Author/s:
Kumari, S;Semira, C;Lee, M;Lee, B;Wong, R;Nott, L;Shapiro, J;Gibbs, P

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Kumari Seema (Orcid ID: 0000-0002-4393-9064)

Resection of Colorectal Cancer Liver Metastases in the Older Patient

Seema Kumari[1], Christine Semira[2], Margaret Lee[2-6], Belinda Lee[2,5], Rachel Wong[2,4,6], Louise Nott[7], Jeremy Shapiro[8], Peter Gibbs[2,3,5]

[1]Medical Oncology, Westmead Hospital, NSW, Australia,
[2]Walter and Eliza Hall Institute of Medical Research, Parkville, Australia,
[3]Medical Oncology, Western Health, Footscray, Australia,
[4]Medical Oncology, Eastern Health, Box Hill, Australia,
[5]The University of Melbourne, Parkville, Australia,
[6]Monash University, Eastern Health Clinical School, Box Hill, Australia,
[7]Medical Oncology, Royal Hobart Hospital, Hobart, Australia,
[8]Medical Oncology, Cabrini Health, Malvern, Australia,

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Corresponding author: Dr Seema Kumari, Crown Princess Mary Cancer Centre, Westmead Hospital, Hawkesbury Road, Wentworthville, NSW-2145, Australia, email ID: seemaks18@yahoo.in

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ABSTRACT

Background: Colorectal cancer remains a common cancer in the western world, with liver resection being the only potentially curative option for isolated colorectal cancer liver metastases (CRCLM). Cancer is a disease of aging, with the optimal management of elderly patients with CRCLM presenting an ongoing dilemma.

Methods: We analysed the outcome of CRCLM using prospectively collected patient data from the multidisciplinary TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) registry, collected from July 2009 - July 2018 at 12 Australian hospitals.

Results: Of 2742 patients with metastatic colorectal cancer, liver limited disease was present in 977 patients (36%), of whom 338 (35%) underwent hepatic resection. Resection rates varied with age, including 186 of 428 (43%) patients aged 64 years and younger, 99 of 245 (40%) aged 65 - 75 years and 53 of 303 (17%) aged 76 and older ($p<0.001$). The 30-day mortality rate was 0.9%. Median survival post resection also varied with age, 96 vs 89 vs 68 months ($p<0.001$). In a separate analysis of the oldest patients, those aged over 80 years, where only 11% underwent resection, the median survival was 49 months.

Conclusion: The operative mortality for patients undergoing liver resection at Australian hospitals is low. With advancing age, the rate of liver resection of CRCLM and the post resection survival decline. However, excellent survival outcomes can be achieved in selected elderly patients.

Keywords: liver resection, liver metastases, colorectal cancer, elderly

INTRODUCTION

Colorectal cancer remains the fourth most common cancer in the western world, and is the second most common cause of cancer-related death[1]. At diagnosis or later during surveillance up to 50% of patients with colorectal cancer (CRC) will develop metastatic disease (mCRC), with liver the dominant site.[1] Around 40% will have liver as the only site.[2] Liver resection is the only potentially curative option for colorectal cancer with liver metastases (CRCLM)[3], with multiple studies demonstrating 5-year overall survival rates of 40%-50% for patients post resection.[4-5]

The definition of what constitutes resectable liver metastases continues to evolve but essential elements include the ability to achieve an R0 resection, to maintain critical vasculature and biliary structures and to leave a sufficient functional liver remnant.[6-7] The patient must also be fit for the surgical procedure. Increasingly, systemic therapy is being used as a strategy to convert selected patients with initially unresectable disease into operative candidates, an approach that can achieve good long term outcomes.[8] With continuously improving surgical techniques, anaesthetic and post-operative care, the likelihood of early post-operative mortality continues to decline.[4] Ultimately this means that liver resection becomes a more realistic option even for patients where this was previously precluded due to age, co-morbidity or frailty. However, while the safety of operating in these patients is improving there is also an escalated risk of death from competing causes, which must be weighed against any potential survival gains.

Previous studies suggest that in carefully-selected elderly patients, long-term survival can be achieved with liver resection,[5, 9] but recent data is lacking and this scenario has not been well studied in the Australian context. Here we examine a large cohort of patients recruited from a broad range of Australian centres to further explore the approach and outcomes for patients with CRCLM in the modern era.

