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Running head: Resection of lung metastasis in colorectal cancer

THE ROLE OF LUNG METASTASES RESECTION IN IMPROVING OUTCOME OF COLORECTAL CANCER PATIENTS: RESULTS FROM A LARGE RETROSPECTIVE STUDY.

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Key words: colorectal neoplasms; lung metastases; lung surgery; overall survival

ABSTRACT

Background: The role of surgery of lung metastases (LM) secondary to colorectal cancer remains controversial. The bulk of evidence derives from single surgical series, hampering any definitive conclusion. The aim of this study was to compare the outcome of colorectal cancer patients with LM submitted or not to surgery.

Patients and Methods: Data about 409 patients with LM as first evidence of advanced disease were extracted from a database of 1411 patients. The patients were divided into three groups: G1 comprised patients (n=255) with pulmonary and extra-pulmonary metastases; G2 patients with LM only and not submitted to surgery (n=104); G3 patients with LM only and submitted to surgery (n=50).

Results: No difference in response rates emerged between G1 and G2. Median PFS (95%CI) was: 10.3 (9.4-11.2), 10.5 (9.6-11.4), and 26.2 (10.4-42.0) months for groups G1, G2, and G3, respectively. No difference in PFS was observed between G1 and G2, whereas there was a statistically significant difference between G2 and G3. Median OS was 24.2 (21.5-26.9), 31.5 (28.8-34.2), and 72.4+ (40.7-104.1) months, respectively. Survival was longer in the resected patients: 17 survived for more than 5 years and 3 more than 10 years. In the patients with LM only and not submitted to surgery, 4 survived for 5 years and none longer than 10 years.

Conclusions: Even though patients with resectable LM are more likely to be those with a better outcome, our study provides evidence suggesting an active role of surgery in improving survival in this patient subset.

INTRODUCTION

The clinical outcome of patients with metastatic colorectal cancer (CRC) has improved, with an increase in median overall survival from 8-12 months in the 1990s to currently more than 20 months, along with a not negligible proportion of patients still alive at 5 and 10 years. This improvement in treatment efficacy has been achieved mainly following the clinical use of highly active cytotoxic agents (e.g., irinotecan, oxaliplatin) and, more recently, of molecular targeted therapies (e.g.,cetuximab, panitumumab, and bevacizumab) (1) and through the multidisciplinary management of patients. Resection of liver metastases upfront or after neoadjuvant chemotherapy has been consistently demonstrated to prolong survival (2).

At the time of advanced disease presentation, pulmonary CRC metastases are revealed in approximately 10-15% of the patients (3). The best estimate of isolated lung metastases (i.e. without localization in other organs) lie between 1.7% and 7.4% (4). The management of this latter subgroup of patients is a matter of debate. Surgical resection is a widespread clinical practice. Several studies describing single institution series of resected patients reported 5-year survival rates between 21% and 61.4%, exceeding those normally associated with metastatic colorectal cancer (5-7). This notable difference in 5-year survival rates within surgical studies reflects the quality of evidence for pulmonary metastasectomy that is insufficient to draw definitive conclusions (8). In fact, while some Authors demonstrated stage of the primary tumor, distribution of the metastases, disease free interval, CEA, gender, age, complete resection (R0), number of lung metastases, and vascular and lymphatic invasion to be variables influencing 5-year survival rate, others reported opposite findings (9). Moreover, inclusion criteria guidelines for lung metastasectomy published by several institutions lie on the experience of the single institution (10-12). Despite these discrepancies, the reported outcomes are widely held to corroborate the benefit gained from lung surgery when compared to historical series. To solve the debate, a phase III prospective randomized clinical trial designed to compare patients with lung metastases to be allocated to “active monitoring” or “active monitoring with pulmonary metastasectomy” has been advocated (13).

To our knowledge, there is no study which compared the outcome in CRC patients with lung metastases, surgically resected or not, followed and treated at the same institutions and in the same timeframe. In this retrospective study we searched the databases of three institutions and extracted the data on patients consecutively followed and treated from the time of first appearance of metastatic disease. We then compared their outcomes according to whether they were submitted or not to lung metastasectomy.

PATIENTS AND METHODS

Patients

Clinical databases of three institutions (University of Torino, Oncology Unit, San Luigi di Orbassano Hospital; University of Torino [center 1]; Institute for Cancer Research and Treatment [IRCC] Candiolo [center 2]; and University of Eastern Piedmont, Maggiore della Carità Hospital, Novara [center 3]) were retrospectively investigated. In these databases the clinical characteristics and outcomes of all metastatic CRC patients followed and treated from the time of first diagnosis of metastatic disease have been recorded since 1993. The data from patients with pulmonary metastases diagnosed between January 1st 1994 and June 30th 2010 were then extracted and entered into a new database generated for the purpose of this study. The database included: patient demographics; primary tumor characteristics; prognostic and predictive factors (e.g., disease-free interval); carcinoembryonic antigen, lactate dehydrogenase and alkaline phosphatase level at baseline (pre-chemotherapy or pre-thoracotomy); number and distribution of lung metastases; date of surgical intervention; chemotherapy history; date of first progression; and date of death or last follow-up visit. When exceeding 25 the number of lung metastases was put into the database with the absolute value of 30 and described in the results as “>25”.

