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ORIGINAL ARTICLE

Morbidity and mortality in a large series of surgical patients with pulmonary metastases of colorectal carcinoma: a prospective multicentre Spanish study (GECMP-CCR-SEPAR)†

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Abstract

OBJECTIVE: Little information is available on postoperative morbidity and mortality after pulmonary metastasectomy. We describe the postoperative morbidity and mortality in a large multicentre series of patients after a first surgical procedure for pulmonary metastases of colorectal carcinoma (CRC) and identify the pre- and intraoperative variables influencing the clinical outcome.

METHODS: A prospective, observational and multicentre study was conducted. Data were collected from March 2008 to February 2010. Patients were grouped into Groups A and B according to the presence or absence of postoperative complications. Variables in both groups were compared by univariate and multivariate analyses. *P*-values of <0.05 were considered statistically significant.

RESULTS: A total of 532 patients (64.5% males) from 32 hospitals were included. The mean (SD) ages of both study groups were similar [68 (10) vs 67 (10) years, *P* = NS). A total of 1050 lung resections were performed (90% segmentectomies or wedge, *n* = 946 and 10% lobectomies or greater, *n* = 104). Group A included 83 (15.6%) patients who developed a total of 100 complications. These included persistent air leaks in 18, atelectasis in 13, pneumonia in 13, paralytic ileum in 12, arrhythmia in 9, acute respiratory distress syndrome in 4 and miscellanea in 31. Reoperation was performed in 5 (0.9%) patients due to persistent air leaks in 4 and lung ischaemia in 1. The mortality rate was 0.4% (*n* = 2). Causes of death were sepsis in 1 patient and ventricular fibrillation in 1. In the multivariate analysis, lobectomy or greater lung resection [odds ration (OR) 1.9, 95% confidence interval (95% CI) 1.04–3.3, *P* = 0.03], respiratory co-morbidity (OR 2.3, 95% CI 1.1–4.6, *P* = 0.01) and cardiovascular co-morbidity (OR 2, 95% CI 1–3.8, *P* = 0.02) were independent risk factors for postoperative morbidity. Video-assisted surgery vs thoracotomy showed a protective effect (OR 0.3, 95% CI 0.1–0.8, *P* = 0.01).

CONCLUSIONS: The first episode of lung surgery for pulmonary metastases of CRC was associated with very low mortality and reoperation rates (<1%). The postoperative morbidity rate was 16%. Independent risk factors of postoperative morbidity were major lung resection and respiratory and/or cardiovascular co-morbidity. Video-assisted surgery showed a protective effect.

Keywords: Lung resection • Metastases • Morbidity • Mortality • Risk factors • Pulmonary complications

INTRODUCTION

Recurrence is a common event in colorectal carcinoma (CRC). More than half of all patients with CRC develop some synchronous or metachronous metastasis along the course of the disease, most frequently to the liver (33–60%) and the lung (22%). Approximately 8–10% of all patients with CRC develop pulmonary metastasis (PM) [1].

Several studies have shown the benefits of surgery for PM of CRC, with 5-year survival rates between 22 and 74% [2–5]. Surgery is performed to achieve a complete resection of all nodules while saving as much healthy lung parenchyma as possible. Previous reports on results of surgery for PM of CRC have focused on the rates of pulmonary recurrence and/or recurrences in other sites, long-term survival and prognostic risk factors. Postoperative morbidity and mortality after lung metastasectomy have deserved less attention in reported series [6]. Lung metastasectomy is generally perceived as a low-risk procedure. However, based on the wide experience in surgery for primary lung cancer (LC), it is well known that any major pulmonary resection belongs to the group

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of procedures with a high risk of postoperative morbidity and mortality. Independent risk factors of postoperative outcomes after surgery for primary LC are mainly advanced age, co-morbidity and a major surgical procedure.

The objective of this study was to assess postoperative morbidity and mortality in a large series of patients with PM of CRC undergoing lung resection surgery for the first time. A second objective was to identify risk factors for postoperative complications and death.

MATERIALS AND METHODS

Study design

A prospective, observational and multicentre study was conducted [7]. Data were collected from March 2008 to February 2010, using an online database. The Ethics Committees of the participating hospitals approved the study. Written informed consent was obtained from each patient.

Patients

Patients were considered candidates for surgery of PM of CRC as accepted in international standards and had to meet the following conditions: control of the primary CRC, absence of extra-pulmonary metastases except synchronous liver metastases amenable to radical treatment, technical feasibility to achieve a complete resection of all pulmonary lesions and cardio-respiratory fitness for the planned lung resections, which was preoperatively assessed as recommended by the European guidelines [8]. Patients were included in the study if they met the following criteria: first episode of planned surgery for PM of CRC, absence of macroscopic disease at the end of the surgical procedure and histological confirmation that at least one of the lesions excised actually was a PM of CRC. Patients were grouped as having presented (Group A), or not (Group B), postoperative complications.

