Second primary lung cancer: importance of long term follow up

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ABSTRACT   Review of histopathological and clinical data showed that 153 patients at one hospital developed a second primary lung cancer during 1980–6, 10% of all those with lung carcinoma. There were 64 synchronous tumours (interval less than one year) and 89 metachronous tumours (interval over one year). The average interval between metachronous tumours was 6·1 years. The criteria for diagnosing a second primary lung cancer were any of the following: (1) different histological type; (2) different lobe; (3) interval between the two tumours of at least three years. The incidence of second primary tumours increases with survival, and close follow up is required for their early detection.

Introduction

The incidence of a second primary neoplasm varies considerably, according to the organ affected. In general, it is 1·7–3·9% when a different organ is affected,[1 2] but reaches 5% for primary tumours of the head and neck region in combination with primary lung tumours.[3] Undoubtedly, the development of a second tumour is sometimes a coincidence, but on occasion the same aetiological agent may be responsible: cigarette smoking, for example, is related to carcinomas of both the larynx and the lung.[3] Second primary tumours in the same organ are best recognised for the colon, breast, and ovary.[4] Second primary carcinomas of the lung are also well recognised but are rare, the reported incidence being 1·6–3·0%. This compares with figures of up to 10% for a second primary carcinoma in the breast.[4-7] In those surviving more than three years, however, the incidence of second primary lung carcinoma rises to 10–25%.[7-10] Unfortunately, the criteria used to define a second primary lung carcinoma are often imprecise, and despite the high prevalence of lung cancer few studies of second primary lung tumour have been published.

Methods

During 1980–6 1540 patients with primary carcinoma of the lung were seen at St Antonius Hospital. Of these, 153 had a second primary lung tumour. Some patients had had their first primary tumour diagnosed before the study period.

Any of the following criteria were used to define a lung tumour as being a second primary tumour: (1) different histological type from that of the first tumour; (2) location in a different lobe; (3) diagnosis at least three years after diagnosis of the first tumour.

Patients with bilateral tumours and mediastinal lymph node invasion and those with distant metastasis at the time of diagnosis were excluded from this study, being regarded as having metastatic disease rather than double primaries. The two tumours were classified as being synchronous if they occurred within one year of each other and metachronous if the interval was longer.

Pathological diagnoses were made histologically on bronchial biopsy or resection specimens, often supported cytologically by transbronchial aspirates or bronchial brushings or secretions. Histological types were determined according to the revised WHO classification.[12]

The tumours were staged by chest radiography, bronchoscopy, mediastinoscopy; liver function tests and echohepatography; computed tomography of the brain; and bone scanning.[13] In the light of the results of

this clinical staging procedure (cTNM) 498 patients, including 77 of those with a second tumour, were treated by surgery. The remaining 76 patients with a second tumour were considered inoperable. Survival studies were restricted to the 77 patients who had both tumours treated by surgery and who could therefore be assessed by extensive mediastinal lymph node mapping[14] and evaluation of the surgical specimens (surgicopathological staging: pTNM). The expected survival of these patients was calculated with the aid of the product limit method (Kaplan Meier) and the Mantel-Cox statistic for testing the equality of the survival curves.[15]

Finally, the patients' smoking habits were ascertained to determine whether stopping cigarette smoking increased the interval between the two tumours.

Results

DATA ON PATIENTS

Of the 153 patients with a second primary tumour, 148 were male and five female; in 64 the two tumours were synchronous and in 89 they were metachronous. Patients with synchronous tumours varied in age from 43 to 77 (mean (SD) 63·3 (7·2) years). Patients with metachronous tumours were aged 31–72 (mean 58·7 (7·3) years) at diagnosis of the first tumour and 49–83 (mean 65·3 (6·9) years) at the time the second tumour was diagnosed. The average interval between the first and the second metachronous tumour was therefore 6·6 years (maximum 17·5 (4·2) years). A smoking history was available for 38 of the 45 patients with metachronous resected lung tumours. All were smoking at the time of detection of the first tumour. Eighteen of the 38 continued to smoke until the diagnosis of their second tumour; in these patients the mean interval from the first to the second tumour was 79 (range 16–253) months. Twenty of the 38 patients stopped smoking after resection of the first tumour; the mean interval until the second tumour was 76 (range 16–191) months. The difference between these time-intervals was not significant (unpaired Student's *t* test).

