilobectomy in 21 (4%), lobectomy in 174 (33%), and a segmentectomy or wedge resection in 232 (45%) *(11,18–26,29,31,39–42)*. The operative mortality in 12 studies is 29 (8%) of 386 surgical procedures *(18–20,23–26,31,32,40–42)*. Eight authors have collected survival information on all of their patients who develop second primary lung cancers rather than only on those undergoing surgery. The median survival from the time of diagnosis of second primary lung cancer is 1–2 years and is quite similar in all seven studies. The 5-year survival, however, is quite variable (range, 4%–32%). The two studies reporting the lowest 5-year survival (4% and 8%, respectively) started their patient accrual the earliest (1940s and 1950s, respectively), potentially explaining their shortened survival. Most of the studies show a 5-year survival between 18% and 32%, a figure that we believe is more consistent with modern follow-up and secondary treatment.

Table 3. Secondary treatment of second primary lung cancers after developing an initial non-small-cell lung cancer

Authors (reference No.)	No. of patients with second primary lung cancer	No. resected	Median survival, y*	5-year survival, %*
Van Meerbeck et al. *(11)*	23	12	1.1	—
Ribet and Dambron *(19)*	51	17	1–2†	>30†
Antakli et al. *(29)*	34	21	1.3†	8
Verhagen et al. *(18)*	40	33	1–2†	18
Saito et al. *(17)*	13	6	—	—
Rosengart et al. *(21)*	78	57	2	23
Fleisher et al. *(39)*	19	9	2	32
Deschamps et al. *(20)*	73	44	—	—
van Bodegom et al. *(22)*	89	45	—	—
Smith et al. *(32)*	45	11	—	—
Razzuk et al. *(26)*	29	12	1.0	4
Total	494	267 (54%)	1–2 years	4%–32%

*The dashes in the columns represent data that were not present in the publication and were not obtained by correspondence with the author.

†Not specifically stated in the publication but obtained from written correspondence with the author, evaluating the actuarial curves, or estimated from median follow-up, patients at risk, and numbers of cases.

Surveillance of patients with resected non-small-cell lung cancer. The survival of patients who develop second primary lung cancers is only 20% at 5 years after the diagnosis of their second cancer. One half of the patients followed after a successful resection of their non-small-cell lung cancer present with a second lung cancer that cannot be resected, split nearly equally between patients with tumor dissemination and those with inadequate pulmonary reserve to tolerate additional pulmonary resection. Therefore, more effective surveillance programs of patients may potentially be useful for detecting cancers when they can be treated with resection or ablation. We could not identify any studies that prospectively compared different types of surveillance strategies, but several studies have reported on different aspects of surveillance testing.

The information provided on surveillance includes a prospective study following patients with resected stage I non-small-cell lung cancer, the current reported practice of thoracic surgeons, the ability to detect lung cancer while the patient is asymptomatic, and comparative studies on the rate of developing tumors and the resectability of these tumors. A prospective study followed 346 patients with pathologically documented stage I non-small-cell lung cancer two to three times per year with history and physical examination, blood studies, sputum cytology, and chest radiograph *(30)*. The stage I definition for patients included in this study also had 18 patients with T1N1 disease (currently stage II), because this study predated the more current staging system introduced in 1986 *(43)*. Twenty-seven (77%) of the 35 patients who developed second primary lung cancers were identified at the time of their bi- or tri-yearly scheduled examination. Thirty (86%) of the 35 patients were asymptomatic when their second primary lung cancer was diagnosed: four were identified by sputum cytology and 26 by chest radiograph. Therefore, regularly scheduled follow-up visits for patients with resected stage I non-small-cell lung cancer can identify new lung cancers before symptoms develop.

Two other studies of patients surgically treated for early stage lung cancer retrospectively compared the survival *(44)* or detection of second primary lung cancers in patients followed more often and/or with more investigations to those patients followed less intensively *(45)*. The prospective study of 350 patients with resected stage I non-small-cell lung cancer described above were compared with 124 patients with stage I non-small-cell lung cancer who retrospectively were identified as being resected during the same time period but were not enrolled on the pro-