Study variables

In all patients, the following data were recorded: demographics, preoperative work-up studies, CRC-related data, details of current pulmonary surgery and histopathological results. The dependent variable was the short-term postoperative (30 days) clinical outcome, including morbidity, reoperation rate and mortality. 'Morbidity' or 'complication' was defined as any disease of new appearance during the first 30-day period after surgery that needed any specific treatment and/or implied any increase in the length of hospital stay. Among postoperative complications that merited definition were nosocomial pneumonia, persistent air leaks and respiratory failure. Nosocomial pneumonia was defined as an inflammatory lung process that was infectious in origin, absent at the time of hospital admission and developed >48 h after having been hospitalized. Clinical diagnostic criteria were the appearance of a new infiltrate on the chest X-ray plus two of the three following conditions: purulent secretions, fever >38°C and leucocytosis or leucopaenia [9]. Persistent air leaks were considered if present for >7 days. Respiratory failure was defined as a measure of the partial arterial pressure of oxygen (PaO_2) <60 mmHg, with or without hypercapnia, while breathing ambient air.

Statistical analysis

Variables in Groups A and B were compared with the Student's *t*-test or the Mann–Whitney *U*-test for continuous data according to the normal or non-normal distribution. Chi-square (χ^2) test or Fisher's exact test was used for categorical variables. The independent risk factors were studied in a multivariate analysis using a binary logistic regression test with a forward stepwise method gradually incorporating the model variables, which proved to be statistically significant in the univariate analysis. The Hosmer–Lemeshow test was used to fit the multivariate model, and precision was calculated via C-statistics. The level of statistical significance was set at $P < 0.05$. Due to the small number of deaths found in the study, univariate and multivariate analyses were not performed to find predictors of mortality risk. Statistical analysis was carried out with SPSS version 19.0 statistical packages (IBM Company®, USA).

RESULTS

We collected data of 544 patients from 32 participating hospitals. Twelve patients were not included in the analysis, as some information was missing. Characteristics of the 532 patients finally included in the study are described in Table 1. As shown in the table, age was not different between groups. Our series included 230 (43%) patients aged over 70 years, which is considered a cut-off point for advanced age and thus, for an increased risk in surgery for primary LC. Interestingly, we did not find significant differences when comparing patients younger and older than 70 years ($P = 0.1$).

Table 2 summarizes the characteristics of the primary CRC and lung metastases. The total number of pulmonary lesions seen preoperatively in the computed tomography scan of the chest were 1002. In fact, 1133 nodules were actually resected, 17.7% ($n = 201$) of them were >3 cm. Of the resected lesions, 948 (84%) were PM of CRC.

Table 1: Demographic data and co-morbidity characteristics

Patient's features	No morbidity group total patients: 449 (patients/% patients)	Morbidity group total patients: 83 (patients/% patients)
Age mean ± SD (range)	67 ± 10 (35–91)	68 ± 10 (42–85)
Gender		
Male	284 (63.3%)	59(71.1%)
Female	165 (36.7%)	24(28.9%)
Co-morbidity	260 (58%)	60 (72.3%)
Hypertension	148 (33%)	24 (29%)
Diabetes mellitus	54 (12%)	16 (19.3%)
Respiratory disease	38 (8.5%)	15 (18%)
Cardiovascular disease	55 (12.2%)	19 (23%)
Renal disease	15 (3.3%)	5 (6%)
Other neoplasms	36 (8%)	12 (14.5%)
Other co-morbidities	90 (20%)	24 (28.9%)

Digestive disorders. Endocrinology and metabolic disorders except diabetes. Neurological and Psychiatric disorders.

