Role of Surgery in isolated hepatic metastasis from breast carcinoma, melanoma or sarcoma

Jose Ramos

University of the Witwatersrand
Donald Gordon Medical Centre

Evolution of liver resection

- Better understanding of hepatic anatomy, pathophysiology and response to resection
- Increasing expertise in liver resection by suitably trained HPB surgeons in centres of excellence
- Better understanding of tumour biology and natural history
- Emergence of multimodality treatment and establishment of multidisciplinary teams (MDT)
- Expansion in the indications for and extent of liver resection

Overcoming limitations

- Downstaging of liver tumours
- Portal vein embolisation (PVE)
- Trans-arterial chemotherapy (TACE) and radiotherapy (TARE)
- Combination of resection and ablation
- Staged hepatic resection

Requirements for successful liver resection

- Correct indication for resection
- Assessment by a multidisciplinary team
- Patient is fit for major surgery
- Resection performed by suitably trained HPB surgeon in a centre of excellence
- Ability to achieve complete resection
- Healthy liver amenable to safe resection
- Adequate remnant liver portal venous, hepatic arterial and biliary inflow, and hepatic venous outflow

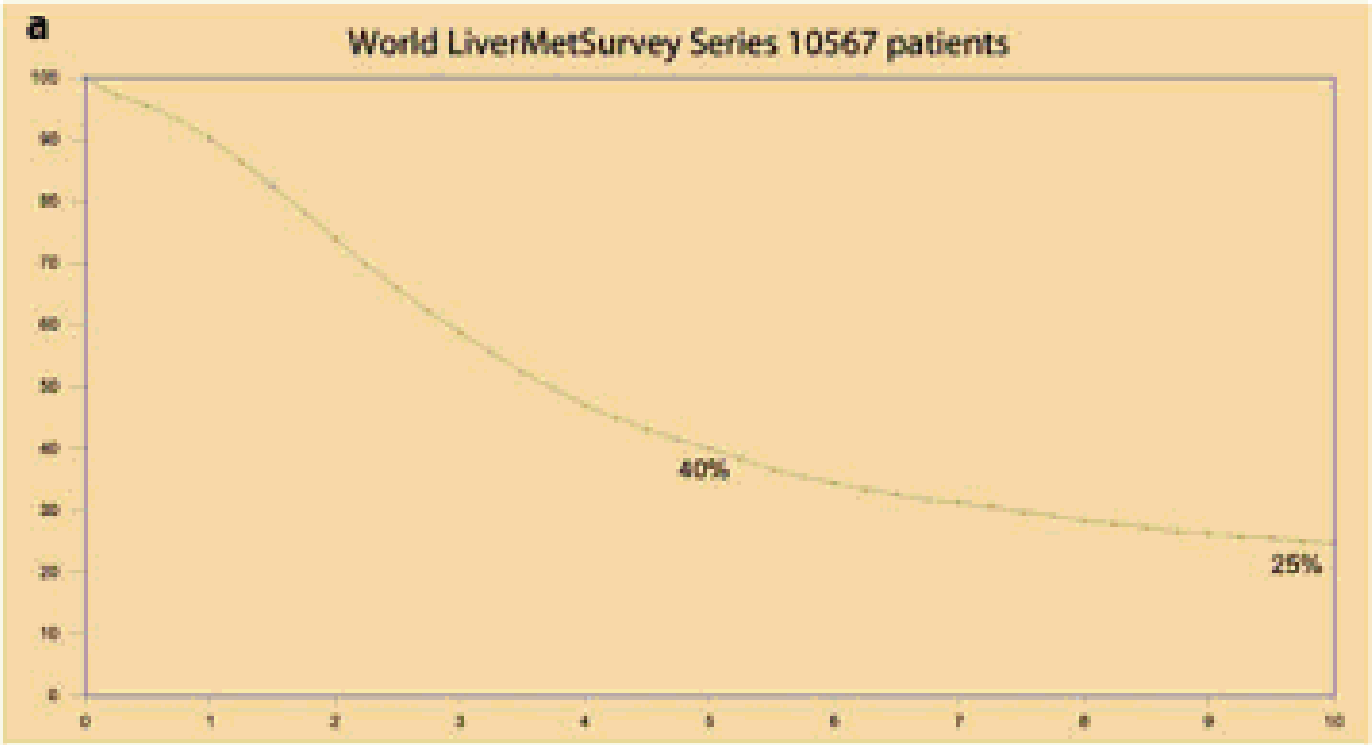
Rationale for liver resection in metastatic malignancy

- Resection with curative intent
  - Favourable tumour biology
  - R-0 resection
  - Primary tumour controlled
  - No unresectable extrahepatic metastases
- Resection for palliation
  - Only indicated for functional neuroendocrine tumours

Is there a role for liver resection in the management of hepatic metastases?

