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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Baseline and Postoperative C-reactive Protein Levels Predict Long-Term Survival After Lung Metastasectomy

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ABSTRACT

Background. Blood level of C-reactive protein (CRP) at diagnosis is a well-know prognostic bio-marker in different primary tumors, but its role has not been investigated in resectable lung metastases. The aim of our study is to assess the predictive value of baseline (CRP0) and 3rd postoperative day (CRP3) levels on long-term survival of patients undergoing lung metastasectomy.

Methods. A total of 846 consecutive patients underwent the first pulmonary resection for lung metastases between January 2003 and December 2015, including 611 (72%) single surgical procedures, 235 (28%) multiple metastasectomies, 501 (59%) epithelial primary tumors, 276 (33%) sarcomas, 66 (8%) melanomas, 286 (33.8%) with 0 risk factors (CRP0 $\leq$ 2 and CRP3 $\leq$ 84 mg/L) and 560 (66.2%) with $\geq$ 1 risk factor ($CRP_0 > 2$ and/or $CRP_3 >$ 84 mg/L).

Results. Cumulative 5-year survival was 57% in patients with low CRP (0 risk factors) versus 43% in high CRP ($\geq$ 1 risk factor, $p < 0.0002$), 62% versus 50% respectively for epithelial tumors ($p < 0.0140$), and 51% versus 34% for sarcomas ($p < 0.0111$). Multivariable Cox analysis confirmed a mortality hazard ratio of 2.5 at 1-year and 1.5 at 5-years in patients with high CRP.

Conclusions. Baseline and postoperative CRP levels predict survival of patients with resectable lung metastases. These data provide a rationale for prospective clinical trials testing the efficacy of anti-inflammatory or immune-modulating agents as "adjuvant" therapy after lung metastasectomy, in patients with elevated pre- and/or postoperative CRP levels.

Metastatic disease is the major cause of cancer death, and chemotherapy still has limited success in blocking tumor progression. The lung is the most common site of metastases in sarcomas and, after the liver, the second one in epithelial tumors.[1] Only 2–3% of patients with pulmonary metastases from colorectal cancer are eligible for surgical resection with curative intent.[2]. Nonetheless, metastasectomy is a frequent thoracic surgical procedures and represents 15% to 50% of the workload in European thoracic surgical departments.[1]

In the early 1970s, curative potential of pulmonary metastasectomy was investigated in childhood osteosarcoma, and the benefit was confirmed by repeated and systematic use as salvage surgery in this disease.[3–5] The favourable outcome of metastasectomy also was reported

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from selected clinical series, including multiple primary tumor.[6] The landmark publication was the 1997 report from the International Registry of Lung Metastasectomy (IRLM), which included 5,206 patients from Europe and North America.[7] For the first time, this study demonstrated that lung metastasectomy could achieve 10- to 15-year survival and established a prognostic system based on resectability, disease-free interval, and number of metastases, which has been adopted worldwide to predict the outcome and potential cure rate in each primary tumor type.

During the past 20 years, a variety of blood markers have been tested to refine cancer patient selection and monitor postoperative course (i.e., CEA, CYFRA-21, PSA, CA19-9, and CA15-3, but a strong clinical efficacy has emerged only for alpha-feto protein (AFP) and beta chorionic human gonadotropin (bHCG) in germ cell tumors).[8]

Given the well-documented association between cancer and inflammation, the search of ease-to-use tumor markers related to immune-status also was intriguing.[9–11] Blood level of C-reactive protein (CRP) at diagnosis is a well know prognostic biomarker in different tumors as well as in chronic obstructive pulmonary disease (COPD).[12–14] In operable lung cancer, we have demonstrated that increased levels of pre- and postoperative (3 days after surgery) CRP are associated with significantly higher postoperative 30-day mortality and poorer 5-year survival.[15]

Prognostic role CRP levels has been scarcely evaluated in lung metastases, and no studies have investigated the predictive value of baseline or postoperative CRP levels in resectable lung metastases.[16] The purpose of the present study was to address this issue in a large unselected series of patients undergoing lung metastasectomy.

