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ORIGINAL ARTICLE

Systemic cytokine response after emergency and elective surgery for colorectal carcinoma

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Abstract
Background Systemic cytokines (SC) are accepted mediators of host immune response. It is debated if long-term survival is influenced by emergency presentation of colorectal cancer, and the role of immunitary response is still unknown. The aim of this prospective study was to compare the SC response after emergency resection with that after elective resections of colorectal carcinoma.
Materials and methods One hundred six consecutive subjects with colorectal cancer were submitted to emergency (complete bowel obstruction; EMS, $n=50$) or elective resection (ELS, $n=56$) of the tumour. Sera were collected before surgery and at appropriate time points afterward and assayed for interleukin-1beta (IL-1β), tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP). Five-year survival was analysed according to Kaplan–Meier test. The Cox proportional hazard model was used for the multivariate analysis.
Results Pre-operative levels of IL-1β, IL-6 and CRP were statistically higher in the EMS group. Levels of TNF-α were not elevated after surgery and there was no difference between the groups. Five-year survival was significantly lower in the EMS group ($p<0.05$).
Conclusions Immunitary response, as reflected by SC, was better after elective resection than after emergency resection of colorectal carcinoma and this difference may have implication in the long-term survival.

Keywords Cytokine response · Emergency surgery · Colorectal carcinoma

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Introduction

Surgery induces a generalised state of immunodepression [1]. Cytokines produced by cells of the immune system and other tissue act as mediators of the immune and acute phase response. Tumour necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β) and interleukin-6 (IL-6) are the major mediators of the acute phase response in humans [2,3]. The post-operative levels of these cytokines have been found to correlate with the magnitude of the surgery and the presence of complications [4–6]. They have, therefore, been accepted as markers of tissue trauma after surgery [7,8].

Approximately one third of patients with colorectal cancer present as an emergency [9]. Previous studies have highlighted the poor survival associated with emergency presentation [10]. Other recent paper has not confirmed this poor survival of emergency-treated patients compared to elective ones [11].

This prospective study compared the cytokine response after elective and emergency presentation in patients with colorectal carcinoma. The aim was to evaluate if there was a difference in immunitary response of emergency-treated patients and if this difference influenced short-term results and 5-year survival.

The primary end-points were cytokine, C-reactive protein (CRP) levels and 5-year survival; clinical parameters were recorded as secondary end-points.

Materials and methods

Patient selection and pre-operative, operative and post-operative management

Since November 1999 to November 2001, all patients with colorectal cancer seen in the Emergency Surgery Department of St. Orsola-Malpighi University Hospital (Bologna, Italy) eligible for the study were enrolled.

Patients with medium-lower rectum tumours were excluded.

All elective patients underwent pre-operative colonoscopy and biopsy of the tumour (ELS). Computed tomography (CT) scan was also performed in all elective and emergency patients.

The bowel was prepared only in elective-treated subjects the day before surgery.

Systemic prophylactic antibiotics (cefotaxime 2 g and metronidazole 500 mg) were administrated intravenously at induction of anaesthesia and afterward according to National Nosocomial Infections Surveillance System Score [12]. A urinary catheter and a nasogastric tube were routinely used.

Emergency indications for surgery (EMS) were complete bowel obstruction confirmed by plain radiograph films and gastrografin enema: a CT scan was also performed for cancer staging.

At laparotomy, patients with caecal diastatic perforations or other forms of peritonitis were excluded.

Anaesthetic technique was standardised. Anaesthesia was induced with propofol (2 mg/kg) and fentanyl (2 γ/kg) given intravenously. Endotracheal intubation was facilitated by the administration of vecuronium (0.08–0.1 mg/kg). Anaesthesia was maintained with mixture of 40% oxygen and air and 2–1.5% sevoflurane titrated to clinical needs. Non-depolarising neuromuscular blockade was maintained with vecuronium 1 mg/h. Intra-operative analgesia consisted of fentanyl 1–2 γ/kg/h.

The operations were performed by seven experienced surgeons with open surgery techniques.

The standard treatment was resection and primary anastomosis with intra-operative colon lavage. Subtotal colectomy was performed in case of colon ischaemia (EMS group) or in case of multiple malignancies (ELS and EMS groups).

