Liver metastases of colon cancer. New therapeutic approaches. Neoadjuvant chemotherapy

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Summary

Colon cancer witnesses one of most exciting and evolving times in the latest years. About 30% of patients with isolated liver colon metastases can now be cured through a multidisciplinary approach of the disease. New systemic treatments have moved the median survival of metastatic disease from 12 months four years ago to 20 months and beyond. Incorporation of new biologic treatments into the neoadjuvant setting may help to further improve historical outcomes and offers promise to continue this trend.

Appropriate surrogate endpoints and optimal designs of clinical trials on neoadjuvant therapy as first or second-line of treatment are needed.

Key words:

Liver metastases. Colon cancer. Neoadjuvant chemotherapy.

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Resumen

El cáncer de colon está presenciando en los últimos años un desarrollo científico espectacular. Aproximadamente el 30% de los pacientes con metástasis hepáticas como única localización, pueden curarse actualmente con un planteamiento multidisciplinar de la enfermedad. Los tratamientos sistemáticos han desplazado la mediana de supervivencia de los 12 meses que se alcanzaban hace cuatro años a 20 meses e incluso más allá. La incorporación de nuevos tratamientos biológicos en el contexto de los tratamientos neoadyuvantes, podría mejorar los resultados históricos y mantiene la esperanza de que prosiga esta tendencia.

Se considera esencial un diseño correcto de los ensayos clínicos y la elección de objetivos apropiados, con tratamientos tanto en primera como en segunda línea, administrados con intención neoadyuvante.

Palabras clave: Metástasis hepáticas. Cáncer de colon. Quimioterapia neoadyuvante.

Nearly half of all patients with colon cancer will develop liver metastases and many will die with disease confined to the liver. The treatment of metastatic colorectal cancer has changed dramatically over the last ten years. The use of systemic therapy as a neoadjuvant treatment for patients with colon hepatic metastases is a relatively new approach and combination chemotherapy has gained wide acceptance as first line reference. Until the availability of the new drugs such as irinotecan and oxaliplatin, the efficacy of chemotherapy was so low that made such a strategy illogical. The emerging data with the new combinations, including new drugs like bevacizumab or cetuximab suggest a second dramatic step-up in antitumour efficacy, making up one of most exciting scenarios of our days.

In 2005, nearly one third of patients with disease confined to the liver can look forward to possibly curative liver surgery. A strategy of sequenced multiple treatments are moving the treatment of colorectal liver metastases to a new multidisciplinary medico-surgical field¹.

Anatomical basis and natural history of liver metastases

The liver is the largest internal organ in the body, accounting for 2 to 3% of the total weight of an adult. Cancer cells travelling by hematogenous spread, have a high likelihood of arriving and lodging within the sinusoids of the liver. The liver is also the first major organ reached by venous blood

draining from the gastrointestinal tract, and hence the most common site for distant metastatic disease in colon cancer, partly as a result of portal venous drainage of the gastrointestinal tract. The liver bleeds copiously and it is often the first organ to be injured in blunt abdominal trauma. To balance these negative characteristics it has two great attributes: its ability to regenerate after massive loss of substance, as well as its ability to forgive insult. A good knowledge of the anatomy is a prerequisite for modern surgery of the liver. Based on external appearance, four lobes are traditionally described: right, left, quadrate and caudate. Based on arterial and portal venous blood supply, biliary and hepatic venous drainage, the liver is divided into functional lobes and segments. The best known and most widely employed conceptions of hepatic segmentation are those of Couinaud (1954), those of Healy and Schroy (1953), simplified by Goldsmith and Woodburne (1957), and those of Bismuth (1982)². Recently, a new terminology called the Brisbane 2000 Terminology of Liver Anatomy and Resections has been unanimously recommended and accepted by the scientific committee of the International Hepato-Pancreato-Biliary Association in order to resolve the existing confusion³.

Each one out of the 8 anatomic segments of the liver has an independent biliary drainage and vascular inflow and outflow. Consequently an individual segment can be removed without disrupting the blood flow or biliary drainage of the remaining segments.