METHODS

Study Population

The cohort consisted of all patients with lung metastasis who underwent a single or multiple metastasectomies at the Thoracic Surgery Division of the National Cancer Institute of Milan, from January 2003 to December 2015. Patients with germ cell tumors were excluded. Surgery was performed in most cases through a minimal, lateral muscle-sparing thoracotomy, followed by one or more sublobar lung resections, such as precision and wedge resections. Anatomical segmentectomies, lobectomies, and pneumonectomies were less frequently applied, for large size or centrally located lesions. For patients undergoing more than one surgical procedure, only the first procedure has been evaluated. All metastases were completely resected in all cases.

Data Collection and Follow-Up

Gender, age, other clinical information, and CRP_0 were recorded at baseline (lung resection date). In addition, CRP was evaluated 3 days after metastasectomy (CRP_3), as well as the maximum value observed in the postoperative course (CRP_{max}). CRP was quantified by immunoturbidimetry using a Roche automated clinical chemistry analyzer (Roche Diagnostics, Belleville, NJ) from the same laboratory through the entire study period. Of 894 first resections, we excluded 48 (5%) patients with germ cell tumors. Patients were followed-up from surgery date until the occurrence of death or the end of September 2016, whichever came first.

Statistical Analysis

Descriptive statistical analysis was performed on patients with a single metastasectomy or multiple metastasectomies to exclude major demographic and clinical differences. The two groups were then combined in subsequent analyses.

Patients were classified in two mutually exclusive groups based on CRP values at baseline (CRP_0) and 3 days after resection (CRP_3). In particular, patients with CRP_0 and CRP_3 below the median value (2 and 84, respectively), considered the reference group (0 risk factors), were contrasted with patients with at least CRP_0 and/or CRP_3 above the median value ($\geq$ 1 risk factor, 2/1 respectively). The choice of third postoperative day was determined by prior analyses on primary lung cancer.[15]

The cumulative risk of overall survival at 5 years was estimated using the Kaplan–Meier method. Stratified analyses were made for primary tumor site (epithelial tumors and sarcomas). Time-to event comparisons were made using log-rank test.[17] The effect of potential predictors on 1 and 5 years survival was estimated by Cox proportional hazards models adjusted for age, gender, and tumor groups. All analyses were performed using the Statistical Analysis System Software (version 9·4; SAS Institute, Cary, NC). Statistical significance was set at the 0.05 level. All p values were two-sided.

RESULTS

Patient Characteristics

We identified 846 patients who underwent the first pulmonary resection for lung metastases between January

TABLE 1 Demographic and clinical characteristics of study patients by number of resections

	Overall cohort (N = 846)	Single metastasectomy (N = 611)	Multiple metastasectomies (N = 235)
Age			
Mean (SD)	57.2 (13.7)	58.6 (13.7)	55.3 (18.2)
Gender			
Female	392 (46.3%)	281 (71.1%)	111 (28.3%)
Male	454 (53.7%)	330 (72.2%)	124 (27.3%)
Tumor group—No. (%)			
Epithelial	501 (59.4%)	361 (72.1%)	140 (27.9%)
Sarcoma	276 (32.7%)	189 (68.5%)	87 (31.5%)
Melanoma	66 (7.8%)	58 (87.9%)	8 (12.1%)
CRP_0			
Median (IQ range)	2 (4)	2 (4)	2 (3)
CRP_3			
Median (IQ range)	84 (77)	85 (76)	81 (77)
CRP_{max}			
Median (IQ range)	97 (89)	99 (87)	89 (92)
Follow-up duration—years			
Median (IQ range)	2.7 (3.6)	2.3 (3.4)	3.5 (3.6)
5-year probabilities of death			
	48%	46%	52%

