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Epidemiology, management and prognosis of colorectal cancer with lung metastases: a 30-year population-based study

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ABSTRACT

Objective Epidemiological data on synchronous and metachronous lung metastases from colorectal cancer are scarce. The aim of this study was to determine trends in the incidence, treatment and survival in colorectal cancer with lung metastases in the general population.

Design and patients All cases of lung metastases from colorectal cancer registered in the Burgundy digestive cancer registry between 1976 and 2005 were included. Trends in the incidence of synchronous colorectal cancer lung metastases were estimated. A Cox model was used to analyse the risk of developing a metachronous metastasis. Multivariate analyses were performed using a relative survival model with proportional hazard applied to the net survival by interval.

Results Overall, 11.0% of patients had synchronous lung metastases. The frequency of synchronous lung metastases significantly increased for both sexes over time, with a nearly threefold increase between the periods 1976–1985 and 1996–2005. The overall 5-year cumulative risk of developing metachronous lung metastases was 5.8%. It did not significantly vary with time. Compared to colon cancer, rectal cancers had a higher risk of developing synchronous (OR: 2.80 (1.65–4.76)) and metachronous (OR: 2.63 (1.69–4.08)) lung metastases. Overall, 4.1% of synchronous lung metastases and 14.3% of metachronous lung metastases were resected for cure. The 3-year relative survival was 11.3% for synchronous lung metastases and 13.8% for metachronous lung metastases. It was, respectively, 53.0% and 59.2% after resection for cure. In multivariate analysis, the relative risk of death for the 1996–2005 period was about one fifth of that for the 1976–1985 period.

Conclusions The incidence of synchronous lung metastases increased over time, whereas the incidence of metachronous lung metastases remained stable. Lung metastases were more frequent in rectal cancer than in colon cancer. Unless surgical resection is possible, the prognosis for lung metastases remains very poor.

Significance of this study

What is already known about this subject?

- The lung is the most common extra-abdominal site of metastases from colorectal cancer
- The real frequency in the general population for both synchronous and metachronous lung metastases is not known
- There are no population-based studies reporting survival data on patients with lung metastases from colorectal cancer

What are the new findings?

- There was a nearly threefold increase in the frequency of synchronous lung metastases between the 1976–1980 and 2001–2005 periods
- The 5-year cumulative rate of metachronous lung metastases was 5.8% and remained stable over time
- Compared to colon cancer, rectal cancers had a higher risk of developing lung metastases

How might it impact on clinical practice in the foreseeable future?

- Patients with rectal cancer may benefit from a specific surveillance strategy

INTRODUCTION

Colorectal cancer (CRC) is a major public health problem in France as in many areas of the world. It is estimated that 412 900 new cases occurred in the European Union in 2006, representing 15% of all cancers[1]. Recurrence after surgery for cure is a major reason for failure[2]. The lung is known to be the most common extra-abdominal site of metastases from CRC. However, the real frequency for both synchronous and metachronous lung metastases (LMs) is not known. Population-based studies are difficult to perform because they require the participation of the entire medical profession and accurate follow-up over a long period which is seldom performed by cancer registries. Several non-population-based surgical studies have reported that resection of pulmonary metastases is associated with a 5-year survival rate of more than 50%.[3 4] Prolonged survival after resection of lung metastases is comparable to that observed after liver resection.[5] However, the rare data available are reported by specialised teams and therefore unavoidably biased.[6] They cannot be used as reference values. The objective of this population-based study was to report on the incidence of synchronous and metachronous lung metastases, their management and their prognosis, using data from a population-based series in France, covering a period of 30 years.

METHODS

Population

A population-based cancer registry records all digestive cancers in the administrative area of Côte-d'Or (Burgundy, France). This area has

a population of 507 000 according to the 1999 census. Patients were treated in a university hospital (including a comprehensive cancer centre), in four public general hospitals and in five private hospitals. Cancer registration began in 1976. Information is regularly obtained from pathologists, hospitals, private physicians (gastroenterologists, surgeons, oncologists and radiotherapists, general practitioners), as well as from the French National Health Service and a monthly review of death certificates. Because of the multiplicity of information sources, it was assumed that nearly all newly diagnosed cancers had been registered. The data reporting was robust since the beginning. Computerised recording of pathology reports, used by all pathology laboratories in the area, was available since 1975 and participation was enthusiastic. The quality and comprehensiveness of registration is certified every 4 years by an audit performed by the National Institute of Health and Medical Research (INSERM) and the National Public Health Institute (InVS).