After surgery, analgesia was administrated according to a standard protocol and diet was resumed as soon as bowel function returned clinically.

The following parameters were prospectively collected: demographic data, operation time, transfusion, duration of hospital stay, complications and death. The staging was based on Dukes' classification. All patients were followed up regularly at 6 months interval. Adjuvant chemotherapy

Table 1 Demographic data and clinical outcome parameters

Parameter	EMS	ELS	*p* value
Number of patients	50	56	n.a.
Age, mean±SD	71.8±12.7	67.7±12.3	n.s.
Sex ratio (M/F)	1.1	0.8	n.s.
Pre-operative CEA (μg/L), median (range)	6.8 (1.7–153)	1.6 (0.5–97)	<0.05
Pre-operative TNF-α (pg/mL), median (range)	8.1 (4.2–10.4)	5.3 (3.7–6.2)	n.s.
Pre-operative IL-1β (pg/mL), median (range)	0.7 (0.1–2.3)	0.3 (0.05–0.9)	<0.05
Pre-operative IL-6 (pg/mL) median (range)	30.1 (8.2–39)	3 (1–12)	<0.05
Pre-operative CRP (mg/L), median (range)	2.5 (1.3–5)	0.6 (0.3–17)	<0.05
ASA score (1/2/3/4)	0/16/29/5	3/28/25/0	<0.05
Number of patients with RH/LH/SC/ARR	13/31/4/2	18/26/1/11	<0.05
Number of resected lymph nodes	21.3±3.2	22.4±4.1	n.s.
Dukes' staging (A/B/C/D)	0/16/22/12	18/13/10/15	<0.05
Number of patients with plasma blood transfusion	30	20	<0.05
Number of patients treated with post-operative NSAID	20	27	n.s.
Number of patients with post-operative fever	14	20	n.s.
Mortality	2	0	n.s.
Leaks	3	2	n.s.
Other morbidity	9	5	n.s.
Hospital stay (days), median (range)	8 (1–51)	9 (2–35)	n.s.

CEA carcinoembryonic antigen, *RH* right hemicolectomy, *LH* left hemicolectomy, *SC* subtotal colectomy, *ARR* anterior rectal resection, *n.a.* not applicable, *n.s.* not significant, *NSAID* post-operative therapy with non-steroidal anti-inflammatory drugs

(5-fluorouracil combined with folinic acid) was offered and performed in all patients with Dukes' C stage. Dukes' D stage patients were treated with palliative therapy with 5-fluorouracil combined with folinic acid, oxaliplatin and irinotecan and submitted to liver resections if feasible.

Blood samples and statistics

Blood samples were taken (with ethical committee approval) before surgery, at 2, 8 and 24 h and every day after surgery up to 1 week. CRP was also evaluated after 2, 3 and 4 weeks. Specimens were allowed to clot and were centrifuged. The serum collected was stored at −70°C for cytokine and CRP assay. TNF-α, IL-1β and IL-6 were measured by enzyme-linked immunosorbent assay.

Statistics The chi-square test, the Student's *t* test and Mann–Whitney test were used as appropriate. We compared peak values and we performed analysis of variance with repeated measures. Kaplan–Meier was used to analyse survival. $p<0.05$ was considered as significant. The Cox proportional hazard model was used for the multivariate analysis.

Results

From November 1999 to November 2001, 106 consecutive patients treated for colorectal cancer in elective end emergency conditions were enrolled.

The demographic and clinical outcome data are reported in Table 1. EMS subjects needed more pre-operative/post-operative transfusions ($p<0.05$). EMS patients had a significantly worse ASA score and Dukes' stage compared to ELS patients ($p<0.05$). Mortality was (two out of 50) in the EMS group vs (zero out of 56) in the ELS group (p=n.s.). Morbidity was (12 out of 50) in the EMS group vs (seven out of 56) in the ELS group (p=n.s). Surgical resection margins (*R* status) were negative in all patients.

There was also no difference in the numbers of resected lymph nodes between the two groups.

