

# World Journal of *Gastrointestinal Surgery*

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## In advanced gastric cancer: Prognosis and treatment of patients with positive peritoneal cytology

Francesco Frattini, Stefano Rausei, Corrado Chiappa, Francesca Rovera, Luigi Boni, Gianlorenzo Dionigi

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**Core tip:** Gastric cancer staging is still matter of debate as it evolves along with introduction of new diagnostic tools. Use of laparoscopy and washing cytology in gastric cancer staging has identified a particular category of patients with no macroscopic peritoneal disease but with positive peritoneal cytology. Prognosis and management of such patients still remains a controversial issue.

Frattini F, Rausei S, Chiappa C, Rovera F, Boni L, Dionigi G. In advanced gastric cancer: Prognosis and treatment of patients with positive peritoneal cytology. *World J Gastrointest Surg* 2013; 5(5): 135-137 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v5/i5/135.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v5.i5.135>

### Abstract

Positive peritoneal cytology in gastric cancer is classified as M1 disease by the 7<sup>th</sup> Edition of American Joint Committee on Cancer staging system. With the introduction of laparoscopy and peritoneal washing cytology in the staging of gastric cancer a new category of patients has been identified. These are patients with no macroscopic peritoneal metastases but with peritoneal cytology positive (POC1). Prognosis and treatment of such patients represent a controversial issue. We evaluate the state of the art of staging system in gastric cancer and discuss standardisation in staging and treatment procedures. There is still a lack of uniformity in the use of laparoscopy with peritoneal cytology in clinical decision making and in the surgical treatment for gastric cancer. Survival of this patient subset remains poor. Multimodal therapies and new therapeutic strategies are required to improve the survival of these patients.

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**Key words:** Advanced gastric cancer; Peritoneal washing cytology; Staging laparoscopy; Reverse transcription-polymerase chain reaction

### COMMENTARY ON HOT TOPICS

Gastric cancer is the second most frequent cause of cancer death worldwide<sup>[1]</sup>. Unfavourable prognosis, mainly in Western countries, is related to the advanced stage of the disease at the diagnosis. The peritoneum is the most common site of metastasis in patients with gastric cancer. Since accurate staging of patients with locally advanced disease is critical for selecting the appropriate treatment strategy, in addition to visible macroscopic peritoneal metastases, only positive peritoneal washing cytology is included in the American Joint Committee on Cancer (AJCC) staging system (7<sup>th</sup> edition) definition of M1 disease<sup>[2]</sup>. The standardization of peritoneal cytological examination is essential, and staging laparoscopy is necessary in patient selection for neoadjuvant chemotherapy. The management of patients with positive peritoneal cytology as the only evidence of M1 disease is largely unknown. Though patients with intraperitoneal free cancer cells (IFCC) have traditionally been offered palliative care, prognosis could be improved by a multimodal approach. Both neoadjuvant and adjuvant treatment strategies are

currently being evaluated.

How should we regard patients negative for macro/microscopic peritoneal seeding, but with positive peritoneal cytology: locally advanced disease or metastatic disease? What is the best treatment option for this subset of patients: neoadjuvant therapy or resection and adjuvant therapy?

In their retrospective study Lee *et al*<sup>[3]</sup> included 1072 patients who underwent surgery for gastric cancer and peritoneal washing cytology: 84% had negative cytology, 16% positive cytology. The patients were stratified into four subgroups: P0C0 (no peritoneal metastases, negative cytology), P0C1 (no peritoneal metastases, positive cytology), P1C0 (peritoneal metastases, negative cytology), P1C1 (peritoneal metastases, positive cytology). Median overall survival was best in the P0C1 subgroup (20 mo) and decreased to 14 and 10 mo respectively for P1C0 and P1C1 subgroups. Patients with P0C1 disease seem to have significantly better survival than those with P1C1 disease. This is probably due to the combination of aggressive surgical resection with lymph node dissection and adjuvant chemotherapy. This is confirmed by the reduction in peritoneal recurrence with associated improvement survival using the aggressive approach reported by Kuramoto *et al*<sup>[4]</sup>.

On the other hand, Mezhir *et al*<sup>[5]</sup> have essentially abandoned gastrectomy as positive peritoneal cytology even in absence of gross peritoneal disease suggests a poor outcome.

So identifying prognostic factors within P0C1 patients may be crucial for planning the most suitable therapeutic option. Again, the multivariable analysis by Lee *et al*<sup>[3]</sup> showed that P0C1 group (with N0/2 patients) after resection and adjuvant chemotherapy had a significantly better prognosis.

Lorenzen *et al*<sup>[6]</sup> demonstrated that gastric cancer patients, whose IFCC status was converted from positive to negative following neoadjuvant therapy, had an improved median survival after surgery, suggesting that surgeons should selectively offer aggressive resection in patients in whom there is a response to induction chemotherapy.

A recent study by Mezhir *et al*<sup>[5]</sup> has proposed a new approach to patients with M1 disease based solely on IFCC positivity. After chemotherapy for 6-12 mo, if there is no clinical progression, repeat cytology is performed. Patients who remain positive for IFCCs are treated palliatively. Patients who become IFCCs negative have repeat laparoscopy after a further 3-6 mo. If they revert to M1 status, they are treated palliatively. If they remain IFCC-negative and have good performance status, they are considered for gastrectomy. Using this strategy, the authors reported a resection rate of 74% for ICC-positive patients who were converted to negative cytology.

A third option, not included in the analysis, is intraoperative chemotherapy (IPC). Some studies have demonstrated the efficacy of this procedure in patients with advanced peritoneal dissemination and have shown improvement in survival rates and a decrease in the incidence of peritoneal recurrence<sup>[7]</sup>.

Currently there are no level 1 data to support a specific

treatment plan. As reported by the review of Matharu *et al*<sup>[7]</sup> the methodological quality of most studies on intraperitoneal chemotherapy is poor, owing to selection and observer bias. Intraperitoneal chemotherapy can be administered preoperative, intraoperative and postoperative. Yano *et al*<sup>[8]</sup> treated with neoadjuvant IPC, 25 patients with T3/T4 tumors, no macroscopic carcinomatosis, (in only one case positive peritoneal lavage cytology) and achieved disease T downstaging in 48% of cases.

The use of extensive intraoperative peritoneal lavage followed by intraperitoneal chemotherapy has been demonstrated, in a randomized controlled trial, to improve the 5-year survival in patients with positive peritoneal cytology and no macroscopic peritoneal carcinomatosis<sup>[4]</sup>. So, IPC may reduce the frequency of peritoneal recurrence in patients with locally advanced gastric cancer in the absence of macroscopic peritoneal seeding, but is clearly unable to prevent recurrence or disease progression completely. Studies seem to demonstrate that IPC is more effective in preventing peritoneal carcinomatosis than in treating macroscopic carcinomatosis.

The methods for detecting IFCCs represent yet another controversial issue. The sensitivities of conventional cytology, immunoassay, immunohistochemistry (IHC), and reversetranscription polymerase chain reaction (RT-PCR) in predicting peritoneal recurrence are low and vary considerably<sup>[8]</sup>. Such low sensitivities suggest that a significant number of patients negative for IFCCs are developing recurrent disease. RT-PCR for the detection of a single tumor marker, CEA mRNA, in the peritoneal lavage increases the detection of subclinical peritoneal disease and is more sensitive than conventional cytology. PCR was positive in a significantly greater number of patients with advanced-stage disease or vascular and perineural invasion than in those who were cytology positive. Multiple studies have shown that patients with no visible peritoneal disease at laparoscopy (LAP-) and positive for PCR have a worse survival and earlier recurrence than PCR-patients<sup>[9]</sup>.

A significant challenge when applying such a sensitive technique is to determine the best threshold and the true predictive role of PCR, thus avoiding overinterpretation of the clinical significance of a false-positive PCR<sup>[10]</sup>. Future studies will also help determine whether analysis of multiple tumor markers rather than a single gene may increase the diagnostic yield and independent predictive value of RT-PCR.

In conclusion, the evaluation of peritoneal cytology in gastric cancer patients is still a grey zone with regards to staging and treatment options. There is lack of uniformity in the utilization of peritoneal cytology in the algorithm of gastric cancer treatment. The optimal management of patients with IFCCs still remains debatable. Therefore, identifying prognostic factors and stratifying patients with IFCCs will be crucial in targeting therapeutic options.

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## Management of potentially resectable colorectal cancer liver metastases

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### Abstract

Colorectal cancer is a very common malignancy worldwide and development of liver metastases, both synchronous or metachronous, is a common event. Of all patients with metastatic colorectal cancer, up to 77% have a liver-only disease and approximately 10%-20% of patients with colorectal liver metastases are considered resectable at the time of diagnosis. Surgical resection of liver metastases remains the best treatment option and it is associated with a survival plateau and a 20%-25% of long-term survivors. Perioperative chemotherapy for resectable liver metastases may improve resectability of liver metastases and disease free survival, but its impact on overall survival is still unclear and more studies are needed. Moreover, preoperative chemotherapy can increase postoperative complications. Further studies are needed to define the role of adjuvant chemotherapy after a R0 resection of liver metastases and to define the criteria for a better selection of patients candidate to hepatectomy. New strategies such as targeted therapies are emerging with promising results. Optimal management requires a multidisciplinary approach, local and systemic, but it is a still pending question. Colorectal liver metastases represent a major challenge for oncologists and surgeons. In this review will be analyzed available data about assessment and

management of the patients with potentially resectable colorectal liver metastases.

