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TOPIC HIGHLIGHT

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Evolution in the treatment of metastatic colorectal carcinoma of the liver

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Abstract

Metastatic colorectal cancer to the liver is associated with a uniform poor prognosis without treatment. Advances in therapy over the past decades have now allowed surgical resections of the liver to occur with a low morbidity and mortality. Improvements in chemotherapy regimes have paralleled technical improvements and now allow a new group of patients to become eligible for surgical resection. This chapter will review the recent advances in surgical and chemotherapeutic regimes in metastatic colorectal cancer to the liver.

Key words: Ethical tensions; Metastatic; Colorectal Carcinoma; Liver

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INTRODUCTION

Colorectal cancer is the 3rd leading cause of cancer related deaths in males and females. In 2005 it is estimated to afflict 72 915 males and 71 004 females in the United States. (www.cancer.org) Autopsy studies have shown that the liver is the most common site of distant disease in colorectal cancer (Welch J 1979), and approximately 60% of patients will develop liver metastases at some point during the course of their disease.(Kemeny 2005)

Malignant tumors of the liver were once considered a lethal disease. Untreated metastatic colorectal carcinoma has a median survival of 6 to 9 mo. (Khatri 2005) Today multiple studies have demonstrated the safety and efficacy of hepatic resection. This chapter will review the history and evolution of hepatic resection for metastatic colorectal cancer to the liver.

SURGICAL CONSIDERATIONS

While reports of liver resections extend back from before the 19th century (Keen 1899), there was significant mortality associated with these procedures. Couinaud, Goldsmith and Healey substantially aided our understanding of the segmental anatomy of the liver and this has contributed substantially to the development of safe hepatic surgery. (Healey 1953; Couinaud 1954; Goldsmith 1957; Couinaud 1999) Surgical resection is the primary treatment for metastatic liver lesions, as patients who do not undergo resection do not survive 5 years. (Scheele J 1995) Large studies by experienced hepatobiliary surgeons have demonstrated a mortality of less than 5% for liver resections (Coppa 1985; Fong 1999), with a five year survival of 20%-38% (Gayowski TJ 1994; Fong Y 1997) for lesions confined to the liver. Additional studies have demonstrated that larger tumors and multiple tumors can also be removed safely (Adson 1980; Adson 1984; Fong 1999). An area undergoing evolution is extrahepatic spread, which traditionally was considered a contraindication for surgery. However, colorectal metastases to the lung do warrant resection in patients along with liver metastases (Regnard JF 1998), and more recently, 5-year survival after surgery for hepatic and extrahepatic disease has been reported to be as high as 29% in carefully selected patients (Elias 2004). Future randomized trials will have to be performed to delineate if resection of extrahepatic disease constitutes a sustained survival benefit for patients.

Optimization of surgical techniques has also aided in reducing peri-operative mortality from liver resections. Measurements of functional liver reserve can be evaluated by bilirubin, prothrombin time, and percent indocyanine green retention. (Miyagawa S 1995) If a large resection is planned, or there is concern regarding the function of the remaining liver, pre-operative portal vein embolization (PVE) offers a method to maximize the size of the hepatic remnant. (Makuuchi M 1990) A study of patients with

metastatic colorectal cancer to the liver demonstrated the efficacy of PVE. Preoperative PVE was performed in patients with a CT-scan estimated post-resection volume of 40% or less, all of whom had received pre-operative chemotherapy. The median increase in CT scan estimated liver volume was 42%, and 63% of the patients were able to undergo an extended liver resection (17/19 resections involved 4 or more segments). (Azoulay D 2000)