Three subgroups of patients were identified : group 1 (G1) including patients with at least one organ involved other than the lung; group 2 (G2) including patients with lung metastases as the sole site of advanced disease and not submitted to lung surgery; group 3 (G3) patients with lung metastases as the sole site of advanced disease and submitted to lung surgery (Figure 1).

Outcome evaluation

Response evaluation was performed under the standard assessment criteria used at each institution for the considered timeframe. Up to 2001, treatment response was classified according to International Union Against Cancer (UICC) criteria (14), wherein complete response was defined as the complete disappearance of all clinically detectable malignant disease, partial response as a decrease ≥50% in the sum of the products of the two longest perpendicular diameters of all measurable lesions, and progressive disease as an increase of at least 25% in the size of measurable lesions and the development of new lesions. After 2001, centers were invited to classify responses according to the RECIST criteria (15), wherein response was defined as a decrease >30% in the sum of the longest diameters of target lesions, and a progressive disease as an increase >20% of this sum. Only the best tumor response was recorded.

Progression-free survival and overall survival were estimated from first-line treatment onset till progression or death from any cause or date of the last follow-up. The cut-off date for the collection of data was January 31st, 2011. Patients not progressing or alive or lost to follow-up at the time of the cut-off date were censored at the time of the last follow-up examination.

Surgical criteria

All patients with lung metastases were considered for lung resection at two thoracic surgery centers, one located at University of Torino, San Luigi Gonzaga Hospital (also referral center for the Oncology Unit at IRCC Candiolo) and the second one at University of Eastern Piedmont, Maggiore della Carità Hospital, Novara. While each institution evaluated patient eligibility for lung resection

according to its own internal diagnostic work up procedures and by a multidisciplinary team which included the thoracic surgeon, the mandatory criteria requested for the inclusion in this retrospective study were: resection with curative intent and with a predicted adequate residual pulmonary reserve after surgery in the absence of unresectable non-pulmonary localization. Surgery was performed upfront when resectability criteria were met. A surgical re-evaluation was planned in case of tumor response or stabilization after chemotherapy.

Statistical analyses

Differences between proportions were evaluated using the chi-square test with Yates correction, when necessary. Differences between groups of non parametric unpaired variables were validated by the Mann-Whitney U test when comparing two groups or the Kruskal-Wallis Analysis of Variance when analyzing multiple groups. Logistic regression analysis was performed to eliminate confounding parameters when examining dichotomous variables. Survival curves were plotted using the Kaplan-Meier method and validated using the log-rank test. Multivariate survival analysis was performed according to the Cox proportional-hazards model. All statistical computations were performed using SPSS for Windows Ver 16.0 and STATISTICA for Windows Ver. 6.0 software.

RESULTS

Patient characteristics

Data from 1411 CRC patients (Table 1) were retrospectively considered, 409 of which presented with lung metastases and composed the primary dataset for the present analyses. Patients were grouped as follows: G1 composed of patients with lung and extra-pulmonary metastases (n= 255); G2 composed of patients with the lung as the sole metastatic site and not submitted to lung resection (n=104); G3 included patients submitted to resection (n=50) (Figure 1). Surgery was performed after neoadjuvant chemotherapy in 19 out of 50 patients. Table 2 summarizes the characteristics of the 409 patients included in the study.

The three groups were comparable for gender, Eastern Cooperative Oncology Group (ECOG) performance status, and circulating serum prognostic factors such as lactate dehydrogenase (LDH), carcinoembrionic antigen (CEA) and alkaline phosphatase (ALP). There was an expectedly higher proportion of colon cancers in group 1 than in the other two groups but no difference was observed between G2 and G3. Patient age and tumor stage at diagnosis were fairly similar in G1 and G2. The median age was significantly lower in G3 than in group 2 (60.8 and 65.9 years, respectively; p <0.004) and there was a higher proportion of metachronous tumors in G3 than in G2 (88% and 56.7%, respectively; X^2 p <0.0001). Median disease free interval was higher in G3 than in G2 and G1 (23.7, 5, and 0.5 months, respectively. ANOVA p<0.001).

Chemotherapy and lung surgery

A total of 371/409 (98.1%) patients received chemotherapy as first-line treatment; 7/409 were not treated because of poor performance status (n=2), concomitant invalidating diseases (n=2), and unknown reasons (n=3). Thirty-one patients in G3 received lung surgery upfront and were not subsequently evaluable for chemotherapy response. The choice about systemic chemotherapy was left to each investigator center discretion. The majority of patients (262/371, 70.6%) received an oxaliplatin-containing doublet, 51/371 (13.8%) received an irinotecan-based chemotherapy, and 56 (15.1%) a fluoropyrimidine-based chemotherapy. Two patients received a triplet. Nineteen patients in G2 (18.5%) received a single agent fluoropyrimidine chemotherapy as they were considered unfit (older patients or those with other comorbidities), and one patient in G3 received a triplet. No more difference in the type of chemotherapy administered between G2 and G3 was found (Table 2). The overall response rate was 38.0% (141/371 patients): 36.1% (90/249) in G1; 35.9% (37/103) in G2; and 73.7% (14/19) in G3, respectively. There was no difference between the three groups. All 31 patients submitted to pulmonary resection upfront received chemotherapy within 2 months of surgery. Most received 12 cycles of FOLFOX; only 3 received 12 courses of FOLFIRI.