Synchronous lung metastasis had to be diagnosed during the diagnostic work-up or within 3 months following the diagnosis of the CRC. LMs were defined as metachronous when occurring at least 3 months after the diagnosis of the CRC. Thus, the risk of developing metachronous lung metastasis was only calculated for patients resected for cure who survived at least 3 months after the CRC. Lung metastases were identified from clinicians' records (general practitioners and specialists) on the occasion of iterative surveys conducted to identify recurrences. The last survey was conducted in January 2008 for patients diagnosed until 2004. Only the first metachronous event was recorded. Patients with a diagnosis of chronic ulcerative colitis, HNPCC syndrome or familial polyposis were excluded. Non-epithelial cancers (lymphomas, sarcomas, malignant digestive endocrine tumours) and anal cancers were also excluded.

Between 1976 and 2005, 7022 newly diagnosed colorectal adenocarcinomas were recorded. Metastatic status was unknown for 26 cases. The characteristics of synchronous lung metastases were analysed from the remaining 6996 CRC cases. The risk of metachronous lung metastases were analysed in patients with colorectal adenocarcinomas resected for cure between 1976 and 2004. Overall, 4957 patients were resected for cure, 285 of whom died postoperatively during the first month following surgery (5.7%), 20 died during the second and third month following surgery and 310 were lost to active follow-up. Overall, 4342 cases were analysed in the metachronous lung metastases study. Throughout the study period, a yearly chest x-ray during the 5 years following diagnosis was recommended for the detection of lung metastases.

Studied variables

Demographic, clinical and tumour-related characteristics were routinely collected. Time at diagnosis was tabulated into three periods (1976–1985, 1986–1995 and 1996–2005). Age was classified in two categories: <75 and 75 and over. The cancer site was classified according to the International Classification of Diseases for Oncology, 3rd revision. The location of the tumour was divided into right colon: caecum, ascending colon, hepatic flexure and transverse colon (C18.0 to C18.4); left colon: splenic flexure, descending colon, sigmoid and rectosigmoid junction (C18.5 to C19.9); and rectum: rectal ampulla (C20). Cancer extension at the time of diagnosis was classified according to the TNM classification (stage I: T1–2 N0 M0; stage II: T3–4 N0 M0; stage III: N1–2 M0).[5] Macroscopic gross features (fungating, ulcerofungating or ulceroinfiltrating) were recorded from pathology reports. Treatment of the lung metastases was classified into three categories: surgery for cure (macroscopic resection of all malignant tissue and no microscopic evidence of spread into the surgical margin), palliative surgery (failure to resect all tumoral tissue and surgical biopsy), chemotherapy and best supportive care.

Statistical analysis

Associations between categorical data of patients with synchronous metastases were analysed using χ^2 tests for homogeneity. Multivariate logistic regression was used to identify risk factors independently and significantly associated with the presence of synchronous metastases. Cumulative metachronous metastases rates were calculated using the actuarial method and were expressed with standard errors. Patients who died were censored at the time of death, and patients who developed metachronous metastasis were censored at the time of occurrence. A multivariate Cox model was used to obtain odds ratios associated with the probability of developing metachronous metastasis according to the characteristics of the CRC.

On 1 January 2008, the vital status was known for 97.3% of patients. Survival was calculated from the date of diagnosis of LMs. Relative 1- and 3-year survival rates were calculated, these being defined as the ratio of the observed survival rate to the expected survival rate in a general population with similar gender and age distribution. It reflects excess mortality relative to background mortality. Results are given with their 95% confidence intervals. To evaluate the effects of prognostic factors on survival, a multivariate analysis was performed using a relative survival model with proportional hazards applied to the net survival by interval (Dickman model). The significance of covariates was tested by the likelihood ratio test. Analysis was carried out using Stata Statistical Software V.9.