METHODS

Data were obtained from the TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) database, a registry designed for the collection and management of information relating to the diagnosis, treatment and outcomes of consecutive patients with mCRC. All patients enrolled from July 2009- July 2018 were included. Patients with dual primary malignancies were excluded from the analysis.

Patient demographics, clinical characteristics, histopathologic factors as well as survival outcomes were collected. Chi square analysis was done to determine any significant differences in patient population. Kaplan-Meier analysis and log-rank test was used to obtain survival estimates. Overall survival (OS) was calculated from the date of diagnosis of first liver metastasis to death from any cause or the date of last follow-up. Progression-free survival was calculated from the date of diagnosis of first liver metastasis to the date of first subsequent progression or the date of last follow-up without progression. This study was approved by the Melbourne Health ethics committee (ethics ID: HREC/18/MH/28).

SPSS version 23 was used for all statistical analyses.

RESULTS

PATIENT CHARACTERISTICS

Across all hospitals contributing patients to the TRACC registry, 2742 patients with mCRC were identified, of whom 977 patients had isolated CRCLM (Figure 1). Of these, 338 (35%) underwent hepatic resection, including 186 (43%) of those that were <65 years old, 99 (40%) of those that were 65-75 years of age, and 53 (17%) of those that were >75 years old (Table 1). Gender, performance status, Charlson co-morbidity score and primary tumour site data is summarised in Table 1. The Charlson comorbidity score was higher in the older age group ($p<0.001$). By age group there was a significant difference in liver metastases resection rates (43% vs 40% vs 17%, $p<0.001$) as well as neoadjuvant chemotherapy usage (23% vs 11% vs 4%, $p<0.001$), (<65 years vs 65-75 years and >75 years respectively). In the very elderly subset (>80 years), shown in Table 2, the resection rate was 11% (19/169). Only two (1.1%) of these patients received neoadjuvant chemotherapy, and the oldest patient to undergo resection was 91 years old.

SURVIVAL OUTCOMES ACCORDING TO AGE GROUP

Of the 338 patients that underwent resection, only three (0.9%) died within 30 days of the operation, including two < 65 years and one in the 65-75 years age group. The cause of death is not recorded in the registry.

Progression-free and overall survival data for each of the age groups for the patients that underwent liver resection and those who did not undergo liver resection are shown in Table 3. Additionally, figures 2 and 3 reflect the survival outcomes in the elderly and very elderly group.

Liver resection versus no liver resection in the <65 years age group was associated with longer PFS and OS (median PFS 67.2 months versus 10.4 months, p<0.001; median OS 96.4 months versus 20.1 months, p<0.001). Similarly, an advantage was seen in the 65-75 years age group [Figure 2 (A); median PFS 31.9 months versus 9.4 months, p<0.001; median OS 88.9 months versus 18.7 months, p<0.001] and in the elderly [Figure 2 (B); median PFS not reached versus 8.2 months, p<0.001; OS 68.4 months versus 13.3 months, p<0.001]. In the very elderly age group, those undergoing resection lived longer than those treated with palliative intent (Figure 3; median OS 48.6 months versus 11 months).

DISCUSSION

Marked gains in the survival outcome for patients with mCRC have been achieved over the last few decades, driven principally by advances in medical therapy, improved diagnostics to better identify patients suitable for curative intent treatment, and the increased use of hepatic resection. Among the entire population, average life expectancy also continues to rise. According to 2016 data from the Australian Institute of Health and Welfare, the median age at death of an Australian female was 84 years and for males 78 years.[10] For someone who was in their 80s during the years 2015-2017, the estimated life expectancy is 92.3 years for a female and 91.3 years for a male.[11] The incidence rate of CRC also increases with age,[12] resulting in a steadily increasing proportion of older patients with CRC. Defining the optimal multi-modality management of these older patients, including potentially liver resection, is the role of the multidisciplinary team. These decisions should continue to be informed by local and contemporary outcome data.

