Liver Resection of Colorectal Metastases in Elderly Patients

Prashant Bhangui[1] and Rene Adam[2]

1. Clinical and Research Fellow, Hepatobiliary Centre, Paul Brousse Hospital; 2. Professor of Surgery, Faculty of Medicine, Paris South University, and President, Medical Board and Head, Onco-surgical Unit, Hepatobiliary Centre, Paul Brousse Hospital

Abstract

The ageing population, the specific epidemiology of colorectal cancer (CRC) and the high incidence of colorectal liver metastases (CRLM) have all led to a significant increase in elderly patients with CRLM seeking surgical management. Due to physiological and functional changes with advancing age (which may decrease the ability of the elderly to sustain aggressive treatment) and the lack of validated guidelines, surgeons still hesitate to plan surgical resection of CRLM in the elderly. Recently, a few studies have suggested that resection of CRLM in the elderly is feasible and yields good short- and long-term outcomes in the context of an intention-to-treat strategy. This article discusses the relevant literature and tries to put forth possible recommendations for the surgical management of elderly patients with CRLM. No chronological upper age limit should contraindicate curative treatment and well-selected elderly patients with advanced CRC can be offered a similar chance of long-term survival with the use of an optimal onco-surgical strategy.

Keywords

Colorectal liver metastases, elderly, liver resection, peri-operative results, long-term outcomes, onco-surgical strategy

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Correspondence: Rene Adam, Centre Hepato-Biliaire, AP-HP, Hopital Paul Brousse, 12 Avenue Paul Vaillant Couturier, F-94804 Villejuif, France. E: rene.adam@pbr.aphp.fr

Colorectal cancer (CRC) is a major public health problem (1,200,000 new cases per year worldwide) and increasingly affects older people; the current median age at diagnosis is 71, and for CRC-related death is 75 years.[1] After 50 years of age, the incidence doubles every seven years, and 76% of patients with newly diagnosed CRC are between 65 and 85 years of age. The liver is the most common site of CRC metastases, involved in approximately half of the patients at the time of diagnosis. Thirty-five to fifty per cent of the patients with colorectal liver metastases (CRLM) who are >70 years of age at the time of diagnosis.[2–5]

Life expectancy has increased dramatically over the years; it is now 75–77 years for men and 80–81 years for women in the developed world.[6] It has been projected that by 2015 there will be a 22% increase of CRLM in people over 65 years of age and a 50% increase in people over 80 years of age in Europe.[7] With an ageing population, the number of elderly patients requiring treatment for CRLM is increasing, and optimal treatment recommendations in this population are warranted.[8]

Resection of CRLM continues to be the only curative treatment. In older series on resection of CRLM only 8–20% of patients were >70 years of age;[9,10] this low rate may reflect a selection process favouring palliative medical treatment in the elderly. However, recent studies have shown that patient age does not seem to be a significant determinant of long-term prognosis following resection of CRLM.[11–16] In light of these studies demonstrating five-year survival rates between 21 and 44% after CRLM resection, elderly patients are increasingly being subjected to similar treatment strategies to those used in younger patients, including chemotherapy and surgery.

On the other hand, one needs to be cautious when using 'aggressive therapies' and 'extended criteria' in the aged. Ageing is associated with myriad physiological and functional changes that may compromise the ability of elderly patients to sustain these therapies. Liver surgery is not without complications, and the need to balance risks and costs against the potential improvement in survival in the elderly continues to leave many clinicians reluctant to propose surgical resection in these patients. Some may also argue that a limited life expectancy in the elderly goes against extending the indications for hepatic resection. However, life expectancy for people between 80 and 85 years of age is still eight years, and six years for those >85 years of age. Moreover, the risk of cancer-related death diminishes with increasing age; it is estimated to be 40% for those between 50 and 70 years of age, falling to 10% for those >90 years of age.[17]

In the presence of continuing contradictions and a lack of strict recommendations in this ever-increasing group of elderly patients with CRLM, this article will discuss the relevant literature and provide possible recommendations for surgical management in these elderly patients.