RESULTS

Characteristics of synchronous lung metastasis

Overall, 1331 newly diagnosed CRC (19.0%) had detectable synchronous metastases. Among them 146 (11.0%) were lung locations. Most of these cases (N=89) had both lung and liver synchronous metastases, 45 had lung metastasis alone and 12 had metastases in other locations as well as LMs. The frequency of synchronous LMs significantly increased for both sexes over time, rising from 5.7% to 17.0% of colorectal cancer patients between the periods 1976–1985 and 1996–2005.

The characteristics of the patients who developed synchronous lung metastases are shown in table 1. Among metastatic patients, the frequency of lung locations increased over time, from 5.7% between 1976 and 1985 to 17.0% between 1996 and 2005 ($p<0.001$). Sex and age were not associated with the proportion of lung metastases, whereas the incidence increased from proximal CRC sites to distal sites ($p=0.002$).

In the multivariate analysis, after adjustment for age, sex and period, the effect of CRC site persisted (table 1). The risk of developing synchronous lung metastasis was higher in cancers of the left colon (OR=1.73, $p=0.017$) and rectal cancers (OR=2.80, $p<0.001$) than in right colon cancers. The risk of synchronous lung metastases was almost four times higher after 1996 compared to the earliest study period.

Among patients with synchronous lung metastases, 4.1% (6/146) were resected for cure (three cases of lung location alone, three cases with another associated metastatic location), 31.5% (46/146) had palliative resection, 30.1% (44/146) had palliative resection with chemotherapy, 9.6% (14/146) received chemotherapy alone and 24.7% (36/146) only received supportive care.

Table 1 Proportion of patients with synchronous lung metastasis among patients with metastatic colorectal cancer at initial diagnosis and risk factors associated with synchronous lung metastases

	N	Lung metastasis	p*	OR	CI 95%	p§
Sex						
Male	780	11.2%		1		
Female	551	10.7%	0.198	1.08	(0.75 to 1.56)	0.672
Age at diagnosis†						
<75 years	849	11.2%		1		
≥75 years	481	10.6%	0.742	0.94	(0.65 to 1.37)	0.756
Period of diagnosis						
1976–1985	368	5.7%		1		
1986–1995	387	7.0%		1.36	(0.75 to 2.47)	0.305
1996–2005	576	17.0%	<0.001	3.77	(2.29 to 6.79)	<0.001
Subsite‡						
Right colon	399	7.5%		1		
Left colon including rectosigmoid junction	706	11.2%		1.73	(1.10 to 2.71)	0.017
Rectal ampulla	215	16.7%	0.002	2.80	(1.65 to 4.76)	<0.001

*χ^2 test, Multivariate logistic regression.
†Unknown: one case.
‡Unknown: one case
§Likelihood ratio test.

Characteristics of metachronous lung metastasis

The overall cumulative rate of developing metachronous LMs was 0.9% at 1 year, 4.2% at 3 years, and 5.8% at 5 years (table 2). At 5 years, these rates did not significantly differ by sex, age at diagnosis and period of diagnosis of CRC. It was 2.1% for stage I cancers, 4.9% for stage II and 13.4% for stage IIII (p<0.001). Rectal cancers were significantly more likely to have lung metastasis as compared to left or right colon cancers, as were cancers with macroscopic ulcerative growth features as compared to fungating features.

Among patients diagnosed with metachronous metastasis, 4.8% (210/4342) had at least one LM. Among these, 114 had metastases confined to the lung. The median time-lag for the diagnosis of the metachronous LMs was 24.6 months (interquartile: 15.8–40.9 months). It was 25.1 months (interquartile: 16.0–37.1 months) for the 1976–1985 period and 23.3 months for the 2001–2004 period (interquartile: 14.6–34.2 months). In multivariate analysis (table 2), rectal cancer was associated with a risk of 2.63 ((1.69–4.08), p<0.001) for developing metachronous lung metastasis, as compared to other locations. Stage at diagnosis remained a risk factor for lung metastasis ($HR_{stage\ III\ vs.\ I}$: 5.64 (3.46–9.20), p<0.001), as did growth features ($HR_{ulcerative\ vs\ fungating}$: 1.72 (1.16–2.54), p=0.006).