The median number of lung metastases (range) was 5 (1->25), 5 (1-15), and 1 (1-6) in G1, G2, and G3, respectively (ANOVA p<0.001). A higher proportion of unilateral distribution was recorded in G3 (64%) than in G2 (37.5%) or in G1 (37.6%) (X^2 p=0.01). Resection was performed in 50/154 (32.5%) patients (31 upfront and 19 after neoadjuvant chemotherapy) with only metastatic lung disease. Reasons for surgery delay were: primary tumor not deemed controlled in 12 patients, and complete resection not considered technically possible in 7 patients. Wedge resection was performed in 34 (68%) patients, lobectomy in 10 (20%), segmentectomy in 5 (10%), and bilobectomy in 1 patient (2%). No postoperative mortality or major complications were reported. Resection was complete (R0) in 49/50 patients. In only one patient residual tumor was microscopically documented in the surgical margins. One other patient underwent a second complete lung resection 1 month after the first surgical treatment.

Twenty-one patients in G2 who present resectable disease, surgery was not performed due to lung disease or other health conditions (mainly poor lung function reserve or cardiac disease). Eight patients in G1 with liver and lung metastases were submitted to liver and then to lung resection.

The proportion of patients submitted to lung resection was higher in those centers with in house thoracic surgery facilities: 21/53 (39.6%) in center 1; 15/32 (46.9%) in center 3; 14/69 (20.3%) in center 2 (center 1 vs. center 2, X^2 p=0.01). However, there was no difference between centers in the proportion of patients with 6 or less lung metastases (the upper range of G3) not submitted to surgery (i.e. patients in G2), nor in their distribution (ANOVA p>0.5 for both analyses).

Clinical outcomes

At the time of data computation (January 31st 2011), 334/409 (81.7%) patients had progressed. The median progression-free survival of the entire population was 11.3 months. Figure 2 reports the progression-free survival curves for each group. The median duration of progression-free survival (95%CI) was 10.3 (9.4-11.2) months in G1, 10.5 (9.6-11.4) months in G2, and 26.2 (10.4-42)

months in G3 (p <0.001). While the duration of progression-free survival was similar for the patients with lung metastases as the sole site of disease not submitted to resection (G2) and those with lung and extra-pulmonary metastases (G1) (10.5 vs. 10.3 months; p=ns; HR 1.09, 95%CI 0.96-1.22), it was longer in the resected patients (G3) than in those with the lung as the sole metastatic site and not submitted to surgery (G2) (26.2 vs. 10.5 months; p <0.0001; HR 0.24, 95%CI 0.01-0.47). In the 19 patients who had received neo-adjuvant chemotherapy before surgery, the median duration of progression-free survival was 26.4 months, comparable to that of the patients undergoing upfront surgery (26.2 months).

At the cut-off date of data collection (January 31st 2011), the overall median survival of the entire population was 29.4 months. Figure 3 reports the Kaplan-Meier estimated curves for each group. The median duration of overall survival (95%CI) was: 24.2 (21.5-26.9) months (G1); 31.5 (28.8-34.2) months (G2); and 72.4+ (40.7-104.1) months (G3), respectively (p <0.001). Survival was longer in those patients with the lung as the sole metastatic site as compared to those with pulmonary and extra-pulmonary metastatic sites (31.5 vs. 24.2 months; p <0.03, HR 0.76, 95%CI 0.62-0.90). Patients who had undergone surgical resection of pulmonary metastases (G3) survived strikingly longer than those who had not (G2) (72.4+ vs. 31.5 months; p<0.0001; HR 0.17, 95%CI 0.01-0.33). No statistically validated difference in overall survival emerged between patients submitted or not to neoadjuvant chemotherapy (70.1+ vs 72.4+ months; p=0.9).

At the cut-off date of data collection, 14/50 resected patients (G3) (28%) had died. The remaining 36 patients still alive were followed for a median of 41.3 months (range, 4.0-134.1). Seventeen (34%) were alive for more than 5 years (five of them without sign of disease) and 3 (6%) for more than 10 years (two disease-free) after diagnosis of advanced CRC, whereas only 4 (4.8%) of those patients in group 2 (patients with lung metastases not submitted to resection) were alive after 5 years (all with progressive disease).

Multivariate analyses

Logistic regression analysis for surgery (value=1) vs no surgery (value=0) stratified for center confirmed age (HR; 95%CI: 0.96; 0.94-0.98), disease free interval (1.03; 1.02-1.04), ECOG performance status (0.54; 0.17-0.91), and the number of lung metastases (0.70; 0.62-0.70) as independent factors. Date of surgery, gender, tumor grade, CEA, LDH, ALP, distribution of lung metastases, and site of the primary did not enter the model.

In order to eliminate confounding variables, multivariate Cox analyses for predictors of progression-free survival and overall survival were performed in the entire population of 1411 patients with metastatic disease (Table 3 and 4).