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**Key words:** Colorectal cancer; Liver metastases; Perioperative chemotherapy; Surgical resection; Targeted therapies

**Core tip:** Colorectal cancer is a very common malignancy and its incidence is rapidly increasing worldwide. Of all patients with metastatic colorectal cancer, up to 77% have a liver-only disease and about 10%-20% of them are considered resectable at the time of diagnosis. Surgery actually still represents the best option of treatment, but new strategies such as perioperative chemotherapy and targeted therapies are emerging with promising results. However, optimal management requires a multidisciplinary approach, both local and systemic. This review aims to critically analyze the management of potentially resectable colorectal liver metastases.

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### INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality<sup>[1]</sup>. The liver is the most common site of CRC metastases and nearly 25% of patients with CRC present with synchronous liver metastases at the time of initial diagnosis and 50%-75% of patients within three years after primary colonic surgery at the time of disease recurrence<sup>[2-5]</sup>. Though most of

these patients have a poor prognosis, there is a subset of patients with liver metastases, both synchronous or metachronous, that can benefit from radical surgery and possibly even achieve cure<sup>[6]</sup>. In fact, from 25% to 50% of patients with surgically resected colorectal liver metastases (CLM) today can survive five or more years after surgery<sup>[7-11]</sup>. Unfortunately, only a small percentage of patients, estimated at 10%-20%, exhibits with initially resectable liver metastases<sup>[12]</sup> and up to 2/3 of patients with resected CLM will experience a recurrence in the majority cases just in the same organ<sup>[13,14]</sup>. In the last two decades, we have observed remarkable advances in the treatment of CLM, both from a medical point of view with the advent of new chemotherapeutic and biologic agents, and with the improvement of surgical techniques and a better definition of the resectability criteria. However, up to now, strong scientific evidences about what is the best strategy for the treatment of CLM are still debated. One of the obstacles to be addressed is the difficulty in defining “Who is resectable?”. The indications for resection of CLM changed significantly over the years. In the late eighties, Ekberg defined restrictive criteria for resectability: less than four metastases (uni or bilobar), absence of extrahepatic disease, and resection margin of at least 1 cm. Moreover, Steele suggested resection of liver metastases only from colorectal primary, three or less lesions, R0 resections, absence of comorbidities and extrahepatic disease<sup>[5,15]</sup>. Starting from the nineties, these criteria were gradually extended, in relation to location and size of tumor, number of lesions, and absence of extrahepatic disease<sup>[16]</sup>. Currently, the number or size of hepatic nodules in the hands of trained surgeons and in high-volume liver departments, are no longer considered an absolute contraindication to hepatectomy if the remnant healthy liver is > 25%-30%<sup>[17]</sup>. Preoperative liver magnetic resonance imaging and intraoperative ultrasound offer the optimal assessment of the number, size, and proximity of tumors to key vascular and biliary structures. Moreover, recent guidelines from the National Comprehensive Cancer Network (NCCN) (v3.2013) recommend a staging positron emission tomography scan for patients with potentially surgically curable metastatic colorectal cancer. Even the simultaneous presence of potentially resectable extrahepatic disease is no longer an absolute contraindication to surgery of liver metastases, particularly if the extrahepatic disease is surgically resectable lung or ovarian metastases. From 1996 to 2009 were identified at least twelve prognostic scoring-systems, in an attempt to predict survival after resection of CLM as a function of the number of risk factors present in the patient’s medical history<sup>[18]</sup>. One of these scoring-systems was tested by Fong *et al*<sup>[3]</sup> and assessed five risk factors on approximately 1000 patients: presence of metastatic nodes at the time of the surgery of the primary tumor, disease-free interval < 12 mo, > 1 metastatic lesion; size > 5 cm and a value of Carcinoembryonic Antigen (CEA) > 200 ng/mL. The 5-year OS ranges from 14% in patients with five risk fac-

tors to 60% in those without risk factors<sup>[19]</sup>. In an attempt to confirm these results, Tomlinson *et al* have validated the reliability of this “score”, recording a 10-year OS of 21% in resected patients with a low score (0-2) and of 10% in those with a high-risk score (3-5)<sup>[20]</sup>. On the other hand, Nordlinger score included seven risk factors: age  $\geq$  60 year, extension into the serosa of the primary cancer, lymphatic spread of the primary cancer, interval less than 2 years from primary tumor to metastases, number of metastases  $\geq$  4, largest size of liver metastasis  $\geq$  5, defining three risk groups (low, intermediate, high) with different 2-years survival rates<sup>[21]</sup>. Finally, there are increasing clinical evidences that medical perioperative treatment may improve the outcome of these patients<sup>[22,23]</sup>.

## NEOADJUVANT CHEMOTHERAPY

Surgery remains the treatment of choice for cure or prolonged survival if it is possible to obtain a radical resection (R0) and with the preservation of a residual functioning liver of 25%-30% of the original liver volume. The term “neoadjuvant chemotherapy” is reserved for chemotherapy for resectable and potentially resectable liver metastases prior to surgery. The role of neoadjuvant chemotherapy in the management of potentially resectable CLM is still controversial and debated<sup>[24]</sup>. In fact, not infrequently, in patients with favorable prognostic factors, “upfront” surgery of liver metastases is the preferred strategy. An argument in favor of the use of preoperative chemotherapy is that this may be a good test *in vivo* to evaluate the chemosensitivity of the tumor. Tumor progression while on preoperative treatment is almost always associated with a poor prognosis, even if the metastases will be resected<sup>[25]</sup>. Perioperative treatment of resectable liver metastases is supported by the phase III European Organization for Research and Treatment of Cancer (EORTC) 40983 trial (Table 1). This study randomized 364 patients with 1-4 resectable CLM to 6 cycles of preoperative and 6 cycles of postoperative 5-fluorouracil-leucovorin-oxaliplatin (FOLFOX4) compared with surgery alone. The primary endpoint was progression free survival (PFS). If we consider all of the 364 enrolled patients (182 per arm), the gain in PFS at 3 years was 7.3% in the perioperative chemotherapy arm compared with surgery alone, although this difference was not statistically significant ( $P = 0.058$ ). If you take into account only the patients who underwent a surgical resection of CLM, then the increase in favor of the perioperative treatment reaches the statistical significance (difference in PFS between the two arms of 9.2%,  $P = 0.025$ )<sup>[22]</sup>. In a recent update of the study after a median follow-up of 8.5 years, the 5-years OS (secondary endpoint) was found of 7 mo longer in the experimental arm (an increase of 3.4%, HR = 0.88; 95%CI: 0.68-1.14,  $P = 0.339$ ), but also in this case not such to reach a statistical significance. Note that in the experimental arm only 2/3 of resected patients has been able to receive the programmed postoperative

**Table 1** European Organization for Research and Treatment of Cancer 40983 Trial

	<i>n</i>	Treatment	HR for progression	3-yr PFS	5-yr PFS	Postoperative OS complications
All pts	364	CHT	0.79	35.4	51.2	-
		Surgery alone	<i>P</i> = 0.058	28.1	47.8 ( <i>P</i> = 0.339)	-
Eligible pts	342	CHT	0.77	36.2	52.4	-
		Surgery alone	<i>P</i> = 0.041	28.1	48.3 ( <i>P</i> = 0.303)	-
Resected pts	329	CHT	0.73	42.4		25%
		Surgery alone	<i>P</i> = 0.025	33.2		16%

Reproduced from reference Nordlinger *et al*<sup>[22]</sup> and Sorbye *et al*<sup>[23]</sup>. pts: Patients; CHT: Chemotherapy; HR: Hazard ratio; PFS: Progression free survival; OS: Overall survival.