The proportion of metachronous lung metastases resected for cure was 14.3% (30/210). It was 24.1% for lung location alone and 3.3% in case of other associated metastasis locations. Chemotherapy with palliative surgery was performed in 37.1% (4/210 with palliative resection and 70/210 with stomy or biopsy) and best supportive care was given in 48.6% of cases (102/210).

Survival

Overall 1-, 3- and 5-year relative survival after diagnosis of the metastasis was 45.5%, 11.3% and 6.9%, respectively, for CCR patients with synchronous lung metastases. Corresponding survival for metachronous metastases was 50.4%, 13.8% and 4.6 %. Survival did not vary with sex and age at diagnosis for either synchronous or metachronous metastases (table 3). Treatment was an important determinant of survival (p<0.001). The 3-year relative survival after resection for cure was 53.0% for

Table 2 Cumulative metachronous lung metastasis rates after curative resection for colorectal cancer and risk factors associated with metachronous lung metastases

	N	1 year	3 years	5 years	p¶	HR	CI 95%	p§
All patients	4342	0.9	4.2	5.8				
Sex								
Male	2412	0.7	4.3	5.8		1		
Female	1930	1.1	4.1	5.8	0.882	1.02	(0.74 to 1.36)	0.951
Age (years)*								
<75 years	2727	0.9	4.4	6.2		1		
≥75 years	1612	0.9	3.8	5.1	0.268	0.87	(0.63 to 1.20)	0.405
Period of diagnosis								
1976–1985	1131	0.7	4.8	6.4		1		
1986–1995	1511	1.0	3.1	4.7		0.65	(0.44 to 0.96)	0.033
1996–2004	1700	0.8	4.7	6.3	0.136	1.03	(0.72 to 1.47)	0.863
Tumour location†								
Right colon	1144	0.5	3.0	4.1		1		
Left colon including rectosigmoid junction	2262	1.0	3.8	5.3		1.38	(0.92 to 2.08)	0.114
Rectal ampulla	932	0.9	6.5	9.1	0.001	2.63	(1.69 to 4.08)	<0.001
TNM stage								
I	1323	0.2	1.3	2.1		1		
II	1816	0.6	3.6	4.9		2.09	(1.26 to 3.46)	0.004
III	1195	2.0	9.5	13.4	<0.001	5.64	(3.46 to 9.20)	<0.001
Macroscopic growth‡								
Fungating	1556	0.2	1.7	3.1		1		
Ulcerofungating or ulceroinfiltrating	2648	1.2	5.6	7.5	<0.001	1.72	(1.16 to 2.54)	0.006

*Age unknown for three cases.
†Subsite unknown for four cases, multivariate Cox model.
‡Gross features unknown for 138 cases.
§likelihood ratio test.
¶Logrank test.

Table 3 Relative survival for synchronous and metachronous lung metastases

	Synchronous				Metachronous			
	Lung metastases				Lung metastases			
	1 year	3 years	5 years	p†	1 year	3 years	5 years	p†
All patients	45.5%	11.3%	6.9%		50.4%	13.8%	4.6%	
Sex								
Male	46.9%	12.2%	4.7%	0.639	51.8%	11.5%	6.0%	0.612
Female	43.4%	9.9%	nc*		48.7%	16.6%	3.6%	
Age								
<75 years	44.3%	13.4%	8.1%	0.803	54.8%	13.6%	5.2%	0.119
≥75 years	48.5%	7.4%	nc*		38.8%	15.3%		
Tumour location								
Right colon	47.8%	10.3%	4.6%	0.985	32.7%	7.6%	nc*	0.006
Left colon including rectosigmoid junction	46.1%	10.0%	8.2%		55.5%	14.6%	3.8%	
Rectal ampulla	43.2%	14.7%	6.2%		51.1%	16.1%	3.8%	
Period of diagnosis								
1976–1985	5.2%	nc*	nc*		33.6%	4.3%	1.7%	<0.001
1986–1995	40.5%	nc*	nc*		32.9%	4.2%	2.6%	
1996–2005‡	55.8%	14.9%	7.5%		74.2%	27.9%	7.2%	
Metastasis location								
Lung metastasis alone	60.2%	23.1%	15.7%	0.008	55.3%	20.2%	7.5%	<0.001
Lung + other metastasis	39.3%	6.3%	3.5%		44.7%	6.8%	1.3%	
Treatment								
Resection for cure	84.6%	53.0%	nc*	<0.001	94.2%	59.2%	29.8%	<0.001
Palliative chemotherapy	60.0%	15.3%	8.4%		85.6%	14.4%	0%	
Symptomatic treatment or palliative resection§	8.9%	3.0%	1.3%		26.4%	1.2%		