Rectal localization, disease-free interval (as a continuous variable), hemoglobin level >12 g/dl, ECOG performance status, and surgery of liver and lung metastases were found to be independent factors for progression-free survival (Table 3). Age, treatment center, tumor stage at diagnosis, grading, gender, and number of metastatic sites did not enter the model.

Disease-free interval (as a continuous variable), the presence of liver metastases, hemoglobin level >12 g/dl, number of metastatic sites, and surgery of liver and lung metastases were found to be independent factors of overall survival (Table 4). Age, treatment center, tumor stage at diagnosis, grading, gender, ECOG performance status, and rectal localization did not enter the model.

DISCUSSION

In this large retrospective study in metastatic CRC patients we observed a remarkably longer duration of progression-free survival and overall survival in patients submitted to resection with radical intent of their pulmonary metastases compared to those who received chemotherapy alone. This is the first study to compare outcomes in the same series of patients and not against historical reports.

The incidence of synchronous lung metastases was higher in our study population than that previously reported (16): 29% of patients presented synchronous lung metastases and 10.9% had only lung localizations. This may be explained in part by the fact that the staging procedure

included thoracic computed tomography (CT), which has been demonstrated to be more sensitive than conventional X-ray (17). Nearly one third of the patients (50/154) with the lung as the sole metastatic site underwent surgery. This number does not include the 8 patients submitted to liver and subsequently to pulmonary resection, as they were included in G1 (patients with lung and extra-pulmonary metastases) in an intention to treat analysis.

Not surprisingly, patients submitted to surgery were, on average, younger. The incidence of chronic lung diseases such as chronic obstructive pulmonary disease increases with age. As a consequence of these chronic comorbilities, older subjects more frequently have poor lung function reserve and are ineligible for surgery, as it was the case for 21 patients in this study. This might represent a selection bias, as younger patients are assumed to have a longer duration of survival, even if other series have not shown this difference (18), or even reported an opposite pattern (19).

Quite unexpectedly, a higher number of tumors with metachronous lung metastases was observed in the resected subgroup. Synchronous metastases of CRC are considered to carry a worse prognostic value compared with metachronous metastases, but there are few and conflicting reported data. A large retrospective study from the CAIRO study of the Dutch Colorectal Cancer Group (DCCG) concluded that, despite unfavorable clinical-pathological features in patients with synchronous metastases, no difference in the median duration of overall survival was observed (20). A possible explanation could be the relative chemoresistance of metachronous metastases due to adjuvant treatments. In our study, 31/42 (73.8%) patients in G3 and 34/59 (57.6%) patients in G2 received adjuvant chemotherapy. Although not statistically validated, this difference is worth of consideration.

As demonstrated by the logistic regression analysis, age, disease free interval and the number of metastases are the variables that drove surgeons through the decision process. Even though discrepant results have been reported in literature on the possible prognostic role of these three variables, it is reasonable to think that resected patients were those destined to have *per se* a longer

survival as they were younger, presented with a longer disease free interval and a lower number of lung metastases than those not submitted to surgery.

One open question concerns whether the strikingly longer survival of patients submitted to lung resection is due to the beneficial effect of surgery itself or to the selection bias above described (21, 22). There is a large body of literature reporting survival benefits gained from lung resection (5-7, 18-22). However, a sort of citation cascade of the same few studies reporting these survival benefits excluding those with negative results might have resulted in an unfounded "authority of claim" as recently demonstrated by Fiorentino et al. (8). Optimally this question could be definitively answered by a phase III trial (13). However, if it could be indirectly demonstrated that surgery is effectively beneficial in curing patients or at least prolonging survival, such a comparative trial would have lower priority from a medical oncology point of view; such was the case for surgery for the treatment of liver metastasis.

Our data confirm a better outcome in those patients submitted to surgery than in those treated with chemotherapy alone in the same institutions and during the same period of time. In the resected subgroup, 17 patients are alive after more than 5 years and 3 more than 10 years after the diagnosis of advanced cancer, whereas only 4 of those in G2 are alive after 5 years. Interestingly, of the 8 patients in G1 submitted to liver and subsequently lung resection, the duration of survival was 5 years in 2 patients and 10 years in 1 patient.

Several published studies have discussed the importance of finding surrogate end points as outcome indicators. Response rate and progression-free survival after first-line treatment have been proposed and validated in CRC patients (23-25) as their evaluation allows a reliable quantitative estimate of the efficacy of new drugs or new techniques with a lower degree of potential bias. In our retrospective study, patients were treated with chemotherapy (G1 and 2) or with surgery. Response to first-line treatment was similar in G1 and G2 (36.1 and 35.9%, respectively). Determining treatment response in G3 patients was difficult because 31 patients received surgery before chemotherapy: if we take into account only the 19 patients who received chemotherapy before

surgery, the response rate was 73.7%; if we consider, however, surgery as an active first-line treatment, the response rate of the whole group was 98%, as residual tumor after surgery (R1) was evident in only 1 patient. Patients submitted to surgery presented a median duration of progression-free survival of 26.2 months, more than twice that recorded in those not resected (10.5 months). Interestingly, the duration of progression-free survival was similar for G1 and G2 (10.3 months). At multivariate analyses of the complete patient dataset of 1411 subjects, liver and lung surgery emerged as independent factors for both progression-free and overall survival. These findings further suggest that surgery is a more active treatment than chemotherapy alone.