chemotherapy and that the post-surgery morbidity was more significant (25% *vs* 16%, *P* = 0.04), although reversible, in patients treated with preoperative chemotherapy. Operative mortality was 1% in both treatments group<sup>[23]</sup>. It remains unresolved the question whether the benefit in PFS observed in this study is mainly due to the perioperative treatment in toto or primarily to adjuvant post-resection treatment, in favor of which there are several studies that confirm its effectiveness<sup>[26-31]</sup>. Two other small phase II trials support the use of a preoperative treatment with FOLFOX/XELOX (Capecitabine plus Oxaliplatin) and XELOX with bevacizumab<sup>[32,33]</sup>, but before we could say a definitive word on the best approach to the treatment of potentially resectable CLM we still need further dedicated studies, with or without new biological agents. Another aspect to consider in these challenging economic times is cost-effectiveness: according to literature, the use of neo-adjuvant chemotherapy could be convenient because it could possibly avoid hepatic resection in those patients who do not respond to this treatment. Nevertheless this analysis is controversial for synchronous resectable metastases<sup>[34,35]</sup>. Neoadjuvant chemotherapy can induce damage to the remnant liver and the risk of hepatic toxicity and surgical complications increase with the duration of pre-operative treatment<sup>[36,37]</sup>. Steatosis has been associated with both fluoropyrimidines and irinotecan. Vauthey *et al*<sup>[38]</sup> reported 20% patients receiving irinotecan having steatohepatitis and this was associated with increased 90-d mortality and morbidity after hepatectomy. Hepatic sinusoidal obstruction syndrome can emerge in patients treated with oxaliplatin but does not seem to be strongly associated with increased postoperative mortality<sup>[37,39]</sup>. A recent retrospective study evaluated histological specimens from 366 resected patients for CLM after preoperative chemotherapy and found that the two independent prognostic factors for OS after hepatectomy were the overall pathologic response > 75% and, surprisingly, fibrosis > 40% and not necrosis as expected<sup>[40]</sup>. Another problem with preoperative chemotherapy includes the shrinkage of viable disease, known as “vanishing metastases”, so it is not visible and therefore not resected at laparotomy. However, in many cases, this clinical complete response does not match with pathologic complete response. According to Adam *et al*<sup>[41]</sup>, the

predictive factors for a complete pathologic response are: age ≤ 60 year, size of metastases ≤ 3 cm, CEA levels at diagnosis ≤ 30 ng/mL, and objective response following chemotherapy. Patients who achieved a complete pathologic response after neoadjuvant chemotherapy had high survival rates (76% at 5 year). Patients should be carefully monitored during chemotherapy and receive surgery before metastases disappear. Therefore, response to neoadjuvant therapy must be closely monitored and it is recommended to reevaluate disease after no more than 2 mo of treatment<sup>[42]</sup>. The duration of treatment *in toto* (preoperative and adjuvant) should not exceed 6 mo<sup>[43]</sup>. In summary, many oncologists feel that perioperative therapy is the best current option of treatment for resectable CLM and the recent European Society for Medical Oncology guidelines define this subset of patients with clearly R0-resectable CLM as “Group 0”. The treatment aims of patients placed in “Group 0” is cure and decrease risk of relapse. Hence, the intensity of neoadjuvant treatment will be “nothing” (upfront surgery) or “moderate” (FOLFOX)<sup>[44]</sup>.

## ADJUVANT THERAPY AFTER RESECTION OF LIVER METASTASES

Nearly 70% of patients relapse after an hepatic resection for CLM and most of them just in the liver and within the first two years after surgery<sup>[13,14,45]</sup>. In an attempt to improve the outcome of these patients was thus adopted the rationale of adjuvant therapy. Two randomized phase III studies and a subsequent meta-analysis of data extracted by them, have evaluated the role of the combination of bolus fluorouracil and leucovorin (5-FU/LV) for 6 mo after R0 surgery of CLM *vs* surgery alone<sup>[26-28]</sup>. The results of these studies, although showing a trend in favor of adjuvant chemotherapy both in PFS and OS, do not provide a strong evidence in favor of postoperative treatment, probably due to their limited statistical power and the use of a chemotherapy regimen that actually does not represent the best combination to be administered in patients considered as metastatic patients. There are two additional meta-analyses that support the use of an adjuvant fluoropyrimidine-based treatment<sup>[29,30]</sup>. In the study of Ychou *et al*<sup>[31]</sup>, the regimen FOLFIRI, as expected, has

**Table 2** Phase III trials of adjuvant chemotherapy after resection of colorectal liver metastases

Ref	n	CHT	Median PFS (mo)	Median OS (mo)
Langer <i>et al</i> <sup>[26]</sup>	129	5-FU/LV	No difference	No difference
Portier <i>et al</i> <sup>[27]</sup>	173	5-FU/LV	24.4 vs 16.6 ( <i>P</i> = 0.028)	62.1 vs 46.4 ( <i>P</i> = 0.13)
Mitry <i>et al</i> <sup>[28]</sup>	278	5-FU/LV	27.9 vs 18.8 ( <i>P</i> = 0.059)	61.1 vs 46.9 ( <i>P</i> = 0.125)
Ychou <i>et al</i> <sup>[31]</sup>	306	FOLFIRI vs 5-FU/LV	24.7 vs 21.6 ( <i>P</i> = 0.44)	No difference

CHT: Chemotherapy; PFS: Progression free survival; OS: Overall survival; 5-FU/LV: 5-fluorouracil/Leucovorin; FOLFIRI: 5-FU/LV/Irinotecan.

failed to show advantage in disease free survival (DFS) compared to 5-FU/LV (Table 2). It was argued, as in the classical adjuvant therapy after surgery of the primary tumor, that an oxaliplatin-based regimen<sup>[46]</sup> may be more effective, but there are no definitive data and studies with the FOLFOX or XELOX regimens with or without biologic agents, are currently ongoing. Several interesting experiences, but difficult to reproduce on a large scale especially for technical difficulties and specific toxicities (*i.e.*, sclerosing cholangitis), were obtained with the administration of a derivate of fluorouracil (floxuridine, FUDR) plus high-dose dexamethasone in the hepatic artery (HAI), using the rationale of the prevalent arterial vascularization of liver metastases and of lower risk of systemic toxicities despite higher doses of chemotherapy<sup>[47-53]</sup>.

In conclusion, it is common practice to administer a postoperative chemotherapy in patients with resected CLM due to the high-relapse rate expectations and the positive impact on PFS, but unfortunately definitive data in favor of adjuvant therapy after R0 resection of CLM are still lacking. Nevertheless, actually the preferred regimen to be administered in these patients are empirically an oxaliplatin-based regimen.

Hence, it will be crucial to identify subsets of patients at increased risk of relapse and candidate to receive adjuvant treatment.

## TARGETED THERAPIES

More recently, the introduction of new biological drugs in the available arsenal of the oncologist has improved the results obtained in the treatment of metastatic colorectal cancer. In particular, anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab in patients with *K-RAS* wild-type<sup>[54-60]</sup> and anti-vascular endothelial growth factor (VEGF) antibody bevacizumab<sup>[61-64]</sup> have shown a synergistic action when associated to classical chemotherapy regimens with two or three drugs, thus increasing significantly the PFS, the overall response rate and hence also the rate of hepatic resection for CLM if compared with chemotherapy alone, especially when used as “conversion” treatment for unresectable liver metastases. Whether these results provide a real OS advantage, it still remains unclear. Unfortunately, data about targeted therapies in the perioperative or neoadjuvant setting of resectable CLM are lacking.

Gruenberger *et al*<sup>[32]</sup> reported their experience of a phase II study with oxaliplatin, capecitabine and bevacizumab in 56 curable CLM patients. This regimen showed a high response rate (73%) with R0 hepatic resections in 52 out of 56 patients and 5 complete pathologic responses. Actually, phase III studies with anti-EGFR antibody cetuximab and with anti-VEGF antibody bevacizumab are ongoing to better define the role of these biological agents in the treatment of potentially resectable CLM.

## CONCLUSION

CLM are a common problem, but many patients are able to undergo R0 liver resection, and a significant proportion of those patients may achieve cure or at least obtain prolonged DFS<sup>[65]</sup>. A multidisciplinary team approach is important for coordinating care of patients with CLM. Surgery is the treatment of choice for resectable CLM and requires that an adequate liver remnant remains after surgery. Perioperative chemotherapy with FOLFOX regimen for six mo according to the results of the EORTC 40983 randomized trial improves the outcome of these patients and it is actually recommended for most patients<sup>[66-69]</sup>. When it an upfront surgery of CLM is performed, then adjuvant chemotherapy with an oxaliplatin-based regimen is a reasonable option. Based on our experience we suggest a close follow up schedule for patients who underwent CLM resection. The role of targeted therapies in neoadjuvant setting of potentially resectable CLM remains to be defined and needs further studies. Finally, where a local approach to CLM is indicated and surgery is contraindicated, the radiofrequency ablation of liver metastases is often considered a good alternative, although generally less effective than surgery in terms of relapse rate and OS<sup>[70-76]</sup>.

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## Operative terminology and post-operative management approaches applied to hepatic surgery: Trainee perspectives

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### Abstract

Outcomes in hepatic resectional surgery (HRS) have improved as a result of advances in the understanding of hepatic anatomy, improved surgical techniques, and enhanced peri-operative management. Patients are generally cared for in specialist higher-level ward settings with multidisciplinary input during the initial post-operative period, however, greater acceptance and understanding of HRS has meant that care is transferred, usually after 24-48 h, to a standard ward environment. Surgical trainees will be presented with such patients either electively as part of a hepatobiliary firm or whilst covering the service on-call, and it is therefore important to acknowledge the key points in managing HRS patients. Understanding the applied anatomy of the liver is the key to determining the extent of resection to be undertaken. Increasingly, enhanced patient pathways exist in the post-operative setting requiring focus on the delivery of high quality analgesia, careful fluid balance, nutrition and thromboprophylaxis. Complications can occur including liver, renal and respiratory failure, hemorrhage, and sepsis, all of which require prompt recognition and management. We provide an

overview of the relevant terminology applied to hepatic surgery, an approach to the post-operative management, and an aid to developing an awareness of complications so as to facilitate better confidence in this complex subgroup of general surgical patients.

