Improved survival in patients with peritoneal metastases from colorectal cancer: a preliminary study

H Mahteme*, 1, J Hansson1, Å Berglund2, L Pählman1, B Glimelius2, P Nygren2 and W Graf1
1Department of Surgical Sciences, Akademiska Sjukhuset, Uppsala, Sweden; 2Department of Oncology, Radiology and Clinical Immunology Akademiska Sjukhuset, Uppsala, Sweden

Peritoneal or local metastasis from colorectal cancer implies a poor prognosis. However, aggressive treatments by debulking surgery and infusional intraperitoneal (i.p.) chemotherapy have been tried and appear to benefit selected patients. We assayed the effects of debulking surgery and i.p. chemotherapy with respect to survival and compared the results with matched control patients treated by intravenous (i.v.) chemotherapy. In all, 18 patients with peritoneal and/or local metastases from colorectal adenocarcinoma underwent debulking surgery followed by 5-fluorouracil (5-FU) 550 mg m\(^{-2}\) day\(^{-1}\) i.p. and leucovorin (LV) 60 mg m\(^{-2}\) day\(^{-1}\) i.v. The chemotherapy was started the day after surgery and was given daily for 6 days and repeated monthly for totally eight courses. The control patients, matched for age, gender, performance status and metastatic site, were randomly selected from controlled clinical chemotherapy trials and treated with i.v. 5-FU + LV or i.v. methotrexate + 5-FU + LV. There was no treatment-related mortality. The median survival among i.p. patients was 32 months compared to 14 months in the control group. In all, 11 patients who underwent macroscopically radical surgery had a longer survival than those who were not radically operated \( (P = 0.02) \). These results indicate that patients with peritoneal metastases and/or locally advanced cancers but without distant metastases may benefit from cytoreductive surgery combined with i.p. chemotherapy.

Keywords: colorectal cancer; peritoneal metastases; intraperitoneal chemotherapy

Patients with peritoneal or local metastasis from colorectal cancer have a poor prognosis. However, aggressive treatments by debulking surgery and infusional intraperitoneal (i.p.) chemotherapy have been tried and appear to benefit selected patients. We assayed the effects of debulking surgery and i.p. chemotherapy with respect to survival and compared the results with matched control patients treated by intravenous (i.v.) chemotherapy. In all, 18 patients with peritoneal and/or local metastases from colorectal adenocarcinoma underwent debulking surgery followed by 5-fluorouracil (5-FU) 550 mg m\(^{-2}\) day\(^{-1}\) i.p. and leucovorin (LV) 60 mg m\(^{-2}\) day\(^{-1}\) i.v. The chemotherapy was started the day after surgery and was given daily for 6 days and repeated monthly for totally eight courses. The control patients, matched for age, gender, performance status and metastatic site, were randomly selected from controlled clinical chemotherapy trials and treated with i.v. 5-FU + LV or i.v. methotrexate + 5-FU + LV. There was no treatment-related mortality. The median survival among i.p. patients was 32 months compared to 14 months in the control group. In all, 11 patients who underwent macroscopically radical surgery had a longer survival than those who were not radically operated \( (P = 0.02) \). These results indicate that patients with peritoneal metastases and/or locally advanced cancers but without distant metastases may benefit from cytoreductive surgery combined with i.p. chemotherapy.

The aim of this study was to explore the effects of cytoreductive surgery followed by repeated courses of i.p. chemotherapy with respect to feasibility, side effects and survival, and to compare with the results obtained using systemic chemotherapy.

**PATIENTS AND METHODS**

**Patients characteristics**

In all, 18 patients (nine women, nine men, mean age 54 years, range 31–74) were included in the study. The study was approved by the regional ethics committees. The protocol was set up in 1991 and the last patient was included in September 1999. The inclusion criteria were primary colorectal adenocarcinoma (colon 16, rectal 2), with local or peritoneal tumour deposits either resectable or suitable for debulking surgery, and without hepatic or other extra abdominal tumour growth as judged from laparotomy, chest X-ray and ultrasonography/CT scan, age <75 years and American Society of Anesthesiologists (ASA) classification grades 1–2. Informed consent was obtained from each patient. The diagnosis of the primary tumour and the metastases were verified histopathologically. One patient was not treated according to the protocol because of extensive irreversible peritoneal tumour growth. The remaining 17 patients were treated by either total macroscopic removal (11) or debulking (6) of the metastases followed by i.p. chemotherapy. In four patients, the diagnosis of