*nc: not calculated, because no more survivors or no more events.
†Three-year univariate relative survival compared with the likelihood ratio test.
‡Last period being 1996–2004 for metachronous metastases.
§36 symptomatic treatments and 34 palliative surgery for synchronous lung metastases, 102 symptomatic treatments and 0 palliative surgery for metachronous lung metastases.

synchronous metastases and 59.2% for metachronous metastases. A multivariate relative survival model including sex, age, period of diagnosis and metastases locations was performed (table 4). Compared to the period 1976–1985, the relative risk of death for synchronous lung metastases for the period of diagnosis 1996–2005 was 0.14 ((0.08–0.25), p<0.001). It was 0.28 ((0.19–0.42), p<0.001) for metachronous lung metastases. The presence of another metastatic location associated with the LMs significantly worsened the prognosis compared with LMs alone (HR synchronous LM: 2.00 (1.31–3.05), p=0.004, HR metachronous LM: 1.99 (1.44–2.75), p<0.001).

DISCUSSION

To our knowledge, this study is the first population-based study to report time trends on the incidence and prognosis of synchronous and metachronous LMs from CRC. Population-based studies have the advantage of providing a non-biased and detailed view of changes in incidence, management and prognosis.

Table 4 Prognostic factors for synchronous and metachronous lung metastases. Multivariate relative survival model

	Synchronous			Metachronous		
	RR	95% CI	p*	RR	95% CI	p
Sex						
Male	1			1		
Female	1.00	(0.69 to 1.46)	0.594	0.86	(0.62 to 1.19)	0.357
Age						
<75 years	1			1		
≥75 years	1.38	(1.93 to 2.08)	0.111	1.45	(1.01 to 2.07)	0.045
Period of diagnosis						
1976–1985	1			1		
1986–1995	0.26	(0.14 to 0.49)		0.99	(0.68 to 1.45)	
1996–2005	0.14	(0.08 to 0.25)	<0.001	0.28	(0.19 to 0.42)	<0.001
Tumour location						
Right colon	1			1		
Left colon including rectosigmoid junction	0.74	(0.46 to 1.18)		0.79	(0.51 to 1.21)	0.27
Rectal ampulla	0.74	(0.42 to 1.30)	0.452	0.76	(0.48 to 1.22)	0.490
Metastasis location						
Lung metastasis alone	1			1		
Lung + other metastasis	2.00	(1.31 to 3.05)	0.001	1.99	(1.44 to 2.75)	<0.001

*Likelihood ratio test.

Our results demonstrate that synchronous LMs are rare in CRC. At time of diagnosis, only 2% of the patients had synchronous lung metastases. They were isolated in one-third of the cases and associated with another metastasis, particularly with liver metastases in two-thirds of patients. This rate was much lower than the 14.5% of synchronous liver metastases reported by the digestive cancer registry of Burgundy during 1976–2000[7]. The frequency of synchronous LM significantly increased for both sexes over time, with a nearly 3-fold increase between the periods 1976–1985 and 1996–2005. It seems likely that these trends are mainly related to the improvement in diagnostic procedures with the increasing use of CT-scan over time.[6] The centralisation of services treating colon and rectal cancers cannot explain the improved diagnosis of LM. The disease was managed in various centres throughout the study period. The CRC subsite was strongly associated with the rate of synchronous LMs, even though the reasons for the preferential occurrence of synchronous LMs in rectal and left colon cancer remain unclear.