INFUSION PUMPS

As systemic therapy for colorectal liver metastases was historically ineffective, studies were undertaken to look at direct infusion of higher doses of chemotherapy directly into the hepatic arterial system. Cancers of the liver have been shown to primarily derive their blood supply from the hepatic artery. (Breedis C 1954) Therefore, chemotherapy delivered through the hepatic artery will directly target the cancer cells before the drug has an opportunity to be metabolized. The rationale behind hepatic directed chemotherapy is based on three principles. (1) a five fold increase in the concentration of drug reaching the liver by avoidance of initial systemic dilution (20% of systemic blood flow goes to the liver); (2) the arterial supply to tumors and predominantly portal venous supply to normal liver increases drug delivery to the tumor with relative sparing of normal liver tissue; (3) hepatic metabolization of certain drugs reduces the hepatic venous concentration minimizing systemic toxicity. Confirmation of the benefit of hepatic administration *vs* portal administration of chemotherapy comes from a small randomized trial in which patients received chemotherapy with floxuridine via the hepatic artery or the portal vein. Fifty-percent of patients receiving arterial chemotherapy responded to treatment, but, there were no responders in patients receiving chemotherapy via the portal vein. One third of patients from the portal treatment group who crossed over to arterial chemotherapy subsequently had a response to treatment. (Daly JM 1987)

Systemic (IV) chemotherapy was first compared to hepatic artery infusion (HAI) chemotherapy in patients with unresectable colorectal liver metastases randomized to receive 5-fluorodeoxyuridine (FUDR) IV or by HAI. Fifty percent of patients receiving HAI infusion had a decrease in measured tumor burden, compared with a 20% response rate for systemic IV infusion ($P = 0.001$). Some patients with tumor progression on IV therapy crossed over to HAI therapy and 33% of these patients responded or had stabilization of disease. Patients receiving HAI had a higher incidence of extrahepatic disease compared to the systemic IV treatment (56% *vs* 37%, $P = 0.092$). Complications of HAI treatment included biliary sclerosis (8%) and ulcers (17%). (Kemeny N 1987) A similar randomized trial from the National Cancer Institute also demonstrated the efficacy of HAI chemotherapy. Sixty-two percent of patients receiving HAI had tumor regression, while only 17% of patients receiving IV therapy had a response. HAI patients had significant rates of biliary sclerosis (21%) and ulcer disease (17%), however, HAI therapy improved survival benefit at two-years to patients without hepatic artery nodal disease. (Chang AE 1987) Additional randomized trials have shown an improved tumor regression and preservation of quality of life with HAI infusion in carefully selected patients compared to selected controls. For example, the survival benefit existed only in the subset of HAI patients with less than 30% liver involvement, treated at specialized centers, and only when the comparison group received either systemic chemotherapy or only supportive care. (Rougier P 1992; Allen-Mersh TG 1995) A meta-analysis of all treatment groups at this time did not demonstrate a survival benefit for patients receiving HAI therapy over systemic therapy. (Harmantas A 1996) However, a more recent prospective trial has shown a survival benefit of HAI. In this trial 117 patients were randomized to IV versus systemic 5-FU and leucovorin. Similar to other trials, an increased response rate (47% *vs* 24%, $P = 0.12$), and time to hepatic progression (9.8 *vs* 7.3 mo, $P = 0.034$) was seen in HAI as compared to systemic therapy. Despite an increase in extrahepatic disease progression, overall survival was improved in patients with HAI (24.4 *vs* 20 mo, $P = 0.0034$). Importantly, quality of life assessments also showed an improvement in physical functioning at 3 and 6 mo of follow-up. (Kemeny N 2006)

The technique to place the catheter for drug delivery has been modified over the years such that current treatment involves an open laparotomy to cannulate of the gastroduodenal artery, and cholecystectomy. An analysis of 544 consecutive hepatic artery pumps in patients with unresectable colorectal cancer, revealed increased complications in patients with variant anatomy, pump insertion into an artery other than the GDA, and placement by a surgeon performing < 25 cases. However, the study also showed that only 16% of pumps had failed by two years. (Allen P 2005)