Defining the Elderly – Should They Be Considered as Different?

The age limit to define the elderly population has been used arbitrarily in various studies (65, 70 or 75 years of age; see *Table 1*). Seventy years of age has been most commonly used cut-off to differentiate the young from the elderly, and we used the same cut-off in our recently published series.[18] However, more important are the oft-posed questions of whether it is correct to consider only the

Table 1: Reported Series on Hepatic Resection for Colorectal Liver Metastases in the Elderly

First Author, Year of Publication	Number of Patients	Age Cut-off (Years)	Peri-operative Morbidity (%)	Peri-operative Mortality (%)	3- and 5-year Overall Survival (%)
Zieren, 1994[14]	18	>70	28	6	25 (5-year)
Fong, 1995[15]	128	≥70	42	4	35 (5-year)
Fong, 1997[12]	83	>65	47	4	50 (3-year)
Brunken, 1998[13]	25	≥70	28	4	44 (5-year)
Brand, 2000[34]	41	≥70	29	7.3	–
Zacharias, 2004[11]	61	>70	41	1.6	21 (5-year)
Nagano, 2005[35]	62	≥70	19.7	0	34.1 (5-year)
Figueras, 2007[16]	160	≥70	41	8	36 (5-year)
Nojiri, 2009[37]	64	≥75	29.6	0	33.2 (5-year)
Adam, 2010[18]	1,624	≥70	32.3	3.8	57 (3-year), 36 (5-year)

chronological age of a cancer patient when taking an oncological decision and whether an age limit alone should be considered as a deterrent to surgical treatment.

Several physiological and functional changes that occur with ageing to a great extent reduce the ability of the elderly to sustain the stress of a surgical procedure. Over half a century ago, in his large series of abdominal operations in patients over 70 years of age Welch reported a peri-operative mortality rate of 20.7%. He concluded that surgery itself was safe but that the elderly require greater attention in the peri-operative period.[19] However, current evidence suggests that the health of the extreme elderly is improving and interventions can be successfully undertaken at later ages. Over the last two decades, the mortality and morbidity rates associated with hepatic resection have decreased in elderly patients (<5 and 20–30%, respectively) due to an improved knowledge of surgical hepatic anatomy, better resection techniques and advances in anaesthetic and intensive care.

In addition, in studies reporting resection of CRLM, age did not appear as a risk factor influencing short- and long-term outcomes.[9,20–23] Moreover, the results of resection in the elderly were not very different from those in the younger population. Thus, it is not chronological age alone that determines post-operative mortality, morbidity and long-term survival after surgery.[24–26] A true limit in terms of chronological age should not exist for resection, which indeed continues to be the sole potentially curative treatment; instead functional status should be taken in account when planning an intention-to-treat onco-surgical strategy.

The Necessity and Feasibility of Liver Resection in the Elderly with Colorectal Liver Metastases

The liver is the most common organ for distant metastases from CRC.[27] It has been documented that CRC in the elderly may be a biologically low-grade malignancy compared with that in the younger population.[28] Unfortunately, little is known about the clinico-pathological characteristics of CRLM specifically in the elderly. The natural course of unresectable CRLM is limited to 4.5–6.5 months of survival; similarly, patients treated by chemotherapy alone have a median survival of 9.2–16.5 months.[4,29–31] Chemotherapy is capable of downstaging the disease and rendering CRLM resectable, and a combination of chemotherapy and curative surgery has been shown to achieve survival rates of up to 58%.[10,22,32,33] Hence, it is essential that complete surgical resection be the therapeutic goal in these patients.