The cumulative rate of liver resection of 12.3% for all patients and 34.6% for patients with liver only metastases is consistent with recent reports from other countries, although there is notable variation. In a population based study by Manfredi et al. (2006), the rates of liver resection between years 1976-2000 in France were 23% (6.3% for synchronous and 16.9% for metachronous CRC).[13] A US series based on data from 2006 reported a liver resection rate approaching 20%.[14] In the Netherlands the resection rate was 24% in 2012.[15] In a recent analysis

of data from the United Kingdom only around 5% of patients with mCRC underwent at least one liver surgery, with the rate plateauing around 2012.[16] It is worth noting that the resection rates in elderly (>75 years old) in Netherlands between years 2008-2010 were fairly similar to our study at around 13.9%.[4]

All series report a number of factors that impact the rate of liver resection, including age. In our Australian cohort, the rate steadily declines with age, most likely due to decreasing fitness for major surgery. Older patients may also not wish to undergo major operations, even if these are potentially curative, so patient preference may also be having an impact but this is not captured in the registry. There is also less use of neoadjuvant chemotherapy in older patients undergoing resection, so fitness for neoadjuvant therapy is also a factor where the aim is to convert borderline or inoperable candidates into resectable cases. A study by Adam et al (2010) also reported decreasing rate of liver resection and in the use of neoadjuvant chemotherapy with advancing age.[17]

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Multiple series over recent decades have reported that the operative mortality from liver resection has continued to decline. In our series there were only 3 deaths within 30 days of operation, including two in the youngest cohort, which also constituted the largest number of patients. Notably no early deaths were observed in the 53 patients aged over 75 years that underwent liver resection. The overall operative mortality for this Australian series of 0.9% is similar to that reported elsewhere. A study by Rees et al (2008) showed a 30-day post-op mortality of 1.2%[18], and similarly a 60-day post-op mortality of 1.6% was reported in another study[17] in CRCLM patients undergoing liver resection.

The median overall survival post liver resection in our study ranges between 43 months to 96 months, varying significantly by age subgroup. This is somewhat higher than other series published over the past 10 years which reported a median overall survival anywhere between 36 months to 55 months.[15, 18-20] This data is consistent with high quality patient selection and treatment delivery in the Australian context coupled by increasing use of neoadjuvant chemotherapy over years.

A key finding of our series is that excellent outcomes can be achieved in even the oldest patients. For patients over 75 years the median progression free survival has not been reached and median

overall survival was 68.4 months. For the 11 patients in the very elderly subgroup (≥80 years of age) the median survival was over 4 years, well in excess of what could be achieved with medical therapy alone.

Limitations of our series include that the reasons for patients not undergoing surgery, including technical operability, fitness for surgery and patient preference were not documented. The rationale for the use of any preoperative chemotherapy was also not recorded and a number of patients with initially resectable disease likely received upfront chemotherapy. Lastly, there are a number of prognostic factors that are not well captured in the database, including tumour volume. These along with ECOG performance status would impact progression free survival in the elderly population studied.

CONCLUSION

Liver resection in the elderly population selected for surgery is associated with excellent early post-operative and long-term survival outcomes in this multi-centre Australian series. Patients should not be excluded as operative candidates on the basis of age alone.

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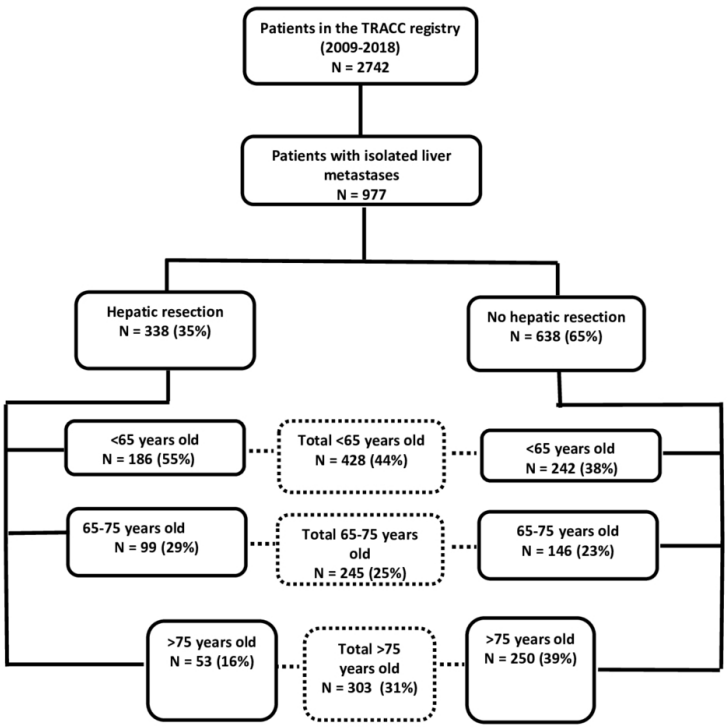
FIGURE LEGENDS:

Figure 1. Consort Diagram, TRACC patients with isolated liver metastases, 2009-2017.

