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Australian Contemporary Msanagement of Synchronous Metastatic Colorectal Cancer

ABBREVIATED TITLE:

Management of synchronous metastatic colorectal carcinoma.

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TEXT: 2738 words including main text, tables and figures but excluding abstract, references and acknowledgements.

Abstract

Introduction

This article outlines current Australian multidisciplinary treatment of synchronous metastatic colorectal adenocarcinoma and assesses the factors that influence patient outcome.

Methods

This is a retrospective analysis of the prospective "Treatment of Recurrent and Advanced Colorectal Cancer" registry, describing the patient treatment pathway and documenting extent of disease, resection of the colorectal primary and metastases, chemotherapy and biological therapy use. Cox regression models for progression-free (PFS) and overall survival (OS) were constructed with a comprehensive set of clinical variables. Analysis was intention to treat, quantifying the effect of treatment intent decided at the multidisciplinary team meeting (MDT).

Results

1109 patients presented with synchronous metastatic disease between July 2009 and November 2015. Median follow-up 15.8 months. 4.4% (group 1) had already had curative resections of primary and metastases prior to MDT, 22.2% (group 2) were considered curative but were referred to MDT for opinion and/or medical oncology treatment prior to resection; 70.2% were considered palliative at MDT (group 3).

Overall, 83% received chemotherapy, 55% had their primary resected and 23% had their metastases resected; 13% of resections were synchronous, 20% were staged with primary resected first and 62% had only the colorectal primary managed surgically.

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Performance status, metastasis resection (R0 v R1 V R2 v no resection), resection of the colorectal primary and treatment intent determined at MDT were the most significant factors for progression-free and overall survival.

Conclusions

This is the largest Australian series of synchronous metastatic colorectal adenocarcinoma and offers insight into the nature and utility of contemporary practice.

Australian Contemporary management of Synchronous Metastatic Colorectal Cancer

INTRODUCTION

Synchronous metastatic colorectal cancer represents 25% of colorectal carcinoma presentations and yet the management strategies are remarkably heterogeneous. The current paradigm suggests that we focus on the control of metastatic disease unless both primary tumour and all metastases can be resected(1-4) but only 20-30% have resectable metastases(5); the remaining 70-80% might be offered chemotherapy but 13.9 -18% subsequently obstruct(6), 3% have a significant haemorrhage and 6.1% perforate(5) such that 23% of those with initially unresectable distant disease ultimately need their primary managed, irrespective of any down-staging. Those with a sufficient response to neoadjuvant chemotherapy might proceed to curative resection but the proportion can be as low as 4%(5).

The published literature focuses on younger patients with good performance status having aggressive treatments(2, 3, 7-11), so there is limited documentation of the outcomes for the frailer, older patients often seen in routine practice and even less evidence to guide their treatment(12-14).

Treatment intent determines the management pathway. This treatment decision is made in the multidisciplinary setting (MDT). The effect of this decision on outcomes has never been explored.

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Noting the lack of randomised clinical trials evaluating the optimal sequence of treatment, our primary objective in this article is to prospectively document the treatment pathway and treatment outcomes of a large Australian cohort of patients presenting with synchronous metastatic disease; to assess the effects of clinical variables and contemporary multidisciplinary treatment on progression-free (PFS) and overall survival (OS).

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Methods:

The Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry is a prospective database of metastatic colorectal cancer with 14 contributing centres Australia-wide(15). Data have been collected since July 2009 and are entered at point of care.

The registry was validated prior to analysis by comparison to clinic records. All patients presenting with histologically-confirmed synchronous metastatic colorectal adenocarcinoma from July 2009 to November 2015 were included in the analysis. Appropriate ethical approval was obtained for this analysis.

Treatment intent was classified as curative or palliative; curative patients either had their primary tumour and distant disease resected prior to referral (group 1) or were referred for medical oncology input and/or treatment prior to a possible resection (group 2) while the remainder (group 3) were managed with palliative intent.

Demographic statistics and Cox regression analysis were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA.). Results are presented as hazard ratios (HR). Final Cox models were created by stepwise backward elimination. Analysis was intention to treat.

The development and maintenance of the registry has been sponsored in part by Roche Pty ltd (Australia).

RESULTS

1109 patients had synchronous metastatic colorectal adenocarcinoma within a cohort of 1890 patients. Demographics and disease characteristics are displayed in table 1.