In conclusion, the results of our retrospective study provide evidence suggesting that surgery is a more active treatment than chemotherapy alone when performed as first-line treatment. Although resectable patients are probably those destined to have a more indolent form of the disease as they have theoretically favorable prognostic factors, surgery can further improve their outcome. In our study we recorded 10-year survivors only in G3 and G1 (1 patient submitted to liver and then lung resection), but not in G2 in which some potentially resectable patients might have been included. Moreover, resected patients had a longer duration of progression-free survival, a validate surrogate end-point for clinical outcome. From a statistical point of view, our findings are insufficient to definitively solve the question of whether surgery is beneficial in resectable patients as this can be demonstrated only with a prospective randomized phase III trial. From a medical oncology point of view, however, our results add evidence to the debate whether such a study is still necessary.

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TABLE 1. Patient characteristics of the entire database of subjects followed and treated from the time of the first appearance of metastatic disease at three different institutions.

		(%)
No. of patients	**1411**	
Oncology centers		
San Luigi, Orbassano	601	42.6
IRCC Candiolo	540	38.3
Novara	270	19.1
Median age (yrs)	63.2	
(range)	(26.8-87.4)	
Gender		
Male	848	60.1
Female	563	39.9
Site of primary tumor		
Colon	1040	73.7
Rectum	371	26.3
Stage at diagnosis		
A	6	0.4
B	182	12.9
C	389	27.6
D	834	59.1
ECOG performance status at chemotherapy onset		
0-1	887	62.9
2	56	4.0
3	9	0.6
unknown	459	32.5
Adjuvant Chemotherapy		
Stage B	94/182	51.6
Stage C	297/389	76.3
Distant Metastases		
No. of sites		
1 site	1073	76.0
>1 site	338	24.0
Sites involved		
Liver	975	69.1
Lung	409	29.0
Abdomen	318	22.5
Surgery of metastases		

Liver	286	20.3
Lung	58	4.1

TABLE 2. Patient characteristics of the subjects enrolled into this study. Data are summarized as overall, group 1 (patients with lung and extra-pulmonary metastases), group 2 (patients with the lung as the only site of metastases not submitted to surgery), and group 3 (patients with the lung as the only site of metastases submitted to surgery). Data are expressed as number of patients (%).

No. of patients	**Overall** **409**	**Group 1** **255**	**Group 2** **104**	**Group 3** **50**
Centers				
San Luigi, Orbassano	158 (38.6)	105 (41.2)	32 (30.8)	21 (42)
IRCC Candiolo	148 (36.2)	79 (31.0)	55 (52.9)	14 (28)
Novara	103 (25.2)	71 (27.8)	17 (16.3)	15 (30)
Median age (yrs) (range)	64.3 (26.8-87.4)	63.9 (31.1-87.4)	65.9 (36.1-77.6)	60.8 (26.8-86.5)
Gender:				
Male	241 (58.9)	147 (57.6)	62 (59.6)	32 (64)
Female	168 (41.1)	108 (42.4)	42 (40.4)	18 (36)
Site of primary tumor				
Colon	265 (64.8)	176 (69)	60 (57.7)	29 (58)
Rectum	144 (35.2)	79 (31)	44 (42.3)	21 (42)
Stage at diagnosis				
A	3 (0.7)	1 (0.3)	0 (0)	2 (4)
B	58 (14.2)	26 (10.2)	17 (16.3)	15 (30)
C	138 (33.7)	69 (27.1)	42 (40.4)	27 (54)
D	210 (51.4)	159 (62.4)	45 (43.3)	6 (12)
Adjuvant Chemotherapy				
Stage B	31/58 (53.4)	12/26 (46.2)	8/17 (47.1)	11/15 (73.3)
Stage C	94/138 (68.1)	48/69 (70.0)	26/42 (61.9)	20/27 (74.1)
Disease free interval median (5°-95° percentile)				
Months	1.37 (0-58.5)	0.5 (0-45.4)	5 (0-76.4)	23.7 (0-118.8)
ECOG performance status at therapy onset				
0-1	314 (76.8)	195 (76.4)	77 (74)	42 (84)
2	18 (4.4)	16 (6.3)	1 (1)	1 (2)
3	2 (0.5)	1 (0.4)	1 (1)	0 (0)
Unknown	75 (18.3)	43 (16.9)	25 (24)	7 (14)
First-line chemotherapy				
Doublet with oxaliplatin	262/371 (70.6)	181/249 (72.7)	68/103 (66.0)	13/19 (68.4)
Doublet with Irinotecan-	51/371 (13.8)	30/249 (12.0)	16/103 (15.5)	5/19 (26.3)

