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Specialist Interest Articles

Gram-positive Bacteraemia in Granulocytopenic Cancer Patients

EORTC International Antimicrobial Therapy Cooperative Group

In the four EORTC International Antimicrobial Therapy Cooperative Group trials, the frequency of gram-positive isolates has increased significantly from 29% of single-organism bacteraemias in trial I (1973–1976) to 41% in trial IV (1983–1985). In trial IV febrile and neutropenic (less than 1000 polymorphonuclear lymphocytes per μl) cancer patients were randomized prospectively to receive either azlocillin plus a long course (at least 9 days) of amikacin, or ceftazidime plus a short course (3 days) of amikacin, or ceftazidime plus a long course of amikacin. Without modification of the allocated antibiotics, the overall response rates for gram-positive bacteraemias were similar for all three regimens (19/37 [51%], 8/23 [35%] and 14/30 [47%]), respectively. However, in patients with prolonged and severe neutropenia, treatment with azlocillin plus amikacin was significantly more effective than with ceftazidime plus 3 days' amikacin (7/10 vs. 0/7). The overall response rate for these infections was significantly lower than that observed in trial I (46% vs. 74%), but this was not associated with increased mortality. The response to treatment was significantly influenced by the susceptibility of the infecting strain to the beta-lactam. Multivariate analysis revealed that increasing age, presence of a central venous catheter and resistance to beta-lactam adversely affected outcome. Future studies should be designed to improve the outcome of gram-positive bacteraemia in neutropenic patients with cancer.
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INTRODUCTION

BACTERIAL INFECTION remains a major problem in patients undergoing aggressive chemotherapy for the treatment of neoplastic diseases, especially when accompanied by granulocytopenia. Early empirical antibacterial therapy has improved infection-related morbidity and mortality. However, many centres report a change in the distribution of microorganisms causing bacteraemia in neutropenic cancer patients with a shift toward gram-positive bacteria [1–4]. Moreover, methicillin-resistant *Staphylococcus aureus* and *Staph. epidermidis* are increasing in frequency [5–8]. Although mortality associated with gram-positive bacteraemia is supposed to be lower than that due to gram-negative rods, other factors should be considered, such as prolonged fever, delays in antineoplastic therapy and the need to use toxic and/or expensive drugs.

Beta-lactam–aminoglycoside combinations are widely used as empiric treatment of febrile neutropenic patients, but these combinations are not always the best for methicillin-resistant staphylococci and other gram-positive organisms [1, 3–7]. We have reviewed gram-positive bacteraemia in the four trials done by the EORTC International Antimicrobial Therapy Cooperative Group [9–12] and report the results of treatment of such bacteraemia in the fourth trial. In this trial we compared the efficacy of azlocillin plus a long course of amikacin, the most effective regimen for gram-negative bacteraemia in the third trial [11], to that of ceftazidime plus amikacin, given either for 3 or at least 9 days.

Correspondence to: C. Viscoli, Department of Infectious Disease, G. Gaslini Scientific Institute, University of Genova, Largo G. Gaslini 5, 16148 Genova, Italy.
Writing committee: C. Viscoli, S.H. Zinner, M.P. Glauser, J. Klastersky, H. Gaya, T. Calandra and F. Meunier.
Data review committee: T. Calandra, F. Meunier, M. Rossi, M. Sanz and J.C. Wade.
Consultant: S.C. Schimpff.
Statisticians: P. Bruzzi, Institute for Tumor Research; L. Boni, G. Gaslini Children's Hospital, Genova, Italy; R. Sylvester, EORTC Data Center, Brussels, Belgium.
Data Manager: F. Woussen.
Other investigators: A. Padmos, Riyadh; P. Togni, Lausanne; J. Gallagher, Danville; R. Hemmer, Luxembourg; J.A. Child, Leeds; R. De Bock, Edegem; I.M. Hann, Glasgow; P. Martino and F. Mandelli, Rome; A. Porcellini, Pesaro; G. Masera, Milan; G. Hoffken, Berlin; G. Todeschini, Verona; L. Massimo, Genova; J. Levy, Brussels; J.C. Legrand, Charleroi; M. Rey and J. Beytout, Clermont-Ferrand; F. Menichetti and A. Del Favero, Perugia; A. Lopez, Barcelona; M. Fopp, St. Gallen; J. Nikoskelainen, Turku; G.L. Ridgway and A.H. Goldstone, London; K.H. Mayer, Providence.
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PATIENTS AND METHODS