Figure 2: (Top) PFS and OS curves for 65 to 75-year-old patients. Median PFS with resection = 32 months; median PFS without resection = 9.4 months, p<0.001. Median OS with resection = 89 months; median OS without resection = 18.7 months, p<0.001.

(Bottom): PFS and OS curves for elderly/ >75-year-old patients. Median PFS with resection = not reached; median PFS without resection = 8.3 months, p<0.001. Median OS with resection = 68.4 months; median OS without resection = 13.3 months, p<0.001

Figure 3. PFS and OS curves for very elderly (≥ 80-year-old) patients: Median PFS with resection = not reached; median PFS without resection = 8.2 months, p<0.001. Median OS with resection = 48.6 months; median OS without resection = 11 months, p<0.001.



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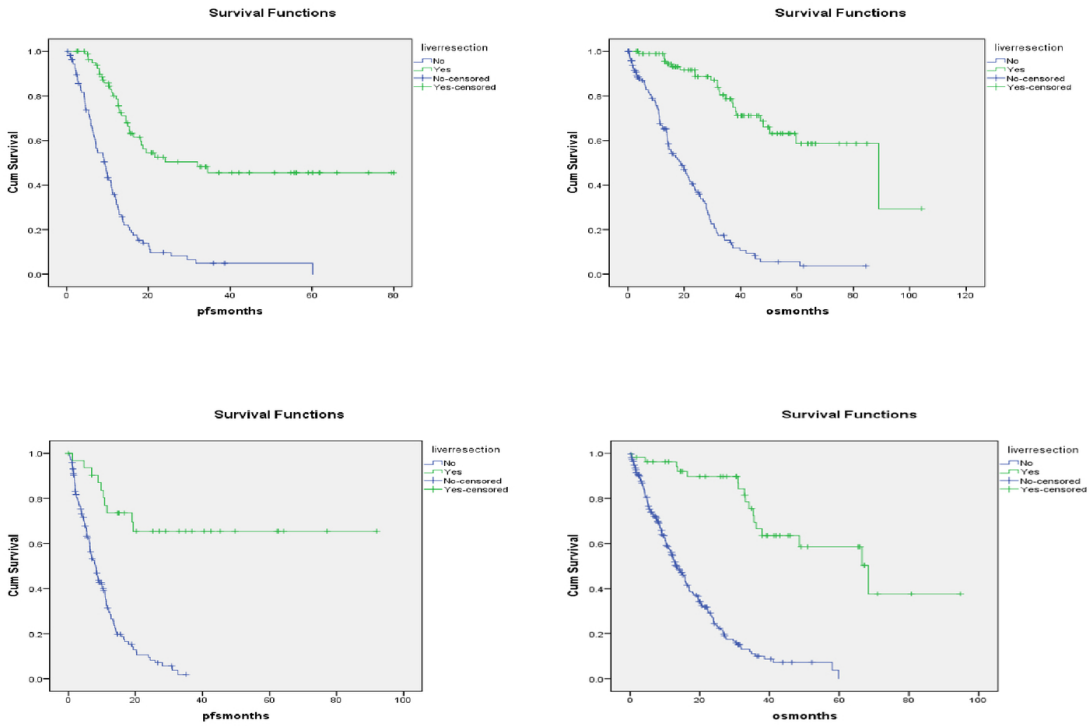