Approximately 50% of patients with colorectal

cancer develop liver metastases and 20% present with liver involvement at the time of diagnosis⁴. Interestingly, in some 20-35% of patients with advanced disease, metastases are confined to the liver⁵. Several retrospective studies have indicated that the outcome for patients with untreated liver metastases is poor, with a median survival of 8-12 months^{6, 7}. However, there are occasional long-term survivors and considerable disparity between mean and median survival. The factors that independently predict outcome on multivariate analysis are: performance status, extent of liver disease, abnormal liver tests and site of primary tumour⁸. In general, patient factors (i.e., gender or age) do not influence survival, whereas factors reflecting tumour burden (i.e. performance status) do.

Treatment of liver-only metastases

Surgical resection of liver-only metastases, where feasible, offers a significant survival advantage and should be considered for selected patients. Some have criticized that the improved survival rate seen in patients with resection (versus no resection) could be due to the superior performance and low tumour burden and therefore more favourable prognosis in patients considered for resection. Unfortunately, a randomized clinical trial will not be possible anymore given the compelling results for liver surgery, that seem to confer a survival benefit by itself⁹. The modern era has ushered in an aggressive approach to liver surgery because of the advances in imaging modalities, improved anaesthetic management, enhanced knowledge of functional liver anatomy and an appreciation of the functional reserve of the liver as well as the vast potential for hepatic regeneration. A number of issues remain subject to debate, including criteria for operability or nonresectability, optimizing surgical outcome with neoadjuvant or adjuvant therapy and the role of other regional therapies including hepatic arterial infusion of chemotherapy.

The goal of the pre-operative evaluation is to identify the best candidates for resection and to discriminate these from those with limited survival benefit or those who will be found at the operation to have unresectable disease. Whereas age alone is not a contraindication to resection, comorbid diseases

may preclude major surgical resection. An evaluation to exclude the presence of extrahepatic disease should be done. The overall detection rate of helical CT in detecting colorectal liver metastases is approximately 85% and the positive predictive value is 96%¹⁰. It is the imaging modality used most frequently to assess the extent of disease both within and outside the liver. MRI can distinguish benign cysts or hemangiomas from malignant lesions. FDG-PET scanning identifies additional disease or excludes metastases in 20% of patients¹¹. CEA and Ca 19.9 must also be determined.

A conceptual approach would support the idea of administering systemic chemotherapy for all patients before surgery. The theoretical disadvantage would be the possibility of progressing to an unresectable situation. Of note, it seems that patients who progress to chemotherapy have anyway a poor prognosis^{12, 13}. The fact is that some multidisciplinary teams are using neoadjuvant therapy even if the resection is technically feasible (at least for synchronous metastases), in order to control the systemic disease. Tumour control before surgery is crucial to offer a chance of prolonged remission in patients with multiple metastases. Optimal sequencing of systemic and local therapy remains an area of active debate.

Ablative and destructive therapies

The description of these techniques exceeds the purpose of this review. However it should be mentioned that they are very useful when surgery is not possible or sometimes as a complementary treatment. Radiofrequency ablation uses high-frequency alternating current to produce heat. It has proven to be an extremely safe procedure with complication rates of less than 10%, being very useful for small lesions¹⁴. It is contraindicated in the proximity of the principal biliary ducts. It can be performed percutaneously, laparoscopically or even through open laparotomy, having replaced other ablative techniques as the preferred method of interstitial ablation. For strictly unresectable liver metastases, the association of hepatic resection, radiofrequency and chemotherapy, results in 3-year survival rate of 47%. Unfortunately, it doesn't provide survival comparable to radical surgery¹⁵ but it seems to be better than the obtained with only-chemotherapy¹⁴.

¹⁶. Results from EORTC 40004 (FOLFOX vs FOLFOX plus radiofrequency ablation) are expected.

Percutaneous ethanol injection is less effective in metastatic hepatic colon cancer lesions in comparison to primary hepatocellular carcinomas. There is little evidence to support its use in metastatic colon cancer¹⁷.

Hepatic resection

Several significant advances have been made over the last 10 years, that make liver resection a more routine procedure with minimal patient morbidity. The main goal of liver resection is to precisely remove the involved portion of liver with an adequate surgical margin and preserve sufficient hepatic reserve. Intraoperative ultrasonography is the most sensitive modality currently available for detecting otherwise occult liver metastases. Its overall sensitivity is reported to be up to 98%¹⁸. The role of laparoscopy before surgical exploration remains to be defined.