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Patterns of chemotherapy and biologic agent use

928 patients (83.7%) received chemotherapy: 55% FOLFOX, 15% single agent 5-Flourouracil and 12% XELOX. Reasons for ceasing first line chemotherapy and the proportion receiving a second-line agent are outlined in figure 1. Palliative patients commenced their first-line chemotherapy regimen within a median 36 days of diagnosis (range 0 days to 2.3 years).

579 (52.2%) patients had Bevacizumab therapy, 8 had Cetuximab and 48 patients had SIRT sphere therapy to the metastases.

Patterns of surgical management

612 patients had their primary tumour resected (55.2%) and 253 patients had their metastases resected (22.8%); 13.2% were synchronous, 19.7% were staged "primary first", 3.3% were "liver first" and 382 patients only had the primary tumour resected (62.4%). 391 (63.8%) had their primary tumour resected before chemotherapy commenced, while 123 (20.1%) had chemotherapy upfront.

The majority of patients (814, 73.4%) were considered palliative (i.e. group 3) at MDT. This palliative intent group still had 45.5% (370 of 814) of their colorectal primary tumours resected and 8.6% (70 of 814 patients) had their metastases resected. Reasons for primary resection in the palliative group were surgeon decision (45%), obstruction (33%) but 4% achieved curative resection of metastases. Figure S1.

160 liver resections were performed (14.4%), 11 lung resections (1.0%) and 83 resections of other disease (7.5%), the majority being peritoneal deposits resected with the colorectal primary. Resection of metastases was R0 in 76.0%, R1 in 6.6% and R2 in 17.4%.

Rectal cancer management is explored in supporting document 1.

Elderly patients

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174 of the patients were 80 years or older. 11.5% were curative and 88.5% were palliative. 85 (48.9%) had chemotherapy; the most common first-line regimen received was single agent capecitabine (19.5%). Only 10 of 174 (5.7%) had both primary and metastases resected. Mean duration of first-line chemotherapy was 68.3 days compared to 141 days for those under 80 years of age (P<0.001) and the older group were less likely to use a second line agent (13.8% v 53.0% p<0.001). Median PFS and OS were lower in this older age group when compared to those less than 80 years of age (PFS 9.0 v 12.2 months p<0.001, OS 12.5 v 24.9 months P<0.001).

Progression free and overall survival

Unadjusted Hazard ratios and Cox modelling for PFS and OS are shown in table 2. Five-year progression-free survival was 41% for group 1, 16% for group 2 and 2% for group 3. Five-year overall survival was 84% for group 1, 41% for group 2 and 5% for group 3. 664 patients (59.9% of all patients) have subsequently progressed or recurred at a median follow-up of 15.8 months. Figure S2 contains relevant Kaplan Meier survival curves.

Examining the effect of receiving curative treatment

Surgery is the only chance for cure in metastatic colorectal carcinoma(11). Analysis of those having both primary and metastases resected showed that male sex (HR 1.5 p 0.02), poor performance status (HR 5.3 p 0.009) and synchronous resection (HR 1.65 p 0.01) influenced progression-free survival while age (HR 1.02 p 0.03) and treatment intent (HR 8.4 for palliative p <0.0001) were the only variables that influenced overall survival.

Median PFS for synchronous resection was 13.4 months, metastases-first 26.5 months and primary-first 25.0 months (p <0.0001). Median OS for those synchronously resected was 44.0 months, those having the metastases resected first was 40.8 months (p 0.001); median OS for those having the primary resected first could not be calculated as more than 50% were alive at analysis at 93 months.

Figure 2 outlines the pathway for the subset of resected patients having curative resections (R0/R1)

DISCUSSION:

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This paper outlines real-life, contemporary patient management and to our knowledge, represents the largest Australian cohort of patients with synchronous metastatic colorectal carcinoma.

Performance status is the most significant determinant of PFS and OS. The inclusion of elderly and poor performance status patients in this analysis is critical to a comprehensive overview; their reduced use of chemotherapy and reduced tolerance of first-line chemotherapy regimens is in keeping with the literature(12, 16).

Curative intent had a marked effect on survival compared to palliation. Indeed, it remained influential even when modelled with variables used to determine the feasibility of curative treatment. Curative intent significantly improved both PFS and OS when compared to a palliative approach even though almost half of the palliative group had their primary tumour resected and most patients received some form of chemotherapy, reinforcing the importance of considering aggressive surgical and medical therapy for all fit patients. Although most patients were considered palliative, 4% of the palliative group achieved curative resection demonstrating that a small proportion do have a better than expected response to treatment.