In studies investigating the role of surgery in CRLM in the elderly, differences in patient selection, limited numbers of patients and the arbitrary definition of elderly patients have made the interpretation of results difficult. Thus, we recently published a study that compared the outcomes of CRLM resection in patients at least 70 years of age compared with those in younger patients.[18] This study was performed in a large prospective multicentre cohort (the International LiverMetSurvey register). Twenty-one per cent of patients (out of 7,764 patients resected for CRLM) were at least 70 years of age. The trend in recent years of operating on elderly patients was shown by the fact that 29% of resected patients were at least 70 years of age in 2006 compared with only 5% in 1990. The post-operative mortality rate in the elderly was <5% (3.8%), which compares favourably with published data. Post-operative complication rates were similar between younger and older patients (28.7 versus 32.3%). In addition, we found that there was a prevalence of metastases from colon carcinoma, significantly smaller and fewer metastases (≤3) and more metachronous and unilateral metastases in the elderly compared with younger patients. All these observations point to a better selection of patients, which made curative resection feasible (the rate of liver curative and globally curative resection was higher in the elderly) and thus helped in attaining good post-operative results.

When Fong et al.[15] compared the results of CRLM resection in elderly and younger patients, they found no difference in peri-operative morbidity (younger group 40% versus older group 42%) or mortality (4% for both groups). Similarly, Zieren et al.[14] reported that there was no difference in peri-operative mortality (3 versus 6%) or major morbidity (10 versus 16%) among elderly and younger patients.

Figueras et al.[16] reported results in 160 elderly patients (≥70 years of age) undergoing liver resection for CRLM. Elderly patients had higher peri-operative mortality than younger patients, but in recent years that difference had markedly reduced. Excluding post-operative mortality, the overall survival (OS) and disease-free survival (DFS) were similar in both groups. The authors concluded that the criteria to indicate surgery must essentially be the same in both groups. Noting these results, one would be justified in saying that resection of CRLM in the elderly is indeed feasible and yields comparable peri-operative outcomes to those in younger patients.

Zacharias et al.[11] showed that not only a first liver resection but also repeat liver resection for CRLM can be performed safely in elderly patients (>70 years of age). However, in their study the short-term results (mortality rate of 7% and morbidity rate of 38%) and long-term outcomes (three-year OS of 25% and no survivors at five

years) with repeat resection were poor. They suggested that a repeat resection should be performed only in patients without risk factors for recurrence and particularly without extrahepatic disease.

By contrast, in our series[18] well-selected older patients had a similar benefit from repeat hepatectomy to younger patients (three-year survival rate 76.1 versus 78.3%). Moreover, the post-operative mortality rate after repeat hepatectomy was zero, confirming the fact that these patients should not be denied an aggressive surgical approach. Furthermore, in terms of the effect of increasing age on immediate post-operative outcomes, post-operative mortality in our series was 4% for patients 70–75 years of age, 5% for those 75–80 years of age and 8% for patients at least 80 years of age (p=0.047). Therefore, patients up to 80 years of age seem to have similar outcomes to younger patients, whereas beyond 80 years of age the short-term results seem to be less optimal.

Long-term Outcomes of Colorectal Liver Metastasis Resection in the Elderly

In addition to acceptable morbidity and mortality rates, recent studies have suggested that hepatic resection for CRLM should be the preferred therapeutic option in elderly patients in view of the good long-term outcomes (see *Table 1*).[13–15,34,35]

In most studies, the five-year OS in patients >70 years of age was between 15 and 35%.[14,15,34] The long-term survival for older patients was slightly less than for younger patients, but still considerably long and acceptable.

Fong et al.[15] reported a median survival of 44 months in the elderly patients after resection (compared with 40 months in younger patients). The five-year OS was 35%. It is pertinent to note that a significant number of patients (64%) in their study underwent major resections (defined as resection of at least three segments).

In a population-based study analysing the utility of hepatic resection in patients ≥65 years of age, Cummings et al.[36] reported a five-year OS of 32.8% in resected patients compared with 10.5% in patients who did not undergo hepatic resection of CRLM (p<0.0001). Lack of hepatic resection was associated with a 2.78-fold increase in the risk of death.