*Correspondence: Dr H Mahteme; E-mail: Haile.Mahteme@kirurgi.uu.se
Received 26 March 2003; revised 7 September 2003; accepted 13 November 2003
Surgical treatment

The mean operating time was 3.7 h (range 0.9–6.7). The surgical procedure, the metastatic location and the treatments are detailed in Table 1. At the end of surgery, a PORT-A-CATH (No. 21-2000-04, SIMS deltec, Inc., St Paul, MN, USA) was placed subcutaneously just above the periost of the lower ribs and a catheter was tunneled through the abdominal wall and directed towards the principal tumour site. Finally, a drainage no. 18 was placed in the abdominal cavity. The drainage was plugged while the chemotherapy was given, but opened for drainage of peritoneal fluid for 1–2 h just before the next i.p. infusion. This drainage was removed at the end of the first treatment course.

Intraperitoneal chemotherapy

The i.p. chemotherapy was started the day after surgery. 5-Fluorouracil was given i.p. (550 mg m⁻² day⁻¹) dissolved in 500 ml saline 0.9%. At 60 min after the start of the infusion, an i.v. infusion of leucovorin (LV) (60 mg m⁻²) was administered. The pharmacokinetical rationale for this sequential treatment is to obtain simultaneous tissue peak concentration of 5-FU and LV (Spears et al, 1989). The 5-FU dose was selected after a pilot study, showing that an i.p. 5-FU dose of 550 mg m⁻² day⁻¹ during 6 days was possible to give directly after major abdominal surgery without causing an increased risk for postoperative complications (Graf et al, 1994c). The chemotherapy treatment was given daily for 6 days with 4–6 weeks intervals. Any possible symptoms and side effects of the treatment were registered. Before the second course of treatment, a single photon emission computed tomography (SPECT) (General Electric, GE Maxxus, Milwaukee, WI) (Technetium-labelled albumin (⁹⁹Tc⁰ Albures) at volume of 500 ml) was performed to judge the potential distribution of the drug in the abdominal cavity. The distribution of the drug was calculated using a computer-based measurement (FBP, Nuclear Diagnostics AB, Stockholm, Sweden). After the fourth course, a clinical evaluation was carried out. Another run of four courses was given if the patients responded well, tolerated treatment and clinical evaluation was carried out. Another run of four courses was given if the patients responded well, tolerated treatment and showed a median abdominal cavity distribution volume of 2896 ml (range 32–11 557). In one patient, treatment was withdrawn after SPECT because of the lack of widespread distribution in abdominal cavity. In five patients the PORT-A-CATH was reoperated. There was no mortality related to surgery or to the i.p. treatment. In one patient who was not treated with cytoreductive surgery, no i.p. chemotherapy was administered.

Survival

The median survival in i.p. patients was 32 months (95% confidence interval (CI) 22.2–62.6 months), whereas in the i.v. control group it was 14 months (95% CI 5.6–24.9 months), (P = 0.01, Figure 1). A 2 and 5 years survival in i.p. patients were 60 and 28%, whereas corresponding values in the i.v. control group were 10 and 5%. In all, 11 patients who were considered macroscopically tumour free after the tumour reduction procedure had a longer survival (34.5 months, 95% CI 28.7–75.7) than those who did not undergo macroscopically radical surgery (10 months, 95% CI 15.7 to 70.0, (P = 0.02, Figure 2). Five patients in whom radical surgery could be performed are still alive (median 8.3 years, range 6.8–9.1) after surgery. One patient who underwent radical surgery survived only 4 months. One patient who was considered not to be macroscopically tumor free after the tumor reduction procedure is still alive and has survived 10.8 years. In total, 10 patients in whom radical surgery was not performed survived median 13 months (range 3 months–10.8 years).