Patients

1074 patients from twenty-four institutions were included in the trial. After excluding patients with doubtful infections and those with proven non-bacterial infections, 872 episodes were evaluable. In each participating centre, granulocytopenic (less than 1000 polymorphonuclear lymphocytes [PMN] per μl) febrile (over 38°C) patients with leukaemia, lymphoma or solid tumours were eligible. Patients with fever from causes other than infection (underlying disease, infusion of blood products, cytotoxic drugs) and patients who had received intravenous antibiotic therapy during the 4 days before randomization were excluded. Other exclusion criteria were refusal to participate in the study (informed consent was required) and a history of severe allergy to one of the protocol antibiotics or to penicillin. Each patient had a complete history and physical examination, chest X-ray, cultures of blood, urine and any material from clinically relevant sites, measurements of serum electrolyte and creatinine levels and a complete blood cell count, including differential leukocyte count.

Treatment

Each patient was randomly allocated by drawing consecutive sealed cards to receive either azlocillin plus amikacin, ceftazidime plus six doses (3 days) of amikacin or ceftazidime plus a long course of amikacin. In responding patients, treatment was continued for 9 days or until complete resolution of infection. Investigators were free to administer oral antibiotic prophylaxis.

Ceftazidime, amikacin and azlocillin were diluted in 5% dextrose in water and infused separately over 15 min. Azlocillin was administered at 300 mg/kg per day in four divided doses (average adults received 5 g four times a day). Ceftazidime was given at 100 mg/kg per day in four divided doses (average adults received 1.5 g four times a day). Amikacin was administered at 7.5 mg/kg twice daily (average adults received 500 mg every 12 h). Doses of antibiotics were adjusted in patients with renal insufficiency.

Assessments

Each febrile episode was classified as: microbiologically documented infection with or without bacteraemia, clinically documented infection, possible infection or doubtful infection [9–11, 13].

Gram-positive bacteraemia was defined as the presence of clinical signs and symptoms of infection together with the isolation of a gram-positive microorganism from the blood. For an episode to be ascribed to a coagulase-negative staphylococcus, at least two positive blood cultures were required. Each specimen was microbiologically processed according to classical methods [14]. Antibiotic susceptibility was evaluated with the Kirby–Bauer disk method [15]; a strain was considered susceptible to amikacin if the zone diameter was 17 mm or more and to azlocillin and ceftazidime if the zone was larger than 18 mm.

All case reports were blindly reviewed by the data review committee. Each patient was evaluated on the 4th and 9th day after randomization and at the end of therapy.

Response was evaluated as: improvement—complete and lasting resolution of all major symptoms and signs of the defined infection, without modification of the protocol regimen; or failure—(1) absence of clinical response (i.e. persistence of fever and progression of infection), (2) persistence of pathogen at the site of infection or in blood and (3) death from infection within 9 days after the start of therapy.

The efficacy of the three treatments was evaluated separately in patients who had experienced prolonged and severe neutropenia, i.e. those who had less than 100 PMN/μl for at least 9 days after randomization. Patients who responded to the protocol were assessed for the emergence of any further infection at the same or other sites during antibiotic therapy or within a week after its discontinuation and caused by an organism other than the initial infecting pathogen.

Statistics

We used the χ^2 test for heterogeneity to assess the association between binary or multinomial variables. When one of the variables had more than two levels (trials, years, protocols), the χ^2 test for trend was used to assess the significance of the linear component of the correlation.

The independent role of bacterial susceptibility to the allocated antibiotics in predicting response was evaluated by the Mantel–Haenszel test. To assess simultaneously the predictive relevance of all variables on response to treatment and to identify spurious associations due to confounding factors, a multivariate logistic model was fitted. Response was used as the dependent variable. Treatment, age, sex, underlying disease, PMN count at onset, presence of an indwelling central catheter at onset, antibiotic prophylaxis, presence of a clinically detectable site of infection at onset, aetiology and *in vitro* susceptibility to the antibiotic were included as independent variables. A step-down procedure based on a likelihood ratio test was used.