Triplet	2/371 (0.5)	1/249 (0.4)	0/103 (0)	1/19 (5.3)
5FU-based	56/371 (15.1)	37/249 (14.9)	19/103 (18.5)	0/19 (0)
Clinical parameters at therapy onset[$]				
LDH >240 U/L	175/235 (74.5)	122/156 (78.2)	29/44 (65.9)	24/35 (68.6)
CEA >5 ng/ml	165/251 (65.7)	130/168 (77.4)	22/48 (45.8)	13/35 (37.1)
ALP >120 U/L	140/236 (59.3)	110/156 (70.5)	15/45 (33.3)	15/35 (42.9)
Distant metastases				
No. of sites				
1 site	154 (37.7)	-	-	-
>1 site	255 (62.3)	-	-	-
Sites				
Liver	227 (55.5)	227 (89)	-	-
Lung	409 (100)	255 (100)	-	-
Abdomen	68 (16.6)	68 (26.7)	-	-
No. of lung metastases				
Median (range)	4 (1->25)	5 (1->25)	5 (1-15)	1 (1-6)
Distribution of lung met				
Unilateral	167 (40.8)	96 (37.6)	39 (37.5)	32 (64.0)
Bilateral	226 (55.3)	145 (56.9)	63 (60.6)	18 (36.0)
Unknown	16 (3.9)	14 (5.5)	2 (1.9)	0

[$]Only for centers 1 and 3. LDH: lactate dehydrogenase (abnormal values >240 units/L); CEA: carcinoembryonic antigen (abnormal values >5 ng/mL); ALP: alkaline phosphatase (abnormal values >120 units/L).

TABLE 3. Multivariate Cox proportional-hazards analyses of predictive factors in 1411 patients with colorectal cancer followed from the time of first appearance of metastatic disease. Progression-free survival.

Variable		**HR**	**95% CI**	**P value**
Rectal cancer		0.85	0.78-0.92	0.01
Disease-free interval*		0.99	0.98-1.00	0.01
Hemoglobin >12 g/dl		0.70	0.61-0.79	<0.001
ECOG performance status		1.01	1.00-1.02	0.05
Liver surgery		0.47	0.39-0.55	<0.0001
Lung surgery		0.46	0.31-0.57	<0.0001
CEA >5 ng/ml		1.48	1.37-1.59	<0.001
CA 19-9 >37 U/l		1.22	1.12-1.32	0.03

*Continuous variable.

Age, center, tumor stage at diagnosis, grading, gender, number of metastatic sites, number of lung metastases, LDH and ALP levels, and the presence of liver metastases did not enter the model.

TABLE 4. Multivariate Cox proportional-hazards analyses of predictive factors in 1411 patients with colorectal cancer followed from the time of first appearance of metastatic disease. Overall survival.

Variable		**HR**	**95% CI**	**P value**
Liver metastases		1.42	1.33-1.51	<0.0001
Hemoglobin >12 g/dl		0.72	0.62-0.82	<0.001
ECOG performance status		1.01	1.00-1.02	0.10
Liver surgery		0.26	0.16-0.36	<0.0001
Lung surgery		0.26	0.06-0.46	<0.0001
CEA >5 mg/ml		1.49	1.36-1.62	<0.001
CA 19-9 >37 U/l		1.44	1.33-1.55	<0.001

Age, center, tumor stage at diagnosis, grading, gender, number of metastatic sites, disease-free interval, LDH and ALP levels, and rectal cancer did not enter the model

Figure Legend

Figure 1. CONSORT diagram of the study.

Figure 2. Kaplan-Meier estimate curves for progression-free survival according to patient subgroup (see text). A statistically significant longer survival was evident only in patients with lung metastases submitted to surgery (group 3).

Figure 3. Kaplan-Meier estimate curves for overall survival according to patient subgroup (see text) . Differences were evident and validated between each group.

Figure 1.