Anatomic resection is a superior oncologic resection than wedge or atypical resection. Segment-oriented liver resection represents the virtuosity of hepatic surgery. It is unique in its oncologic efficacy and safety. The technique promotes tumour clearance while preserving uninvolved parenchyma. Preoperative American Society of Anesthesiologists (ASA) classification, presence of steatosis, simultaneous extrahepatic resection and perioperative blood transfusion have been found to be independent predictors for the development of postoperative complications¹⁹.

5-year overall survival rate following resection is increasing over the years. At the same time, surgical mortality rate is decreasing. Whereas survival rate examining patients treated from the 60's through the mid 90's was reported to be 33%-36%^{9, 20}, most recent reports show figures of 58%^{21, 22}. Mortality rates go down from 2,8% to 0,9%. The overall survival for patients operated on between 1984 and 1992 at John Hopkins Hospital was 31%, compared to 58% for the more recent period (1993-1999)²¹. The mortality reported in more than 1800 consecutive cases from the Memorial Sloan Kettering Cancer Center (1991-2001) decreased from 4% in the first 5 years to 1,3% in the last two years²³. These higher survival and lower mortality rates, probably reflect

improvement in perioperative care, multidisciplinary treatment and an appropriately aggressive approach to safe hepatic resection. Patients who undergo liver resection for colorectal metastases and have no recurrence for 4 years thereafter have a cumulative probability that parallels people without cancer¹.

The two main disadvantages for liver resection are that only a limited number of patients are suitable for surgery and that disease-free survival is low²⁴. Fortunately, many presentations of hepatic disease that would previously have been considered unsuitable for surgery are now considered amenable to resection. Strategies designed to increase the proportion of patients to be candidates for complete surgical treatment are emerging, such as neoadjuvant chemotherapy²⁵, preoperative portal vein embolization²⁶ and 2-stage resection approaches²⁷.

An additional issue regarding liver resection after neoadjuvant therapy is how managing the type of resection in patients who had unresectable disease and then responded. Currently the trend is to resect all sites within the liver that contained disease. Actually it should be clarified if it is necessary to resect the volume in which the initial disease resided or it would be enough to take the nidus of residual disease.

Redefining eligibility for resection and prognostic factors

Historically, only 10% of patients with liver metastases, had traditionally been considered for resection (1-3 unilobar metastases, < 5 cm in size, ideally presenting metachronously). The limiting factor is nowadays, whether it is technically possible to remove all the tumour, regardless the number of nodules, as long as no more than 70% of the liver needs to be removed. The definition of resectability is currently evolving and a number of clinical scores have been devised in order to guide patient selection.

Although surgical resection can cure some patients, the majority will eventually develop recurrent disease. Therefore, several groups have identified some prognostic factors for recurrence. Metachronous detection of colorectal metastases, usually carries a better prognosis than synchronous liver metastases. Regarding *primary tumour related factors*, positive lymph node status and a disease-

free interval of less than one year (between resection of the primary tumour and liver metastases) are both associated with poor outcome. Several groups have noted that the site of primary tumour was also an independent predictor of survival. Rougier et al demonstrated that patients whose primary tumours arose in the right colon fared worse than those developed elsewhere in the colon or rectum⁸. However, other investigators have reported a worse survival for patients with rectal tumours^{24, 28}. High-grade⁹ and stage^{1,29} of primary tumour correlate with poorer survival. With respect to the *liver metastases*, factors that reflect advanced tumour burden have been shown to predict shorter survival: number of lesions^{21, 29}, size of largest lesion, bilobar distribution of disease (this is not generally accepted), percent hepatic replacement and weight of resected specimen³⁰. While patients with a small tumour size have a better prognosis than those with a large tumour, these ones may still benefit¹. Though 5 cm was the historical threshold, more updated reviews have shown that tumour size exceeding 10 cm has a poorer prognosis²⁵. No long-term survivors have been reported when more than 50% of the liver was replaced by metastatic colorectal cancer at the time of the surgery⁹. Elevation in preoperative serum carcinoembryonic antigen (CEA) levels is consistently associated with poorer outcome^{20, 21, 29-31}. Ca 19.9, less often studied, could also be one of most important prognostic factors²⁵. Alkaline phosphatase and albumin were independent prognosticator in a recent study²⁹. Regarding *technical factors*, a positive or close resection margin are predictive of poor outcome^{21, 32}. Anatomical resections have a significant survival benefit over lesser procedures in some analysis⁹ and the non-curative pattern of hepatectomy is identified as a prognostic factor²⁵. Though all tumours should be removed with an adequate margin, in some situations, such as contact with the contralateral portal triad sheath, the resection margin may be zero, if a macroscopic R0 resection can be achieved with potentially curative intent. Of course, resection must be achieved without cutting across the tumour (R1 resection), and a true positive margin remains a contraindication to curative surgery¹. The optimal width of the negative surgical margin remains controversial.