- Liver is affected in 40% of patients dying of metastatic malignancy
- In CRC, metastases isolated to the liver in only 20% - 25% of cases, less so in other malignancies
- No randomised trials to prove the benefit of resection of liver metastases.
- Major benefit in PFS and OS compared to other treatments especially in CRC, NETs, others

LiverMetSurvey (CRCLM)



Survival %

Time	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Percent	90%	74%	59%	47%	40%	34%	31%	28%	26%	25%

Number of exposed patients

Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
10567	7205	4612	2858	1778	1172	762	562	414	304	230

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Multimodal therapy of metastatic malignancy

- Chemotherapy
- Hormonal therapy
- Targeted and biological therapy
- Radiofrequency (RFA) and Microwave (MWA) Ablation
- Radiotherapy
- Angiographic embolisation (TACE and TARE)
- Surgery

Are all liver metastases equal?

- Portal vein route
- Hepatic arterial route
- Are these the same?
  - Pathology
  - Natural history

Breast Cancer Liver Metastases (BCLM)

Breast cancer metastases

- 40% - 50% of pts with breast carcinoma (BC) develop metastatic disease (Stage IV)
- 20% - 25% have liver metastases
- 12% - 15% have predominant liver metastases
- 5% will have metastases only in the liver

Survival in metastatic BC

- Median survival 4 – 14 months with standard traditional chemotherapy
- Median survival 24 – 33 months with combination of modern chemotherapy, targeted therapy and hormone blockade

  21% - 25% 5-year survival in modern era

Published series of resection for BCLM

Table 1 – Demographic characteristics of hepatectomy studies for breast cancer liver metastases (NR refers to not reported).

First author	Country of origin	Institution city	Year published	Study period	Level of evidence	Total breast cancer patients (*n*)	Patients undergoing surgery for liver metastases			Resections per year (*n*)
							Explored (*n*)	Resected (*n*)	Unresectable (*n*)	
Rubino[6]	Italy	Milan	2010	1997–2005	III	2500	22	18	4	2.0
Hoffmann[11]	Germany	Heidelberg	2010	1999–2008	III	NR	50	41	9	4.1
O'Rouke[21]	UK	Basingstoke	2008	1986–2006	III	NR	NR	11	NR	0.7
Lubrano[15]	France	Rouen	2008	1989–2004	III	NR	20	16	4	1.0
Caralt[10]	Spain	Barcelona	2008	1988–2006	III	NR	NR	12	NR	0.7
Thelen[19]	Germany	Berlin	2008	1988–2006	III	NR	NR	39	NR	2.2
Kollmar[17]	Germany	Saar	2008	2000–2007	III	NR	NR	27	NR	3.4
Reddy[22]	USA	Durham NC	2007	1995–2005	III	NR	NR	20	NR	1.8
Lendoire[24]	Argentina	Multicentre	2007	1989–2006	III	NR	NR	19	NR	1.1
Martinez[12]	USA	Santa Monica CA	2006	1995–2004	III	NR	NR	20	NR	2.0
Adam[9]	France	Villejuif	2006	1984–2004	III	NR	108	85	23	7.7
Cordera[20]	USA	Rochester MN	2005	1988–1998	III	NR	NR	10	NR	0.9
Weitz[23]	USA	New York	2005	1981–2002	III	NR	NR	29	NR	1.3
Sakamoto[7]	Japan	Tokyo	2005	1985–2003	III	11000	NR	34	NR	1.8
Ercolani[18]	Italy	Bologna	2005	1990–2003	III	NR	NR	21	NR	1.5
Vlastos[13]	USA	Houston	2004	1991–2002	III	NR	33	31	2	2.6
Elias[14]	France	Villejuif	2003	1986–2001	III	NR	65	54	11	3.4
Selzner[8]	USA	Durham NC	2000	1987–1999	III	6041	33	17	16	1.3
Pocard[16]	France	Cedex	2000	1988–1997	III	NR	52	49	1	4.9
Total	–	–	–	–	–	–	–	553	–	–
Range	–	–	–	–	–	–	–	10–85	–	0.7–7.7
Median	–	–	–	–	–	–	–	21	–	1.8