Only one series, by Nojiro et al.,[37] showed that long-term results are statistically worse in the elderly. This could be related to the high rate of death in elderly patients due to other diseases. However, in their series, compared with the five-year survival of 33.2% in elderly patients who underwent hepatic resections, the long-term outcomes in unresected patients were poor.

In our series of 1,624 elderly patients ≥70 years of age who underwent resection of CRLM, the three- and five-year OS were 57 and 36%, respectively.[18] These outcomes were similar to the 60.2 and 42% three- and five-year OS in younger patients resected for CRLM during the same period (although statistically the five-year survival was better in younger patients). With a median follow-up of 22 months (range 1–230 months) for the entire study population, 28.1% of patients developed tumour recurrence in the elderly group compared with 35.6% in the younger group. The three- and five-year DFS rates were 37 and 25%, respectively, in patients at least 70 years of age or 70 years of age or more. These rates were again not significantly different from those in younger patients. Sixty-three per cent of the elderly patients were alive at last follow-up compared with 57% of the younger patients.

Median OS after resection in the elderly was lower than in younger patients, but elderly patients undergoing CRLM resection had a much higher OS than those receiving palliative chemotherapy[38] or best supportive care.[28] In addition, our study showed no deterioration in long-term survival with increasing age. For patients ≥80 years of age, three-year OS was similar to that for people 70–75 years of age. These results show that increasing age is not a deterrent for good long-term results, and thus further justify the surgical treatment of CRLM in elderly patients.

Safety and Role of Chemotherapy in the Elderly

Recent demographic trends, along with the likelihood of CRC being metastatic at the time of diagnosis in about 60% of cases, suggest an enlarging population of onco-geriatric patients who will be evaluated for adjuvant or palliative chemotherapy to prolong survival. More importantly, the best results in CRLM can be achieved using a combination of surgery and chemotherapy (up to 58% OS at five years).

Palliative chemotherapy may prolong the survival of patients with unresectable disease.[29,39–41] Neoadjuvant chemotherapy may downsize to resectability patients previously judged inoperable,[42] whereas adjuvant chemotherapy may prolong the time to recurrence after resection of hepatic metastases.[43]

However, chemotherapy is associated with possible toxic effects, and advanced age is widely considered to increase these risks.[44] Older patients are more likely than younger individuals to have multiple, long-standing or advanced co-morbid conditions and to use concurrent medications. However, the degree to which elderly patients metabolise cytotoxic compounds differently, or differ in terms of susceptibility to toxicity compared with younger patients, remains unconfirmed.

Exposure to highly active regimens is the foundation of current chemotherapy, and response improves with exposure to more, rather than fewer, effective agents.[30,39,45–47] The tolerability and improvement in survival in elderly patients with optimal chemotherapy (oxaliplatin- or irinotecan-based) and novel biologic agents (such as bevacizumab) have been demonstrated by several studies.[48–52] Popescu et al.[53] noted that elderly patients with good performance status tolerated adjuvant and palliative chemotherapy for CRC as well as younger patients.

It is true that limited prospective data currently exist and definitive conclusions cannot be drawn. However, the studies that are available stipulate that age alone should no longer be considered a contraindication to an active chemotherapy regimen with known tolerability and efficacy, and elderly patients can receive similar protocols to younger ones in the absence of strict contraindications.

The current recommendations[54] suggest that in potentially resectable metastases after chemotherapy, if the patient is fit, a three- (or two-) drug combination should be used; if pre-frail or vulnerable, a single agent (capecitabine or 5-fluorouracil-leucovorin [5FU-LV] ± bevacizumab) should be considered; and in frail patients, best supportive care is the preferred option.

Are There Any Prognostic Factors for Peri-operative and Long-term Outcomes?

The results of liver resection for CRLM in well-selected elderly patients are favourable, thus the next step would be to determine whether there are prognostic factors that predict better or worse outcomes of resection in these patients. Proposals for a prognostic model in this select group of patients have been made, but to date none has been validated.