spective study. This study reported on four patients not included in the study published 3 years later *(30)* who were subsequently found to have primary nonpulmonary cancers that had metastasized to the lungs. The patient characteristics and the survival in the two groups were similar; the patients followed more intensively tended to live longer, although it was not statistically significant with a *P* value of .21 *(44)*. Another retrospective study determined the outcome of 120 patients with resected stage I–IIIA non-small-cell lung cancer who were followed at least four times per year with clinic visits, chest radiographs, or multichannel blood tests, or who had at least one computerized tomography of the chest, bronchoscopy, or sputum cytology during the follow-up period. Their outcome was compared with that of 62 patients followed less often without these tests *(45)*. More second primary lung cancers were identified in the intensive follow-up group than in the less intensive follow-up group (four versus none); however, the survival was similar in both groups. Therefore, in these retrospective studies, closer follow-up could detect more second primary cancers, and neither of these studies suggested any impact on survival of patients with early stage lung cancer.

The current stated practice of thoracic surgeons following patients with lung cancer has been assessed by a survey of the Society of Thoracic Surgeons for the current practice of follow-up for patients with lung cancer in the first 5 years after complete surgical resection *(46)*. The stated follow-up showed an average of four clinic visits with chest radiographs per year in the first year, gradually decreasing to yearly clinic visits with chest radiographs over 5 years. Complete blood cell counts and liver function tests are done once per year at the time of the clinic visits. Computerized tomography of the chest and sputum cytology are performed once during the 4 years. The benefit of this surveillance was not addressed. The other information about the potential utility of screening tests comes from information about detecting second cancers with chest radiographs, sputum cytology, and fiberoptic bronchoscopy while the patients are asymptomatic and the stages at which they present. Nine studies reported on the symptoms in 317 patients diagnosed with second primary lung cancers *(18–20,24,26,30,31,40,47)*. Two hundred twenty patients (69%) were reported to be asymptomatic and were identified by interval chest radiograph or sputum cytologic examination. There was no dramatic difference in the number of cancers identified in cohorts of patients that had a stated policy of follow-up chest radiographs and sputum and those that did not have a stated policy. A stronger statement about these two groups cannot be made at this time because the duration at risk was not matched, the cumulative risk was not defined, and the groups were not randomly assigned. Although many studies noted whether patients could or could not be resected, we could identify only two studies that noted the stages of all second primary lung cancers arising in 97 patients treated for an initial lung cancer *(21,39)*. Sixty-four (66%) patients had stage I non-small-cell lung cancer, nine (9%) had stage II, 15 (15%) had stage IIIa, four (4%) had stage IIIb, and five (5%) had stage IV. As would be expected, the majority of patients diagnosed in these cohorts had relatively early stage cancer.

Patients With Small-Cell Lung Cancer

The risk of developing a second lung cancer after an initial small-cell lung cancer. The problem of developing second primary lung cancers in patients surviving small-cell lung cancer has been recognized for more than 10 years *(48–50)*. The second lung cancers typically are non-small-cell lung cancers arising in different anatomic sites from the patients' initial small-cell lung cancer. A slightly different definition of second primary lung cancer for non-small-cell and small-cell lung cancer has been proposed by us (Table 1). We have provided information on the relative risk of different cancers other than lung cancer in both our own cohort of patients as well as in a combined cohort *(4,51)*. Ten other studies *(2,3,5,49,52–57)* provided information on the development of second primary cancers other than lung cancer, but they did not provide adequate follow-up information to determine relative risk or percent risk per year. Therefore, there is little new information on risk of cancers other than second primary lung cancers, so this portion of the review will only cover the development of second primary lung cancers.

One hundred seventy-four to 3681 patients have been followed either in a single institution or in multiple institutions. The patients have been followed from the 1970s when combination chemotherapy was introduced for small-cell lung cancer. None of the reports goes back to patients treated in the 1940s, 1950s, or 1960s as some of the surgical series have. Nearly all of the patients have been studied during the time period that fiberoptic bronchoscopy and computerized tomography of the chest have been available. Those that have evaluated patients for the development of second primary lung cancers have studied patients who have already survived for 2–3 years after the start of initial treatment. Nearly all of the patients who died less than 2–3 years after the start of initial treatment for small-cell lung cancer died of their original lung cancer.

Only 7% (range, 6%–12%) of the patients treated for small-cell lung cancer survived for 2 years or longer (Table 4). This has prompted half of the investigators to combine patients from multiple institutions to report on patients surviving for 2 or more years after the start of initial treatment for small-cell lung cancer. Despite combining patients from different institutions, the number of patients followed for longer than 2 years is quite small (range, 14–217) compared with the number of patients followed after initial surgical treatment for early stage non-small-cell lung cancer (Table 2). The small numbers of patients available even after combining institutions prompted us to amalgamate patients from 10 institutions for further analyses of 2-year cancer-free survivors of small-cell lung cancer *(4)*.