Adam and co-workers have recently updated its experience with initially considered unresectable

colorectal liver metastases after neoadjuvant chemotherapy. They have found four preoperative risk factors that could help to select the patients most likely to benefit from this strategy. Rectal primary, three or more metastases, maximum tumour size of 10 cm and Ca 19.9 > 100 UI/L have been reported as preoperative factors associated with decreased survival²⁵. Extrahepatic disease had no significant impact on survival except metastatic lymph nodes of the hepatic pedicle.

Possible contraindications for surgery: Resection may be considered in all patients fit enough to tolerate general anaesthesia. Absolute contraindications for resection of colorectal liver metastases have not been clarified, but most would agree that patients should not be offered resection if they have uncontrolled primary disease or such widespread intrahepatic involvement that the residual liver function after resection would be inadequate. Most authorities would agree that presently it would be safe to resect up to 70% of a healthy liver. One factor that theoretically precludes potentially curative liver resection is the involvement of lymph nodes at the hepatic hilum. However, some studies suggest benefit from radical excision of nodes in the region of the hepatic pedicle³¹. Though the presence of extrahepatic disease significantly reduces the likelihood of long-term survival, there are some instances where patients with extrahepatic disease can be considered for resection with potentially curative intent. These cases include direct diaphragmatic invasion, resectable local colorectal recurrence and resectable lung metastases that are readily resectable and few in number³³. Patients with adrenal gland metastases may survive for more than 5 years¹.

Relative contraindications include situations where resections are not easily performed such as those involving the caudate lobe or tumours invading the inferior vena cava or the portal vein confluence.

Neoadjuvant chemotherapy

Neoadjuvant therapy refers to the use of chemotherapy in patients who present localized or locally advanced cancer. However, this term can also be used for referring to some treatments administered before what is considered a curative treatment such as liver disease secondary to colon cancer. In this

setting, neoadjuvant therapy refers to “primary induction treatment for advanced disease followed (if possible) by surgery with curative intention”.

The feature of administering chemotherapy before surgery is the preservation of the tumour mass as a biologic marker of chemosensitivity of the drugs. A hypothetical advantage would be accessing tissues while they are fully oxygenated and vascularized, diminishing micrometastases or circulating tumour cells³⁴. As we mentioned before, chemotherapy itself could spare ineffective surgical treatment¹³. The question remains whether the response to chemotherapy simply identifies patients with a favourable prognosis or could modify the course of the disease.

What we can learn from other diseases with regards to neoadjuvant treatment is that it has allowed the sparing of some organs (such as bladder, larynx, anal sphincter or other). It also decreases the rate of post-operative complications in rectal cancer. And finally, in lung cancer, the neoadjuvant treatment impacts the survival at some stages.

The introduction of new chemotherapeutic regimens, may convert up to one third of non-resectable patients to resectability with curative intent (see Table I)³⁵⁻³⁹. A recent report reviews 1439 consecutive unresectable cases treated with surgery after neoadjuvant chemotherapy. The mortality rate was

0.7%, 5-year disease free and overall survival of 22% and 33% respectively and 10-year disease free and overall survival of 17 and 23%²⁵. This report offers a considerable support to both feasibility and results in initially unresectable patients treated with neoadjuvant chemotherapy. Although several studies demonstrate the utility of chemotherapy in rendering unresectable liver metastases resectable, full clinical evidence is missing, since no randomized trials have been completed with this purpose.