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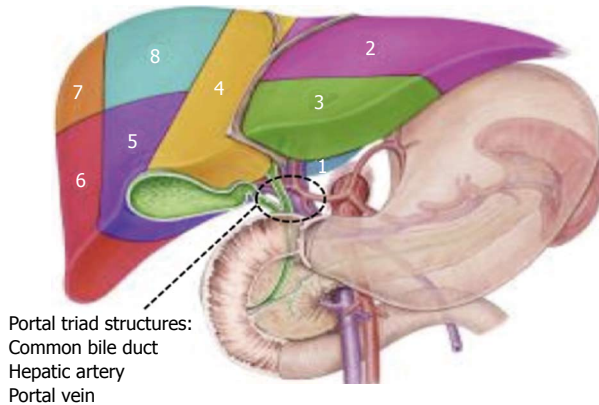
**Key words:** Hepatic surgery; Terminology postoperative management; Complications; Training

**Core tip:** Applied anatomy as used in hepatic surgery is different to the traditional morphological teaching. Applied hepatic anatomy is complex but trainees require an understanding of the basic principles to allow an appreciation of the operations performed. Complications require a low threshold of suspicion as they often have important consequences in relation to patient outcome. Recognition of such with rapid alerting of senior staff can facilitate timely and effective management. To date, no universal protocol exists for management of the post-operative period and varies from centre to centre. We provide a practical overview of the terminology, post-operative management, and complications associated with hepatic surgery.

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### INTRODUCTION

The structural design and unique innate property of the liver to regenerate functioning parenchyma after tissue loss forms an important basis of hepatic resection sur-



**Figure 1** Couinaud classification of hepatic segmental anatomy. The liver is made up of 8 segments: Segment 1 is the caudate lobe and is closely related in position to the inferior vena cava posteriorly; Segments 1-4 make up the left hemi-liver; Segments 5-8 make up the right hemi-liver. Couinaud divided the liver into functional left and right hemi-livers, and the plane between the two runs in Cantlie's line. This line runs from the middle of the gallbladder fossa anteriorly to the IVC posteriorly.

gery (HRS). Early experience was associated with significant mortality and morbidity but these are now reported at 1%-4% and 15%-35% respectively in high volume centres<sup>[1-5]</sup>.

Outcomes have improved as a result of advances in the understanding of hepatic anatomy, improved surgical techniques, and enhanced peri-operative management. Patients are generally cared for in specialist higher-level ward settings with multidisciplinary input during the initial post-operative period but greater acceptance and understanding of HRS has meant that care is transferred, usually after 24-48 h to a standard ward environment. The surgical trainee will be presented with such patients either electively as part of a hepatobiliary firm or whilst on-call, and it is therefore important to understand the key points in managing HRS patients.

Herein we provide an overview of the relevant terminology of hepatic surgery, an approach to the post-operative management, and provide hints to heighten awareness of complications so as to facilitate better confidence in this complex subgroup of general surgical patients.

## INDICATIONS FOR HRS

In the United Kingdom and Europe the commonest indication for HRS remains colorectal liver metastasis (CRLM). Resection is also performed for other benign and primary malignant hepatobiliary tumours [cholangiocarcinoma (CCA) and hepatocellular carcinoma (HCC)], donation for transplantation and trauma<sup>[6-8]</sup>. Most resections performed for CRLM are on liver with otherwise normal or mildly diseased parenchyma such as post-chemotherapy fatty livers. Less frequently in the United Kingdom, HRS is performed for HCCs arising in cirrhotic patients, and such resections are associated with a higher complication rate<sup>[9,10]</sup>.

## LIVER ANATOMY AND SURGICAL TERMINOLOGY

Unlike other general surgical operations where the nature of the procedure is readily grasped, HRS requires some knowledge of hepatic anatomy, and specific nomenclature is applied to such resections<sup>[11]</sup>. The surgically applied anatomy of the liver is different to the traditional (morphological) teaching in undergraduate medical school. The core principle relates to the Couinaud classification of liver anatomy<sup>[12]</sup>.

In this system the liver is divided into eight functionally independent segments (Figure 1). Each segment has its own vascular inflow, outflow and biliary drainage. In the centre of each segment there is a branch of the portal vein, hepatic artery and bile duct. In the periphery of each segment is the vascular outflow *via* the hepatic veins which link to form the right, middle and left hepatic veins. These in turn drain into the inferior vena cava. Crucially, the segmental portal and hepatic blood supply, together with the biliary drainage are unique, and allow for contiguous segments to be resected without compromising the vascular supply to the adjacent tissue.

In addition, the liver is separated into four sectors by the hepatic veins (Figure 2). Briefly, the right hepatic vein divides the right lobe into anterior and posterior segments; the middle hepatic vein divides the liver into right and left lobes (hemi-livers) and the left hepatic vein divides the left lobe into medial and lateral sectors.

This knowledge forms the basis of the consensus nomenclature outlined in the Brisbane 2000 terminology guidelines for hepatic resections<sup>[13]</sup>. In Table 1 the operation titles and number of segments are illustrated. While complex, it is more important perhaps for the trainee to be aware as to what constitutes a minor and major hepatic resection, as the extent of resection is associated with mortality and morbidity. A major resection was traditionally defined as  $\geq 3$  segments but more recently established as  $\geq 4$  segments<sup>[14]</sup>.

## DETERMINING THE LIMITS OF SAFE RESECTION

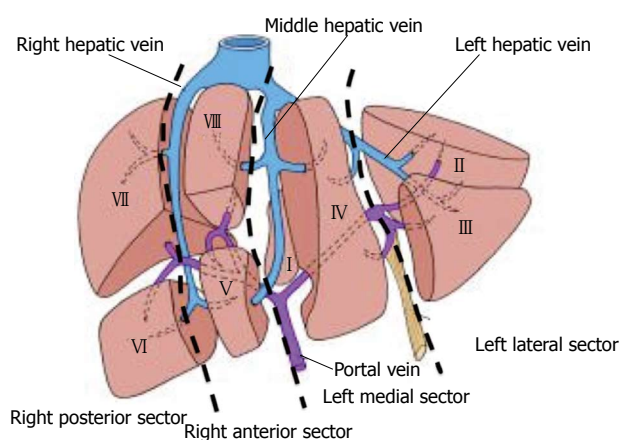
In the case of CRLM, the extent of resection that can be safely performed is now governed by two factors: the ability to resect all malignant tissue, and an adequate predicted volume of hepatic tissue remaining, the so-called functional liver remnant (FLR)<sup>[15,16]</sup>. As such during the pre-operative work-up it is important that surgeons work as part of a multi-disciplinary team with radiologists, oncologists and gastroenterologists to plan HRS to assess these factors<sup>[17]</sup>.

The primary investigations used in determining the extent of resection are cross-sectional imaging studies with computed tomography (CT)  $\pm$  magnetic resonance imaging (MRI) and if there is concern regards extra-hepatic disease, positron emission tomography (PET) scans

**Table 1** Brisbane consensus nomenclature 2000 for describing hepatic resectional surgery based on liver segmental and sectorial anatomy

Anatomical term	Couinaud segments	Term for HRS	Major or minor resection
Right hemi liver	5, 6, 7, 8	Right hemihepatectomy or right hemihepatectomy	Major
Left hemi liver	2, 3, 4 ( <sup>1</sup> / <sub>1</sub> )	Left hemihepatectomy or left hemihepatectomy	Major
Right anterior section	5, 8	Right anterior sectionectomy	Minor
Right posterior section	6, 7	Right posterior sectionectomy	Minor
Left medial section	4	Left medial sectionectomy or resection segment 4 or segmentectomy 4	Minor
Left lateral section	2, 3	Left lateral sectionectomy or bisegmentectomy 2, 3	Minor
-	4, 5, 6, 7, 8, ( <sup>1</sup> / <sub>1</sub> )	Right trisectionectomy or extended right hemihepatectomy or extended right hepatectomy	Major
-	2, 3, 4, 5, 8, ( <sup>1</sup> / <sub>1</sub> )	Left trisectionectomy or extended left hemihepatectomy or extended left hepatectomy	Major

"Non-anatomical" resections are also performed either as the main index procedure or in combination with the above anatomical hepatic resectional surgery. A non-anatomical resection refers to a situation in which there is a small tumour that is excised with a negative margin but leaving a remnant segment – a so-called "chip-shot" or metastectomy.



**Figure 2** Sectorial anatomy of the liver based on the hepatic veins. The liver is divided into a right and left hemi-liver by the middle hepatic vein (lies in Cantlie's line). The right hemi-liver is divided into anterior and posterior sections by the course of the right hepatic vein; The left hemi-liver is divided into lateral and medial sections by the left hepatic vein.

are useful<sup>[18]</sup>. If there is concern regards the FLR then portal vein embolization of the diseased portion of the liver can be performed to induce hypertrophy of the remaining parenchyma. For otherwise normal parenchyma the ratio of FLR to total estimated liver volume should be in the order of 25% but 40% may be required in the presence of cirrhosis or other liver disease<sup>[19-24]</sup>.