RESULTS

Of the 872 evaluable patients 219 (25%) had single-agent bacteraemia, 90 (41%) due to gram-positive and 129 (59%) due to gram-negative bacteria. The results for gram-negative bacteraemia have been reported [12].

Gram-positive pathogens in EORTC trials

The work of the EORTC International Antimicrobial Therapy Cooperative Group began in 1973. Four trials of empirical antimicrobial therapy have been completed.

From trial I to IV (Table 1), gram-positive bacteraemia increased significantly from 29% to 41% of all cases of single-organism bacteraemia ($P = 0.01$). Despite this increase, the distribution of gram-positive bacteria did not change significantly from trial II to IV (Table 2) (data for trial I are not

Table 1. Distribution of single gram-positive and single gram-negative bacteraemia in the four EORTC trials

Trial	Evaluable cases	Bacteraemia		
		Single agent	Gram-positive	Gram-negative
I (1973–1976)	453	145	42 (29%)	103 (71%)
II (1977–1980)	419	111	37 (33%)	74 (67%)
III (1980–1983)	582	141	58 (41%)	83 (59%)
IV (1983–1985)	872	219	90 (41%)	129 (59%)

Overall $P = 0.01$.

Table 2. Gram-positive bacteria causing septicaemias in trials II, III and IV

Microorganism	Trial II	Trial III	Trial IV
Staph. aureus	10 (27%)	14 (25%)	25 (28%)
Staph. epidermidis	9 (24%)	24 (41%)	18 (20%)
Other gram-positive bacteria	18 (49%)	20 (34%)	47 (52%)
Total	37 (100%)	58 (100%)	90 (100%)

Overall $P = 0.07$.

retrievable). There was a non-significant increase in streptococcal isolates from trial III to IV (from 18 of 58 [31%] to 37 of 90 [41%]. Most of the streptococcal isolates in trial IV were α-haemolytic streptococci (21 of 37 [57%]); 10 of these strains were not further characterized, while the others were identified as *Streptococcus sanguis* (5) and *Strep. mitis* (6). Among the other 16 streptococcal isolates, 6 were identified as *Strep. pneumoniae*, 5 *Strep. faecalis*, 3 *Strep. pyogenes* and 2 *Strep. agalactiae*.

Patients with gram-positive bacteraemia in trial IV

Of the 90 patients with gram-positive bacteraemia (Table 3), 37 (41%) were treated with azlocillin plus amikacin, 23 (26%) with ceftazidime plus 3 days of amikacin and 30 (33%) with ceftazidime plus a long course of amikacin. There were no significant differences among the groups in age, sex, underlying disease or distribution of pathogens. 36 (40%) patients had a central intravenous catheter at the onset of fever. They were evenly distributed among the treatment groups (43%, 48%, and 30%, respectively). 51 of the 90 patients (57%) were severely neutropenic (less than 100 PMN/μl) at the onset of fever and they were also evenly distributed among the groups; 24 (27%) were still severely neutropenic at day 9: 27%, 30%, and 23%, respectively, not statistically significant. Only 3 patients had shock.

*Table 3. Trial IV: characteristics of patients**

	Azlocillin plus amikacin	Ceftazidime plus amikacin (3 days)	Ceftazidime plus amikacin (long)
No. of patients	37	23	30
Age (yr)			
Median (range)	28 (2–79)	42 (3–76)	38 (1–69)
Mean	35	40	34
M/F	23/14	12/11	12/18
Underlying diseases:			
Leukaemia	21 (57%)	11 (47%)	19 (63%)
Lymphoma	3 (8%)	2 (9%)	5 (17%)
Solid tumour	2 (5%)	2 (9%)	4 (13%)
Others	11 (30%)	8 (35%)	2 (7%)
Patients at randomization with:			
Granulocytes < 100/μl	22 (59%)	13 (57%)	16 (53%)
Shock	0	1	2
Central catheter	16 (43%)	11 (48%)	9 (30%)

*No significant differences between groups.

In 27 of the 90 patients (30%) prophylactic protocols included oral neomycin plus framycetin; gentamicin, vancomycin, neomycin or other non-absorbable antibiotics. 6% of patients (5/90) received co-trimoxazole and 6% received co-trimoxazole with colistin or neomycin; only 3% of patients received a quinolone (2 norfloxacin and 1 ciprofloxacin). 50 patients (56%) did not receive any antibiotic prophylaxis. These patients were evenly distributed among the treatment groups (21, 11 and 18, respectively).