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Results of resection of BCLM

- Morbidity 0% - 44%
- Mortality 0% - 6%
- Overall survival 15-47 months
- 5-year survival 21% - 80% (median 40%)

Meta-analysis of BCLM resection

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Babiera 2005	-0.69	0.44	1.3%	0.50 [0.21, 1.19]
Bafford 2008	-0.75	0.25	3.5%	0.47 [0.29, 0.77]
Blanchard 2007	-0.34	0.124	9.4%	0.71 [0.56, 0.91]
Cady 2008	0	0		Not estimable
Fields 2007	-0.63	0.119	9.8%	0.53 [0.42, 0.67]
Gnerlich 2007	-0.48	0.029	19.0%	0.62 [0.58, 0.65]
Khan 2002 (1)	-0.49	0.029	19.0%	0.61 [0.58, 0.65]
Khan 2002 (2)	-0.29	0.027	19.1%	0.75 [0.71, 0.79]
Leung 2009	0	0		Not estimable
Rapiti 2006 (1)	-0.51	0.234	3.9%	0.60 [0.38, 0.95]
Rapiti 2006 (2)	0.26	0.246	3.6%	1.30 [0.80, 2.10]
Ruiterkamp 2009	-0.48	0.102	11.3%	0.62 [0.51, 0.76]
Total (95% CI)			**100.0%**	**0.65 [0.59, 0.72]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 47.04$, df = 9 ($P < 0.00001$); $I^2 = 81\%$
Test for overall effect: $Z = 8.38$ ($P < 0.00001$)

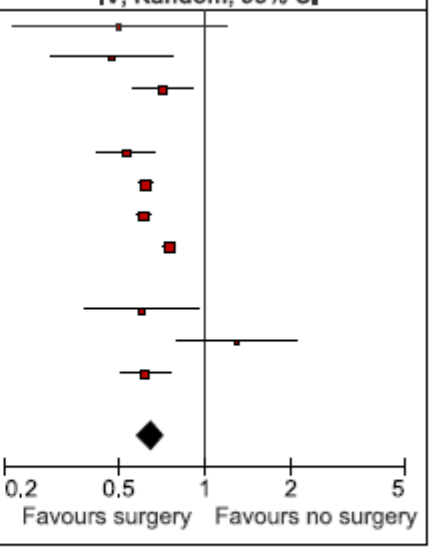

Fig. 1. Pooled analysis of Hazard Ratios for overall mortality for surgery versus no surgery for patients with stage IV breast cancer. (1): patients with free surgical margins; (2): patients with positive surgical margins.

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Ablation of BCLM

Results of studies regarding minimally invasive techniques as treatment of breast cancer liver metastases

Author (year)	Pt.	Period	Study	No. mets	Technical success	Survival						
						Overall					Median	Mean
						1	2	3	4	5		
RFA												
Livraghi (2001) [38]	24	1996–1999	two	64	92%						n.a.	
Gillams (2005) [39]	19	n.a.	single	n.a.	n.a.			42%			n.a.	
Gunabushanam (2007) [40]	14	2002–2005	single	16	100%	64%					n.a.	
Sofocleous (2007) [41]	12	1999–2005	single	14	93%	100%		70%		30%	5.0 yrs	
Jakobs (2009) [42]	43	1999–2006	single	111	96%	92%		70%		39%	4.9 yrs	
Meloni (2009) [43]	52	1996–2008	single	87	97%	68%		43%		27%	2.5 yrs	
Laser												
Mack (2001) [44]	127	1993–2000	single	332	n.a.	97%	75%	65%		34%		4.3 yrs
Mack (2004) [45]	232	1993–2002	single	578	n.a.	96%	80%	63%		41%		4.9 yrs
Vogl (2010) [46]	161	2001–2007	single	n.a.	n.a.	89%	56%	37%		14%		2.7 yrs
Microwave												
Abe (2005) [47]	8	2000–2004	single	11	91%						n.a.	n.a.

n.a. = not available.