It is a subject of debate when to operate (after neoadjuvant therapy). Some groups suggest that surgery must be performed as soon as resectability is technically possible. The date of operation should be chosen to avoid a long interval between the last chemotherapy and surgery.

The main criticism for most reported as neoadjuvant studies, is that they do not evaluate prospectively the outcomes related to resectability. The criteria for non-resectability differed between the studies and were poorly defined. Poor prognosis does not imply non-resectability, and some surgeons could be prone to classify as non-resectable a poor prognosis patient, hoping that neoadjuvant therapy could change some prognosis factors. And it does change them. What is not so clear is if either the decrease of the number of nodules or the decrease of the size of nodules actually translate into a better survival. This question could only be answered through a randomized clinical trial which is unlikely to be launched.

When designing clinical trials for neoadjuvant therapies, the inclusion of appropriate surrogate endpoints (obviously final endpoint is overall survival) should be kept in mind. It has been clearly demonstrated that new agents improve survival, but improvement of response rates is not less important in this setting since a good shrinkage is necessary to allow the further surgery. The objective response rate has been recently associated with the resection rate of metastases⁴⁰. When tumour size is the non-resectability criterion, chemotherapy is the best option.⁴¹ In patients with synchronous metastases, the response to neoadjuvant chemotherapy may even be a prognostic indicator of survival and might assist in the selection of patients⁴². Some additional endpoints for trials in the neoadjuvant setting would be tumour shrinkage, patients eventually resected with curative intention, R0 resection rates, rates of com-

TABLE I

Resection rates after chemotherapy in initially inoperable patients

<i>Author</i>	<i>Patients</i>	<i>Surgery Rate (R0)</i>
Oxaliplatin-based		
Alberts 2003 ³⁵	42	36%
Adam 2004 ²⁷	1439	12.5%
Tournigand 2004 ⁴⁵	111	22%
Delaunoit 2005 ³⁶	267	4%
Irinotecan-based		
Ducreux 2003 ³⁷	55	31%
Pozzo 2004 ⁴¹	40	33%
Tournigand 2004 ⁴⁵	109	9%
Delaunoit 2005 ³⁶	264	1%
Oxiri-based		
Falcone 2004 ³⁸	74	26%
Quenet 2004 ³⁹	34	37.5%
Delaunoit 2005 ³⁶	265	4%

plete response, tumour necrosis in the pathological specimen, etc.

The choice of upfront therapy when considering the possibility of being a neoadjuvant therapy is critical. The most relevant indicator of the effectiveness of chemotherapy is the rate of complete response. The main requirement for drugs or combinations to be used in the neoadjuvant setting is to have documented evidence for its clinical efficacy in the advanced disease setting. The recent advances in treatment of advanced colorectal cancer have brought significant improvements in overall response rates and survival, yet have not translated into an actual cure for the disease. The reason is that the complete response rate for these regimens has been lower than 10% and no patient with advanced cancer has ever been cured without first achieving a complete remission. A new (fortunate but infrequent) challenge is the management of the complete responders⁴². The best approach to these infrequent situations has not been defined yet, and a case-by-case decision has to be made.

Prospective randomized studies are now underway in an attempt to define the utility of adjuvant therapy in the treatment of liver-only metastases from colorectal cancer. A randomized phase III study (40983) of the European Organization for Research and Treatment of Cancer study has tested the impact of preoperative and postoperative chemotherapy in resectable liver metastases. Surgical morbidity and mortality (0,9 and 1,6% in the chemotherapy and only-surgery arms respectively) were low. Results on survival are still pending. This trial will generate some information with regards to the role of chemotherapy but we will have no information regarding the right moment to administer chemotherapy (before or after surgery). One trial, N014A, is evaluating the surgical resectability rate after cetuximab plus oxaliplatin fluoracil and leucovorin, of patients with advanced colorectal cancer confined to the liver, initially considered suboptimal for resection.