Clinical presentation at onset of fever

49 of 90 patients (54%) presented with fever alone as the initial clinical manifestation of their infection and they were evenly distributed among the groups. In the other 41 patients focal signs of infection were present in addition to fever. These signs were localized to the upper respiratory tract in 17 patients (19%) and to the central intravenous catheter (tunnel or exit site) in 7 patients (8%); 10 further patients (11%) had a skin or soft tissue infection and 7 (8%) had pneumonia. In 7 of the 36 patients with an indwelling central catheter the intravenous device was considered to be the primary site of infection (19% of patients with a central catheter and 8% of all patients). No major difference in the type of clinical presentation was observed among the groups.

Response to therapy

As reported previously [12], 49 patients (54%) failed to respond to the allocated regimen; in 41 of these the failure consisted of absence of clinical response. Failures and consequent changes in treatment were observed after a median of 4 days in the three groups, with ranges of 2–9 days (azlocillin plus amikacin), 2–8 (ceftazidime plus 3 days' amikacin) and 2–7 (ceftazidime plus a long course of amikacin). The median duration of treatment in the responding patients was 9 days in all three groups. Overall, the effectiveness of the regimens was similar (19 of 37 [51%]; 8 of 23 [35%]; 14 of 30 [47%], respectively).

*Table 4. Trial IV: response by susceptibility and evaluation of independent role of bacterial susceptibility to allocated antibiotics in predicting response**

Susceptibility		Microorganisms Total	Microorganisms Responding
Beta-lactam Amikacin	S S	23	13 (57%)
Beta-lactam Amikacin	S R	24	15 (63%)
Beta-lactam Amikacin	R S	25	7 (28%)
Beta-lactam Amikacin	R R	8	2 (25%)

*Role of susceptibility to beta-lactam drug adjusted for susceptibility to amikacin: $P = 0.007$. Role of susceptibility to amikacin adjusted for susceptibility to beta-lactam drug: $P = 0.79$ (Mantel-Haenszel test). S = sensitive, R = resistant.

Patients with prolonged and severe neutropenia had a lower overall response rate than other patients (9 of 24 [38%] vs. 34 of 66 [52%], not statistically significant). In this subgroup with severe neutropenia the response rate was significantly higher for azlocillin plus amikacin compared with ceftazidime plus a short course of amikacin (7 of 10 vs. 0 of 7, $P = 0.01$). Azlocillin plus amikacin showed a non-significant superiority over the third group (7 of 10 vs. 2 of 7). The response by type of organism has been reported [12].

In univariate analysis, patients not receiving any oral antibiotic prophylaxis responded better than patients who did (overall response: 14 of 40 [35%] vs. 29 of 50 [58%], respectively, $P = 0.05$). However, in multivariate analysis, this difference was no longer significant.

Response by susceptibility to antibiotics

Susceptibility data were available for 80 of the 90 (89%) infecting organisms (Table 4). Successful outcome depended on the susceptibility of the infecting pathogen to the beta-lactam agent ($P = 0.007$) rather than to the aminoglycoside ($P = 0.79$) (Mantel–Haenszel test). However, in univariate analysis, the *in vitro* susceptibility of a given isolate did not accurately predict the *in vivo* response; indeed, 10 of 23 patients (43%) whose infecting strains were susceptible to both protocol antibiotics failed therapy.

Multivariate analysis

All variables potentially affecting the response to therapy were entered into a logistic regression model (Table 5). Increasing age, presence of a central venous catheter and resistance to the beta-lactam antibiotics adversely affected outcome regardless of treatment regimen.

Mortality

2 patients with *Staph. aureus* bacteraemia and 2 with *Strep. pneumoniae* bacteraemia died as a result of the presenting infection. The overall mortality rate in primary gram-positive bacteraemias was 4%. 4 other patients primarily affected with a gram-positive bacteraemia (4%) died from a further infection not due to a gram-positive organism. In the present trial, primary gram-negative bacteraemias showed a significantly higher mortality rate than primary gram-positive bacteraemias (12% vs. 4%, $P = 0.03$) [12].