DATA ON TUMOURS

In two thirds of cases, synchronous as well as metachronous, both tumours were located in the upper lobes, equally divided between right and left. Only 11 of the 64 synchronous and eight of the 89 metachronous double tumours were located in adjacent lobes. The histological findings are shown in table 1. The tumour type was the same in 117 (76%), and of these it was squamous cell carcinoma in 97 (83%) and adenocarcinoma in 20 (17%). Combinations of small cell and non-small cell carcinomas occurred, three synchronous and four metachronous;

Table 1 *Histological types of double tumours (numbers of tumours)*

Identical		Different		
64 SYNCHRONOUS TUMOURS				
Squamous cell	42	Squamous cell and adenocarcinoma		5
Adenocarcinoma	10	Large cell and small cell		3
		Others		4
Total	52	Total		12
89 METACHRONOUS TUMOURS				
		Tumour 1	*Tumour 2*	
Squamous cell	55	Adenocarcinoma	Squamous cell	13
Adenocarcinoma	10	Squamous cell	Small cell	4
		Small cell	Squamous cell	2
		Large cell	Squamous cell	2
		Others		3
Total	65	Total		24

in the latter group one patient had a small cell carcinoma as the first tumour. The tumours fulfilling our three criteria for being double are shown in table 2; many fulfilled more than one criterion. Histological type was different in 12 of 64 synchronous tumours and in 24 of 89 metachronous tumours. Location was different in 61 of 64 synchronous tumours and in 86 of 89 metachronous tumours. The interval was more than three years in 72 of the 89 metachronous tumours.

STAGING AND SUITABILITY FOR SURGERY

In 40 of the 64 patients with synchronous tumours one or both tumours were in the prognostically unfavourable stage 3 (table 3a). The staging results for the metachronous tumours (table 3b) show that, whereas 77 of the 89 patients had stage 1 disease at the time of the first tumour, only 35 of these patients despite intensive follow up had their second tumour diagnosed in stage 1.

Of the 64 synchronous tumours, 27 were inoperable; a further five patients were unfit for surgery because of poor lung function. Of the 89 patients with metachronous lung cancers, 77 had stage 1 disease at the time of the first tumour, but in only 45 could the second tumour be resected: at this time 24 had inoperable clinical stage 3 disease, and 20 were unfit for operation as judged by lung function testing. Thus, of the 77 patients who underwent resection of the second primary lung cancer, 45 had a metachronous

Table 2 *Criteria used to classify a tumour as a second primary tumour*

Criterion	Synchronous	Metachronous
Different histological type	12/64 (19%)	24/89 (27%)
Different location	61/64 (95%)	86/89 (97%)
Interval > 3 years	0	72/89 (81%)

Table 3 *TNM (pTNM) stage of double tumours*

		Tumour 2			
		S 1	S 2	S 3	Total
64 SYNCHRONOUS LUNG CANCERS					
Tumour 1	S 1	18 (15)	2 (2)	10 (4)	30 (21)
	S 2	3 (2)	1 (1)	1 (1)	5 (4)
	S 3	6 (6)	0 (0)	23 (1)	29 (7)
	Total	27 (23)	3 (3)	34 (6)	64 (32)
89 METACHRONOUS LUNG CANCERS					
Tumour 1	S 1	35 (32)	3 (3)	39 (5)	77 (40)
	S 2	1 (0)	0 (0)	3 (1)	4 (1)
	S 3	2 (2)	1 (1)	5 (1)	8 (4)
	Total	38 (34)	4 (4)	47 (7)	89 (45)

TNM—tumour, node, metastasis; p—pathological stage.