Discussion

Our experience, with treatment of peritoneal colorectal metastases, is promising. We believe patients without hematogenous metastases (e.g. liver, lung, etc) from colorectal cancer might have a survival benefit if cytoreductive surgery is combined with i.p.
Table 1  Surgical procedures of the 18 patients in the i.p. group

| Pat. | Primary tumour site | Surgical procedures at primary tumour surgery | Completing surgical events before inclusion | Metastatic site at inclusion | Surgical procedures at inclusion | Macroscopically radical | Remnant tumour location | Additional surgical tumour procedures | PAC reop. |
|------|---------------------|-----------------------------------------------|---------------------------------------------|----------------------------|----------------------------------|-------------------------|-------------------------|----------------------------------------|----------|
| 1    | Colon               | Colectomy, IRA                               | Rectal res. SBR × 2                         | Small bowel, abdominal wall, peritoneal | SBR, AWR, local excision        | Yes                     | Pelvic                  | SBR                                    | Yes      |
| 2    | Colon               | R. hemicolecotomy                            | R. hemicolectomy                            | Ventricule, duodenum, small bowel × 2 | ICR, duodenal resection, local excision, EC | Yes                     | Pelvic                  | Scapula and costae resection           | Yes      |
| 3    | Colon               | Sigmoid resection, SOE                        | Pelvic wall                                 | Peritoneal                   | Local excision, EC              | Yes                     | Pelvic                  | Yes                                    | No       |
| 4    | Rectum              | APR                                           | Pelvic wall                                 | Peritoneal                   | Local excision, EC              | No                      | Pelvic                  | R. hepatectomy, aorta resection, SBR   | No       |
| 5    | Colon               | Ileoacal resection                           | Ileoacal anastomosis, jejenum, abdominal wall | ICR, SBR, local excision     | Yes                             | Pelvic                  | Pelvic                  | SBR, recto sigmoid resection, ureterolysis | No       |
| 6    | Colon               | Sigmoid resection, L, hemicolecotomy, splenectomy | Abdominal wall, small bowel                 | AWR, SBR, local excision     | Yes                             | Pelvic                  | Pelvis                  | Yes                                    | No       |
| 7    | Colon               | Sigmoid resection                            | Ileoacal anastomosis                        | ICR, local excision          | Yes                             | Pelvic                  | Pelvis                  | Yes                                    | No       |
| 8    | Colon               | R. hemicolecotomy                            | Ileoacal anastomosis, sigmoid, uterus, ovary, vagina, peritoneal | ICR, local excision, SOE, hysterectomy, EC | No | No | R. hepatectomy, aorta resection, SBR | No |
| 9    | Colon               | L. hemicolecotomy                            | Colectomy+IRA, SOE                          | Abdominal wall, pelvic wall, peritoneal | AWR, local excision, EC        | No                      | Pelvic                  | No                                     | Yes      |
| 10   | Colon               | R. hemicolecotomy                            | Pelvic wall, urinary bladder                | Urinary bladder resection, urostoma, local excision | No | No | Pelvis                  | No |
| 11   | Colon               | ICR                                           | Abdominal wall, ileacal anastomosis         | R. hemicolecotomy, AWR, Local excision | Yes | No | No | No |
| 12   | Colon               | Sigmoid resection                            | Pelvic wall, rectum, small bowel, L.A, ilaca int, L. ureter | AR, ilaca int resection, local excision | Yes | No | No | No |
| 13   | Colon               | R. hemicolecotomy                            | Abdominal wall, small bowel, sigmoid colon | AWR, SBR, sigmoid resection | Yes | No | Pelvis                  | AWR |
| 14   | Colon               | Ileoacal resection                           | R. colon, small bowel, ovary, peritoneal    | R. hemicolecotomy, SOE, local excision, EC | Yes | No | No | No |
| 15   | Rectum              | APR, sigmoideal stoma                        | Pelvic local, hep, caecum                  | ICR, Liver resection, local excision | No | No | Pelvis                  | Yes |
| 16   | Colon               | Sigmoid resection, pelvic wall resection      | Ovary small bowel, colon transversum, peritoneal | Transversum resection, SBR, local excision, EC | No | No | Pelvis                  | Yes |
| 17   | Colon               | Sigmoid resection, pelvic wall resection      | Peritoneal, locally advanced               | Local excision               | No | No | Peritoneal              | Recto sigmoid anastomosis |
| 18   | Colon               | R. hemicolecotomy                            | Peritoneal, locally advanced               | None                        | No, No PAC | Peritoneal, locally advanced | No |