2003 and December 2015. Among them, 611 (72%) had a single surgical procedure, and 235 (28%) had multiple metastasectomies. Table 1 shows the baseline and follow-up characteristics, for single and multiple metastasectomies. In summary, 392 (46%) were females, 454 (54%) males, 501 (59%) epithelial tumors (250 from colorectal cancer, 50 from renal-cell carcinoma, 49 from breast cancer, and 152 from other tumors), 276 (33%) sarcomas of various origin, and 66 (8%) melanomas. There were not substantial differences in all variables except for (1) the mean age, higher in patients with single metastasectomy (59 vs. 55 years old), and (2) the prevalence of sarcoma and melanoma tumors. The proportion of multiple metastasectomies was 31.5% for sarcomas, 27.9% for epithelial tumors, and only 12.1% for melanoma. According to CRP levels, 286 patients (33.8%) were classified as 0 risk factors (CRP0 $\leq$ 2 and CRP3 $\leq$ 84 mg/L) and 560 (66.2%) as $\geq$ 1 risk factor ($CRP_0 > 2$ and/or $CRP_3 > 84$ mg/L).

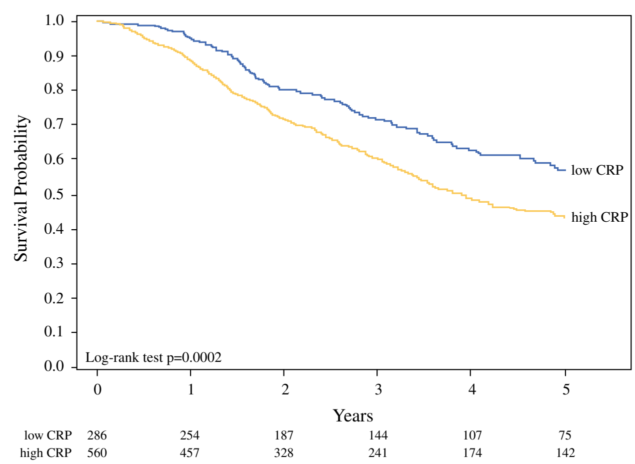

FIG. 1 Kaplan–Meier survival curves for the whole series, according to C-reactive protein measured at baseline (CRP_0) and 3 days after surgery (CRP_3). Low CRP: $CRP_0 \leq 2$ and $CRP_3 \leq 84$-high CRP: $CRP_0 > 2$ or $CRP_3 > 84$

CRP Levels and Long-Term Survival

Cumulative 5-year survival was 57% in patients with low CRP (0 risk factors) versus 43% in patients with high CRP ($\geq$ 1 risk factor, Fig. 1, $p < 0.0002$), 62% versus 50% respectively in epithelial tumors (Fig. 2a, $p < 0.0140$), and 51% versus 34% in sarcomas (Fig. 2b, $p < 0.0111$). Predictive value of CRP was maintained when the analysis was restricted to 626 sublobar resections, representing the prominent and more homogeneous group of metastasectomies (Fig. 3, $p < 0.0002$).

Multivariable Cox model analysis, adjusted for age, gender, and primary tumor type, confirmed the increase in mortality risk, with a hazard ratio (HR) of 2.51 at 1 year and 1.51 at 5 years for patients with high CRP ($\geq$ 1 risk factor) compared with those with low CRP (0 risk; Table 2). The HRs were confirmed also stratifying analysis by the number of metastasectomies (single vs. multiple resections; Table 2).