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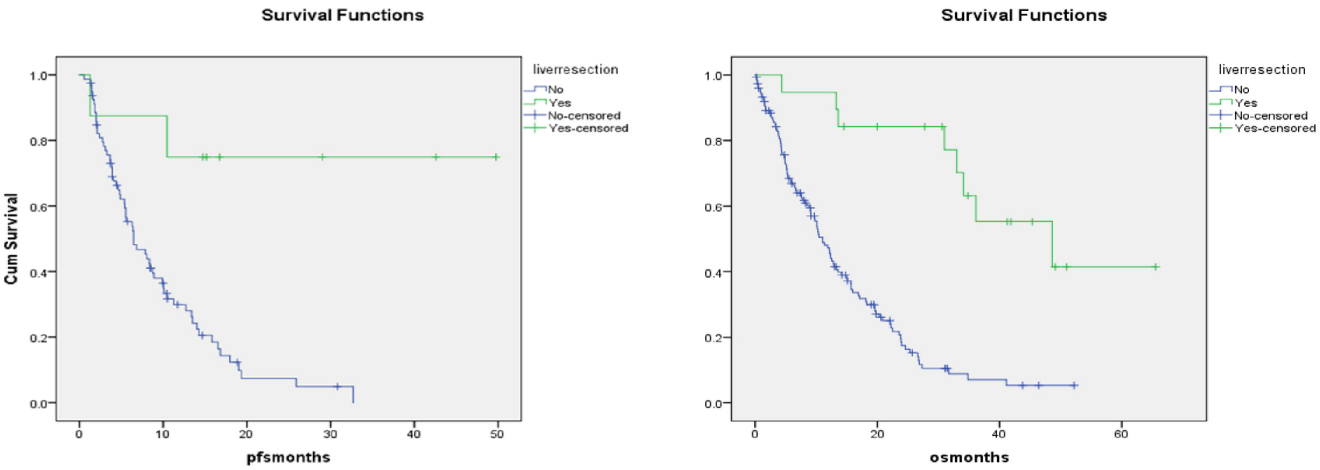

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	<65 (n=428)	65-75 (n=245)	>75 (n=303)	Total	p-value
Gender					<0.001
Male	262 (61%)	180 (74%)	174 (57%)	616	
Female	166 (39%)	65 (26%)	129 (43%)	360	
ECOG					<0.001
0-1	400 (93%)	214 (87%)	204 (67%)	818	
2-4	26 (6%)	28 (11%)	97 (32%)	151	
Missing	2	3	2		
Charlson comorbidity					<0.001
0-2	350 (82%)	54 (22%)	0	404	
>2	76 (18%)	188 (77%)	301 (99%)	565	
Synchronous/metachronous					<0.001
Synchronous	334 (78%)	167 (68%)	200 (66%)	701	
Metachronous	94 (22%)	78 (32%)	102 (34%)	274	
Liver metastases resected					<0.001
Yes	186 (43%)	99 (40%)	53 (17%)	338	
No	242 (57%)	146 (60%)	250 (83%)	638	
Neoadjuvant chemo					<0.001
Yes	100 (23%)	28 (11%)	12 (4%)	140	
No	86 (20%)	71 (29%)	41 (13%)	198	
Primary Site					
Left	310	168	153	631	
Right	97	70	120	287	
NOS	10	6	7	23	
Occult	0	2	10	12	

Table 1. Clinicopathologic characteristics of patients with isolated colorectal cancer liver metastases stratified by age group

	Age ≥80 (n=169)
Gender	
Male	89 (53%)
Female	80 (47%)
ECOG	
0-1	104 (62%)
2-4	63 (37%)
Blanks	2 (1%)
Charlson comorbidity	
0-2	0
>2	169
Synchronous/metachronous	
Synchronous	112 (66%)
Metachronous	57 (34%)
Liver mets resected	
Yes	19 (11%)
No	150 (89%)
Neoadjuvant chemo	
Yes	2 (1.1%)
No	17 (10%)

Table 2. Clinicopathologic characteristics, CRCLM patients ≥80 years old

Age Group	Liver Resection	Median PFS (months)			Median OS (months)		
		Estimate	95% Confidence Interval		Estimate	95% Confidence Interval	
			Lower Bound	Upper Bound		Lower Bound	Upper Bound
<65	No	10.4	9.4	11.5	20.1	18.3	21.9
	Yes	67.2	20.8	113.6	96.4	66.9	125.8
65-75	No	9.4	7.4	11.4	18.7	13.7	23.7
	Yes	31.9	.	.	88.9	47.6	130.3
>75	No	8.2	6.6	9.8	13.3	10.8	15.7
	Yes	NR	NR	NR	68.4	43.3	93.5

a. Estimation is limited to the largest survival time if it is censored. NR= not reached

Table 3: Median PFS and OS with and without liver resection in different age groups