Among Dukes' D stage patients, six EMS subjects and seven ELS subjects were submitted to liver resections

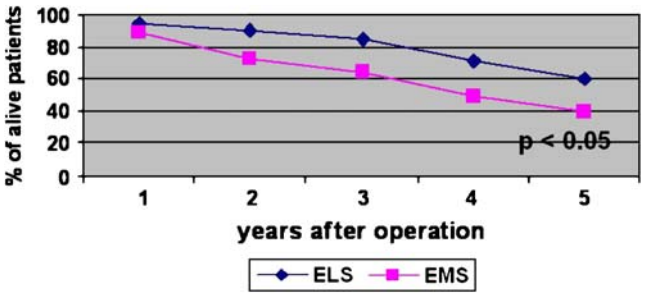

Fig. 1 Five-year survival

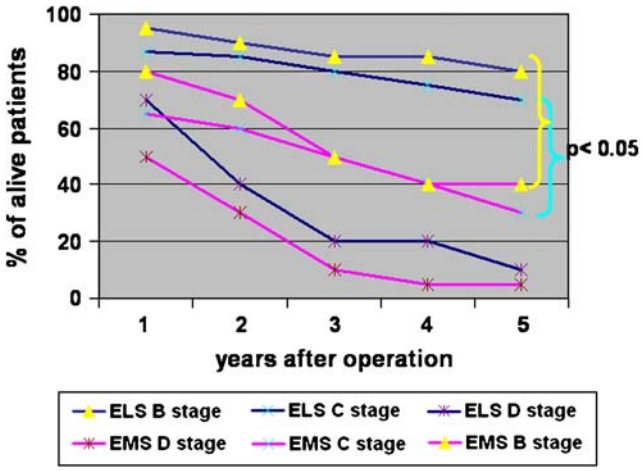

Fig. 2 Five-year survival according to Dukes' stage

(*p*=n.s.). Five-year survival was lower for EMS patients with statistical significance ($p<0.05$) also considering Dukes' B–C stages (Figs. 1 and 2, respectively). No difference in survival between Dukes' B and Dukes' C patients after elective surgery was seen, and Dukes' B and Dukes' C patients after emergency surgery did not differ either.

Causes of deaths after discharge are reported in Fig. 3: there were more cancer-related deaths in EMS patients compared to ELS patients ($p<0.05$).

The cytokine profiles are shown in Figs. 4, 5, 6 and 7. The pre-operative levels of cytokines were different in the two groups ($p<0.05$) with the exclusion of the TNF-α pre-operative level. (Table 1) The TNF-α post-operative level was also not elevated after surgery in both groups without