When proposing operating on cirrhotic livers it is also useful to perform a quantitative assessment of liver function, and in the Far East where HRS is more frequently performed for HCC, indocyanine green clearance (ICG) is carried out in all such patients to confirm the presence of an adequate volume of functioning parenchyma<sup>[25-30]</sup>. In the setting of CRLM, most patients have traditionally been observed to have normal parenchyma. However the widespread use of chemotherapy and its associated risk of liver injury such as steatohepatitis and sinusoidal obstruction syndrome may increase morbidity and potentially mortality associated with resection<sup>[31-33]</sup>. As a consequence such parenchyma may no longer be considered "normal" in this subgroup.

Biopsies of CRLM are not performed pre-operatively if a curative resection is planned because of concerns

of needle track seeding<sup>[34]</sup>. In cases of HCC, biopsies are sometimes performed if imaging is inconclusive and may be indicated to assess the surrounding parenchyma<sup>[35]</sup>.

## INTRA-OPERATIVE STRATEGIES

There are now a wide range of devices and pharmaceutical agents available to the hepatic surgeon. Their collective aim is to reduce blood loss during surgery as blood loss and the need for blood transfusion are regarded as important prognostic indicators for outcome<sup>[36-38]</sup>. The most widely used device is the cavitron ultrasonic surgical aspirator (CUSA) that dissects liver tissue utilizing ultrasound.

A number of clamping maneuvers can also be employed to reduced bleeding during the phase in which the liver parenchyma is transected<sup>[39,40]</sup>. The most commonly performed procedure is the Pringle maneuver in which inflow to the liver is controlled by compressing the hepatic artery and portal vein at the level of the hepatic pedicle. A number of different protocols exist in which the vessels are intermittently clamped and released, usually at 15 min intervals.

## APPROACH TO POST-OPERATIVE MANAGEMENT

Many units are now incorporating HRS patients into enhanced recovery programs with early targets for introduction of enteral diet, mobilization, prompt removal of invasive monitoring devices, reduction in the use of opiate analgesia, and judicious use of intravenous fluids<sup>[41-43]</sup>. These measures mean that most patients will expect to stay less than a week following their surgery. The increasing use of laparoscopic techniques has also contributed to the reduction in hospital stay especially for minor resections<sup>[44-46]</sup>.

## ASSESSMENT OF LIVER FUNCTION

### Liver enzymes

Perhaps one of the most challenging aspects for the junior trainee in the post-operative period is making sense of liver function tests. A transient early rise in serum hepatic

transaminase levels as a result of hepatocellular damage is common, usually peaking at 24-48 h with the extent of derangement being related to the extent of resection<sup>[47]</sup>. A persistent rise should alert the surgeon to the presence of ongoing hepatic ischaemia. Such a problem is more likely in those in whom a vascular reconstruction has been performed or if there has been prolonged clamping of the hepatic pedicle. This is an indication for urgent notification of senior staff and a Doppler study is useful in looking at the patency of the hepatic artery and portal veins. Early intervention by means of re-operation or interventional radiological techniques may be appropriate.

An isolated rise in alkaline phosphatase or an elevation of this enzyme in association with gamma-glutamyltransferase may indicate normal hepatic regeneration rather than a pathological process, with levels of the enzyme peaking at around 14 d<sup>[48]</sup>.

A sustained rise in bilirubin coupled with elevation in alkaline phosphatase should prompt a search for a cause of biliary obstruction. This is uncommon after a minor liver resection and is usually seen after a major resection in which a biliary reconstruction has been performed<sup>[49-52]</sup>. An ultrasound scan is the first line investigation to look for evidence of dilated biliary radicles. Further investigations and management can be arranged depending upon the findings of initial studies.

### Synthetic function

Changes in platelet count, prothrombin International normalized ratio (INR) and activated partial thromboplastin times (aPTT), which are markers of coagulation status, may be deranged and reflect the magnitude of resection. Specifically, a post-operative rise in INR between days 1-5 as well as a decrease in platelet count and fibrinogen levels are common and thought to be due to a combination of decreased synthetic function of the remnant liver and a consumptive coagulopathy<sup>[53-55]</sup>. This is usually self-limiting particularly in the setting of normal liver parenchyma and does not need correction with fresh frozen plasma (FFP) or platelet infusions. While there are no established guidelines for the use of FFP to prevent coagulopathy, some centers do use prophylactic FFP if the INR is > 2, in particular in cirrhotic patients<sup>[56]</sup>. This can be administered in combination with other products including vitamin K and human recombinant factor VIIa to treat clinically significant coagulopathy.

## FLUID AND ELECTROLYTES

Changes in liver function are coupled with fluid and electrolytes imbalances in the post-operative setting. The principles of goal-directed therapy in maintaining adequate fluid balance, haemodynamics and renal function (urine output > 0.5 mL/kg per hour) as outlined in the British Consensus Guidelines on intravenous fluid therapy for adult surgical patients should be followed ([www.bapen.org.uk/pdfs/bapen\\_pubs/giftasup.pdf](http://www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf)). However, there are some important caveats following HRS. In

the setting of cirrhosis, colloids or human albumin solutions are preferred rather than crystalloids. In addition, sodium restriction, judicious use of diuretics, and selective paracentesis are additional important measures to be considered. Under normal circumstances liver gluconeogenesis consumes a large proportion of body lactate but in the post HRS setting serum lactate can rise, as it is not efficiently metabolised. There are a number of reports implicating the negative impact of elevated lactate and base excess on outcomes after HRS, and some centers advocate the use of non-lactate containing solutions<sup>[57]</sup>.

Hypo/hyperglycemia, hypocalcaemia and hypophosphataemia particularly after major resection should not be ignored and require correction. Strict control of glucose levels has been shown to improve outcomes using a variety of techniques and most intensive/high dependency care units have dedicated protocols. Phosphate is an important component of efficient cell energy metabolism. A decreased level can affect many systems and functions including respiratory failure, cardiac and neurological dysfunction, and insulin resistance<sup>[58]</sup>. Replacement can be with phosphate infusions, potassium phosphate solutions and oral and paraenteral replacement. The exact mechanism behind the pathogenesis of hypophosphataemia is likely to be increased renal excretion<sup>[59]</sup>. Hypocalcaemia should be corrected with calcium gluconate or calcium chloride to optimize coagulation status since calcium is critically important in the coagulation cascade and in liver regeneration<sup>[60]</sup>.

## THROMBOPROPHYLAXIS

The prevalence of venous thromboembolism (VTE) after surgery particularly in oncological patients cannot be overemphasised. In HRS there has been reluctance in the past to prescribe pharmacologic thrombo-prophylaxis due to concerns regarding bleeding and so-called 'auto-anticoagulation'. However, VTE can still occur even in the presence of elevated INR and aPTT following HRS<sup>[61]</sup>. Indeed, evidence now confirms patients are more hypercoagulable and the use of pharmacologic thromboprophylaxis lowers the incidence of symptomatic VTE after major HRS without increasing the rate of blood transfusion<sup>[62,63]</sup>. The majority of patients undergoing HRS will undergo placement of an epidural catheter and so low molecular weight heparins should be started on the day of surgery unless explicit instructions from the operating team regarding increased risk of bleeding. During the surgery, pneumatic compression devices are employed to reduce the risk of thrombosis and mechanical should be continued with compression stockings post-operatively.

## ANALGESIA

It is crucial for the junior doctor reviewing a patient to insure they have adequate analgesia as poor pain control leads to prolonged recovery time, inefficient respiratory effort,

a poor appetite and a general slowing down of recovery. There are many options available that can be tailored to the patient, the two most commonly used being patient-controlled analgesia with intravenous agents (opioids or paracetamol), and epidural analgesia<sup>[64]</sup>. Local anaesthetic techniques such as transversus abdominis plane (TAP) blocks and infusion catheters are also useful techniques to spare the use of opioids<sup>[65,66]</sup>. Patients can then be switched to regular and as required oral analgesics according to the world health organization analgesic ladder<sup>[67]</sup>.

As the liver is an important organ for drug metabolism and detoxification it is important to realise potential risks of each modality in the context of liver parenchyma status, magnitude of resection, and concomitant liver or renal failure. Opiates have traditionally been the mainstay of analgesia but can be associated with respiratory depression, excessive sedation, and exacerbation of hepatic encephalopathy<sup>[68]</sup>. As such patients on opiates require close observation in particular after major resections, HRS carried out in the presence of cirrhosis or renal impairment. Better alternatives to simple morphine in cirrhotics include hydromorphone and fentanyl as they are less affected by renal impairment, and are better secreted by the kidney<sup>[69]</sup>. Intramuscular routes should be avoided, as bioavailability is variable. Non-steroidal anti-inflammatory agents are generally avoided post hepatectomy due to concerns in relation to coagulation and renal impairment<sup>[69]</sup>.