Table 4 *Types of resection for the two tumours*

Synchronous tumours	
Lobectomy, lobectomy	14
Pneumonectomy	7
Lobectomy, segmentectomy	6
Bilobectomy, segmentectomy	2
Wedge resection, bilobectomy	3
Total	32
Metachronous tumours	
Lobectomy, lobectomy	25
Lobectomy, bilobectomy	9
Lobectomy, segmentectomy	4
Bilobectomy, segmentectomy	3
Segmentectomy, lobectomy	1
Radiotherapy, lobectomy	1
Radiotherapy, pneumonectomy	1
Chemotherapy, lobectomy	1
Total	45

tumour and 32 a synchronous tumour. The operative treatment of these 77 patients is shown in table 4.

Seven of the 77 patients died from postoperative complications (9%), leaving 70 for survival analysis. The median survival of patients with pTNM stage 1 and 2 cancers, calculated from the time of resection of the second tumour until death or the end of the study (31 December 1987), was 29 (SEM 4·0) months for patients with a synchronous second tumour and 42 (0·9) months for those with a metachronous tumour (fig 1). This difference is not significant. Patients in pTNM stages 1 and 2, however, had a significantly better survival than those in pTNM stage 3, whether the tumours were synchronous or metachronous (Mantel-Cox statistic = 17·8; p < 0·001; fig 2).

Discussion

When the results of different studies are being compared the criteria used to define a second primary lung cancer must be considered. Recently most authors have used the criteria of Martini and Melamed[6]—different histological type, different lobe, interval over two years, any one of the three being sufficient. Unfortunately, all of these criteria are open to criticism: the first because of the possibility of the histological heterogeneity of lung cancer, the second because of the possibility that a tumour located elsewhere could still be a recurrence or metastasis of
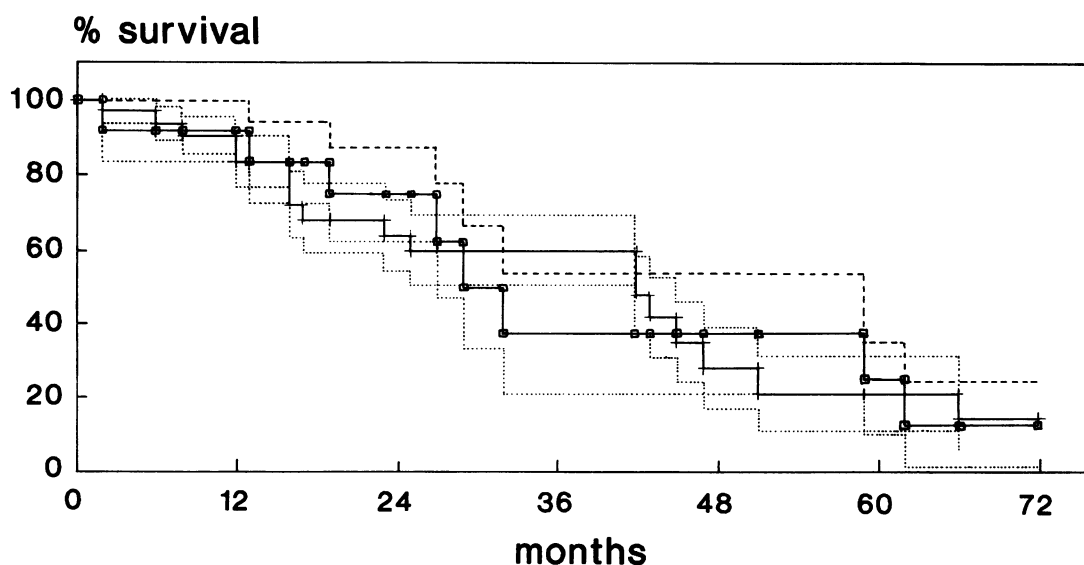