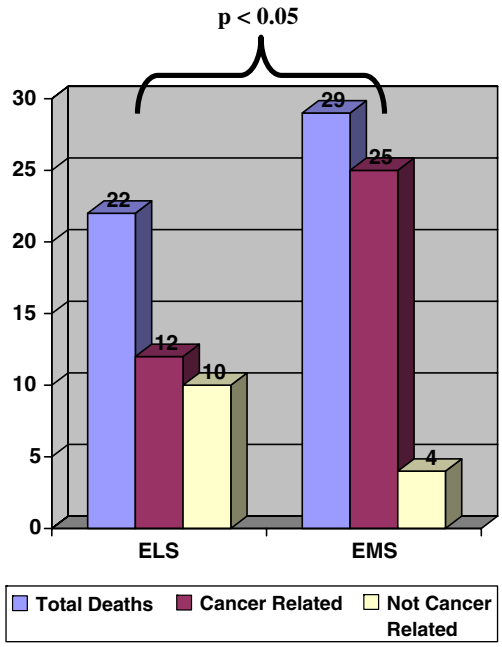

Fig. 3 Patients' death causes after discharge

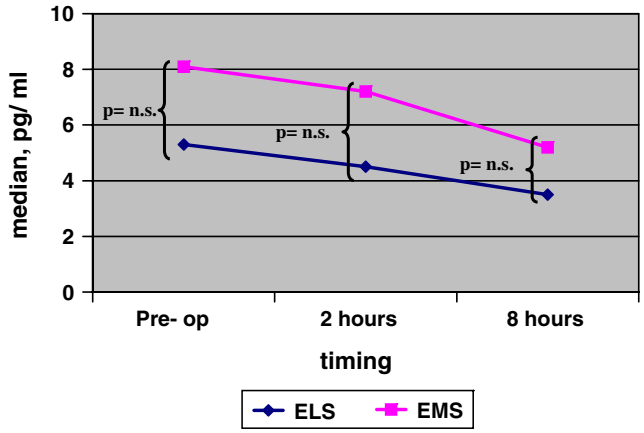

Fig. 4 TNF-α profile

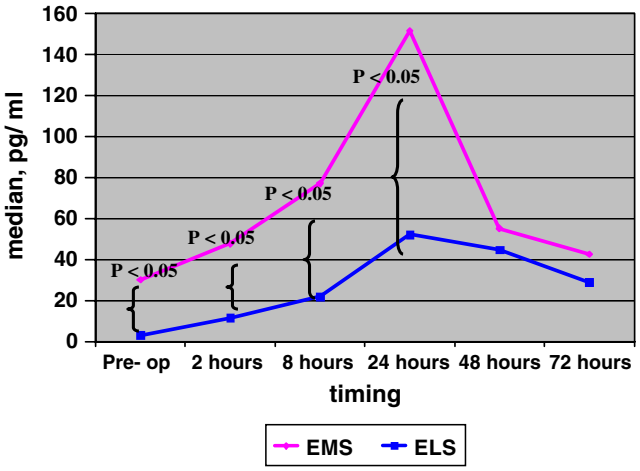

Fig. 6 IL-6 profile

any statistical difference (Fig. 4). However, the levels of IL-1β, IL-6 and CRP rose significantly after surgery (Figs. 5, 6 and 7). IL-1β peaked at 2–8 h after surgery and IL-6 peaked at 2–8 and 24 h after surgery. The differences were statistically significant between EMS group and ELS group.

CRP levels peaked at 48 h after surgery. This difference between the studied groups was again significant.

To look for confounding factors, the natural logarithm of the IL-6 peak level was used as the dependent variable to correlate sex, age, surgical condition (emergency or elective), ASA score, carcinoembryonic antigen levels, blood transfusion, post-operative non-steroidal anti-inflammatory drugs (NSAID) therapy, post-operative fever, complications, mortality and Dukes' staging by multiple linear regressions. Blood transfusion and surgical condition (emergency or elective) were found to be independently related to the IL-6 peak level ($p<0.05$).

Cytokine and CRP levels did not predict complications, in general, and anastomotic leakage, in particular, in the study population.

Emergency presentation (OR=1.88; 95% confidence interval=1.61–2.12), IL-6 peak level (OR=1.77; 95% confidence interval=1.52–1.94), Dukes' stage (OR=1.7–2.9), blood transfusions (OR=1.67; 95% confidence interval=1.41–1.85) were independent prognostic negative factors for survival.

Discussion

Approximately one third of patients with colorectal cancer present as an emergency [9]. Previous studies highlighted the high mortality–morbidity post-operative rate and poor survival associated with emergency presentation [10]. However, many of these studies were small retrospective series based on a single institution, some reported only immediate post-operative mortality and many did not compare the results with a concurrent cohort of elective patients. McArdle confirmed the excess of both cancer-