The number of second primary lung cancers is much smaller than in the surgical series reporting the outcome of patients with resected non-small-cell lung cancer. The median number of second primary lung cancers in each series is four (range, one to 51), sevenfold less than the median number observed in the non-small-cell lung cancer series *(29)*. The predominant histology developing in these patients is squamous cell carcinomas, accounting for 37 (69%) of 54 second primary lung cancers reported in the 14 studies *(1–3,58)*. The large multi-institutional study with some overlap among the series reported that 26 (51%) of 51 non-small-cell lung cancers were squamous cell carcinomas *(4)*.

Thirteen studies of more than 100 patients (range, 14–611, 2- to 3-year survivors) have reported on the development of second primary lung and/or aerodigestive cancers (Table 4). Despite the smaller numbers of patients surviving small-cell lung cancer followed for an extended period of time compared with patients treated for non-small-cell lung cancer, the information on the

Table 4. Rate of developing second primary lung cancers after developing an initial small-cell lung cancer*

Authors (reference No.)	No. of patients	Source of cohort	Years of study	No. of 2-year† survivors	No. of second primary lung cancers	Rate of developing second cancer per patient per year‡
Jacoulet et al. *(5)*	—	Multiple institutions	1986–1997	155 (2.5 years)	9	—
Tucker et al. *(4)*	—	Multiple institutions	1973–1995	611	51	3% (RR = 11; 95% CI = 8.4–15)
Sekine et al. *(3)*	278	Single institution	1977–1991	34	4	—
Lassen et al. *(2)*	1714	Multiple institutions	1973–1991	60 (5 years)	4	—
Johnson et al. *(60)*	578	Single institution	1973–1991	62	16	2%–13%
Szczepek et al. *(58)*	314	Single institution	1976–1985	30	4	4%–6%
van der Gaast et al. *(55)*	—	Multiple institutions	1980–1989	81	5	—
Sagman et al. *(56)*	800	Multiple institutions	1971–1985	—	4	RR = 7; 95% CI = 1.4–20
Heyne et al. *(59)*	446	Single institution	1978–1984	51	8	6%
Souhami et al. *(54)*	3681	Multiple institutions	1978–1986	217	1	—
Fukuoka et al. *(53)*	174	Single institution	1978–1984	14 (3 years)	2	RR = 5; 95% CI = 1–14.5
Osterlind et al. *(49)*	874	Multiple institutions	1973–1981	54	5	—
Vogelsang et al. *(52)*	225	Single institution	1973–1982	25	1	—

*The dashes in the columns represent data that were not present in the publication and were not obtained by correspondence with the author.
†If different from the 2-year survival, the interval is given in parentheses.
‡RR = relative risk. CI = confidence interval.

risk of second cancers with the passage of time is quite consistent and more striking. The risk has been estimated by both an increase in relative risk (observed number of cases divided by the expected number of cases in the general population) as well as the percentage of patients developing a second lung cancer per year of follow-up. The relative risk of developing a second lung cancer is sevenfold to 16-fold higher in the patients surviving small-cell lung cancer for more than 2 years compared with a similar population in the United States and Canada *(4,51,56).* The risk of developing a second primary lung cancer estimated as a percentage per patient per year in this same patient population is at 2%–13% per patient per year *(4,50,58–60).* Both the relative risk and percent per patient per year of follow-up for developing an aerodigestive or non-small-cell lung cancer in patients surviving for 2 or more years increased with the passage of 10 years from twofold to sixfold *(4,51,59,60).* These high rates of developing a second lung cancer result in a cumulative risk of approximately 30% at 10–12 years from starting initial treatment (Fig. 2, A and B). In our series, the predominant aerodigestive cancer is lung cancer, so the curves for cumulative risk of lung cancers and aerodigestive cancers are similar.