The majority of the cohort had their primary tumour resected and the primary was usually resected before the metastases. Resection of the colorectal primary still improved PFS (HR 0.58 $p<0.0001$) and OS (HR 0.57 $p<0.0001$) in the context of modern medical oncology treatment, adding to a growing body of literature supporting routine colorectal primary resection even when the metastases are not resectable(17). However, timing this resection is difficult; although the colorectal lesion may become symptomatic during chemotherapy, the possibility of complications from resection of the primary disease delaying systemic therapy is more concerning (18, 19). Peri-operative mortality is 2.7% and major morbidity is 11.8% (5) when the primary is resected in this context(20) but the alternatives also have significant risks: colonic stenting has a 1.2% immediate and 3.1-5.1% cumulative perforation rate(21, 22) even in the hands of experienced proceduralists(23). No clear pathway for management of the primary tumour has been established.

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Primary tumour location influenced both PFS and OS in this cohort in keeping with evidence suggesting that outcomes are inferior for metastatic right colonic lesions(24, 25). The clinically silent nature of right sided disease, different tumour biology and potentially different patterns of venous drainage contribute to a poorer overall outcome(25, 26).

PFS was poorer for those who had synchronous resection of primary and distant disease rather than staged, but this did not affect OS. Prior literature suggests that neither PFS nor OS should be affected by the timing of resections(27) and that the principal impact is on the use of hospital resources(28). Quality of resection was critical; R0 and R1 resection of metastatic disease resulted in significant improvement in overall survival while R2 resection was little different from no resection.

This analysis represents an update on the Australian management of Stage 4 disease from 2009 to 2015. Level one evidence for the management of stage 4 colorectal adenocarcinoma is lacking due to the difficulty of enrolling patients in available trials: the SUPER trial(29) closed early and no results have been reported from ISAAC(30), SYNCHRONOUS(31) or CAIRO4(32).

There are a number of limitations. Although we account for the number of metastatic sites, we have not strictly assessed the volume of liver disease which has previously been an independent predictor of overall survival(33). Nor do we have a measure of surgical complications for those undergoing resection. Quality of life measures are not assessed in this series.

CONCLUSION:

It is critical that there is appropriate selection of curative intent strategies for patients with synchronous metastatic colorectal cancer because a proportion of patients can be cured with intensive chemotherapy and surgical resection of primary and metastatic disease. There are a significant number of disease and patient variables that must be considered as the appropriate management strategy is formulated, ideally with multi-disciplinary input. High quality prospective data remain elusive and we continue to be guided by the patient's response to treatment as chief determinant of our management strategy.

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Palliation still typically involves colorectal primary resection. Aggressive adjuvant or definitive medical oncology treatment significantly delays progression and improves survival and should be considered for all fit patients irrespective of disease parameters.

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Conflicts of interest

None.

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List of supporting information:

Document S1 "**Management of Synchronous metastatic rectal adenocarcinoma"**

Figure S1 "**Reasons for resection of the colorectal primary in the palliative intent group**"

Figure S2 **"The effect of treatment intent and resection of colorectal primary on progression free and overall survival"**

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Table 1: Demographics and disease characteristics	
Median Age	65.6(range 18-96)
Gender	
Male	621(56.0%)
Female	488 (44.0%)
Hospital	
Private	521(47.0%)
Public	588(53.0%)
ECOG status	
0	384(34.6%)
1	533 (48.0%)
2	116 (10.5%)
3	64 (5.8%)
4	12(1.0%)
Charlson Comorbidity index †	
0	118 (10.7%)
1	156 (14.1%)
2	220 (20.0%)
3	214 (19.4%)
4	162 (14.7%)
≥5	234 (21.2%)
Treatment intent:	
Curative, resections already performed (group 1)	49 (4.4%)
Curative, resection planned (group 2)	246 (22.2%)
Palliative intent (group 3)	814 (73.4%)
Disease by site	
Rectum	284 (25.6%)
Left colon	415 (37.4%)
Right colon	340 (30.7%)
Occult/unspecified	70 (6.3%)
Symptomatic primary at some stage	
Yes	63.1%
no	36.9%
Number of sites of metastatic disease	