AR = anterior resection; SOE = salpingo ofoor ectomy; APR = anterior perineal resection; AWR = abdominal wall resection; EC = electric cautery; ICR = ileoacal resection; IRA = ileorectal anastomosis; PAC = port-A-cath; SBR = small bowel resection.
chemotherapy. Furthermore, a complete remission of the disease is possible for an extended period of time. It seems that a macroscopically radical tumour resection has an impact on survival.

This series is not a prospective-randomised study, and a selection of patients may of course have influenced the results. However, in an attempt to compare the locoregional treatment to standard i.v. chemotherapy, we used historical controls. The two combinations (MFL and FLv) of chemotherapy, both based on biochemical modulation of 5-FU, were equally effective with respect to survival and response rates in one trial (Glimelius et al, 1998). It is therefore reasonable to consider these two combinations as equal and these patients thus received ‘golden standard’ chemotherapy during their treatment period. However, the more recently developed combination regimen (de Gramont et al, 2000; Douillard et al, 2000; Saltz et al, 2000) are even more effective than those used in the Nordic chemotherapy trials.

The relative importance of the i.p. chemotherapy cannot be properly assessed in the present study and further studies are needed to clarify a possible contribution of locoregional chemotherapy to the treatment effect. A possible benefit of a repeated regional treatment has been suggested since the end of 1960s (Long et al, 1969) and several reports have been published since then (Sugarbaker et al, 1996; Stephens et al, 1999; Cavaliere et al, 2000; Elias et al, 2001). One of the major problems is the nonuniform distribution of the chemotherapy to tumour deposits within the abdominal cavity. The SPECTs can be valuable to analyse the drug distribution in the abdominal cavity. If there are several adhesions, the labelled albumin will accumulate only in a limited space and chemotherapy may not reach all possible metastatic sites. To prevent postoperative adhesions and an obliterated abdomen, an early start of i.p. infusion, that is, immediately after surgery or at the latest the first postoperative day may be important.

One of the concerns of i.p. chemotherapy is anastomotic dehiscence. A study in humans indicated that it is possible to give the present regimen a day after surgery without suppressing the collagen accumulation too much (Graf et al, 1994a,b). In addition, an experimental study showed an impaired healing after i.p. 5-FU, but when folic acid was added, no further deterioration occurred (Graf et al, 1992). However, this problem and other chemotherapy-related toxicities have been investigated in several clinical studies and this form of administration has not been associated with an increased complication rate (Graf et al, 1994c; Vaillant et al, 2000).

The antitumoral effect of chemotherapy is believed to be enhanced by hyperthermia (41–42°C), possibly through an increase in cell membrane permeability, alteration of active drug transport, a change in cell metabolism and a decreased interstitial fluid pressure (Hahn and Shiu, 1983; Leunig and Hirth, 1993; Kong et al, 2000). Moreover, recent clinical studies have shown promising results (Beaujard et al, 2000; Cavaliere et al, 2000). However, there is a lack of consensus about the optimal target temperature and a finding of increased morbidity and mortality when a cytoreduction procedure has been followed by hyperthermic i.p. chemotherapy (Jacquet et al, 1996) that warrant further studies. To optimise the i.p. treatment, choosing the appropriate chemotherapy is crucial. An important obstacle to successful treatment of solid tumours is the resistance to cytotoxic drugs (Wright et al, 1998; Germain, 2000; Kepler et al, 2000). In this context, the drug resistance examination is a potential valuable tool (Csoka et al, 1994, 1995).

In summary, a survival benefit can be achieved with cytoreductive surgery followed by repeated courses of i.p. chemotherapy. A complete remission of the disease is possible for an extended period of time. However, a longer period of follow-up is needed to establish if definite cure is possible for this category of patients and a randomised study is necessary to prove the value of this approach definitely.