## DRAINS

Unit guidelines will dictate when drains are used and when they should be removed, as there are no published guidelines. In reality, the decision to remove drains is dependent on the reason the drain was inserted, the type of fluid draining and the volume of that fluid. If bile is observed then senior colleagues should be informed as imaging studies may be indicated especially if drainage persists or volume increases. Some have advocated the “3×3” rule (drain-fluid bilirubin level below 3 mg/dL on day 3 after operation) as criterion for removal of prophylactically placed abdominal drains after hepatic resection<sup>[70]</sup>. Interestingly, a Cochrane review has shown that routine abdominal drainage for uncomplicated liver resection is not needed and if used a closed drain system is associated with less infectious complication and hospital stay than open systems<sup>[71]</sup>.

## NUTRITION

Following major HRS, patients enter a catabolic state and so require early nutritional support to optimise liver regeneration, prevent infections, and promote general recovery. Those undergoing minor resection with normal parenchyma will often only require re-introduction of normal diet the first post-operative day. A systematic review of nutrition following HRS confirmed that early nutrition by enteral route is associated with a lower inci-

dence of wound infections and complications as compared to parenteral, and therefore remains the favoured route of nutritional support<sup>[72]</sup>.

In addition to early feeding, data is now emerging to encourage the use of pre- and pro-biotics (known as symbiotic therapy) in an attempt to address gut barrier dysfunction and microbial flora to reduce the gut-mediated systemic inflammatory response syndrome and encourage liver regeneration<sup>[73,74]</sup>. This therapy is yet to be validated in large randomised controlled trials and not used routinely in current United Kingdom clinical practice.

## RECOGNISING POST-OPERATIVE COMPLICATIONS

The mortality rates in the majority of published series are now in the order of 0%-2%, however, with reported morbidity rates of 25% to 45% it is important to be alert to potential complications following HRS in all patients. Risk factors for complications include: age > 65 years; ASA score  $\geq 3$ ; larger extent of resection (multiple tumours, bilobar disease); requirement for blood transfusion; and involved resection margins<sup>[75]</sup>. Up to 30% can suffer “major” complications; specifically bleeding, liver/kidney/respiratory failure and sepsis and account for the majority of deaths post surgery<sup>[75]</sup>. In an attempt to allow comparison across series, the Clavien-Dindo classification of post-operative complication is now frequently reported<sup>[76]</sup>.

## HEPATIC FAILURE

Around 3%-5% of patients may develop liver failure following their resection and will usually show signs and symptoms from 48-72 h after their surgery<sup>[2]</sup>. These are usually patients undergoing major resections, or resections carried out in the presence of cirrhosis. The International Study Group of Liver Surgery recently developed a consensus definition for post-hepatectomy liver failure namely ‘the impaired ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased international normalized ratio and concomitant hyperbilirubinemia (according to the normal limits of the local laboratory) on or after postoperative day 5<sup>[77]</sup>. They graded the severity of post-hepatectomy liver failure on the basis to its impact on clinical management: Grade A post-hepatectomy liver failure requires no change of the patient's clinical management. The clinical management of patients with grade B post-hepatectomy liver failure deviates from the regular course but does not require invasive therapy. The need for invasive treatment defines grade C post-hepatectomy liver failure.

In our own practice, the following indices are used in the monitoring of hepatic function and identifying dysfunction: (1) persistent hyperbilirubinemia [serum bilirubin level > 4.1 mg/dL (to convert to micromoles per liter, multiply by 17.104)]; (2) coagulopathy with anINR > 2.5,

**Table 2** Abridged version of West Haven criteria

HE grade	Mental state
1	Mild confusion, slowing of ability to do mental tasks, <i>e.g.</i> , serial 7's
2	Drowsiness, inappropriate behaviour
3	Somnolent but rousable, marked confusion
4	Coma

Reproduced with permission from reference Ferenci *et al.*<sup>[79]</sup>.

despite early attempted correction with clotting factors; (3) abdominal ascites (drainage volumes > 500 mL/d); and (4) encephalopathy with hyperbilirubinemia and exclusion of other acute confusional states<sup>[36]</sup>.

Another practical definition of post-hepatectomy liver failure is indicated by a prothrombin time < 50% and serum bilirubin > 50 mmol/L (the "50-50" criteria) and been shown to predictive factor of mortality when measured at days 3 and 5<sup>[78]</sup>.

Patients with significantly impaired hepatic function may exhibit hepatic encephalopathy (HE). The West Haven criteria (Table 2) grades HE from I to IV according to severity and is widely used<sup>[79]</sup>. It is based on changes of consciousness, intellectual function, behavior, and is useful in monitoring patient progress. Ammonia levels should be measured if HE is suspected and lactulose and systemic antibiotics prescribed to alter gut flora and reduce the production and absorption of ammonia<sup>[80]</sup>.

A number of risk factors have been identified for the development of post-hepatectomy liver failure and have been summarised in a recent review<sup>[81]</sup>. When confronted with a picture of liver failure, it is important to attempt to determine the underlying cause, as some elements are correctable. Causes of liver failure are usually multifactorial and include: bleeding; sepsis; hepatic ischaemia; portal vein thrombosis; venous outflow obstruction; and a poorly functioning liver remnant. There hepatotoxic effects of pre-operative chemotherapy on the parenchyma, and the presence of steatosis may also contribute to insufficiency.

Intensivists, senior surgeons and hepatologists lead the management of this most feared complication. The mainstay of treatment is supportive with blood products administered to support synthetic function, aggressive investigation and treatment of infection, and radiological investigation to ensure patency of major vascular and biliary structures. The use of exogenous antioxidants such as N-acetylcysteine (Parvolex<sup>®</sup>) has been used by some including our own unit in attempting to reduce the damage by oxygen free radical associated ischaemic reperfusion injury of the liver<sup>[82]</sup>. However this remains to be accepted as universal practice and currently lacks a strong evidence base<sup>[83,84]</sup>.

## BLEEDING AND TRANSFUSION REQUIREMENTS

Intra- and post-operative bleeding, and the requirement for blood transfusion are associated with increased morbidity, mortality and poorer long-term disease-specific

outcomes in CRLM and HCC<sup>[85,86]</sup>. Kooby *et al.*<sup>[37]</sup> in a study of 1351 liver resections noted a variation in operative mortality between 1.2% for no transfusion to 11.1% when more than 2 units of blood were transfused. A recent review by Dixon *et al.*<sup>[38]</sup> highlighted the negative effects of blood loss on outcome in surgical oncology patients, and suggested that the need for transfusion may be an indicator of the quality of surgery performed.

The operating surgeon and anaesthetist incorporate multiple techniques including: low intra-operative central venous pressure; dynamic intra-operative coagulation monitoring; drugs (aprotinin, tranexamic acid); and haemostatic products on the cut surface of the liver to reduce the occurrence of this complication. As a result median blood loss in overall HRS has significantly reduced and reported to be less than 700-800 mL<sup>[87]</sup>. Indeed, the median transfusion rate in the majority of contemporary series is zero.

Blood loss during surgery should be clearly documented on the operative note. Unit protocols drive the specific haemoglobin criteria for transfusion and should be referred to when assessing the patient in this early stage. During the post-operative phase, patients will have haemoglobin and haematocrit measurements determined regularly. It would be expected that patients would stabilise during the initial 24-48 h and any deterioration following this should trigger referral to senior colleagues and a request for imaging studies. Patients actively haemorrhaging may require re-exploration or radiological embolisation of bleeding vessels.

## POST-OPERATIVE SEPSIS

As evidence grows implicating post-operative complications, in particular infection, in poorer disease-free survival, an important aim must be to pro-actively attempt to minimise infections, and when present to identify and implement treatment in an expedient manner<sup>[75]</sup>. Risk factors known to be associated with infection include: obesity; major resections requiring blood transfusions; presence of co-morbidities (diabetes, chronic obstructive pulmonary disease); and post-operative bile leaks<sup>[88]</sup>. Standard effective interventions to minimise infections include ensuring adequate chest physiotherapy, early patient mobilisation, prompt removal of indwelling devices, and institution of broad-spectrum antibiotics therapy where indicated.

## BILE LEAKS

Bile leakage is an important complication occurring after liver surgery and its reported incidence ranges between 4.8%-7.6% in large series<sup>[89-95]</sup> and is less common in surgery for CRLM than for HCC or CCA. The International Study Group of Liver Surgery has recently proposed a uniform definition of bile leakage and a grading system according to severity, which is based on drain fluid bilirubin concentration of greater than three times the serum

bilirubin concentration on day 3 after surgery or the need for additional interventions<sup>[96]</sup>. Management of bile leaks includes treatment of associated infection, defining the location of leak, externalizing the bile with a radiologically placed drain, and the consideration of insertion of biliary stents and/or reconstructive surgery<sup>[97]</sup>.

## SUMMARY AND FUTURE DIRECTIONS

No consensus protocol exists for the post-operative management of HRS, as each centre will have different guidelines reflecting preferences of senior staff with regards to the finer points of management. It is important to deliver early nutrition, effective analgesia, and promote good respiratory function. Furthermore close observation in the early post-operative period is required to identify and aggressively manage bleeding, infection and prevent the development of liver failure. The surgical trainee is required to have a basic grounding and have the ability to appreciate exactly what resection has been performed in a patient to allow for meaningful assessment. Such knowledge will provide insight into being able to alert senior staff appropriately and expediently in this challenging dynamic subgroup of patients.