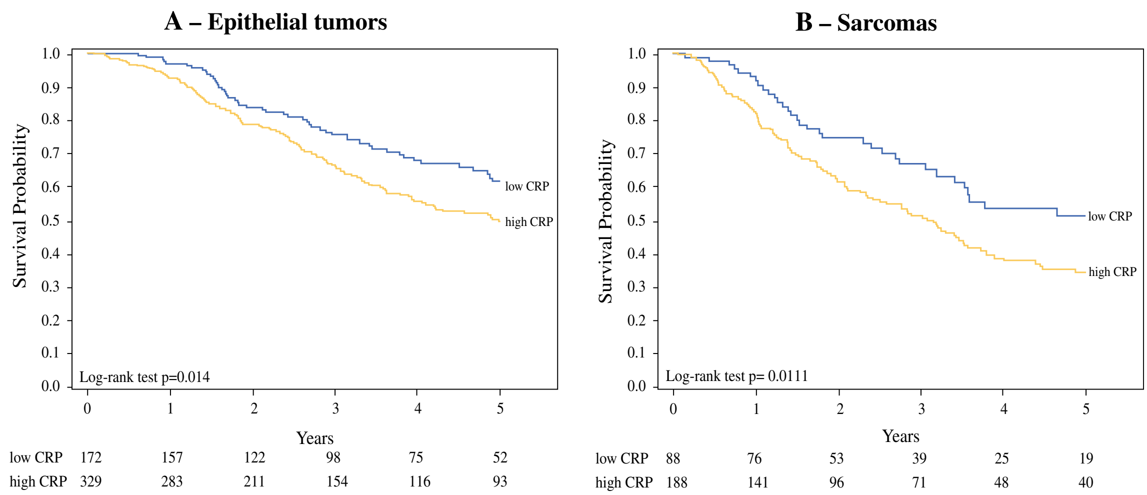

FIG. 2 Kaplan–Meier survival curves by primary tumor type (**a** epithelial tumors, **b** sarcomas), according to C-reactive protein measured at baseline (CRP_0) and 3 days after surgery (CRP_3). Low CRP: $CRP_0 \leq 2$ and CRP3 $\leq$ 84-high CRP: $CRP_3 > 2$ or CRP3 > 84

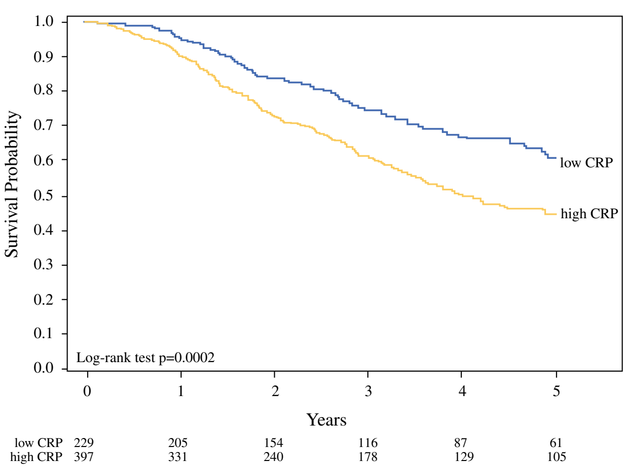

FIG. 3 Kaplan–Meier survival curves of sublobar resections according to C-reactive protein measured at baseline (CRP_0) and 3 days after surgery (CRP_3). Low CRP: $CRP_0 \leq 2$ and $CRP_3 \leq 84$-high CRP: $CRP_0 > 2$ or $CRP_3 > 84$

Supplementary analyses, applied to assess the cumulative 5-year survival of patients with 0 and $\geq$ 1 risk factor stratified by number of surgical procedures showed a similar impact of CRP in patients with single (Fig. S1A, $p = 0.0036$) and multiple metastasectomies (Fig. S1B; $p = 0.044$).

DISCUSSION

It is well known that progression of solid tumors ends in metastatic disease, which is the major cause of cancer death.[18] In this large, unselected series of lung resections for metastatic disease, we demonstrated that CRP values at baseline and 3 days after surgery predict the long-term outcome of all patients undergoing salvage surgery with curative intent. Predictive value of CRP was confirmed in subgroup analyses by primary tumor type (epithelial or

TABLE 2 Adjusted hazard ratio and 95% CI for 1-year and 5-year mortality, according to C-reactive protein measured at baseline (CRP_0) and 3 days after surgery (CRP_3) stratified by number of resections