Table 2: Characteristics of primary CRC tumour and lung metastases

	Number of patients (%)
Primary tumour	
Histology	
Adenocarcinoma	524 (98.49)
Carcinoma adenosquamous	1 (0.2)
Undifferentiated carcinoma	2 (0.4)
No data	5 (0.9)
Location	
Colon	258 (48.5)
Rectum	241 (45.3)
Colon–rectum	33 (6.20)
Astler–Coller classification	
A	10 (1.87)
B	195 (36.65)
C	191 (35.90)
D	120 (22.55)
No data	16 (3)
TNM	
I	43 (8.08)
II	140 (26.31)
III	200 (37.59)
IV	140 (26.31)
No data	9 (1.69)
Lung metastases	
Time of onset	
Synchronous	81 (15.2)
Metachronous	451 (84.8)
Maximum size (cm)	
<3	438 (82.3)
≥3	94 (17.7)
Median number of metastases per patient	1.78 ± 1.91 (1–25)
Distribution	
Unilateral	456 (86)
Bilateral	76 (14)
Chemotheraphy prior to lung metastasectomy	
Yes	113 (21.2)
No	419 (78.8)
Synchronous liver and lung metastases	44 (8.1)
Prior resection of liver metastases	23 (4.32)
Radicality lung metastasectomy (microscopic margin)	
R0	506 (95.1)
R1	24 (4.5)
No data	2 (0.3)
Lymphadenectomy	
Yes	254 (48)
No	278 (52)

Co-morbidities were present in 60% of patients (Table 1). Mean values of forced expiratory volume in one second and KCO [transfer coefficient is diffusing capacity of the lung for carbon monoxide (DLCO) corrected for alveolar volume (VA)] are presented in Table 4. Ninety percent (n = 479) of patients received chemotherapy at any time before lung surgery, and in 21% (n = 113), chemotherapy was specifically indicated for lung metastases before surgery was administered. The use of induction chemotherapy in Group A was 17 vs 22% in Group B (P = 0.28).

The median time between primary CRC resection and surgery for PM was 28 (range 0–189) months. Fourteen percent (n = 76) of patients presented bilateral lung lesions. One-stage surgery was performed in 20 (26%) patients and two-stage procedures in 56 (73%), giving a total of 606 surgical procedures in 532 patients. Surgical approaches were 492 thoracotomies, 12 sternotomies and 102 video-assisted surgeries, the latter in 94 patients. A total of 1050 lung resections were performed (90% segmentectomies or wedge, n = 946 and 10% lobectomies or greater, n = 104). Mechanical staplers were used in 97.6% (n = 519) patients, buttressing materials and/or lung sealants in 32% (n = 169). Lymphadenectomy, either systematic or sampling, was performed in 10 and 38% of patients, respectively. The rates of lymphadenectomy in the two study groups were similar (Group A, 52%; Group B, 47%; P = 0.42).

Table 3: Postoperative complications

Morbidity 83 patients (15.6%)[a]	Number of affected patients/%[b]
Air leaks >7 days	18/3.4
Atelectasis	13/2.4
Pneumonia	13/2.4
Paralytic ileum	12/2.3
Arrhythmias	9/1.7
Acute respiratory distress syndrome	4/0.8
Other complications[c]	31/5.8
Re-interventions	5/0.9
For persistent air leaks	4/0.8
Completion lobectomy for ischaemia of lung segment	1/0.2

[a]% over 532 patients.
[b]Some patients have more than one complication (100 complications in 83 patients).
[c]Pleural cameras: 16; urinary infection: 5; renal insufficiency: 3; phrenic paralysis: 2; congestive heart failure: 2; oedema post-pneumonectomy: 1; bronchopleural fistula: 1.

Group A included 83 (15.6%) patients who developed 100 complications (Table 3). Blood transfusion was required by 2.8% of patients. Also, blood transfusion was significantly more frequent in patients in Group A than in those in Group B (8.4 vs 1.8%, P < 0.01). Reoperations were performed in 5 (0.94%) patients due to persistent air leaks in 4 and pulmonary segment ischaemia requiring a completion lobectomy in 1. Two patients died (mortality rate 0.4%). Causes of death were sepsis in 1 patient and ventricular fibrillation in 1 (Table 3).

Variables significantly associated with complications in the univariate analysis (tumour size of 30 mm or greater, lobectomy or greater lung resection, respiratory and/or cardiovascular co-morbidity as well as video-assisted surgery) (Table 4) were included in the logistic regression analysis. Lobectomy or greater lung resection [odds ratio (OR) 1.9, 95% CI (95% confidence interval) 1.04–3.3, P = 0.03], cardiovascular co-morbidity (OR 2, 95% CI 1–3.8, P = 0.02) and respiratory co-morbidity (OR 2.3, 95% CI 1.1–4.6, P = 0.01) were independent factors significantly associated with postoperative morbidity. Video-assisted surgery vs thoracotomy was inversely associated with complications (OR 0.3, 95% CI 0.1–0.8, P = 0.01) (Table 5).

DISCUSSION

Main findings of our study are that a first episode of lung surgery for PM of CRC was associated with a very low mortality (<1%) and a postoperative morbidity rate of 16%. Independent risk factors of postoperative morbidity were major lung resection and respiratory and/or cardiovascular co-morbidity. Video-assisted surgery showed a protective effect.

