Background: Metastases to the liver is the leading cause of death in patients with colorectal cancer. Methods: The authors review the data on diagnosis and management of this clinical problem, and they discuss management options that can be considered. Results: Complete surgical resection of metastases from colorectal cancer that are localized to the liver results in 5-year survival rates ranging from 26% to 40%. Conclusions: By adding modalities such as targeted systemic therapy and other "local" treatments for liver metastases, further gains in survival are anticipated.

Key words: liver metastases, surgical resection, neoadjuvant chemotherapy, extrahepatic disease, survival benefit

INTRODUCTION

Colorectal cancer is the third most common cancer in both men and women. About 50% of patients diagnosed with CRC will die from their disease, accounting for about 10% of all cancer deaths. Tremendous strides are made regularly in the prevention, diagnosis, and treatment of colorectal cancer, posing a challenge to the clinician who must stay abreast of the most recent advances. In the 1970s, treatment options for patients with advanced colorectal cancer were limited to the fluoropyrimidine 5-fluorouracil (5-FU). Since that time, newer cytotoxic agents, such as capecitabine, irinotecan, and oxaliplatin, have been introduced, extending survival, facilitating administration, and permitting better tailoring of treatment regimens to individual patients. The last 3 years have seen yet further advances with the approval of biologic agents such as bevacizumab in front-line therapy and cetuximab in second- and third-line therapy. The more aggressive chemotherapy regimens can not only control the disease, but also render some advanced metastatic disease into a resectable stage.

BACKGROUND:

The natural history of colorectal cancer metastasis in the majority of patients is dismal. Historically, the median survival is 6 to 12 months if untreated. Even with newer therapeutics such as irinotecan or oxaliplatin, the 5-year survival rate with nonsurgically treated hepatic metastases is low. In contrast, those who undergo a complete resection have 5-year survival rates of 25% to 40%. It can be argued that the patients who undergo resection are selected and may have better outcomes because they have less virulent disease. A trial designed to compare resection vs systemic therapy is unlikely until more efficacious systemic therapy regimens are discovered. Currently, the survival rates reported after curative hepatic resections are 25% to 39% for 5 years and 22% to 23% for 10 years.

RESECTION OF EXTRAHEPATIC COLORECTAL METASTASES

Once suspected, colorectal liver metastases are staged by spiral CT, CT portography and MRI, which have similar overall accuracies. Mortality following liver resection is less than 5% in major centres, with a morbidity rate of 20% to 50%. Prognostic scoring systems can be used to predict the likely cure rate with resection. Pulmonary metastases occur in 10-25% of patients with resected colorectal cancer, but are limited to the lung in only 2% of cases. In these selected cases surgery provides long-term survival in 20-40%, and repeat lung resection has shown similar rates. The presence of thoracic lymph node involvement and elevated carcinoembryonic antigen level before pulmonary resection are associated with reduced survival. For patients with unresectable disease, chemotherapy and ablation techniques have been demonstrated to prolong survival, although chemotherapy alone has been shown to improve quality of life.
LIVER RESECTION FOR COLORECTAL METASTASES

Surgical resection is associated with the best chance for cure of colorectal cancer when complete resection of the tumor-bearing liver can be accomplished. However, historically, only 10% to 20% of patients with colorectal liver metastases have been eligible for resection with radical intent. Recent improvements in preoperative imaging techniques, patient selection, and surgical techniques, as well as the introduction of new cytotoxic and biologic agents for preoperative and postoperative chemotherapy have improved the resectability rate and almost doubled the 5-year survival rate for patients with colorectal liver metastases, from about 30% two decades ago to nearly 60%. Moreover, in patients with nonresectable metastases, modern chemotherapy alone extends median survival to 2 years or more, and 20% of patients with nonresectable metastases are still alive 4 years after detection of nonresectable liver disease. In summary, the care of patients with hepatic colorectal metastases has rapidly changed. Novel chemotherapeutic regimens combining 5-FU, folinic acid, and oxaliplatin and/or irinotecan have been associated with improved response rates (approximately 50%), allowing 10% to 30% of the patients with initially unresectable disease to be successfully treated with liver surgery. In addition, early results from trials evaluating novel biologic agents that target angiogenesis and the epidermal growth factor receptor, bevacizumab and cetuximab, suggest that even more patients with initially unresectable disease may respond to primary treatment with combinations of systemic therapies (response rates up to 70%).