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## Localized pseudomembranous colitis in the cecum and ascending colon mimicking acute appendicitis

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tients with acute abdominal pain who have been treated with antibiotics. We report a case of an older patient with pseudomembranous colitis that was misdiagnosed as acute appendicitis.

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### Abstract

A 61-year-old male was admitted to our hospital due to right lower abdominal pain and watery diarrhea for 3 d. Beginning 3 wk before he arrived in our hospital, he took 3<sup>rd</sup>-generation cephalosporin (cefixime) for 2 wk due to chronic left ear otitis media. Colonoscopic examination revealed yellowish patches of ulcerations and swelling covered with thick serosanguineous exudate in the cecum and ascending colon. After 7 d of oral metronidazole treatment, his symptoms completely disappeared. We report a case of localized pseudomembranous colitis in the cecum and ascending colon mimicking acute appendicitis associated with cefixime.

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**Key words:** Enterocolitis; Pseudomembranous; Appendicitis; Abdomen; Acute; Diarrhea; Cefixime

**Core tip:** Pseudomembranous colitis is mostly related to antibiotics, and it presents symptoms of diarrhea, abdominal pain, fever, hypoalbuminemia and hypovolemia. Diarrhea is the most common manifestation, but in geriatric patients, symptoms of pseudomembranous colitis can be different from those of usual cases, and the disease course can be more aggressive. For these reasons, it can be misdiagnosed. Therefore, physicians must consider pseudomembranous colitis in older pa-

### INTRODUCTION

Patients who are administered antibiotics often experience diarrhea (referred to as antibiotic-associated diarrhea), and when these patients are proven to have inflammation in the colon, it is known as antibiotic-associated colitis. Furthermore, when patients with antibiotic-associated colitis have more inflammation in the colon and show pseudomembrane formation, it is referred to as pseudomembranous colitis.

Here, we present the case of a 61-year-old male patient who was first suspected of having acute appendicitis and had been experiencing right lower abdominal pain, tenesmus, and frequent watery diarrhea for 3 d before visiting the hospital. He also had a history of taking a cephalosporin antibiotic (cefixime) for 2 wk after an outpatient visit to the otolaryngology department to treat otitis media of the left ear 3 wk before visiting us. Based on these findings, we performed hematologic, colonoscopic, and histologic examinations and found pseudomembranous colitis limited to the cecum and the right ascending colon. We also present a literature review.

### CASE REPORT

A 61-year-old male had right lower abdominal pain, frequent watery diarrhea. He was underwent antibiotic treat-



**Figure 1** Abdominal ultrasonographic finding. Non-specific colitis in the ascending colon and the cecum and secondary mild inflammation of the appendix.



**Figure 2** Abdomen computed tomography scan shows circular wall thickening in the cecum and the ascending colon and pericolic infiltration and adjacent lymph nodes.

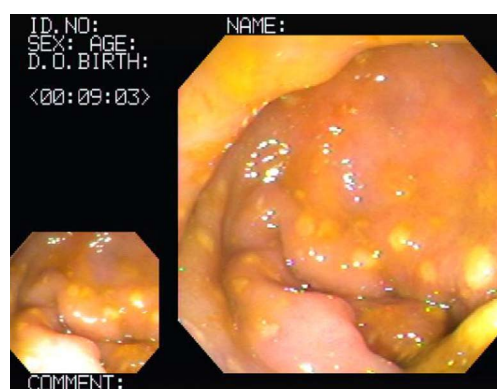
ment for otitis media in the right ear 3 wk previously and had been taking diabetes medications for 19 years. He had no specific history.

### History of present illness

Three weeks before visiting us, he was diagnosed with otitis media in the left ear and had been taking a 3<sup>rd</sup>-generation cephalosporin antibiotic (cefixime) prescribed by the otolaryngology department at our hospital for 2 wk. He stated that a week before the visit, he began to suffer from discomfort in the right lower abdomen, tenesmus, and intermittent and frequent watery diarrhea several times a day. When he made an outpatient visit to the department of surgery, he reported that he had not been able to tolerate the consistent right lower abdominal pain for the previous 3 d.

### Physical findings

When he visited us, his vital signs were blood pressure 110/60 mmHg, pulse rate 80 bpm, respiratory rate 20/min, and body temperature 36 °C but without fever or chills. He presented a slightly decreased appetite, and based on the clinical manifestations found through his physical examination, his bowel sounds were normal. Although the right lower abdominal tenderness and re-



**Figure 3** Colonoscopic finding shows multiple elevated yellowish or white pseudomembranes with hyperemic, edematous mucosa in the ascending colon and cecum.

bound tenderness were obvious, our digital exploration did not find any lump.

### Examination findings

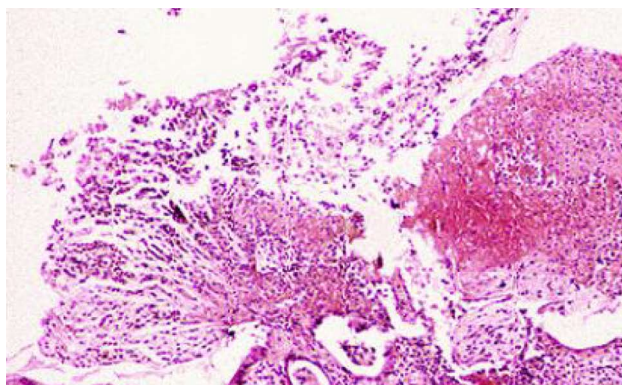
The hematological examination results were peripheral blood white blood cell count 8900/mm<sup>3</sup>, hemoglobin 15.3 g/dL, hematocrit 44%, platelet count 123 × 10<sup>3</sup>/mm<sup>3</sup>, and CRP 15.2 mg/L. Meanwhile, his urinalysis results were normal, except for glucose (+++). His ultrasound results on the day of the visit showed that every layer of the serous membranes of the ascending colon and cecum was hypertrophic, whereas the serous membrane of the appendix was slightly hypertrophic, secondary to inflammatory responses in the colon (Figure 1). The results of an abdominal computed tomography (CT) scan performed the day after the visit showed that the serous membranes of the cecum and ascending colon were generally hypertrophic, and there were inflammatory infiltrates around the colon (Figure 2). A colonoscopy performed on the 4<sup>th</sup> d also found pseudomembranous colitis limited to the cecum and ascending colon; thus, a biopsy was carried out (Figure 3). The biopsy confirmed that he had typical pseudomembranous colitis with crater-shaped ulcers (Figure 4), and the stool analysis showed that he was positive for *Clostridium difficile* (*C. difficile*) cytotoxin (0.09).

### Progress

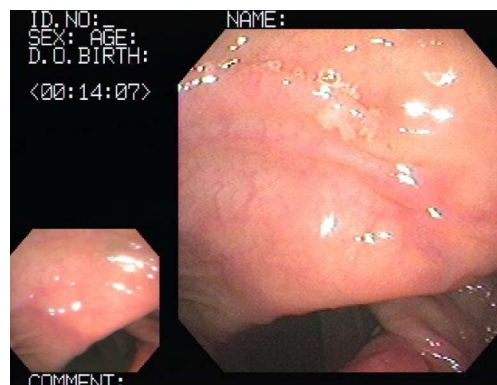
On the day that the biopsy confirmed pseudomembranous colitis, he began oral treatment with 250 mg of metronidazole 4 times a day. After 3 d, his defecation disorder and right lower abdominal pain mostly disappeared. In addition, when he was discharged, he was able to eat properly. He was orally administered metronidazole for 7 d, and through a colonoscopy performed a month after discharge, we were able to confirm that his intestinal mucosa had returned to normal (Figure 5).

## DISCUSSION

Pseudomembranous colitis was first reported in 1893, and it was rare before antibiotics came into widespread



**Figure 4** Histological finding shows the typical volcano-like exudate, inflammatory cells, mucofibrinous material and inflammatory colonic mucosa with erosion (HE stain, × 40).



**Figure 5** Follow-up colonoscopic finding showing normal mucosa in the ascending colon and the cecum.

use. In the early 1950s, as antibiotics began to be widely used, the incidence of pseudomembranous colitis also began to rise. At the time, people suspected that the main cause of pseudomembranous colitis was *Staphylococcus aureus*, one of the most common nosocomial infections. However, in 1974, a prospective study revealed that approximately 20% of patients who were administered clindamycin experienced antibiotic-associated diarrhea, and half of them suffered from pseudomembranous colitis.

In 1935, Hall and O'Toole claimed that *C. difficile* was a normal part of the flora of infants' intestines. They described it as "the difficult clostridium" because an anaerobic gram-positive bacillus was considered the most difficult bacteria to grow in culture<sup>[1]</sup>. In an animal study, it was shown that *C. difficile* could secrete powerful toxins, but its clinical significance was discovered in the late 1970s. At that time, for the first time, *C. difficile* and its cytotoxin were found in the feces of almost every patient with pseudomembranous colitis but not in the feces of healthy people; this indicated that the toxins produced by *C. difficile* caused pseudomembranous colitis.