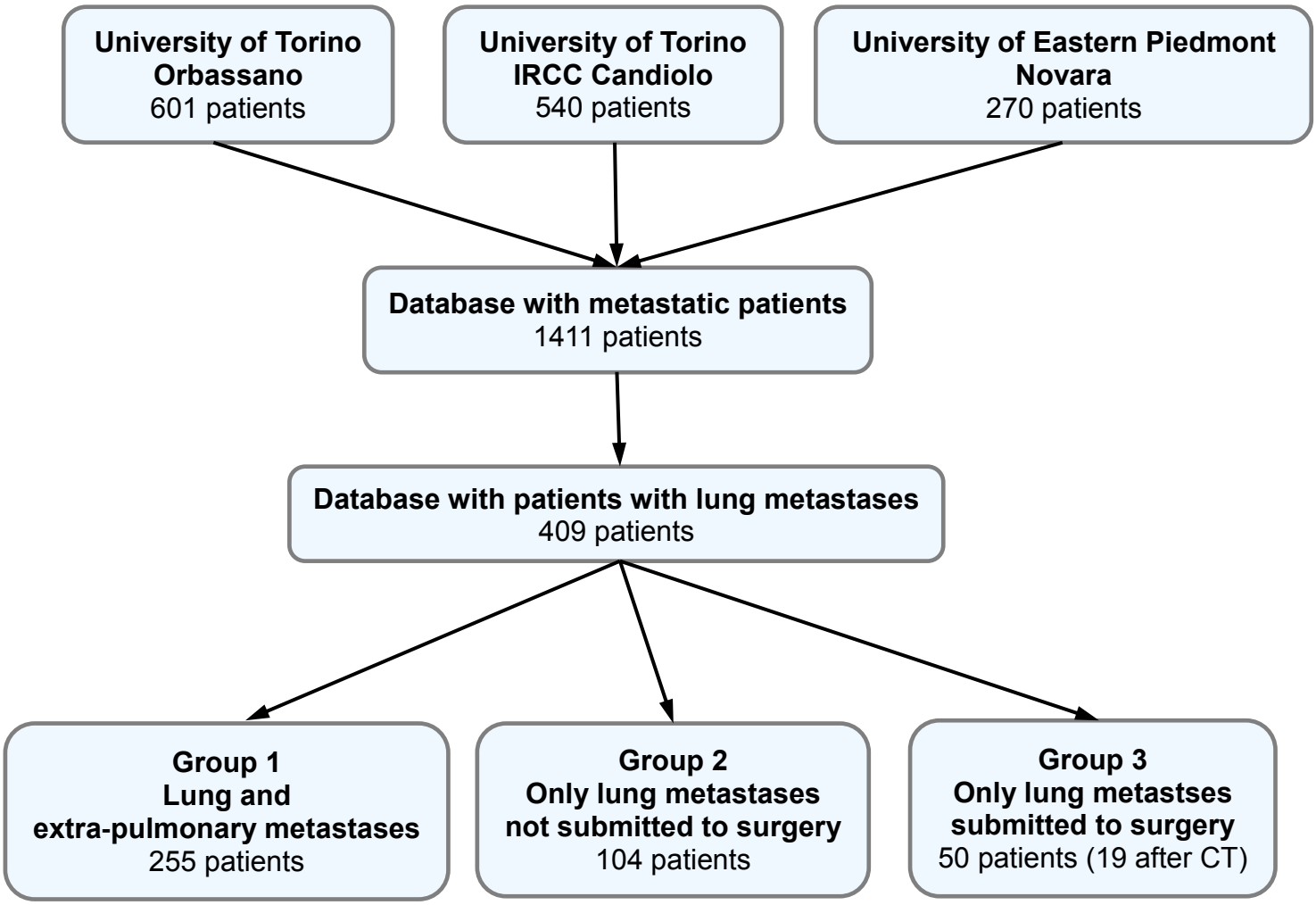
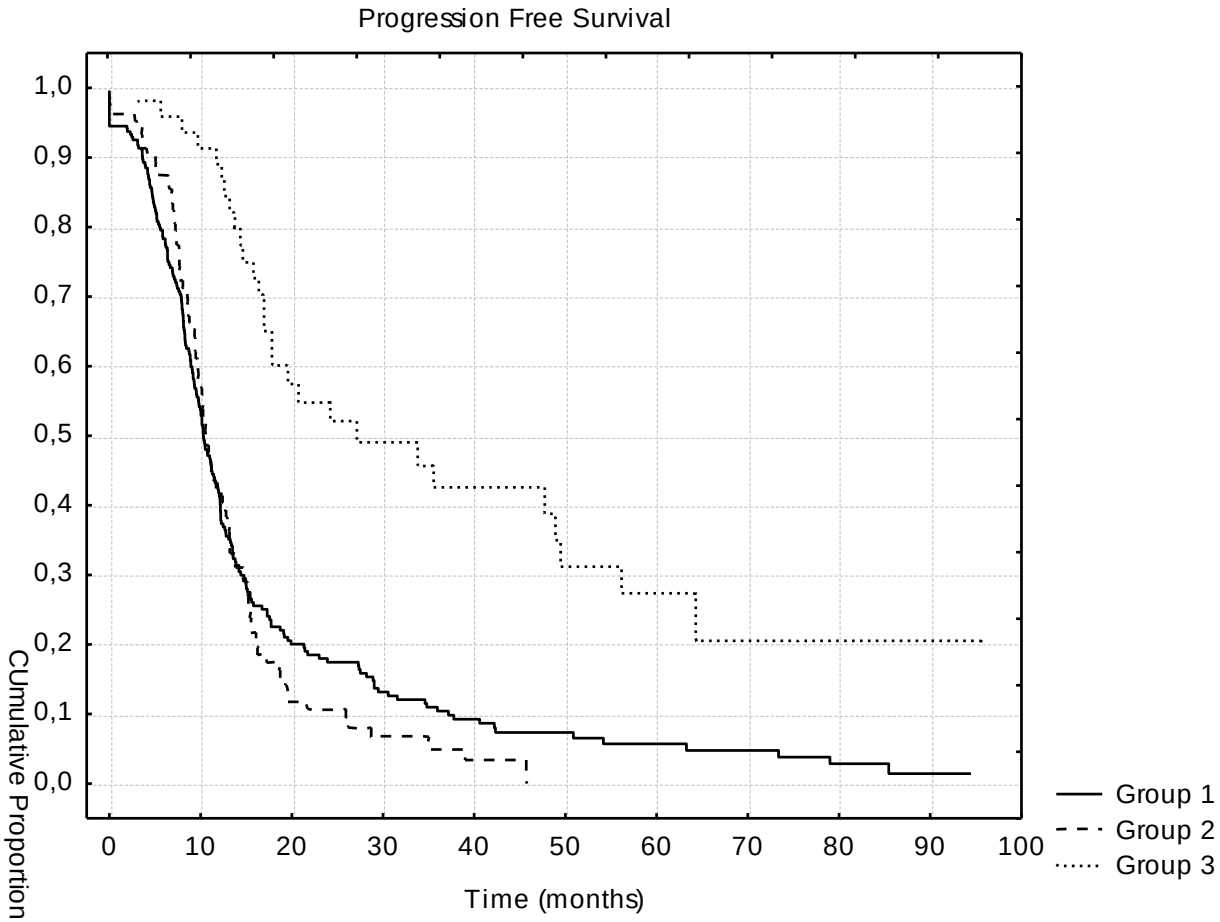