Only 5% of the patients resected for cure who survived for 5 years subsequently developed LMs. The same figure was reported in a large hospital-based series involving 5230 patients.[8] In more than half of these cases, metachronous LMs were isolated, which is a higher proportion than for synchronous metastases. The median time between the diagnosis of CRC and the occurrence of detectable LMs was 24.6 months, which is longer than for liver metastases (17.2 months).[7] In a non-population-based study, late recurrence (more than 5 years after the initial surgery) occurred in 56% of cases with LMs versus 17% of cases with liver metastases.[9] All these findings are consistent with the hypothesis that the majority of CRC metastases develop in discrete steps, first in the liver, next in the lung and, finally, in other sites.[10] Whereas the rate of synchronous LM increased over time, no significant change was observed concerning metachronous LM. However, diagnosis of the two diseases was made earlier over time, suggesting an improvement in periodic screening through the increasing use of CT scan. It is now the most sensitive technique available for the diagnosis of LM and plays a major role in therapy planning since it gives a precise evaluation of the number and size of nodules.[11 12]

In the multivariate analysis, the risk of metachronous LMs occurrence was significantly associated with initial tumour location, stage at diagnosis and macroscopic tumour growth features. This increased risk of LM for rectal cancer is well known.[13 14] Kobayashi *et al* reported a significantly higher risk of LM for rectal cancer (7.5%) than for colon cancer (3.5%) among 5230 patients.[8] This may encourage clinicians to perform closer surveillance in patients with rectal cancer. We also observed an increased risk of LM for infiltrating or ulcerofungating tumours compared with fungating tumours, probably due to the more rapid metastatic cellular diffusion in the former. The association between morphologic appearance and further risk of metastases in general has already been reported in previous studies.[5 16–18] Michelassi *et al* reported metastatic progression in 48.6% of non exophytic tumours with a 5-year survival rate of 54%, whereas the rates were 29.7% and 80%, respectively in exophytic tumours.[15]

The prognosis in LMs remains poor. However, survival in the last study period was twice that in the first study period for both types of metastases suggesting the importance of earlier diagnosis of LMs. Although surgical resection of pulmonary metastases from CRC is feasible and can be performed safely with a low mortality rate,[16] only 4.1% of patients with synchronous and 14.8% of patients with metachronous LMs were resected with a curative intent. This proportion was 24.1% for patients with metachronous lung-only metastases. Data from non-comparative studies suggest that, for a subset of selected patients, complete resection of pulmonary metastases is associated with a 5-year survival rate of 36–63% in hospital-based series.[16–18] These results are confirmed by our population-based study. Several studies have suggested that patients with solitary metastasis potentially benefit more from pulmonary resection than do patients with multiple pulmonary metastases.[16] Some authors have found better results in metachronous versus synchronous metastases,[19–21] the latter being considered more aggressive. This was not the case in our study. As observed with liver resection,[7] curative resection can be proposed as first-line treatment provided that a complete resection can be achieved. Radio-frequency ablation could offer an attractive option in high-risk patients or in those who refuse surgery. It can be used either alone or in combination with surgical resection as a lung-parenchymal sparing approach.[22] However, further randomised controlled trials are needed to determine the place of radio-frequency ablation in the therapeutic strategy. Similarly, stereotactic body radiation therapy (SBRT) has recently been shown to be a promising safe and effective non-invasive therapy for oligo-metastatic disease, but still has to be evaluated.[23]

In most cases, pulmonary metastases are not surgically curable. The proportion of patients treated with best supportive care dramatically decreased at the same time as the use of palliative chemotherapy increased. This, in addition to the development of more effective chemotherapy regimens, probably explains the survival improvement observed for the most recent period of the study.[24]

In conclusion, synchronous pulmonary metastases from CCR are rare. Their rising incidence is explained by progress in diagnostic procedures. The occurrence of metachronous LMs remained stable. Rectal cancer was more frequently associated with LM than was colon cancer and patients with rectal cancer may benefit from a specific surveillance strategy. Unless surgical resection has been performed, the prognosis in LM remains very poor.

Competing interests None.

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