In 1995 Moertel demonstrated the advantage of adjuvant chemotherapy in Stage III colorectal cancer (Moertel C 1995). As hepatic resection became a safer procedure, investigators began to question whether resection followed by adjuvant therapy could offer a survival benefit as well as reduce liver recurrence. The German Cooperative study randomized patients to surgical resection alone versus surgical resection and HAI of 5-FU and folinic acid. Interim analyses did not demonstrate a conclusive survival benefit and the study was terminated. (Lorenz M 1999) However, an additional randomized trial demonstrated a survival benefit for HAI. Patients after liver resection received either HAI with floxuridine, dexamethasone, and, IV fluorouracil and leucovorin, or, systemic therapy alone of fluorouracil and leucovorin. Survival at two years was increased in the group receiving combined HAI and systemic therapy (86 *vs* 72%, $P = 0.03$).(Kemeny N 1999) An intergroup study randomized patients to surgery alone *vs* adjuvant HAI FUDR with IV 5-FU. While 4-year recurrence rate and liver recurrence-free rate were improved with therapy (25% *vs* 46%, $P = 0.04$, and 43% *vs* 67%, $P = 0.03$), the improvement in overall survival did not reach stastical significance. (Kemeny MM 2002) This may have been secondary to the fact that a significant number of patients that were disqualified from the study at the time of surgery, or, that the performance of the study at multiple institutions introduced another

variable.

In summary, HAI can be performed safely in institutions with appropriate experience. In patients with resectable tumors, HAI may offer a survival benefit either alone or when used in conjunction with systemic therapy. The patients with advanced disease that will receive the most benefit from HAI are those without peri-portal nodal disease.

CHEMOTHERAPY

For many years the only chemotherapy option in advanced colorectal cancer was the thymidylate synthase inhibitor 5-FU, given in combination with folinic acid (leucovorin), to potentiate the effect of 5-FU. These drugs had been shown to prolong disease free survival, with a large meta-analysis demonstrating a response rate of 32% and a median survival of 11.5 mo. (Project 1992) The development of newer agents has significantly influenced the management of advanced colorectal cancer.

Oxaliplatin is a third generation platinum drug that forms DNA adducts and results in cell death, with more efficacy and less side effects than previous generation platinums such as cisplatin.(Woynarowski JM 1998) Oxaliplatin used in combination with 5-FU and leucovorin improves disease free survival when used as an adjuvant in stage II or III colorectal cancer.(Andre 2004) In advanced colorectal cancer, the use of oxaliplatin with 5-FU/LV (FOLFOX) improved response rates to 50.7% and increased median survival, although not significant, to 16.2 mo.(de Gramont A 2000)

CPT-11(Irinotecan) and its active metabolite SN38 inhibit topoisomerase I, resulting in single strand DNA breaks and inhibition of DNA synthesis. (Kawato Y 1991) A randomized trial of irinotecan and 5-FU/Leucovorin (FOLFIRI) demonstrated an improved response rate of 39% and improved median survival of 14.8 mo in patients with metastatic colorectal cancer ($P = 0.04$ versus 5-FU/LV). (Salz L 2000) More recent trials have looked at treating patients with FOLFIRI or FOLFOX and with disease progression, transferring the patient from irinotecan to oxaliplatin or vice versa. This trial demonstrated impressive improvement in survival of 21.5 and 20.6 mo, limited only by toxicity profiles.(Tournigand C 2004)

As research in cancer therapy has progressed, more specific targets of cancer cells have been identified. Cancer cells express vascular endothelial growth factor (VEGF) in an effort to promote new vessel growth and tumor survival. Bevacizumab is humanized monoclonal antibody against VEGF. A randomized phase 3 trial of bevacizumab in combination with irinotecan, fluorouracil and leucovorin (IFL) versus IFL alone demonstrated increased disease free progression (10.6 *vs* 6.2 mo respectively) and increased survival (20.3 mo *vs* 15.6 mo). (Hurwitz H 2004) The epidermal growth factor receptor (EGFR) is an integral part of the cell that is the target of many signals regulation cell growth and death. A monoclonal antibody against EGFR, cetuximab, has also been demonstrated to prolong survival in patients with colorectal cancer refractory to irinotecan (8.6 *vs* 6.9 mo). (Cunningham D 2004)