Fig 1 Survival after resection of a second primary lung tumour: comparison of 12 patients with stage 1 and 2 synchronous double tumours (—•—) with 36 patients with metachronous tumours (—|—). The dotted lines indicate standard errors.
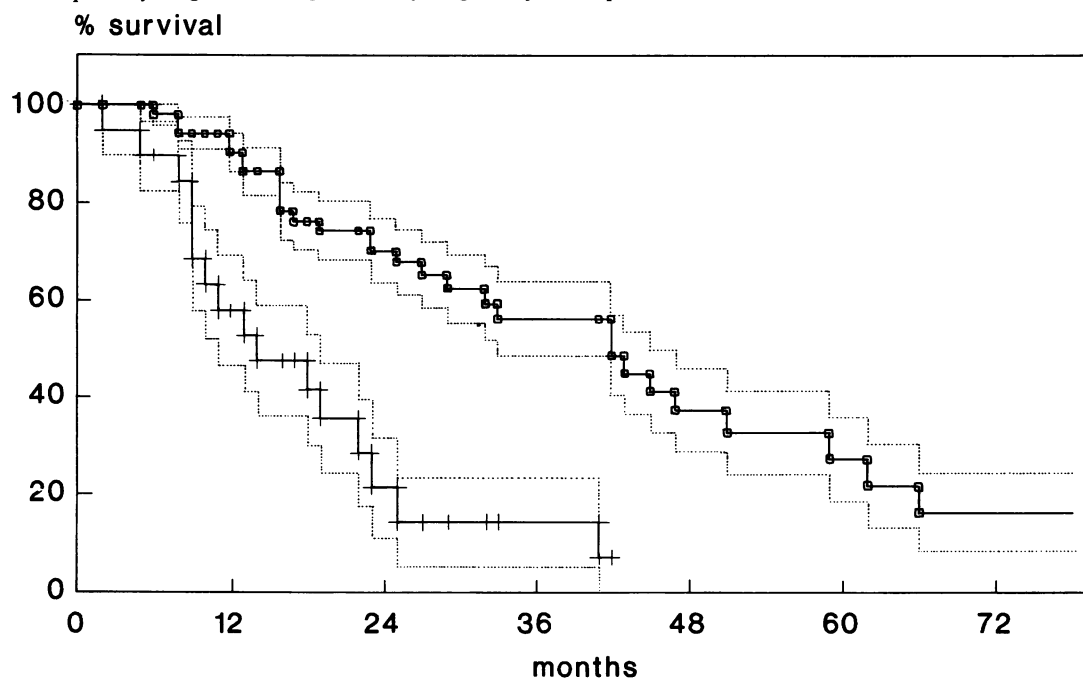
% survival

Fig 2 *Survival after resection of a second primary lung tumour: comparison of 48 patients with stage 1 and 2 second tumours with 22 patients with stage 3 tumours.—•—Stage 1 and 2; —|— stage 3. The dotted lines indicate standard errors.*

the first tumour, and the third because recurrence and metastasis may not appear for several years. We have therefore applied stricter criteria than those used previously. Our first criterion is identical to that of Martini and Melamed, but we modified the second criterion by excluding patients with bilateral synchronous lung cancers of the same histological pattern who also had metastases in mediastinal lymph nodes, believing that these cases might represent a single primary tumour with contralateral metastases. We also modified Martini and Melamed's third criterion by extending the time interval from two to three years. This is more in accord with observations that survival does not stabilise until after the third postoperative year.[8 13] Although we cannot fully exclude the possibility that some of our second tumours may represent a recurrence or metastasis rather than a new primary tumour, we believe that the use of stricter criteria than those of previous workers has made our figures more reliable than those hitherto available.

Our first criterion (different histological type) was the defining feature for 12 (19%) of the 64 synchronous tumours and 24 (27%) of the 89 metachronous tumours. Our second criterion (different location) was fulfilled by 61 (95%) and 86 (97%) respectively, and our third criterion (interval of more than three years) by 72 cases (81% of the metachronous tumours).

Many of the second tumours (64 of 153) appeared within one year. This could be taken as evidence that they represented a recurrence of the first growth rather than a new primary tumour, but there are several arguments against this. Firstly, all the second tumours were related anatomically to a bronchus. Secondly, most (53 of 64) were situated in the contralateral lung, in the absence of mediastinal lymph node invasion. Thirdly, the absence of extrapulmonary metastases makes it less likely that the second growth was a metastasis. Although solitary metastases are well recognised, in the absence of mediastinal lymph node disease solitary pulmonary metastases are extremely rare—there were none in our own series of 126 consecutive necropsies on patients with lung cancer from 1986 to 1988 (Wagenaar and van Bodegom, unpublished observations). We believe therefore that these synchronous tumours are likely to be two primary lung tumours rather than a single primary tumour with a solitary lung metastasis.