Two reports of the same patient cohort and a large retrospective multi-institutional study evaluated the effects of cigarette smoking cessation on the rates of developing second lung cancers in patients surviving small-cell lung cancer. Approximately 60%–75% of the patients discontinued smoking either before or at the time of diagnosis of their small-cell lung cancer *(4,51,60).* These studies show a threefold to fourfold reduction in the relative risks and rate per person per year in patients who stopped smoking before or at the time of starting initial treatment compared with patients who continued to smoke cigarettes *(4,51,60).*

A portion of this increasing risk of a second lung cancer for 10 years after starting initial treatment for small-cell lung cancer may be caused by the administration of chest radiotherapy. The relative risks for second lung cancers of patients treated with chest irradiation increased approximately twofold compared with patients not treated with chest radiotherapy *(4,51).* This was particularly evident in patients who continued to smoke cigarettes where the relative risk increased nearly fourfold *(4).* Despite the increase in relative risk of second lung cancers in

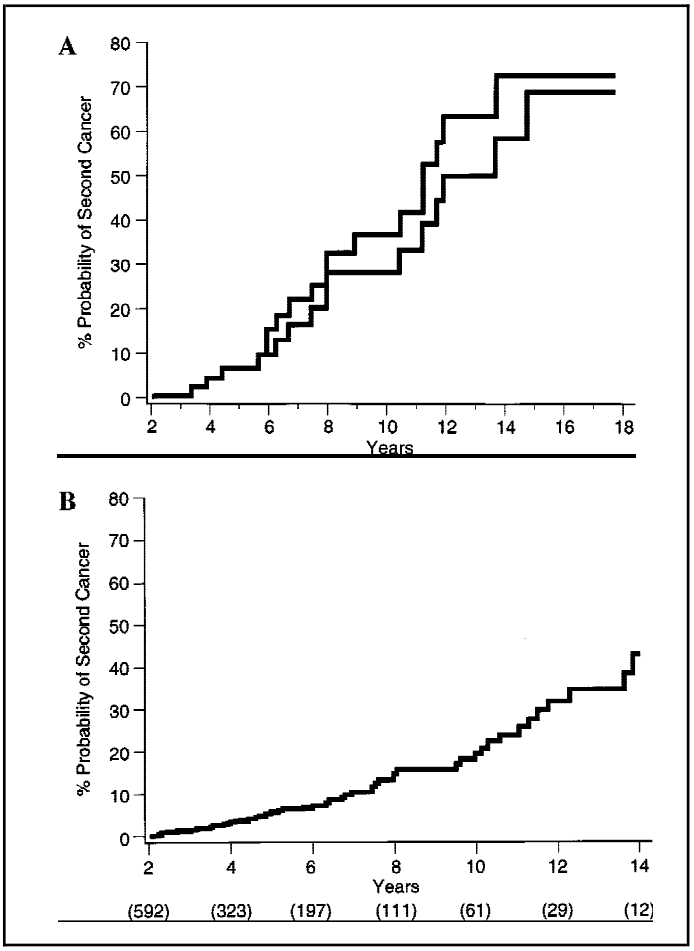

Fig. 2. A) Cumulative actuarial percentage of patients treated for small-cell lung cancer who developed cancer with the passage of time. The upper line represents the actuarial risk for developing a second aerodigestive cancer while the lower line represents the actuarial risk for developing a non-small-cell lung cancer. *Adapted from Johnson et al. (60) with permission.* **B)** Cumulative actuarial percentage of patients treated for small-cell lung cancer who developed lung cancer with the passage of time. The numbers in parentheses at the bottom of the figure represent the number of patients at risk for a non-small-cell lung cancer at that time period. *Adpated from Tucker et al. (4) with permission.* The cumulative risk is determined by the Kaplan–Meier technique with events (deaths and other malignancies) other than these cancers censored.

patients with small-cell lung cancer treated with chest radiation, chest radiotherapy added to combination chemotherapy clearly provides a survival benefit for patients with limited stage small-cell lung cancer *(61,62)*. Therefore, this small increased risk of a second primary lung cancer is currently a price one must pay for the therapeutic success of combined modality therapy.

Secondary treatment of patients developing lung cancer after small-cell lung cancer. There are relatively little data on the secondary treatment of patients with second lung cancers after initial treatment of their original small-cell lung cancer. Twelve different studies of patients surviving small-cell lung cancer have reported on the outcome of attempted secondary surgical treatment of the second primary lung cancers. Six (13%) of 46 patients who developed second primary lung cancers were able to undergo successful surgical resection of their non-small-cell lung cancers *(1,3,58)*. We have defined successful as being able to resect the cancer and have the patients reported as cancer free at their last follow-up. Patients treated for small-cell lung cancer at our institution and at other institutions were followed every 3–12 months. Despite identifying the non-small-cell lung cancer when it had not spread outside the thorax in 14 of our 15 patients, only one patient was able to undergo two successful resections *(60)*. Since the information on survival from the diagnosis of a second primary lung cancer in patients treated for small-cell lung cancer is meager, we have not included it in this review.