NEOADJUVANT CHEMOTHERAPY

The armamentarium for treatment of metastatic colorectal cancer has improved over the years. While surgical resection offers the best outcome, many patients are not resectable and therefore undergo either HAI or systemic chemotherapy as described above. Bismuth was the first to demonstrate that preoperative chemotherapy could downstage tumors and make surgical resection an option. Patients in this study ($n = 330$) had nonresectable colorectal liver metastases, based upon tumor size, location or number of metastases, and underwent treatment with 5-FU, leucovorin, and oxaliplatin. Fifty-three patients responded to chemotherapy such that they became eligible for hepatic resection. The overall 5-year survival of patients undergoing surgery was 40%, with no peri-operative mortality. While 64% of patients had a hepatic recurrence, almost one-half were able to undergo an additional hepatic resection. (Bismuth 1996) These results have been substantiated in additional trials using the same chemotherapy with five-year survival of 35%-50%.(Giacchetti 1999; Adam R 2001)

Analysis of unresectable patients undergoing HAI infusion has only identified a small number of patients that became amenable to surgical resection. The first study was a retrospective analysis of 5-FU based HAI in patients with colorectal and non-colorectal liver cancer. Surgical resection became an option in 5.8% (14/239) of patients. Of these patients, 9 had metastatic colorectal cancer and underwent surgery. Five patients remained free of disease at a mean follow-up of 36 mo. (Elias D 1995) A similar retrospective study by Meric et al identified 383 patients with metastatic colorectal cancer who received HAI with FUDR. Twenty two patients had a response such that they were able to undergo additional procedures. Ten were able to undergo a resection alone while 6 underwent resection with cryotherapy or radiofrequency ablation. At a median post-operative follow up of 17 mo, the majority had recurrence and only 1 patient was alive without evidence of disease. (Meric f 2000) A phase I trial of the chemotherapy regimen of HAI of FUDR and dexamethasone with systemic oxaliplatin ± irinotecan or 5-FU/LV, demonstrated safety and an improved response rate when compared to systemic chemotherapy alone. Despite the fact that the majority of these patients had progression of disease on previous chemotherapy regimens, and 87%-90% had a partial response, seven of thirty-six patients were able to undergo liver resection and 2 had a complete pathologic response. (Kemeny N 2005) These encouraging results warrant further studies on the role of HAI with systemic chemotherapy in patients that fail to respond to other first line chemotherapy regimens.

The ability to respond to neoadjuvant chemotherapy improves survival and may be a significant harbinger of long-term survival. Allen studied patients presenting with colorectal liver metastases presenting within 1 mo of the primary surgery. All patients were resectable by radiological criteria. One group of patients went directly to surgery while the other group of patients received neoadjuvant chemotherapy consisting of 5-FU in combination with either oxaliplatin or irinotecan. The administration of

chemotherapy did not statistically influence survival, and no patients became radiographically unresectable while on chemotherapy. However, the patients on chemotherapy that had stabilization or regression of disease, had significantly improved survival over those patients that had disease progression on chemotherapy. (87% versus 38% 5-year disease specific survival, respectively, P = 0.03). (Allen P 2003) While this paper demonstrates the predictive value of response to chemotherapy, it also shows that patients who had disease progression also benefited from surgical resection.

CHEMOTHERAPY AND HEPATIC TOXICITY

With the knowledge that pre-operative chemotherapy can be given to downstage patients and possibly select those patients that are going have an improved survival, one must consider the effect of the chemotherapy on the liver. A retrospective analysis of 67 patients after liver resection revealed significant increase in morbidity in the group that received pre-operative chemotherapy consisting of 5-FU combined with either oxaliplatin or irinotecan. While there was no mortality, post-operative complications occurred in 37.8% of patients receiving neoadjuvant therapy and only in 13.6% of patients undergoing resection alone (P = 0.03). Transient hepatic failure occurred in 5 patients in the chemotherapy group. Pathologic examination of liver outside of the tumor revealed significantly increased sinusoidal dilatation in the chemotherapy group (49% *vs* 25% respectively, P = 0.005). There was no difference in steatosis or fibrosis. Multivariate analysis revealed preoperative chemotherapy to be one of the factors associated with increased post-operative morbidity. (Karoui M 2006)