Systemic treatment for colon cancer

The antimetabolite 5 FU was until a decade ago the only first line chemotherapeutic option for patients with advanced colorectal cancer. In spite of extensive efforts to improve response by modifying

schedules, doses and modulators, median survival did not exceed 12 months. The modern era of colon cancer chemotherapy began in the mid-1990s, when the two novel chemotherapeutic agents irinotecan and oxaliplatin were found to have significant activity. Since then, the treatment of advanced colon cancer has evolved considerably⁴⁴. Where there had previously been only one effective agent available for palliation, namely 5-FU, there are now a number of effective agents. During the past decade the FDA and the EMEA have approved five new drugs for metastatic colorectal cancer.

Though survival has been the main concern regarding adjuvant and metastatic treatments (at least for Health Authorities approvals), response rates and disease free survival could be more relevant to neoadjuvant therapy. As we mentioned before, the relationship between response and resectability rate has been well established^{40, 41} and would support the strategy of using the most active regimens in potential curable patients. Pozzo et al showed that only 18% of patients with stable disease after neoadjuvant chemotherapy for non-resectable patients underwent surgery⁴¹.

In Europe, where the infusional 5-FU regimens were developed, these drugs have such been combined. The rate of objective responses is now in the range of 40-50%. Response rates obtained with FOLFOX and FOLFIRI are considered to be equivalent^{45, 46}. Though more patients receiving FOLFOX as their first-line were able to go on to have resection⁴⁵. Main differences are found in the toxicity profile. Although the optimal neoadjuvant regimen has yet to be determined most evidence suggest that infusional FU/LV with oxaliplatin or irinotecan are the most effective for this purpose. Table II shows the most active regimens (only regimens tested in phase III are mentioned)⁴⁷⁻⁵³.

The two main reasons for the use of infusional regimens are a more favourable toxicity profile and prolonged thymidilate synthase inhibition.⁵⁴ Infusional administration of 5FU is less toxic, overshadowing issues related to the added cost, inconvenience and chance of catheter-related complications. Median number of cycles before surgery is about 10, and current trends in some groups is to perform surgery as soon as it is technically feasible²⁵. Therefore neurotoxicity does not seem to be a major concern in the neoadjuvant setting. Alopecia may be more

TABLE II

The efficacy of most active (more than 40% RR) chemotherapeutic regimens tested in randomized trials

<i>Regimen</i>	<i>Study</i>	<i>Number pts</i>	<i>RR</i>	<i>Median PFS(months)</i>
Irinotecan first line				
CPT+infFU LV	Douillard 2000 ⁴⁷	199	41%	6.7 mo (TTP)
CPT+AIO FU	Koehne 2003 ⁴⁸	214	54.2%	8.5 mo
CPT+AIO 5FU	Heinemann 2004 ⁴⁹	106	45%	Not reported
FOLFIRI	Tournigand 2004 ⁴⁵	109	56%	14.2 mo
Oxaliplatin first line				
Oxal/FU/LV (chronomodulated)	Giachetti 2000 ⁵⁰	100	53%	6.1 mo
FOLFOX	De Gramont 2000 ⁵¹	210	50.7%	9.0 mo
FOLFOX	Goldberg 2004 ⁵²	267	45%	8.7mo
FUFOX	Grothey 2002 ⁵⁵	118	48.3%	7.9 mo
FOLFOX	Tournigand 2004 ⁴⁵	111	54%	10.9 mo
Bevacizumab first line				
IFL/ Bevacizumab	Hurwitz 2004 ⁵⁹	402	44.8%	10.6 mo
FOLFOX6/Bevacizumab	Hochster 2005 ⁶⁶	71	62%	8.7 (TTP)
CPT11 and oxaliplatin				
IROX	Heinemann 2004 ⁴⁹	109	53%	Not reported
Oxal/CPT/5FU/fol	Souglakos 2004 ⁵³	102	45%	8.9mo

frequently with irinotecan. However if irinotecan is used weekly in doses below 100 mg/m² less than 10% of patients will have alopecia.

It has been suggested that sequence of drugs is not as important as the availability of all of them⁵⁵. A paper recently published by Dr Poston criticizes very harshly the policy of the UK National Institute for Clinical Excellence, stating that many British patients have been denied an effective treatment as a consequence of its 2002 guidance (recommending the use of 5FU-folinic as first line therapy)⁵⁶. We physicians, must do our best in order to achieve the best therapies to be approved as soon as possible. But we must also keep in mind that doubling the median survival in these patients is accompanied by a 340-fold increase in drug costs^{57, 58}. And drugs by themselves remain a palliative option, since there is no evidence that the new therapies increase cure rates. We must look again at multidisciplinary treatments.