Surveillance of patients surviving small-cell lung cancer for more than 2 years. Only 13% of patients developing a second primary lung cancer (both small-cell and non-small-cell types) after initial treatment for small-cell lung cancer can undergo successful surgical resection. The survival of patients who develop a second primary lung cancer after initial treatment for small-cell lung cancer is undefined. There is no systematic information about why patients have been unable to undergo resection. The information on surveillance for patients surviving small-cell lung cancer is scarce. Investigators *(1,49,56)* evaluated patients every 3 months for 2 years and then every 6–12 months, but none of these investigators has given the information about the frequency with which the patients actually were seen. The majority of patients followed present with intrathoracic cancer *(60)*, and two thirds of the patients treated with chest radiotherapy in addition to combination chemotherapy develop their cancer within or at the edge of the radiotherapy portal *(4)*. There is very little information about the symptoms of patients at the time they present with their second cancer. The use of surveillance in patients with small-cell lung cancer is not well documented, and there have been no comparative studies of different schedules of follow-up.

Laboratory techniques to document second primary lung cancers. The definition of second primary lung cancers remains a clinical definition (Table 1). The recent advances in flow cytometry and genotyping of tumors has allowed some insights into the clonality of metachronous cancers. Flow cytometry has been used on six pairs of metachronous tumors to measure the amount of DNA *(63)*. Five of the six patients who met the authors' clinical criteria for metachronous tumors had different DNA histogram patterns, suggesting separate origins of the cancers. Mutations of KRAS2 oncogene *(64)*, TP53 *(65)*, and CDKN2 tumor suppressor genes *(66)* have been described in lung cancers. The initial and subsequent lung cancers from 24 patients have been genotyped for one or more of these genes *(67–70)*. Fifteen (68%) of the 22 patients with two or more non-small-cell lung cancers had discordant mutations in one or more of the genetic loci. Two patients with an initial small-cell lung cancer followed by a non-small-cell lung cancer had both of their cancers genotyped for all three genetic loci *(67)*. One patient had a mutation in the TP53 tumor suppressor gene in the initial small-cell lung cancer and had a KRAS2 mutation in the subsequent non-small-cell lung cancer. The other patient had no mutations in any of the three loci in the initial small-cell lung cancer but had mutations in the TP53 and CDKN2 tumor suppressor gene in the subsequent non-small-cell lung cancer. There were no examples of any of the 24 metachronous lung cancers with the same mutation. Therefore, the different patterns of the DNA histograms and the mutation patterns of KRAS2, TP53, and CDKN2 in the different lung cancers from the same patient strongly support the clinical data that these are indeed metachronous lung cancers.

DISCUSSION

Risk of Second Primary Lung Cancers in Patients Surviving Their Initial Lung Cancer

The information reported about second lung cancers in patients treated for non-small-cell lung cancer is quite different from that reported about patients treated for small-cell lung cancer. Many authors have reported on large cohorts of patients with non-small-cell lung cancer typically treated with surgical resection at single institutions and followed for extended periods of time. There is extensive information about the patients' symptoms, anatomic localization of the lung cancers, histology, secondary surgical treatment, complications of that surgical treatment, reasons for not resecting, and the outcome. In contrast, there have been relatively little data on the risk of developing second primary cancers because of continued cigarette smoking, on the evaluation of the risk of second primary cancers by relative risk, on the effect of chest irradiation on tumorigenesis, and on the impact of surveillance strategies on the outcome.

Authors have reported on small cohorts of patients treated for small-cell lung cancer and have analyzed the contributions of cigarette smoking and various treatment modalities on the risk of developing second primary cancers. The studies have focused on patients surviving longer than 2–5 years after the start of treatment because the events in the first 2–3 years are dominated by deaths from relapsed small-cell lung cancer. A few studies of the development of second primary cancers in patients surviving small-cell lung cancer have shown continued cigarette smoking, chest irradiation, and duration of follow-up contribute to the increasing risk of second primary lung cancer *(4,51,59,60)*. There is a paucity of information about the patients' symptoms, stage of the second lung cancer, subsequent surgical treatment, complications of surgical treatment, reasons for not resecting, outcome after the development of a second primary lung cancer, and impact of surveillance strategies.