The first case of pseudomembranous colitis that occurred in the cecum and appendix was presented in 1997 by Coyne *et al*<sup>[2]</sup>. A 76-year-old female patient who was receiving hemodialysis for chronic renal failure experienced pseudomembranous colitis after being administered clindamycin to treat abdominal pain and diarrhea, but pseudomembranous colitis reoccurred a month after using metronidazole, and this led to her death. Based on the colonoscopy performed when she was admitted to the hospital, she was diagnosed with pseudomembranous colitis in her diverticulum, cecum, and appendix across her transverse colon and descending colon.

In approximately 90% of cases, *C. difficile* is found in the rectum and sigmoid colon on colonoscopy. However, in approximately 10% of cases, it occurs in the distal colon; therefore, patients cannot be diagnosed by sigmoidoscopy alone<sup>[1]</sup>. In 1982, Tedesco *et al*<sup>[3]</sup> carried out a prospective study on patients diagnosed with pseudomembranous colitis. They stated that 77.3% of the

patients were successfully diagnosed through sigmoidoscopy; but in 13.6% of the patients, pseudomembranous colitis occurred between 24 and 60 cm from the anus, and it occurred more than 60 cm from the anus in 9.1% of the patients. Furthermore, in 1999, Lee *et al*<sup>[4]</sup> studied the clinical characteristics of *C. difficile*-associated diseases and claimed that because less than 10% of patients had lesions in the ascending colon alone without invading the descending colon, sigmoidoscopy was sufficient, and colonoscopy was not needed.

When *C. difficile* occurs in the cecum, it can be observed on a CT scan as an "accordion sign", which is caused by the invasion of the tissues surrounding the cecum and cecal bulb as well as a thickening of the cecal folds. Based on these CT scan results, appendicitis should be distinguished from typhlitis, pseudomembranous colitis, inflammatory diseases, diverticulitis of the cecum, inflammatory bowel diseases, cecal volvulus, pneumatosis intestinalis, ischemia and necrosis, solitary cecal ulcer syndrome, and tumors in the cecum in a patient suffering from right lower abdominal pain<sup>[5]</sup>. Our patient's CT scan showed the "accordion sign."

*C. difficile* is an anaerobic gram-positive bacillus that is resistant to antibiotic treatments by forming spores. *C. difficile* is part of the normal flora in the intestine of infants, but this is rarely the case with older children or adults. However, if the normal flora is altered due to antibiotic or antitumor treatments or infections with pathogens, such as *Salmonella* or *Shigella*, *C. difficile* colonization can occur. Therefore, the normal flora in the colon appears to inhibit the growth of *C. difficile*. *C. difficile* secretes powerful exotoxins called toxin A and toxin B, which induce tissue damage to the colon. However, depending on the strain, some exotoxins may be less toxic than others or not toxic at all. Nonetheless, because the level of toxicity is not proportional to the severity of the disease, in general, these toxins are reported as either positive or negative<sup>[1]</sup>.

Almost every antibiotic that shows activity against bacteria can induce antibiotic-associated colitis. The antibiotics that most commonly cause antibiotic-associated colitis are cephalosporin, ampicillin, amoxicillin, and

clindamycin; the ones that cause it less frequently include penicillin, excluding ampicillin, and macrolides (erythromycin, clarithromycin, and azithromycin). In addition, antibiotics that occasionally cause antibiotic-associated colitis include fluoroquinolone, trimethoprim-sulfamethoxazole, metronidazole, tetracycline, and chloramphenicol. It has not yet been clearly established whether sulfonamide, parenteral aminoglycosides, or parenteral vancomycin—as well as other antimicrobial agents against fungi, mycobacteria, parasites, and viruses—can induce antibiotic-associated colitis.

Moreover, *C. difficile*-associated colitis can occur in patients who (1) have had prolonged hospitalization; (2) share a cubicle or ward with a patient suffering from antibiotic-associated colitis; (3) are old; (4) recently had surgery, in particular, gastrointestinal surgery; (5) suffer from intestinal obstruction; or (6) have a malignant tumor<sup>[6]</sup>.

The most distinctive antibiotic-associated colitis induced by *C. difficile* may be pseudomembranous colitis. For example, over 95% of patients diagnosed with pseudomembranous colitis have a positive stool toxin assay. A close examination of their pseudomembrane reveals few normal tissues and raised exudative plaques that have hemorrhagic edematous mucosa with perforated areas. Such plaques can grow and become merged across bowel segments in the final stage of the disease.

The clinical characteristics of antibiotic-associated pseudomembranous colitis vary. One of the most common characteristics is a large amount of watery diarrhea without blood or mucus. Most patients experience severe convulsive abdominal pain and tenderness, fever, and leukocytosis. However, symptoms can vary greatly. On one hand, some patients suffer from diarrhea and show no systemic symptoms. On the other hand, some patients present severe systemic toxicity, high fevers up to 40.0 °C–40.6 °C, and peripheral leukocytosis up to 50000/mm<sup>3</sup>. The results of stool examinations usually show white blood cells.

If left untreated, the clinical course varies between patients. Some patients experience immediate relief from symptoms after discontinuing the drug, while others continuously produce a large amount of feces up to week 8, which can ultimately lead to hypoalbuminemia or electrolyte imbalance. There also have been some reports of severe patients with toxic megacolon and enterobrosis. The mortality rate of severe patients is approximately 30%, while the symptoms of most patients with mild symptoms improve simply by discontinuing antibiotics. In most patients, symptoms begin to appear 4–10 d after antibiotic administration. However, approximately 25% of patients do not experience any symptoms until they discontinue antibiotics, and a few begin to show symptoms after 4 wk of administration. It has been reported that in some cases, symptoms occur within several hours of antibiotic administration and sometimes even after a single administration of antibiotic as a surgical prophylactic measure<sup>[7]</sup>.

Our aged patient had risk factors for developing pseudomembranous colitis and had a history of taking a 3<sup>rd</sup>-generation cephalosporin antibiotic (cefixime) for

approximately 2 wk. On sigmoidoscopy, we observed several pseudomembranes limited to the cecum and the ascending colon, and the pseudomembranes were proven by biopsy. Moreover, the patient's stool toxin assay was positive (0.09).

Pseudomembranous colitis can be treated by discontinuing the antibiotic that has been used and switching to a conservative treatment alone. In such cases, approximately 30% of patients show improved symptoms in approximately 10 d; however, patients with severe enteritis can also take 250 mg of metronidazole orally 4 times daily for approximately 7–14 d. When oral administration is impossible due to paralytic ileus or megacolon, 500 mg can be administered every 6 h through a jugular vein. Because metronidazole is well absorbed in the upper gastrointestinal tract, the downside of oral administration is that its concentrations can decrease in the feces. However, pseudomembranous colitis can increase the permeability of the colonic mucosa and subsequently allow metronidazole to be delivered to the lumen of the colon. Metronidazole is much more affordable than vancomycin, and due to recent concerns over *Enterococcus*, which is resistant to vancomycin, metronidazole is the primary choice to treat antibiotic-associated colitis<sup>[8]</sup>.

Typically, 125 or 500 mg of vancomycin is administered orally 4 times daily for 7–14 d. The 125 mg dose is cheaper than the 500 mg dose, but they appear to have similar treatment effects. Because vancomycin is rarely absorbed when orally administered, the fecal concentration remains high. However, it is less effective when it is administered through a jugular vein, as the concentration is lower in the lumen of the colon. It can be argued that oral vancomycin is highly effective in treating antibiotic-associated colitis because there is no report of *C. difficile* being resistant to vancomycin. Nevertheless, it is still much more expensive than metronidazole, and considering concerns over vancomycin-resistant enterococci, metronidazole should be the primary choice to treat antibiotic-associated colitis; vancomycin should only be used in cases in which metronidazole cannot be used or in patients who do not respond to metronidazole<sup>[9,10]</sup>.

We administered 250 mg of metronidazole orally to our patient 4 times daily; after 3 d, the right lower abdominal pain, tenesmus, and frequent watery diarrhea disappeared. The reoccurrence rate of pseudomembranous colitis after treatment is reported to be approximately 20%, and possible causes of reoccurrence are reinfections by remaining strains and spore formation<sup>[11]</sup>. Our patient was administered metronidazole for 7 d total, and based on the result of a sigmoidoscopy performed one month later, we were able to confirm that his intestinal mucosa had returned to normal.

In conclusion, even when right lower abdominal pain is the major clinical manifestation, if the patient has abnormal bowel habits and a recent history of antibiotic administration, even without the presence of fever, chills, or watery diarrhea (which are common clinical characteristics of pseudomembranous colitis), we recommend that

pseudomembranous colitis should be considered in the differential diagnosis of acute appendicitis.

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- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 DOI:10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ, Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

*No author given*

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

*Volume with supplement*

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/0000-3086-200208000-00026]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

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*Personal author(s)*

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

*Conference proceedings*

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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- 14 **Christensen S**, Oppacher F. An analysis of Koza's computa-

tional effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

#### Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

#### Patent (list all authors)

- 16 Pagedas AC, inventor; Ancel Surgical R&D Inc, assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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