The new targeted agents directed against EGF receptor or VEGF are increasing the efficacy of chemotherapy. Whereas a survival benefit has been seen with bevacizumab in both the first- line with

IFL (irinotecan/5FU, leucovorin)⁵⁹ and second-line settings (FOLFOX), the larger benefit in first line suggests that this agent should now also be considered a standard first line option. Cetuximab when added to patients with irinotecan resistance not only improved the rate of objective response but also prolonged the progression-free survival⁶⁰. Promising data have also been reported when bevacizumab was added to a combination of irinotecan and cetuximab in irinotecan-refractory patients⁶¹. It should be mentioned that addition of bevacizumab to 5FU/fol seems to be as effective in terms of response rates as IFL (irinotecan /5FU/fol)⁶². Bevacizumab increases overall survival by 30%. We could expect a parallel advantage regarding response rates or tumour shrinkage⁶³.

These new agents will be incorporated into neo-adjuvant trials. However, it is essential to define its role in well designed clinical trials, that should also explore potential adverse events related to these new drugs. Bevacizumab could have a deleterious effect in wound healing, as well as bleeding complications, bowel perforations, thromboembolic events etc⁵⁹. On the other hand, as we said before, objecti-

TABLE III

Gene expression and polymorphisms: influence on response and toxicity

<i>5 FU</i>	<i>Irinotecan</i>	<i>Oxaliplatin</i>
Thymidilate synthase	P450 3A4	XPB gene
Dihydropyrimidine Hydrogenase	ATP-binding cassette transporters	Excision repair enzyme XRCC1, ERCC2
Thymidine Phosphorilase	Carboxylesterase	GSH-dependent enzymes
	UGT1A1	EGFR

ves to be achieved with new therapies in every setting must be properly defined.

So far the most appealing results reported in first line, with regards to response rate, included cetuximab combined with FOLFOX (81%)⁶⁴, cetuximab combined with FOLFIRI-AIO (74%)⁶⁵, bevacizumab combined with FOLFOX6 (62%)⁶⁶ and oxaliplatin combined with irinotecan (70%)⁶⁷ all in phase II trials. FOLFOX plus cetuximab and FOLFIRI-AIO plus cetuximab had the same figures for resectability rates: 21%. FOLFOXIRI rendered 26% R0 resected patients. Of note, regimens including cetuximab were only administered to EGFR positive patients, while some EGFR negative patients could benefit from this treatment⁶⁸. Should these results be confirmed in phase III trials, these combinations could become a good option as a neoadjuvant therapy.

PTK/ZK is an orally active small molecule that blocks both angiogenesis and lymphangiogenesis by inhibiting tyrosine kinase signaling. This drug could have a positive effect when added to FOLFOX, mainly in patients with high LDH. This fact can be interesting since most adverse prognostic factors before surgery are related to tumoral volume⁶⁹. Other small molecule VEGF inhibitors, including SU11248 and Bay 43 9006 are also in clinical development.

Data are now accumulating about the efficacy of second –line therapy. We must be prepared to face liver relapses after adjuvant treatment with FOLFOX, that was recently approved by the EMEA in node-positive colon cancer adjuvant therapy. Specific clinical trials designed for these patients would help to clarify the best option. The assumption that 5 FU would be beneficial throughout treatment should also be tested in clinical trials.

Other drugs such as pemetrexed (ALIMTA), epothilones (microtubule-stabilizing drugs), edote-

carin (non-camptothecin topoisomerase I inhibitor) and tezacitabine (nucleoside analog to gemcitabine) could be added to the colorectal armamentarium in the next years. But it is too early to evaluate its possible impact on the neoadjuvant setting.

Incremental improvements in survival, symptom palliation and quality of life have been achieved with the new therapies. Conventional chemotherapy has moved prognosis for patients with metastatic colorectal cancer from 12 months to 20 months and beyond. The emergence of biologic therapies, has expanded the options for treatment. The number of potential combinations has grown such that the complexity of delivering care in colorectal cancer is far greater than in the past.