Patients with non-small-cell lung cancer develop second primary cancers at a rate of approximately 1%–2% per year. The ongoing prospective collection of information on the rates of developing second primary cancers in large cohorts of patients

with non-small-cell lung cancer and head and neck cancer prospectively followed in the large chemoprevention trials should clarify further the rates of development of second primary cancers *(6,7)*. Patients successfully treated for small-cell lung cancer develop second primary lung cancers at an average rate of approximately 6% per year, which increases from 2% to more than 10% per patient per year with the passage of 10 years *(59,60)*. The information beyond 10 years is based on relatively few patients surviving 10 years or more after initial treatment for small-cell lung cancer. Further data are needed to confirm the current observations on rates of second lung cancers in patients with small-cell lung cancer surviving for a decade or more.

The second primary lung cancers appearing in patients with surgically resected non-small-cell lung cancer are four times as likely to be able to undergo a surgical resection as patients treated for small-cell lung cancer (52% versus 13%). The reasons have not been elucidated but could include at least two different factors. Patients with surgically resected non-small-cell lung cancer may have better pulmonary reserve because they have not been treated with chest irradiation. The majority of patients treated for small-cell lung cancer have their non-small-cell lung cancer appear within or near their radiation portal. Since the second primary lung cancers are difficult to recognize within the radiation portal on chest radiographs, patients present with more advanced disease and thus are less likely to be resected.

Two other cohorts of patients studied for the development of second primary lung cancers are patients successfully treated for Hodgkin's disease and breast cancer. A number of similarities exist among the risks for developing second primary lung cancers in patients treated for small-cell lung cancer, Hodgkin's disease, and breast cancer. Patients treated for Hodgkin's disease have a twofold to eightfold increased risk of lung cancer compared with the general population *(71–76)*. Similar to the data in patients successfully treated for small-cell lung cancer, the risk of a lung cancer in patients treated for Hodgkin's disease and breast cancer increases approximately twofold to 20-fold with the passage of 10 or more years from the start of therapy *(72–78)*. Despite the increased relative risks, the chance of developing lung cancer in patients surviving Hodgkin's disease is only 0.1% per person per year *(72,74–76)*, 10–130 times lower than that observed in patients surviving lung cancer.

The factors most often associated with the development of lung cancer in patients surviving Hodgkin's disease and breast cancer appear to be chest radiotherapy and cigarette smoking. Chest radiotherapy increases the risk of lung cancer twofold to sixfold in patients successfully treated for Hodgkin's disease and breast cancer in most studies, particularly in patients surviving more than 10 years after their initial radiation treatment *(72–78)*. The relative risk of developing lung cancer is increased on the ipsilateral side as the breast irradiation and the risk increases with increasing doses of irradiation *(77,78)*. Smoking also increases the risk of lung cancer sixfold to 15-fold in patients treated for Hodgkin's disease and breast cancer *(71,77,79)*, similar in magnitude to patients who have not had a previous cancer *(80)*. The data show a multiplicative interaction between smoking and chest radiotherapy in patients treated for small-cell lung cancer, Hodgkin's disease, and breast cancer *(4,77,79)*.

Recommendation for Future Studies

Future reports on developing second primary cancers in patients surviving lung cancer could provide additional information. The published studies of patients surviving non-small-cell lung cancer are missing different pieces of information than the studies of patients with small-cell lung cancer. Studies of patients surviving non-small-cell lung cancer will benefit from information on the contribution of smoking, chest radiation, and chemotherapy to the development of second primary cancers. This will be particularly important for patients with stage II and III non-small-cell lung cancer treated with chemotherapy plus chest radiotherapy. The analyses of the rates of second primary cancer development also will benefit from relative risk calculations to provide information about the increased risk of cancers less common than lung cancer. The assessment of the patient at the time of development of the cancer can help provide useful information for the efficacy of the follow-up procedures and subsequent treatment of the secondary cancer. Further information on the symptoms, signs, and methods of detection of second primary cancers in patients surviving lung cancer would be helpful in analyzing potential surveillance strategies.