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1	585 (52.6%)
2	326 (29.4%)
3	146 (13.2%)
4 or more	54 (4.9%)

[†] excludes scores pertaining to the metastatic cancer itself

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Table 2: Cox regression Model for progression free and Overall survival

	Progression free survival				Overall survival			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	HR	P	HR	P	HR	P	**HR**	P
Age	1.01	<0.0001			1.03	<0.0001	1.01	0.005
Male sex v female	1.02	0.83			1.02	0.9		
Private hospital v public	0.931	0.3			0.84	0.03		
Modified Charlson score	1.05	<0.001	0.961	0.03	1.1	<0.0001		
Number of metastatic sites	1.22	<0.0001	1.1	0.004	1.3	<0.0001	1.1	0.006
Log (Duration of first-line chemotherapy)	0.914	<0.0001			0.83	<0.0001	0.96	0.002
Biological agent (Bevacizumab) used	0.849	0.02	0.77	0.0002	0.75	0.0002	0.71	0.0003
Primary resection performed	0.47	<0.0001	0.58	<0.0001	0.41	<0.0001	0.57	<0.0001
Primary site								
Left colon (reference group)	1		1		1		1	
Right colon	1.18	0.05	1.2	0.02	1.3	0.006	1.3	0.02
Occult/unspecified primary	1.28	0.08	0.89	0.4	1.9	<0.0001	1.3	0.1
Rectum	0.98	0.8	0.83	0.04	0.98	0.8	0.81	0.05
ECOG status								
ECOG 0 (reference group)	1		1		1		1	
ECOG 1	1.4	<0.0001	1.2	0.02	1.7	<0.0001	1.3	0.004
ECOG 2	2.6	<0.0001	1.7	<0.0001	4.5	<0.0001	2.3	<0.0001
ECOG 3	4.3	<0.0001	3.1	<0.0001	9.3	<0.0001	5	<0.0001
ECOG 4	91.8	<0.0001	76.3	<0.0001	179	<0.0001	84.0	<0.0001
Nature of metastasis resection								
R0 (reference group)	1		1		1		1	
R1	1.8	0.04	1.6	0.1	1.5	0.4	1.2	0.7
R2	2.8	<0.0001	1.9	0.002	4	<0.0001	2.2	0.004

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no resection	3.2	<0.0001	2	<0.001	6.5	<0.0001	2.7	<0.0001
<u>Treatment intent</u>								
group 1 (reference group)	1		1		1		1	
group 2	2	0.002	1.6	0.04	3.7	0.002	2.8	0.02
group 3	4.2	<0.0001	1.9	0.01	13.4	<0.0001	4.2	0.002

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Figure 1: Premature Cessation of First-line chemotherapy and utilisation of second-line treatment