ACKNOWLEDGEMENTS

This study was supported by the Swedish Cancer Society Project No. 4618-B01-01XAA

REFERENCES

Assersohn L, Norman A, Cunningham D, Benepal T, Ross PJ, Oates J. Influence of metastatic site as an additional predictor for response and outcome in advanced colorectal carcinoma. Br J Cancer 1999; 79: 1800 – 1805

Beaujard A, Glehen O, Caillot J, Francois Y, Bienvenu J, Panteix G, Garbit F, Grandclement E, Vignal J, Gilly FN. Intrapitoneal chemohyperthermia with mitomycin C for digestive tract cancer patients with peritoneal carcinomatosis. Cancer 2000; 88: 2512 – 2519

British Journal of Cancer (2004) 90(2), 403 – 407 © 2004 Cancer Research UK
Graf W, Di Filippo F, Botti C, Cosimelli M, Giannarelli D, Aloe L, Arcuri E, Aromatario G, Consolo S, Caloppoli A, Laurenzi L, Tedesco M, Di Angelo P, Giunta S, Cavaliere R. Peritoneal recurrence and hyperthermic antioblastic perfusion in the treatment of peritoneal carcinomatosis. *Eur J Surg Oncol* 2000; 26: 486 – 491.

Colorectal Cancer Collaborative Group. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. BMJ 2000; 321: 531 – 551.

Coka K, Larsson R, Tholander B, Gerdin E, dela Torre M, Nygren P. Cytotoxic drug sensitivity testing of tumour cells from patients with ovarian carcinoma using the fluorometric microculture cytotoxicity assay (FMCA). *Gynecol Oncol* 1994; 54: 163 – 170.

Coka K, Nygren P, Graf W, Pahlman L, Glimelius B, Larsson R. Selective sensitivity of solid tumors to suramin in primary c of tumor cells from patients. *Int J Cancer* 1995; 6: 356 – 360.

Culliford 4th AT, Books AD, Sharma S, Saltz LB, Schwartz GK, O'Reilly EM, Ilson DH, Kemeny NE, Kelsen DP, Guillem JG, Wong WD, Cohen AM, Pfyte PB. Surgical debulking and intraperitoneal chemotherapy for selected peritoneal metastases from colon and appendix cancer. *Ann Surg Oncol* 2001; 10: 787 – 795.

Cunliffe WJ, Sugarbaker PH. Gastrointestinal malignancy: rationale for adjuvant therapy using early postoperative intraperitoneal chemotherapy. *Br J Surg* 1989; 76: 1082 – 1090.

de Graaf M, Aigner F, Seymour M, Homerin M, Himsi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichail D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18: 2938 – 2947.

Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Cucinotta J, Sugarbaker PH. Biochemical modulation of 5-fluorouracil: a randomized trial. *Cancer Treat Res* 1993; 14: 341 – 135.

Elias D, Blot F, El Otmany A, Antoun S, Lasser P, Boige V, Rougier P, Car兼 Tigue P, Gustavsson B, Fro trading R. Folinic acid modulation of 5-fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; 355: 1041 – 1047.

Elis A, Blot F, El Otmany A, Antoun S, Lasser P, Boige V, Rougier P, Duceux M. Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. *Cancer* 2001; 92: 71 – 76.

Germann UA. Detection of recombinant P-glycoprotein in multidrug resistant cultured cells. *Mol Biotechnol* 2000; 14: 131 – 147.

Glimelius B. Biochemical modulation of 5-fluorouracil: a randomized comparison of sequential methotrexate, 5-fluorouracil and levovorin versus sequential 5-fluorouracil and levovorin in patients with advanced symptomatic colorectal cancer. The gastrointestinal tumour adjuvant therapy group. *Ann Oncol* 1993; 4: 235 – 240.

Glimelius B, Jakobson A, Graf W, Berglund A˚, Gadeberg C, Hansen P, Kjaer Vaalli J-C, Nordlinger B, Deuffic S, Arnaud JP, Pelissier E, Favre JP, Jaeck H., et al. Improved survival in patients with peritoneal metastases from adenocarcinoma of the colon. *Cancer Treat Rev* 1996; 22: 247 – 260.