	No. of subjects	1-year mortality		5-year mortality	
		No. of deaths	HR[a] (95% CI)	No. of deaths	HR[a] (95% CI)
All resections					
Low CRP	286	13	1 (Reference)	93	1 (Reference)
High CRP	560	62	2.51 (1.38–4.58)	255	1.51 (1.18–1.92)
Single metastasectomy					
Low CRP	194	10	1 (Reference)	63	1 (Reference)
High CRP	417	53	2.59 (1.32–5.11)	189	1.47 (1.10–1.96)
Multiple metastasectomies					
Low CRP	92	3	1 (Reference)	30	1 (Reference)
High CRP	143	9	2.00 (0.53–7.57)	66	1.56 (1.01–2.42)

Low CRP: $CRP_0 \leq 2$ and $CRP_3 \leq 84$-high CRP: $CRP_0 > 2$ or $CRP_3 > 84$

[a]Adjusted for: age, gender, primary tumor type

sarcoma) or extent of surgery (sublobar resection and number of metastasectomies). Our results are in agreement with Køstner's report that preoperative CRP and number of metastases (but not metastasis size) were predictive of poor survival in colorectal cancer (CRC) patients, thereby supporting the hypothesis that systemic inflammation drives tumor progression, rather than tumor burden.[19]

CRP is an acute-phase protein with long half-life, mainly secreted by hepatocytes during acute-phase reaction in response to tissue damage, and related cytokines (interleukin-6 [IL6], interleukin-1 [IL1], and tumor necrosis factor [TNF]-a), in correlation with the intensity of pathological processes.[18,20,21] CRP binds to the surface of apoptotic cells, microbes, or "mutant" cells (e.g., cancer cells), allowing phagocytosis and interferes with immune cells activity.[20,22] Thereby, rather than a simple inflammatory marker, CRP is part of innate immunity. As shown in primary lung cancer patients, where CRP values predict long-term survival independently from stage, chronic inflammation causes additional DNA injury and hampers effective adaptive immunity, eventually leading to metastatic spread and tumor progression.[15] In the postoperative phase of metastasectomy, inflammatory cells recruited in the attempt of repairing surgical tissue damage can promote further tumor growth and accelerate metastatic progression.

Few biomarkers related to immune status have been investigated in the setting of metastatic patients. Kishiki et al. analyzed different immune-markers in a series of 167 unresectable stage IV (CRC) patients and evidenced a significant association between elevated modified Glasgow Prognostic Score (mGPS, a combination of CRP and albumin values) and poor prognosis.[23] Similarly, the results of NORDIC-VII trial (in which 393 patients with metastatic CRC received first line treatment) outlined that high levels of pretreatment serum IL-6 or CRP were associated with impaired outcome.[24] In patients undergoing liver metastasectomy for oligo-metastatic CRC, novel biomarkers, such as the CRP to albumin ratio, can predict a poor outcome.[25] Also in patients treated with surgical resection for bone and soft tissue sarcoma, SIR and mGPS represent an independent predictor of recurrence-free and cancer-specific survival.[26] Similar results were reported in urothelial carcinoma, where a CRP level < 1 mg/dl before metastasectomy was an independent significant predictor of better progression-free and overall survival.[27]

Taking into account its role as immune modulator, it is not surprising that CRP value may contribute to predict the overexpression of other significant inflammatory cytokines or protein involved in targeted therapies. A recent analysis on 508 resected NSCLC revealed a strong correlation between programmed death-ligand 1 (PD-L1) expression and high CRP value.[28] A similar correlation between serum PD-L1 and CRP levels was reported in advanced pancreatic cancer patients.[29] Similarly, higher levels of CRP (> 5 mg/L) have been associated with "pro-inflammatory cytokine intensity," defined as number of cytokines above the median value (IL-1$\beta \geq 10$ pg/mL; IL-6 ≥ 10 pg/mL; and TNF$\alpha \geq 55$ pg/mL), which predicts progression-free survival in CRC patients.[30] Given its strong association with these molecules, CRP value could be employed to stratify patients for future immunotherapy trials using anti-PD-L1 antibody (e.g., Darvalumab) or interleukin-1β inhibitors (e.g., Canakinumab) in oligo-metastatic patients undergoing salvage surgery.[31,32]