Zacharias et al.[11] noted three independent risk factors that influence the OS and the DFS at multivariate analysis: presence of extrahepatic disease, presence of three or more liver metastases and a high pre-operative carcinoembryonic antigen (CEA) level (>200ng/ml). Patients without these risk factors had a three- and five-year OS of 59 and 36%, respectively, and a median OS of 42 months. Three- and five-year DFS rates were 33%. With one risk factor, three-year OS was 47% and median OS was 33 months, while three-year DFS was 14%. With two or three risk factors, the three-year OS was 20% and median OS was 14 months, with disease recurrence in all patients within the first year.

In a study by Fong et al.,[15] male sex and American Society of Anesthesiologists (ASA) class were significant predictors of complications after liver resection. The extent of resection, operative blood loss and operating time did not emerge as significant factors in multivariate analysis, although they were significant at univariate analysis.

In our study,[18] univariate analysis identified eight pre-operative variables influencing survival: more than three metastases at diagnosis, bilateral metastases, a larger number of pre-operative chemotherapy cycles, non-curative liver resection, 'globally non-curative' resection (presence of extrahepatic disease), combined treatment modalities to improve resectability (radiofrequency ablation, cryosurgery or both used to treat all metastases during surgery), total number of hepatectomies and concomitant extrahepatic disease.

However, at multivariate analysis, three pre-operative variables merged as independent prognostic factors: more than three metastases at diagnosis, bilateral metastases and concomitant extrahepatic disease. In addition, no post-operative chemotherapy independently predicted poor survival. All are well-known poor prognostic factors as they reflect more advanced disease.[9,25,26,55–57] OS at three and five years was 64.6 and 43%, respectively, for patients without any risk factors and ranged from 49.4 to 54.7% and 26 to 32%, respectively, when one factor was present. When two risk factors were present, the OS was 33.7–39.5% and 13–17%, respectively, at three and five years, whereas in the presence of all three risk factors the OS was only 22.3 and 6%, respectively. Our proposed prognostic model is indicative and could be used as a guide, but since it has not yet been validated, it should not be used as a unique cut-off decision-making tool.

Conclusion

Liver resection for CRLM in elderly patients is feasible and results in acceptable peri-operative and long-term outcomes that are similar to those in younger patients. The use of optimal chemotherapy further improves long-term survival. No upper age limit should contraindicate optimal treatment, and well-selected elderly patients can be offered a similar chance of DFS and OS. Although potential co-morbidities should be identified carefully to minimise peri-operative mortality, hepatectomy for CRLM as well as active chemotherapy should not be denied on the basis of age alone. ■

Prashant Bhangui is a Clinical and Research Fellow in hepatobiliary (HPB) surgery and liver transplantation at the Hepatobiliary Centre at the Paul Brousse Hospital in France. He works in the specialised field of HPB surgery with a special interest in liver malignancies and transplantation. He received the Goa Scholar award in recognition of his academic and co-curricular achievements and for pursuance of advanced studies in HPB surgery and liver transplantation. He completed his post-graduate studies in surgery at Goa Medical College, India, where he received the University Gold Medal.

Rene Adam is a Professor of Surgery in the Faculty of Medicine at Paris South University. He is President of the Medical Board and Head of the Onco-surgical Unit of the Hepatobiliary Centre at Paul Brousse Hospital in Villejuif in France. He is actively involved in clinical activity and research into the treatment of hepatocellular carcinoma and liver metastases. He chairs the European Liver Transplant Registry (ELTR) and LiverMetSurvey, an international Registry of Colorectal liver metastases. Professor Adam is on the Editorial Board of *The Oncologist* and a member of several international societies, including the American Society of Clinical Oncology (ASCO), the European Society of Surgical Oncology (ESSO), the European Society of Organ Transplantation (ESOT), the European Surgical Association (ESA) and the International Hepato-Pancreatic and Biliary Association (IHPBA). He has given more than 600 lectures worldwide, and has more than 200 articles published in peer-reviewed journals.

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