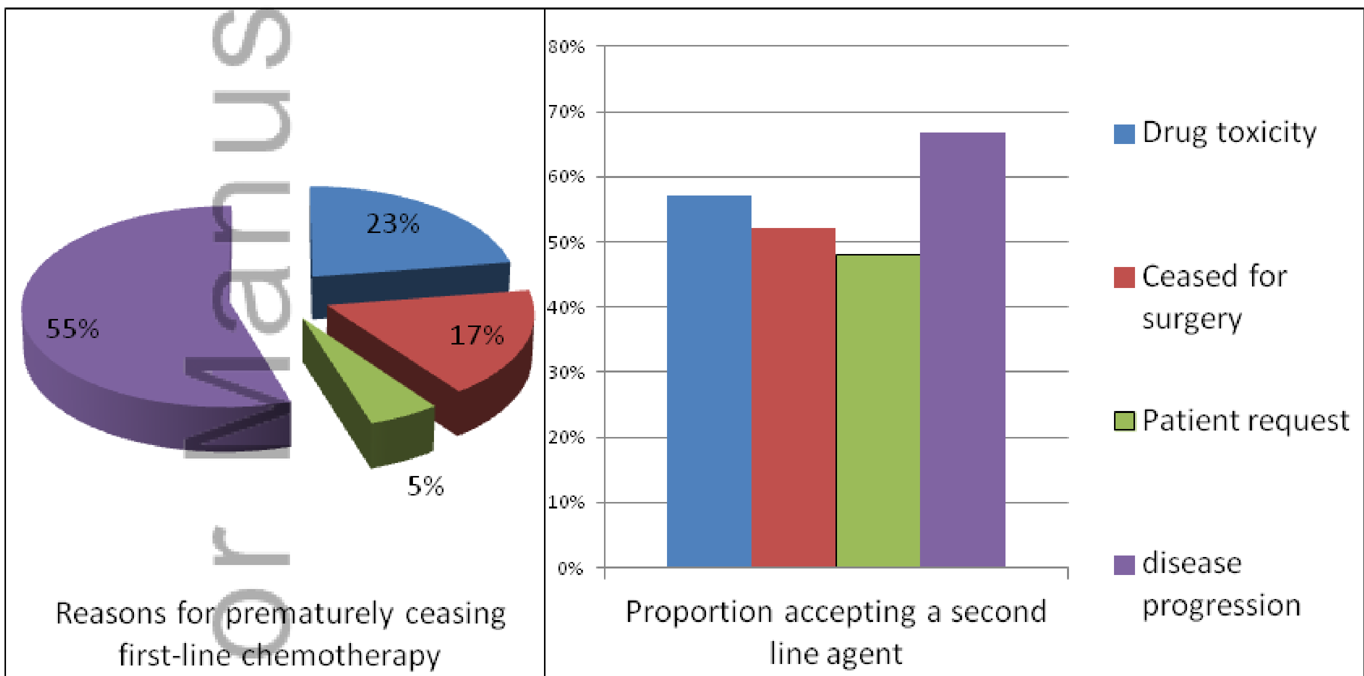

figure 1.tif

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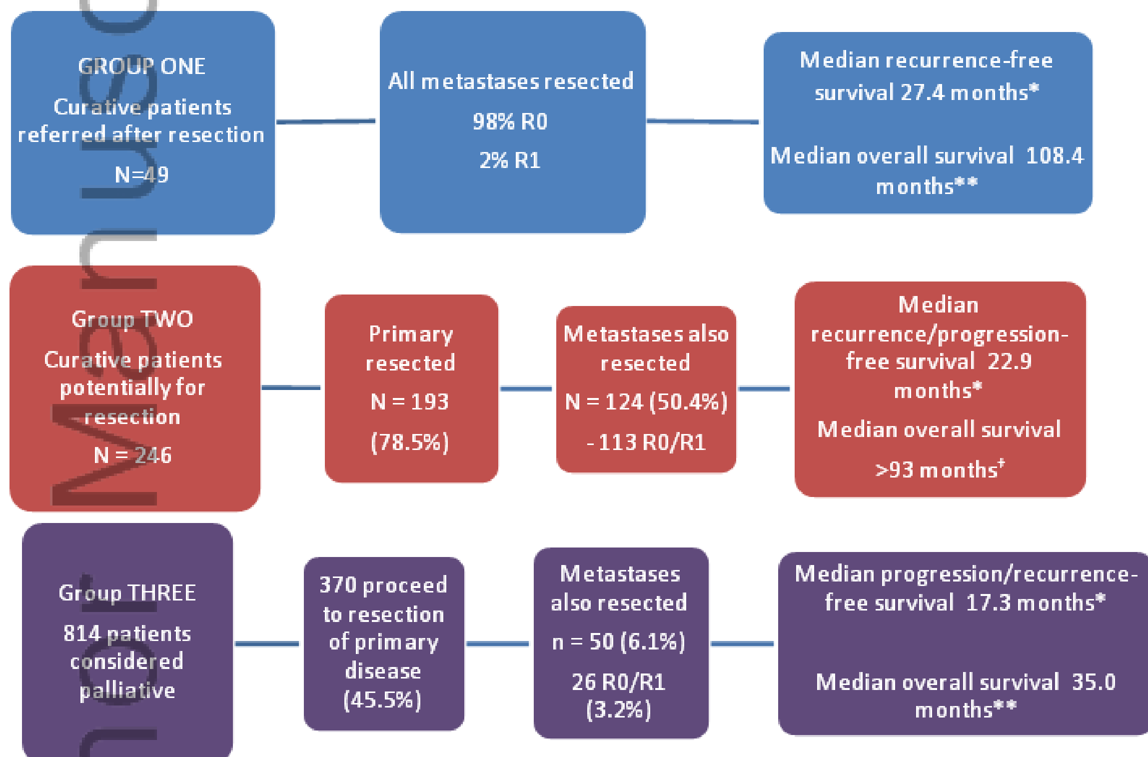

figure 2.tif

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