Nodular regenerative hyperplasia (NRH) is the result of hyperplasia of hepatocytes with obliteration of surrounding liver in the absence of fibrosis. (Steiner 1959) The result is an enlarged liver with large nodules and at times, portal hypertension that mimics cirrhosis. The inciting factor of NRH is not known. A large study of 2500 autopsies demonstrated an incidence of only 2.6%. In this study, there was an increased incidence in older patients with collagen vascular diseases, tumors, and with underlying cirrhosis. (Wanless 1990) Pathologic analysis often noted thrombosis or diminutive portal veins, suggesting that alterations in portal flow influenced the development of NRH. Additional support for modifications in blood flow comes from two described cases of congenital absence of the portal vein, where a liver biopsy confirmed NRH, (Grazioli L 2000), however, many additional studies of NRH have not demonstrated vascular abnormalities.

NRH has also been shown to occur after chemotherapy. A consecutive study of hepatectomy specimens identified NRH in 7% of specimens. (Washington K 1993) All these patients had received pre-operative 5-FU regimen for colon cancer metastatic to the liver. However, there remains a disparity between drug administration and development of NRH, as not everyone in this study who received chemotherapy developed NRH. More recent studies have begun to describe cellular mechanisms of NRH. Notch signaling is a highly conserved intracellular signaling pathway that is fundamental in cell differentiation and embryonic development. In mice and humans, there have been four NOTCH receptors described (NOTCH1-4). In mice, loss of notch signaling is a fatal event. However, if one of the receptors of Notch signaling (Notch1) is inactivated early in postnatal development, this leads to NRH in the absence of vascular abnormalities.(Croquelois 2005) In addition, overexpression of IL-6 has also been shown to lead to NRH in mice.(Maione D 1998) These studies demonstrate pathways that could be targets for future understanding and prevention of NRH.

A retrospective study analyzed adjacent liver in resected liver specimens for metastatic colorectal cancer. All patients received 5-FU, leucovorin and either oxaliplatin or irinotecan. NRH was demonstrated in 4% of specimens. Importantly, 51% of specimens had sinusoidal dilatation with one-half having additional venoocclusive fibrosis. This was most common in patients that had received oxaliplatin therapy. (Rubbia-Brandt 2003)

Bevacizumab has anti-angiogenic properties and it is not yet known if livers resected after this therapy will have alterations in post-resection regeneration or function. At Yale, we have performed hepatic resections after 5-FU based therapy with oxaliplatin or irinotecan. In addition, some patients have also received bevacizumab. NRH has been frequently observed in patients receiving oxaliplatin particularly with extensive treatment. To date however this has not impacted negatively on the postoperative course or on hepatic regeneration.

FUTURE DIRECTIONS

With the progression in the understanding of colorectal disease new therapies will evolve. Instead of a surgical intervention to install an infusion pump to direct therapy into the liver, perhaps a therapy will be targeted to a gene. For example, adenoviral vectors are taken up by the liver and processed safely without evidence of inducing tumors (Bell 2005). These vectors can be used to carry cytokines, genes and apoptotic inducing proteins. Microarray technology has identified profiles of colorectal cancers that are likely to metastasize (Croner R 2005) and may help identify patients that need systemic chemotherapy. Gene profiling has identified characteristics that portend a favorable response to chemotherapy. (Matsuyama R 2006) The challenge will be to translate these studies into meaningful data for the patients with colorectal cancer.

In conclusion, the treatment of liver tumors has evolved substantially over the last century. The best chance for survival is surgical resection, and today liver resection can be performed with a low morbidity in correctly selected patients. Improvements in chemotherapy have improved survival in primary and metastatic colorectal cancer. Furthermore, chemotherapy has been able to downstage patients with advanced disease rendering them surgically resectable. Future studies will need to evaluate the hepatic side effects of newer drug regimens.

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