University of Torino
Orbassano
601 patients
University of Torino
IRCC Candiolo
540 patients
University of Eastern Piedmont
Novara
270 patients
Database with metastatic patients
1411 patients
Database with patients with lung metastases
409 patients
Group 1
Lung and
extra-pulmonary metastases
255 patients
Group 2
Only lung metastases
not submitted to surgery
104 patients
Group 3
Only lung metastses
submitted to surgery
50 patients (19 after CT)

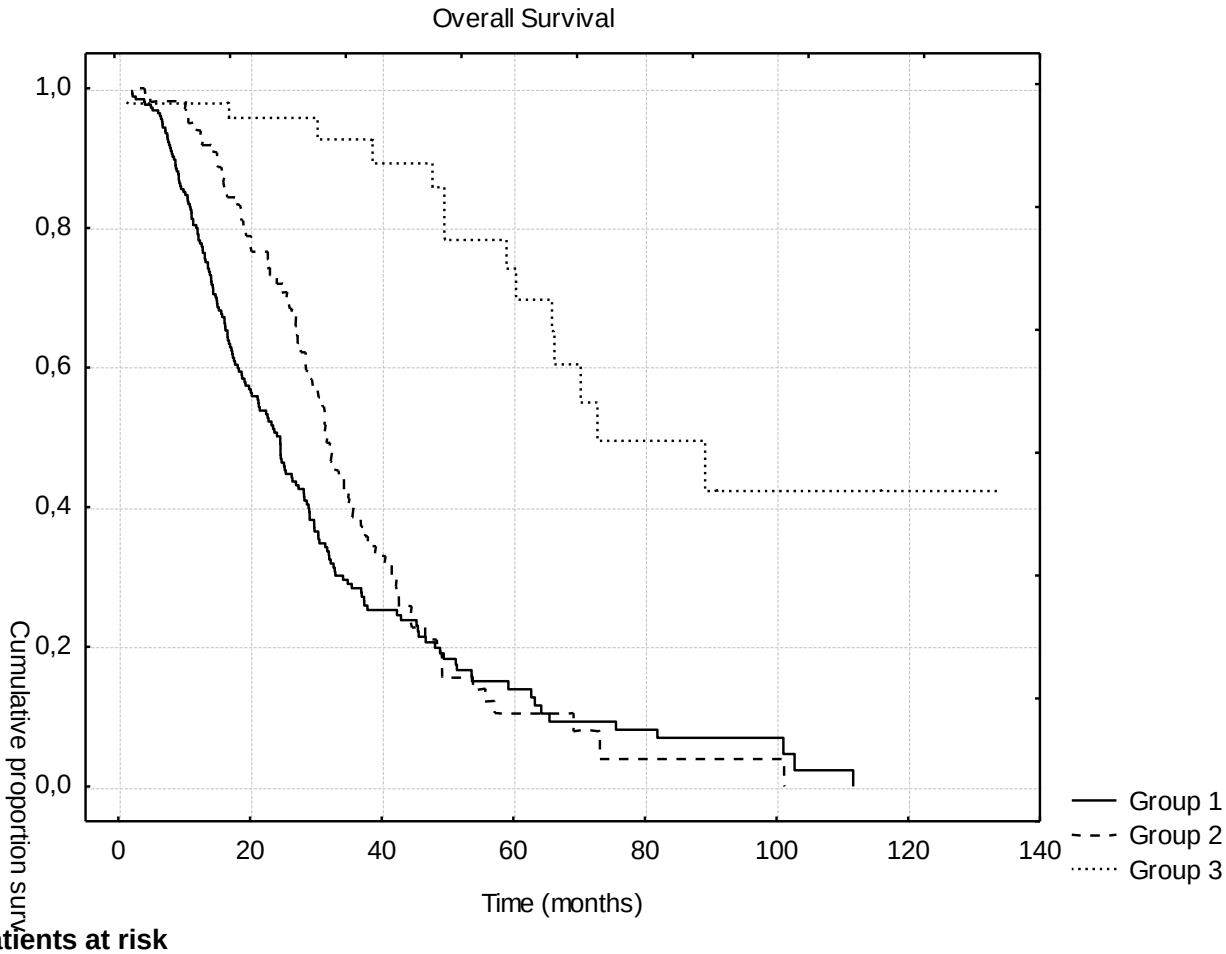
Figure 2.



Patients at risk

Group 1	255	122	40	24	16	9	6	5	3	1
Group 2	104	55	11	5	2	0	0	0	0	0
Group 3	50	40	22	18	13	8	5	3	2	1

Figure 3.



Patients at risk

Group 1	255	112	36	12	7	3	1
Group 2	104	71	23	4	1	1	0
Group 3	50	37	18	17	7	3	3