NEOADJUVANT THERAPY

Most patients with colorectal liver metastases will present with unresectable disease. Beginning in the 1990s, Bismuth et al reported on a small percentage of patients who had a significant downsizing of their hepatic lesion with neoadjuvant chemotherapy. These patients were then brought to surgery for an attempted R0 resection. The 5-year survival rate was 40%, similar to those resected de novo. These results have been reproduced multiple times. Therefore, those patients initially determined to be unresectable should be reevaluated for resectability after neoadjuvant therapy for resectability. More recently, newer effective chemotherapeutic combinations, including FOLFOX or FOLFIRI with bevacizumab, have had more consistent results in downsizing liver metastases from colorectal adenocarcinoma. There is no evidence to support pretreatment with neoadjuvant chemotherapy in patients with respectable disease also response might be a surrogate marker for curative resection and studies will sho the impact of adjuvant therapy after liver resection. 20% will progress while on chemotherapy and will have no benefit from subsequent liver resection.

RECURRENCE FOLLOWING LIVER RESECTION

Approximately 60% to 70% of patients treated with resection will recur. Of those who recur, 30% of recurrences will be isolated to the liver. The liver parenchyma will regenerate or hypertrophy to presurgical size in 3 to 6 months, and significant resection can be performed a second time if the patient’s physical status will allow repeat procedures. Several studies have demonstrated similar morbidity and mortality compared to primary resection. The overall 5-year survival is similar to that of the initial resections and the timetable is reset from the time of the second resection. A recent retrospective study by Petrowsky et al demonstrated similar morbidity and mortality rates compared to primary resection, with a 34% actuarial 5-year survival rate and 15% actual 5-year survivors at the time of follow-up. These results are similar to those published for primary resections and suggest that reintervention is of benefit. The recent emergence of molecularly targeted monoclonal antibody therapy with proven efficacy in metastatic colorectal cancer, provides a significant improvement in the outcomes for patients, but also presenting challenges for clinicians in selecting the most appropriate combination of therapy for their patients after liver resection.

FOLLOW-UP AFTER RESECTION:

Postoperative surveillance evaluates the efficacy of treatment as well as screening for recurrence. According to the 2006 National Comprehensive Cancer Network guidelines, follow-up includes a physical examination, a CEA measurement, and a CT scan of the chest and abdomen every 3 months for 2 to 3 years, then every 6 months for 5 years. Some clinicians limit the use of CT scan until a measurable CEA level is noted. Most recurrences are identified within the first 2 years of operation. The surveillance begins again if a patient has had a re-resection of a liver lesion. A recurrence beyond 5 years of intervention is rare; therefore, routine imaging and laboratory follow-up other than screening colonoscopy are unnecessary.

CONCLUSIONS

With the addition of newer chemotherapeutics, survival has improved in patients treated both medically and surgically for metastatic colorectal cancer. The role of neoadjuvant chemotherapy is being clarified. The current approach is upfront surgery unless a lesion is considered unresectable. Neoadjuvant therapy may soon be recommended more frequently, however, as more predictable responses from the intervention occur. During the preoperative evaluation, attention needs to be focused on considering sufficient liver parenchyma and assessment for extrhepatic disease. Survival benefits in patients undergoing a second liver resection have similar outcomes as those undergoing a primary resection. Regardless of the surgical resection, patients benefit most when tumor-free margins greater than 1 cm are achieved. If the margins are close, RFA or cryotherapy can be added to ensure an adequate depth.

SUMMARY

Hepatic metastases occur in 60% of patients following resection for colorectal cancer. Liver resection is the only curative option, with one third of resected patients alive at five years. In those developing recurrence in the liver fol-
lowing resection, further liver surgery may be curative, with similar 5 years survival rates of about 30%. Until recently surgery was feasible in only 15-25% of patients with colorectal liver metastases. New strategies, such as downstaging chemotherapy, portal vein embolization and two-stage hepatectomy, may increase the resectability rate by 15%. Earlier detection of liver metastases would increase resectability, although good follow-up trials are lacking.

SUMMARY

MULTIMODALNO LEĆENJE METASTATSKOG KOLOREKTALNOG KARCINOMA

Uvod: Metastatska bolest jetre je vodeći uzrok smrti bolesnika sa kolorektalnim karcinomom.

Materijal i metode: Autori analiziraju podatke iz literaturu u vezi sa dijagnozom i lećenjem metastatske bolesti jetre i diskutuju o mogućim načinima lećenja.

Rezultati: Radikalna hirurška resekcija metastaza u jetri poreklim od kolorektalnog karcinoma omogućava petogodišnje preživljavanje u 26 do 40% bolesnika.

Zaključak: Dodavanjem drugih modaliteta lećenja kao što su ciljana sistemска hemoterapija i drugi vidovi lokalne terapije metastaza, mogu se postići bolji rezultati u lećenju metastatske bolesti jetre.

Ključne reči: metastaze u jetri, hirurška resekcija, neoadjuvantna hemoterapija, ekstrahepatična bolest, preživljavanje

REFERENCES


56. Wein A, Riedel C, Kockerling F, et al. Impact of surgery on survival in palliative patients with metastatic colorectal cancer after first line treatment with weekly 24-