It is well known that any major pulmonary resection is associated with a high risk of postoperative morbidity (between 15

Table 4: Univariate analysis of potential risk factors for postoperative complications

Variables	No morbidity group total patients: 449 (patients/%patients)	Morbidity group total patients: 83 (patients/%patients)	*P*-value
Age (mean ± SD)	67 ± 10	68 ± 10	0.46
Gender (male/female)	284 (63.3%)/165 (36.7%)	59 (71.1%)/24 (29%)	0.17
Co-morbidity	260 (57.9%)	60 (72.3%)	0.01
Arterial hypertension	148 (33%)	24 (29%)	0.46
Diabetes mellitus	54 (12%)	16 (19.2%)	0.07
Respiratory Co-morbidity	38 (8.4%)	15 (18%)	<0.01
Cardiovascular co-morbidity	55 (12.28%)	19 (23%)	0.01
Renal co-morbidity	15 (3.3%)	5 (6%)	0.23
Other neoplasms	36 (8%)	12 (14.4%)	0.06
Other co-morbidities	90 (20%)	24 (29%)	0.07
Chemotherapy prior to lung metastasectomy	99 (22%)	14 (17%)	0.28
Video-assisted surgery	89 (19.8%)	5 (6%)	<0.01
Minor lung resections	369 (82.1%)	56 (67.4%)	<0.01
Major lung resections	79 (17.6%)	27 (32.5%)	<0.01
Use of stapler suture	432 (96.2%)	77 (92.7%)	0.15
Lesions ≥3 cm	72 (16%)	22 (26.5%)	0.02
Lymphadenectomy	211 (47%)	43 (52%)	0.42
Respiratory functional test, mean ± SD			
FEV_1 (%)	96 ± 19	91 ± 21	0.06
FVC (%)	97 ± 19	95 ± 24	0.57
KCO (DLCO/VA, %)	95 ± 21	91 ± 27	0.26

Table 5: Multivariate analysis of risk factors of postoperative complications

Variable	Odds ratio (95% CI)	*P*-value
Model 1[a]		
Age	0.9 (0.9–1)	0.7
Gender	1.4 (0.9–2.4)	0.2
Co-morbidity	2 (1.2–3.5)	0.01
Lesions ≥3 cm	1.3 (0.7–2.5)	0.3
Lung major resections	1.8 (1.01–3.2)	0.04
Video-assisted surgery	0.3 (0.1–0.7)	0.01
Model 2[b]		
Age	1 (0.9–1)	0.7
Gender	1.3 (0.8–2.2)	0.3
Respiratory co-morbidity	2.3 (1.1–4.6)	0.01
Cardiovascular co-morbidity	2 (1.1–3.8)	0.02
Lesions ≥3 cm	1.3 (0.7–2.4)	0.4
Lung major resections	1.9 (1.04–3.3)	0.03
Video-assisted surgery	0.3 (0.1–0.8)	0.01

[a]In the development Model 1, the C-statistic (discrimination power) was 0.67 ($P < 0.01$), and the Hosmer–Lemeshow goodness-of-fit statistic was 3.07 ($P = 0.93$).
[b]In the development Model 2, the C-statistic (discrimination power) was 0.68 ($P < 0.01$), and the Hosmer–Lemeshow goodness-of-fit statistic was 8.57 ($P = 0.37$).

and 47%) and mortality (1 and 12%) [10]. The most frequent complications are respiratory, cardiovascular and those related to surgical technique. Acknowledged risk factors for postoperative morbidity and mortality are advanced age, co-morbidity, major extent of lung resection, longer operating time and need for postoperative mechanical ventilation. However, when lung resection is performed, in particular for PM, it is usually perceived as much safer. In the review by Pfannschmidt *et al*. [6], for surgery for PM of CRC, low morbidity (0–22%) and mortality (0–2.5%) rates were reported (Table 6).

In our series, including 1050 lung resections performed in 532 patients, only 2 died postoperatively. For that reason, potential risk factors for mortality were not assessed.

The complication rate rose to 15.6% (83 patients), respiratory and cardiovascular being the most frequent, which is similar to the data reported in other series [6]. Complications related to the surgical technique developed in a few cases, with a re-intervention rate of only 0.4%.