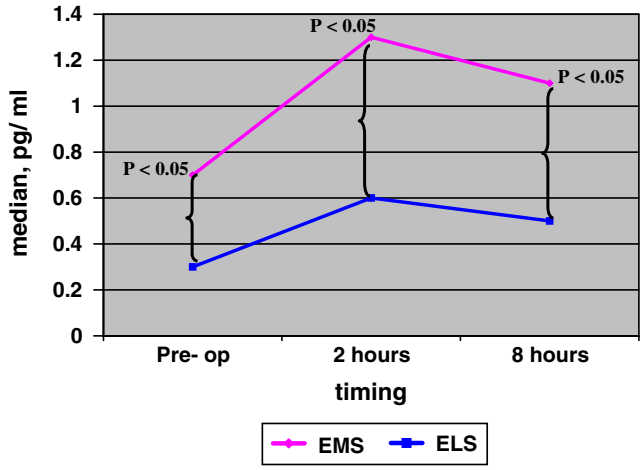

Fig. 5 IL-1β profile

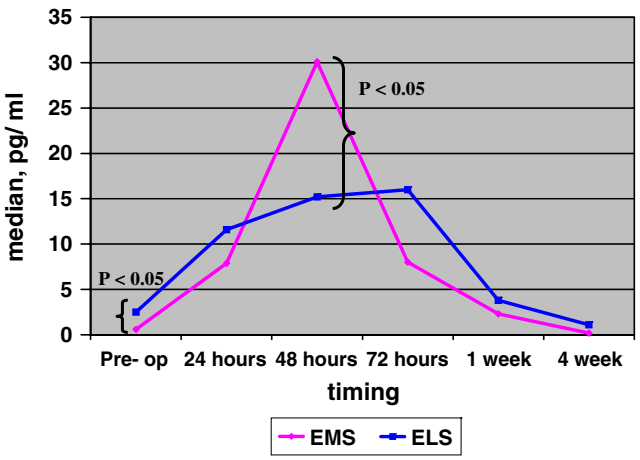

Fig. 7 CRP profile

related and intercurrent death in patients who presented as an emergency in a large comparative case-mix study [13].

Other authors did not confirm this difference in 5-year survival [14] but again many of these studies were retrospective case–control analysis not specifying if elective medium-lower rectum tumours were excluded (in these cases, pre-operative adjuvant therapy might have a fundamental role) [15].

The acute phase response consists of a series of hormonal, metabolic and immunologic changes in response to surgery, trauma or sepsis.

TNF-α, IL-1β and IL-6 are major mediators of the acute phase response in humans [2,3]. TNF-α and IL-1β are responsible for inducing non-hepatic manifestations such as fever, elevated prostaglandin levels, tachycardia and accelerated catabolism [5]. IL-6 is primarily responsible for the hepatic component of the response, resulting in the synthesis of acute phase proteins. It usually peaks at 4 to 48 h (median 8 h) after surgery and falls rapidly thereafter in patients with an uncomplicated post-operative course [6].

CRP, a key representative of acute phase proteins, has a consistent response and provides a dependable overall screening test for acute phase reactions. It usually peaks at 24 and 72 h after surgery and levels may remain elevated for approximately 2 weeks [8]. The levels of the cytokines and CRP were found to be related to the magnitude of surgery and the presence of complications [5,6]. Therefore, they have been used as objective biochemical markers to reflect surgical tissue trauma and immunitary response [16–18].

Some authors reported lower IL-6 levels in laparoscopic surgery and correlate it to a lower surgical trauma [19].

In the present study, immunitary response and short-term to long-term outcomes were evaluated. We also analysed the possible confounding factors by multivariate analysis.

TNF-α differences in the two groups were not significant: this indicated that no significant endotoxemia occurred after surgery in both groups. IL-1β, IL-6 and CRP pre-operative levels were higher in the EMS group: these differences indicated that emergency-treated patients had a worse immunitary response probably caused by the complicated cancer. Cytokine levels rose at the expected time points. The significant differences between the EMS group and the ELS group strongly supported the theory that emergency-treated patients have a bigger immunitary trauma. On multivariate analysis, the natural logarithm of the IL-6 peak level was also found to be related to blood transfusion: this may reflect the extent of the disease, the need for a more extensive surgical procedure or the intrinsic immunosuppressive effect of blood transfusion [20].

In cancer surgery, immunosuppression induced by the disease and the surgery confers a growth advantage to micrometastasis [21]. In emergency, the surgical trauma is increased thus probably reducing the host immunity.

Emergency-treated patients had a poorer 5-year survival independently from Dukes' B and C stages. Emergency colorectal cancer presentation triggers an impairment of the immune system: IL-6 and CRP have anti-inflammatory and immunosuppressive effects that may influence 5-year survival [22].

The excess of cancer-related death in patients with Dukes' B and C stages may, therefore, be exposed by a higher prevalence of residual occult disease and the immunodepression.

As a matter of fact, death causes analysis showed a statistically higher cancer-related mortality in EMS patients compared to elective ones.

So, the immunitary trauma of cancer emergency presentation and treatment may be the cause of continuing excess of deaths that affects survival.

No difference in survival between Dukes' B and Dukes' C patients after elective surgery was seen, and Dukes' B and Dukes' C patients after emergency surgery did not differ either: probably, the power of the study failed to reveal a significant difference.

In conclusion, immunitary response in emergency-treated patients is worse compared to elective ones: probably, this difference plays a major role in the poorer 5-year survival.

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