Studies of patients surviving small-cell lung cancer will benefit from information on the symptoms, signs, radiographic, and bronchoscopic abnormalities of patients developing second primary lung cancers. The limited information available thus far suggests that fewer patients surviving small-cell lung cancer can be resected compared to patients with non-small-cell lung cancer. Information is needed on the stage of second primary lung cancers arising in patients surviving small-cell lung cancer and the reasons patients cannot be resected. Data on survival of patients after their second primary cancer need to be provided.

The opportunity to review these many studies has prompted us to provide what we believe is a comprehensive list of potentially collectable information to provide investigators with an extensive list of data that may be useful (Table 5). This material

Table 5. Recommended data collection and analysis on cohorts of patients followed after initial treatment for lung cancer: information at diagnosis

Patient information
Age, sex, performance status, smoking history, anatomic location, histology, stage, and surgical procedure, chemotherapy, and/or radiotherapy
Cohort information
Institutional setting, years of patient accrual, years of patient follow-up, smoking information, frequency of intended clinic visits, actual frequency of clinic visits, complete blood cell counts, serum chemistries, sputum cytology, chest radiographs, computerized tomography of the chest, and fiberoptic bronchoscopy
Patient information at time of second primary cancer
Age, sex, symptoms, signs, smoking history, method of detection (sputum cytology, chest radiograph, computerized tomography of chest, fiberoptic bronchoscopy), histology, anatomic location, stage, surgical procedure, reason(s) surgical procedure not performed
Patient information after second primary cancer
Patient frequency of follow-up, functional status assessment, survival, third primary cancer (*see* ''Patient information at time of second primary cancer'' above), cause of death.
Analysis of data
Actuarial survival, actuarial risk of developing second primary cancer, percentage risk per patient per year, relative risk calculations, impact of chest radiation, impact of chemotherapy drugs, and impact of continued cigarette smoking

will allow analyses for currently missing data, and investigators can choose among the recommendations for collecting information pertinent to their studies.

The cumulative risk of developing second primary lung cancer in patients surviving non-small-cell lung cancer makes this an important patient cohort to study, and these studies have been summarized recently *(6,7).* Twenty percent to 30% of these patients may develop a second primary lung cancer within 6–8 years, and only 20% of these patients are alive at 5 years. Sputum cytology has been employed systematically in the follow-up of patients with resected early stage non-small-cell lung cancer *(13,27,44).* The systematic use of computerized tomography of the chest and fiberoptic bronchoscopy for patients with resected early stage non-small-cell lung cancer has not been reported. Further research should develop different potential strategies for early detection of lesions that could include sputum cytology *(27),* periodic chest radiographs, spiral chest computerized tomography, and surveillance with white light or fluroescent bronchoscopy *(81,82).*

The high risk of second primary lung cancers also makes these patients excellent candidates for evaluating neoplastic and preneoplastic lesions in the airways and lung parenchyma. New genetic tools are able to characterize the clonality and diversity of the genetic lesions arising in their airways and lung parenchyma *(63,67,69,70,83–87).* These biological techniques can be employed on multiple cancers arising in patients with lung cancer. The definition of metachronous lung cancers is currently a clinical one. It may be useful to genetically type the multiple cancers arising in the same patient that have the same histology to find out how many have the same or different genetic alterations in the tumors. The majority of metchronous cancers have the same histology, and the second cancers may be underestimated because of the difficulty in identifying anatomically distinct lesions. This is particularly important in patients with small-cell lung cancer where fewer than 10 cases of metachronous small-cell lung cancers have been documented *(1).* The majority of the reported metachronous lung cancers arising in patients surviving small-cell lung cancer are squamous cell carcinomas. In contrast, the majority of metachronous lung cancers arising in patients with non-small-cell lung cancers have the same histology as their initial lung cancer. It will be useful to genotype small-cell lung cancers that reappear after a long cancer-free interval to find out if the genotypes suggest that some of these are metachronous cancers rather than late relapses of small-cell lung cancer.

Patients with adequate pulmonary reserve can undergo appropriate pulmonary resections for their metachronous lung cancers. The efficacy of resection and subsequent survival of these patients is well documented if the lesions can be identified at an early stage. Those with inadequate pulmonary reserve may be candidates for local secondary treatment, including laser therapy, cryotherapy, photodynamic therapy, and radiation therapy to the airways. The high rates of developing second primary lung cancer in patients surviving an initial lung cancer are well described, and less than 20% survive for 5 years. This poor survival means this is an important group of patients for whom to design prospective surveillance strategies and/or chemoprevention trials.

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