Hahn GM, Shiou EC. Effect of pH and elevated temperatures on the cytotoxicity of some chemotherapeutic agents on Chinese hamster cells in vitro. *Cancer Res* 1983; 43: 5789 – 5791.

Horsell KW, Merton S, Clingan P, King DW, Morris DL. Peritoneectomy and intraperitoneal chemotherapy in appendix and colorectal cancer. *Aust NZ J Surg* 1999; 69: 729 – 732.

Jacquet P, Stephens AD, Averbach AM, Chang D, Ettinghausen SE, Dalton RR, Steves MA, Sugarbaker PH. Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. *Cancer* 1996; 77: 2622 – 2629.

Kepper D, Kamisako T, Leier I, Yunhai C, Nies A, Tsuji H, Konig J. Localization, substrate specificity, and drug resistance conferred by selective export pumps of the MRP family. *Adv Enzyme Regul* 2000; 40: 339 – 349.

Kong G, Braun R, Dewhirst M. Hyperthermia enables tumor-specific nanoparticle delivery: effect of particle size. *Cancer Res* 2000; 60: 4440 – 4445.

Leung M, Goetz AE, Dillian M, Zetterer G, Garman R, Jain RK, Messmer K. Interstitial fluid pressure in solid tumors following hyperthermia: possible correlation with therapeutic response. *Cancer Res* 1992; 52: 487 – 490.

Long RTL, Spratt Jr JS, Dowling E. *Pseudomyxoma peritonei*. New concepts in management with a report of seventeen patients. *Ann J Surg* 1969; 117: 162 – 169.

Malbran H, Pahlman L, Glimelius B, Graf W. Prognosis after surgery in patients with incurable rectal cancer: a population-based study. *Br J Surg* 1986; 73: 1116 – 1120.

Nordic Gastrointestinal Tumour Adjuvant Therapy gRoup. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol* 1992; 10: 904 – 911.

Ragnhammar P, Hafström L, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in colorectal cancer. *Acta Oncol* 2001; 40: 282 – 308.

Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LR. Irinotecan plus fluorouracil and levovorin for metastatic colorectal cancer. *N Engl J Med* 2000; 343: 905 – 914.

Schellinx ME, von Meyenfeldt MF, Sugarbaker PH. Peritoneal carcinomatosis from adenocarcinoma of the colon. *Cancer Treat Rev* 1996; 21: 247 – 260.

Shepherd N, Baxter K, Love S. The prognostic importance of peritoneal involvement in colon cancer: a prospective evaluation. *Gastroenterology* 1997; 112: 1096 – 1102.

Sears CP, Gustavsson BG, Frössing R. Folinic acid modulation of fluorouracil: tissue kinetics of bolus administration. *Invest New Drugs* 1989; 7: 27 – 36.

Stephens AD, Alderman R, Chang D, Edwards GD, Esquivel J, Steves M, Sugarbaker PH. Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. *Ann Surg Oncol* 1999; 6: 790 – 796.

Sugarbaker PH, Schellinx ME, Chang D, Koslowe P, von Meyenfeldt M. Peritoneal carcinomatosis from adenocarcinoma of the colon. *World J Surg* 1996; 20: 585 – 592.

Vaillant J-C, Nordlinger B, Deuffic S, Arnaud NA, Pelissier E, Favre JP, Jaeck D, Fontquin G, Grandjean JP, Marre P, Letoublon C. Adjuvant intraperitoneal 5-fluorouracil in high risk colon cancer. *Ann Surg* 2000; 231: 449 – 456.

van Ooijen B, van der Burg M, Planting A, Siersema P, Wiggers T. Surgical treatment of gastric drainage only for intestinal obstruction in patients with carcinoma of the ovary or peritoneal carcinomatosis of other origin. *Surg Gynecol Obstet* 1993; 176: 469 – 474.

Wright SR, Boag AH, Valdimarsson G, Hipfner DR, Campling BG, Cole SP, Deleye RG. Immunohistochemical detection of multidrug resistance protein in human lung cancer and normal lung. *Clin Cancer Res* 1998; 4: 2279 – 2289.