Superinfections

Superinfections occurred in 14 patients, and were evenly distributed among the study groups (4, 4 and 6, respectively) and were due to similar organisms. Superinfecting agents were additional gram-positive bacteria (7), fungi (4) and viruses (3), and were isolated from blood (7), lungs (2), mouth (2), skin and soft tissues (2) and the urinary tract (1).

Table 5. Risk factors significantly affecting outcome of gram-positive bacteraemias (multivariate analysis)

	Multivariate coefficient*	SE	*P*
Increasing age	1.05	0.50	0.03
Presence of central venous catheter	1.30	0.53	0.01
Susceptibility to beta-lactam antibiotics	−1.62	0.57	0.007

*Positive coefficient = negative influence on outcome.

Outcome in EORTC trials of gram-positive bacteraemia

A comparison of the previous EORTC trials with the present study showed that the overall efficacy of the early empirical antibiotic regimens in gram-positive bacteraemia decreased over the past 10 years from 74% (31 of 42) in trial I (carbenicillin plus cephalotin, carbenicillin plus gentamicin, cephalotin plus gentamicin) to 46% (41 of 90) in trial IV ($P = 0.004$). However, the decreasing efficacy of the regimens was not accompanied by increased mortality. For example, mortality due to *Staph. aureus* bacteraemia remained unchanged from trial I (11%) to trial IV (8%), despite the decreasing overall response of gram-positive bacteraemias to initial empirical regimens from 70% (7/10) in trial II (carbenicillin plus amikacin, carbenicillin plus amikacin plus cefazolin) to 21% (3/14) and 32% (8 of 25) in trials III (ticarcillin plus amikacin, azlocillin plus amikacin, and cefotaxime plus amikacin) and IV, respectively.

DISCUSSION

Gram-positive bacteria are isolated as causal agents of bacteraemia in cancer patients with increasing frequency. This is clearly shown by the results of the four EORTC trials, which document an increase in gram-positive bacteraemias. Many factors account for this increase, including the widespread use of indwelling central venous catheters [4, 16–18], the progressive shift in beta-lactam antibiotic activity from gram-positive to gram-negative microorganisms and the efficacy of prophylactic antibiotics against gram-negative bacteria [19, 20]. However, a high frequency of gram-positive infections has also been documented by investigators who do not use oral prophylaxis [2]. Since only 3 of the 90 patients in the present trial received a quinolone prophylactically, it is unlikely that these new antibiotics are the major contributors to the increased frequency of gram-positive bacteria, at least in the EORTC studies.

The distribution of the specific gram-positive cocci did not change significantly from trial II to IV, although a relative increase in streptococcal isolates (mostly α-haemolytic streptococci) from trial III to IV was seen. This might be due partly to the use of more aggressive anti-neoplastic regimens with more severe oropharyngeal mucositis.

In this trial the *in vitro* susceptibility to the beta-lactam drug was significantly related to outcome, which has also been observed in gram-negative rod bacteraemia [11, 12]. However, the overall response of gram-positive bacteraemia to the empiric combinations studied was disappointing. Although the combination of azlocillin and amikacin was somewhat better than the two other regimens, statistical significance was approached only for patients with prolonged and severe neutropenia. The poor clinical efficacy of the three regimens against gram-positive bacteraemias was not fully explained by *in vitro* susceptibility data, since 43% of the patients infected with strains sensitive *in vitro* to both antibiotics failed to respond to the allocated regimen. The lack of *in vitro* predictability seen here for gram-positive bacteraemia could possibly reflect a discrepancy between the minimum inhibitory and bactericidal concentrations, which is not often seen with gram-negative organisms

[6, 21, 22]. Moreover, susceptibility testing of streptococci and staphylococci presents several difficulties that might make *in vitro* results only partly predictive of clinical response [21, 23–25].

Multivariate analysis revealed additional factors that adversely affected outcome in these patients: advancing age, presence of an indwelling central venous catheter and resistance to the beta-lactam antibiotic. There was a slightly increased risk of coagulase-negative staphylococcal infection in patients with an indwelling venous catheter. Coagulase-negative staphylococci were isolated from 36% of patients with a central venous catheter, but caused bacteraemia in only 15% of patients without a venous catheter. *Staph. aureus* bacteraemia was distributed evenly between patients with and without a venous catheter. Continued attention to optimal catheter care might reduce the frequency of some of these infections.