The univariate and multivariate analyses identified the same independent factors of risk for postoperative complications, except age, as reported in lung surgery for any diagnosis. Interestingly, in our study, age was not different between groups in the univariate analysis. In our opinion, because of the type of surgery performed in the resection of PM in CRC patients, age was not found to be a relevant factor in contrast to primary LC surgery. As expected, co-morbidity and major extent of the pulmonary resection were independent risk factors. These data should be interpreted in the particular context of the surgical strategy designed for patients with PM, which largely differs from that of patients with primary LC. Surgery for PM is based on lung parenchyma-sparing procedures. In our series, 90% of 1050 lung resections were segmentectomies or wedges. In addition, the number of minor resections performed per procedure, had no impact on the development of complications. Also, the size of the pulmonary lesions, smaller or larger than 30 mm in diameter, although significant in the univariate analysis, lost its significance as an independent factor of risk in the multivariate analysis, which is probably related to the fact that larger sizes are associated with major lung resection procedures.

In the present study, 94 (17%) patients underwent video-assisted surgery. We demonstrated a protective effect of the video-assisted approach on postoperative morbidity, which was also confirmed in the multivariate analysis. However, minimally invasive thoracic surgery is currently under debate as preferable or not approaches in PM. Reported advantages include a decrease in the mean length

Table 6: Results on recent series evaluating morbimortality in patients with pulmonary resection for colorectal cancer

References	No. of patients	Mortality (%)	Morbidity (%)	Surgical procedures (patients)			
				Wedge	Segmentectomy	Lobectomy	Pneumonectomy
Sakamoto *et al.* [11]	47	1.7	NR	29	12	17	1
Moore and McCaughan [12]	47	2.12	12	10		30	3
Headrick *et al.* [13]	58	0	NR	42		6	
Irshad *et al.* [14]	49	4	14.2	21		23	5
Saito *et al.* [15]	165	0	NR	86	17	59	3
Rena *et al.* [5]	80	2	NR	62	9	24	
Ike *et al.* [3]	42	2.4	NR		16	26	
Watanabe *et al.* [16]	49	0	NR	33		16	
Pfannschmidt *et al.* [17]	167	1.8	NR	99	42	69	5
Vogelsang *et al.* [18]	75	0	3	73		31	
Shiono *et al.* [2]	87	0	NR	43	17	26	1
Shah *et al.* [1]	39	0	0	28		11	
Melloni *et al.* [19]	81	0	9	61		26	1
Lee *et al.* [4]	59	0	5	42	3	14	
Welter *et al.* [20]	169	0	NR	140	59	60	5
Welter *et al.*[a] [21]	33	0	22	48	21	24	2
Watanabe *et al.* [22]	113	0	NR	79		33	
Onaitis *et al.* [23]	323	1	10.6	271	25	77	1
Mongil Poce *et al.* [24]	45	2.2	9.8	37	5	12	
Current study	532	0.4	15.6	927	19	100	4

[a]The author analyses repeated lung metastasectomies.

of in-hospital stay and in the postoperative complication rate; however, some concern still persists among surgeons as an extensive palpation of the lung is hampered.

Some of our results, although negative, deserve some comments. Staplers were used in >90% of cases. We observed no statistically significant differences between groups, according to this factor. The incidence of mediastinal lymph node involvement in PM of CRC ranges from 7 to 30%. So, performance of a hilar and mediastinal lymphadenectomy is recommended for a better classification of the disease. Survival in patients with mediastinal involvement is between 0 and 30% at 5 years [6, 20]. In our series, 254 (48%) patients had some type of lymphadenectomy. It did not have any impact on postoperative complications, and so, we conclude that it can be done safely. Preoperative chemotherapy increases the risk of complications in the surgical treatment of primary LC. Martin *et al.* [25] showed morbidity of 38% and mortality of 2.4% after lobectomy and 11.3% after pneumonectomy. There are no available data about the impact of preoperative chemotherapy before surgery for PM on postoperative complications. A total of 113 (21%) patients in our series received chemotherapy immediately before lung metastasectomy. We did not find an increase in postoperative morbidity.

The present findings should be interpreted taking into account some limitations. This was an observational multicentre study, and the surgical approach was not homogeneous among the participating hospitals. However, we consider that our data on 1050 lung resections performed on 532 patients from 32 hospitals accurately reflect the everyday clinical practice. Also, potential risk factors for postoperative mortality, postoperative technical complications, need of transfusion and reoperation could not be assessed due to the very low rates in each of these categories. Finally, this is a selected group of patients undergoing a first episode of surgery for PM of CRC; therefore, conclusions are limited to this type of patients. However, the present findings may be useful when planning pulmonary resections of further metastatic disease in this setting.

In conclusion, resection of pulmonary metastases is a technique associated with low mortality and morbidity, and can be considered a safe procedure. The lower mortality and morbidity in these patients could be explained mainly by a higher percentage of minor resections compared with other diseases. In our series, cardiovascular co-morbidity and major lung resections have proven to be independent risk factors related to the occurrence of complications.

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