To our knowledge, the present study provides the first evidence that both preoperative and postoperative CRP values predict survival in patients undergoing lung metastasectomy, irrespective from the histology of primary tumor. Interestingly, these data are in line with our previous study in which CRP0 (cutoff 3 mg/L) and CRP3 levels (cutoff 126 mg/L) predicted immediate mortality and long-term survival in all stages of operable lung cancer, as well as in the subset of non-smoking patients, confirming the prominent role of SIR in affecting and modulating cancer progression and prognosis.[15] Of note, in this series of lung cancer patients, those with only pre- or postoperative elevation of CRP had the same risk of 30-day mortality of those with low pre- and post-CRP. On the contrary, a significant threefold increase of 30-day mortality was observed in patients with both pre- and postoperative elevation of CRP values. That observation convinced us to reverse the conventional interpretation of CRP as an early marker of postoperative complications, with a new hypothesis of postoperative complications as a consequence of immune deficiency, revealed by chronic inflammatory status and elevated CRP. This may be the explanation for the long-term impact of CRP on mortality at 5-10 years from surgery, which also is evident for pre- or postoperative high values only, but is much greater when pre- and postoperative high values are concurrent. A similar analysis in three levels of risk (low CRP, only pre- or postoperative high CRP, both pre- and postoperative high CRP) was not feasible in the present series of lung metastases because of the relatively small number of patients, heterogeneity of primary tumors, and majority of nonanatomical resections. In addition, we acknowledge that—given the retrospective nature of our study—we did not consistently measure CRP at a later postoperative time, such as 2 weeks or even 1 month, when most of the acute inflammatory phase could have resolved, to further validate our hypothesis. This is why we are now launching a prospective study to look at this more in depth.

Our unselected series confirms the curative potential of surgery for localized and completely resectable metastatic cancer, with a cumulative 5-year survival approaching

50%, but the ability to identify a subset of patients with poorer outcome by CRP levels may be of significant clinical value, to implement systemic treatments designed to modify the inflammatory/immune status. Of interest, multivariable analysis showed a greater impact of elevated CRP on short-term failure (1-year mortality HR 2.5 vs. 1.5 at 5 years). Specifically, the present study confirms that the assessment of immune status is of paramount importance to categorize oligo-metastatic cancer patients in high- and low-risk, according to CRP values. High-risk patients could represent the target of specific interventions to modulate host's innate immune hyperactivity and/or to reeducate immune cells to anti-tumorigenic effect. In this setting, a variety of immune-modulating drugs are being evaluated in literature with interesting results. Chronic use of COX inhibitors or β-blockers in healthy peoples showed a chemopreventive effect against several tumors, including breast and CRC.[33–35] A low daily dose of aspirin (25–50 mg per day) during the first postoperative year improved 5-year survival in patients with early-stage gastric and oesophageal cancer.[36] Furthermore, a retrospective study showed that intraoperative administration of a non-selective COX inhibitor (ketorolac) improved survival in patients undergoing surgery for breast or lung cancer.[37] A randomized trial performed in patients with hepatocellular carcinoma evidenced that daily statin treatment for 16.5 months after chemoembolization resulted in a doubling of survival time.[38] Also the use of omega-3 fatty acids has been reported to reduce postoperative immunosuppression and infection and increases the response rate to chemotherapy and survival in advanced lung cancer patients.[39] In addition, because minimally invasive procedures have been associated with less inflammatory response after metastasectomy, the combination of specific drugs and VATS resection may be used to modulate immune status in high-risk patients with single lung metastasis.[40]

Taken together, all these data provide a further rationale for targeting the host's immune response to improve clinical outcomes of cancer patient. New translational studies, as well as prospective, randomized, clinical trials, are needed in the setting of lung metastasectomy to test the efficacy of anti-inflammatory or immune-modulating agents as "adjuvant" therapy in patients with elevated pre- and/or postoperative CRP levels.

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