In this trial the absolute granulocyte count at the onset did not significantly affect the response in multivariate analysis. However, prolonged and severe neutropenia had a slight adverse effect on outcome, as has also been seen in several other studies.

These data highlight the importance of gram-positive bacteraemia in neutropenic patients with cancer. Several studies of empiric specific anti-gram-positive therapy such as vancomycin or teicoplanin have been reported or are in progress [26–32]. Some of these studies reported favourable results from the early empirical use of an anti-gram-positive drug [28–31], with improved overall response rates, more rapid resolution of first fever, reduction of the use of amphotericin B and reduction of further infections and breakthrough bacteraemias due to gram-positive bacteria. Since the present study showed that mortality associated with gram-positive coccal bacteraemia was lower than that seen with gram-negative rods and did not increase despite an overall decreasing response to empirical treatments, it is likely that the addition of a specific anti-gram-positive drug could await documentation of gram-positive infection in patients who are not responding to traditional empiric regimens. However, centres with a high frequency of resistant staphylococci might consider the early inclusion of an anti-gram-positive antibiotic in the empiric regimen.

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Liver Metastases from Breast Cancer: the Relationship between Clinical, Biochemical and Pathological Features and Survival

Susan M. O'Reilly, Michael A. Richards and Robert D. Rubens

The clinical records of 312 consecutive patients with liver metastases from breast cancer were reviewed. The primary tumours were commonly poorly differentiated, although the majority were steroid receptor positive. At diagnosis of liver metastases, 60% of patients had hepatomegaly, 13% were jaundiced and 7% had ascites. A raised serum aspartate transaminase (AST) was the most common biochemical abnormality (84%), with 54% of patients having an AST of more than twice the upper limit of normal. The median survival from the time of diagnosis of liver metastases was 3.8 months. No feature existing prior to the development of liver metastases influenced subsequent survival. The presence of jaundice ($P < 0.001$), ascites ($P = 0.01$) or hepatomegaly ($P = 0.01$) were all associated with a particularly poor prognosis. While any degree of elevation of bilirubin ($P < 0.001$) or alkaline phosphatase ($P = 0.003$) was unfavourable, a raised AST alone was not predictive of shorter survival. AST only influenced survival significantly when above twice the upper limit of normal ($P < 0.001$), with prognosis then progressively worsening the more elevated the level. Multivariate analysis using the Cox model suggested that the degree of elevation of AST was the single most important prognostic factor for survival after the diagnosis of liver metastases.
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INTRODUCTION

PATIENTS with liver metastases from breast cancer generally have a poor prognosis with a median survival from liver relapse of 2–14 months [1–3]. Treatment of these patients presents a difficult clinical problem. Response to endocrine therapy is uncommon [4], while the administration of chemotherapy can be complicated by the involvement of the liver in the activation or metabolism of several cytotoxic drugs commonly used in the treatment of advanced breast cancer [5, 6]. We report here our experience of all patients with liver metastases from breast cancer seen in this unit over a 13-year period. The clinical and pathological features associated with liver metastases are described and the impact of these features on survival is analysed.

Correspondence to: S.M. O'Reilly, Department of Medical Oncology, Charing Cross Hospital, London W6 8RF, U.K.
S.M. O'Reilly, M.A. Richards and R.D. Rubens are at the ICRF Clinical Oncology Unit, Guy's Hospital, London, U.K.

PATIENTS AND METHODS

Three hundred and twelve patients seen in the ICRF Clinical Oncology Unit at Guy's Hospital between January 1974 and December 1986 had liver metastases from breast cancer diagnosed before death. Liver metastases were diagnosed on radionuclide or ultrasound liver scan in 293 patients (94%). Scanning of the liver was not performed routinely. Liver scans were obtained only if hepatomegaly was detected clinically or if liver biochemistry was abnormal.

Hepatomegaly was assessed clinically. The biochemical profile included serum bilirubin, aspartate transaminase (AST), alkaline phosphatase and albumin. As the laboratory normal range of these biochemical measurements varied during the period covered by this study the results are expressed as a ratio to the upper limit of the normal range at the time of measurement.

Response to treatment for liver metastases was assessed by UICC criteria [7] and refers to response in the liver only. Survival was measured from the date of diagnosis of liver metastases to death. Chi-square analysis was used to assess differences between subgroups of patients and the log-rank test was used to assess the influence of clinical and pathological features on survival