Prediction of chemotherapy response

Our decision to recommend a specific treatment is usually based on tumour and patient-related factors known to influence treatment outcome (efficacy and toxicity). However in many cases all these factors are not sufficiently predictive with respect to treatment response and side effects. We need more precise tools to predict individual response and possible toxicities of drug therapy. The pharmacogenomic profile of individual patients is crucial in order to predict efficacy and toxicity. More information is urgently needed to allow individualization of treatment options for patients (See Table III).

Hepatic arterial chemotherapy (HAC)

The dual blood supply of the liver and the access to the hepatic artery, make it an appealing route for the delivery of therapy directly to the liver. The rationale for HAC is that liver metastases are perfused almost exclusively by the hepatic artery, whereas normal hepatocytes derive most of their blood

supply from the portal vein as well and little from the hepatic artery. The chemotherapeutic agents are delivered via implantable pumps or subcutaneous port. FUDR is the best drug to use for regional therapy because 94 to 99% of FUDR is extracted during the first pass compared to 19 to 55% of 5-FU. Response rates range between 40 and 60%. HAC is superior to intravenous chemotherapy in terms of response rate but not in terms of survival⁷⁰. Some groups incorporate this strategy as neoadjuvant therapy to allow some patients to undergo liver resection⁷¹. There is a risk of extrahepatic progression, and sometimes, both intrahepatic and intravenous infusion are alternatively administered. A recent paper reports an amazing 90% response rate in pretreated patients using this strategy⁷².

Progress in technical procedures (percutaneously placed catheters), progress in treatment modalities (new drugs such as oxaliplatin or angiogenesis inhibitors) as well as in indications (in chemo-resistant patients) mark the future directions of this technique.

Chemotherapy and liver toxicity

Chemotherapy can result in liver toxicity, particularly when administered for prolonged duration. Steatosis denotes the accumulation of fat in the liver and is commonly associated with obesity. Use of oxaliplatin has been recently associated with development of hepatic sinusoidal obstruction and hepatic steatosis. For steatohepatitis to occur, a "second hit" seems to be required and some drugs (as well as parenteral nutrition or other) can act as second-hit. In fact, oxaliplatin and irinotecan can be associated with steatohepatitis. Presence of steatohepatitis is associated with increased hepatic failure after major hepatic resection being more likely to occur in the obese. This liver steatohepatitis can affect hepatic reserve, decreasing rather than increasing resectability and might make the liver resection riskier.⁷³ In this situation, portal vein embolization could be recommended to induce hypertrophy of the uninvolved liver.

What type of chemotherapy is associated with increased hepatotoxicity is not clear. Neither it is the duration of the treatment. We have even less information on newer biologic agents such cetuximab or bevacizumab.

Adjuvant therapy of colon liver metastases

Approximately 70% of patients who undergo hepatic resection experience recurrent metastases within 2 years and approximately one-half recur in the liver. While it would be desirable to perform a clinical trial to test treatment strategies and to know the exact role of adjuvant chemotherapy, the design for such a trial poses logistic and ethical difficulties.

A Memorial Sloan Kettering study of chemotherapy following liver resection compared standard systemic chemotherapy (based on 5FU) with a regimen consisting of systemic 5FU/leucovorin alternating with hepatically infused FUDR. The regimen incorporating hepatic arterial infusion was more effective in terms of improving overall survival⁷⁴. Of note, the median follow-up was only 33 months and the study was limited to patients with fewer than four metastases.

The question of regional versus systemic adjuvant chemotherapy following hepatic metastasectomy is being evaluated by two upcoming trials conducted by the NSABP and the ACSOG in the US.

Re-resection of metastases

After surgery for colon liver metastases, relapse will occur in 60-70% of patients⁷⁵ occurring on the opposite side of the liver in more than a third of cases. The majority of patients who develop recurrence following hepatic resection of colorectal metastases relapse within 2 years of surgery. Therefore aggressive surveillance may improve the early detection of recurrent disease. Approximately 20% of these patients have liver-only recurrence and hence may be suitable for resection. It is well established that even serial hepatectomy for recurrent colorectal metastasis is feasible if the performance status of the patient supports a series of operations. As might be expected, a longer time to recurrence was predictive of a more favourable outcome⁷⁶.

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