In this study second primary lung cancers formed 10% of all lung cancers seen (4·2% synchronous, 5·8% metachronous). This is higher than the figure of 1·6 to 3 per cent reported previously despite the fact that our criteria were stricter. If attention is confined to patients who survived three years after the first tumour the percentage of second primary lung cancer increases to 20%. These figures indicate the impor-

tance of follow up of patients with lung cancer. This should lead to the early detection of a second primary lung cancer, and thus increase the chance that the patient will be suitable for surgery. It would appear advisable to supervise these patients in the strict manner suggested for patients treated for head and neck cancer, as these patients have the same 10% risk of developing a second primary cancer in the lung.[2] It is clear that we underestimated the risk of a second primary lung cancer, because many of our patients (50 of 89) had stage 3 squamous cell cancer when their second tumour was identified.

Men formed 96% of the patients in the present study, a higher proportion than the 80% in previously published reports.[6 7 9 10] The age at diagnosis of the first and second primary tumour, the mean interval between the two diagnoses, and the percentage of tumours of the same histological pattern are all similar to those reported previously.[6-10] Three patients with synchronous and six with metachronous second primary lung cancers had a small cell cancer; in all cases this was combined with a non-small cell cancer, though in only one surgically treated patient the small cell cancer came first. This patient had limited disease treated with chemotherapy, to be followed six years later by a curative resection for stage 1 squamous carcinoma. Tests for highly sensitive tumour markers for small cell cancer gave negative results; but bone metastases, reported as small cell cancer metastases, developed two years later.[16-18] The possibility that the small cell carcinoma bone metastases were dedifferentiated metastases of the squamous cell carcinoma does not appear to have been considered previously. The sequence of small cell carcinoma followed by an independent non-small carcinoma has been noted previously and has stimulated speculation that chemotherapy for small cell carcinoma may have an oncogenic action favouring the appearance of a new type of cancer.[7 19 20]

The high percentage of second primary lung cancers might be considered an argument for limited surgical procedures, but it seems more logical to us to consider each tumour on its merits and maximise the chance of a cure by treating each one aggressively if after full clinical staging it appears operable. Sleeve resection and segmentectomy appear to be successful only if carried out with precise lymph node mapping augmented by frozen section investigation during the operation. In these circumstances survival is the same after segmentectomy as after lobectomy and pneumonectomy.[21 22] Survival time for stage 1 and 2 synchronous and metachronous second primary lung cancers is the same as that for first primary lung cancers of similar histological type and stage, though the age is of course greater if the second tumour is metachronous; the mean ages for our metachronous

tumours were 60·8 and 66·2 years. The prognosis for stage 3 tumours is of course poor, whether the second tumour is synchronous or metachronous: the five year survival rate of these patients is similar to the 10% reported for single stage 3 primary lung cancers.[23] Survival after resection of stage 1 and 2 second primaries in our patients could not be compared with previously reported figures because of the lack of surgicopathological staging in the previous reports on second tumours.[6 11] With stage 1 and 2 tumours figure 2 shows that there was, as expected, a significantly better survival (30% died from relapse within two years) than with stage 3 resected double tumours (85% died from relapse within two years). The poor results obtained with surgery in stage 3 disease, suggest that this form of treatment has no place in the management when the second tumour is so advanced.

Finally, in this study, discontinuing smoking did not extend the interval between the first and the second primary metachronous lung cancers, despite the fact that smoking is the most important factor causing lung cancer. The interval between the first and the second tumours (6·6 years) was probably too short for detecting an effect of giving up smoking, for the risk of lung cancer in ex-smokers approaches that of non-smokers only 15 years after they have given up smoking.[24]

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