Prognostic Factors

- Positive
  - Older age
  - Interval from primary breast cancer > 1 year
  - Oestrogen receptor positive tumour
  - R-0 resection
  - Favourable response to systemic chemotherapy
- Negative
  - Positive resection margin
  - Extrahepatic disease
  - Hormone refractory disease
  - Progressive disease prior to resection

Table 5 – Prognostic clinicopathologic factors of patients undergoing hepatectomy for breast cancer associated with poorer overall survival by univariate analysis.

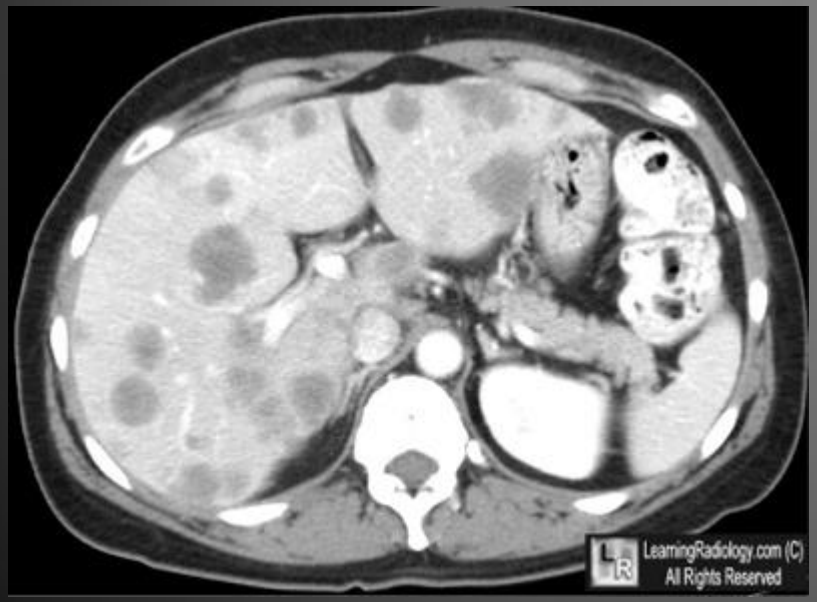
	Association with poorer overall survival	
	Significant (Positive association)	Non-significant (No association)
Younger age	Lubrano,[15] Martinez[12] 2 studies	Hoffmann,[11] Thelen,[19] Adam,[9] Vlastos,[13] Elias[14] 5 studies
Advanced primary tumour		Hoffmann,[11] Lubrano,[15] Thelen,[19] Adam,[9] Sakamoto,[7] Vlastos,[13] Elias,[14] Pocard,[16] 8 studies
Node positive primary	Pocard[16] 1 studies	Thelen,[19] Martinez,[12] Adam,[9] Sakamoto,[7] Elias,[14] Selzner,[8] 6 studies
Poorly differentiated		Lubrano,[15] Thelen,[19] Adam,[9] 3 studies
<1 year to liver metastases		
<1 year	Hoffmann,[11] Selzner,[8] 2 studies	Lubrano[15] (⩽24/>24 months), Caralt[10] (⩽24/>24 months), Adam,[9] Vlastos,[13] Elias,[14] Pocard[16] (⩽24/>24 months) 6 studies
Previous metastases	Thelen[19] 1 study	Hoffmann,[11] Selzner[8] 2 studies
Major hepatectomy		
Major	Lubrano[15] 1 study	Hoffmann,[11] Thelen,[19] Vlastos,[13] Selzner,[8] Pocard[16] 5 studies
Multiple liver metastases	Lubrano[15] 1 study	Thelen,[19] Martinez,[12] Adam,[9] Sakamoto,[7] Vlastos,[13] Elias,[14] Pocard[16] 7 studies
Larger tumour size	Hoffmann[11] 1 study	Thelen,[19] Adam,[9] Vlastos,[13] Elias,[14] Selzner[8] 5 studies
Positive resection margin	Hoffmann,[11] Thelen,[19] Adam[9] 3 studies	Elias[14] 1 study
Extrahepatic disease	Adam[9] 1 study	Hoffmann,[11] Sakamoto,[7] Selzner[8] 3 studies
Hormone sensitive disease	Lubrano[15] 1 study	
Hormone refractory disease	Hoffmann,[11] Martinez,[12] Elias[14] 3 studies	Thelen,[19] Adam,[9] Sakamoto,[7] Vlastos[13] 4 studies
HER2 positive disease	Martinez[12] 1 study	Thelen,[19] Adam[9] 2 studies

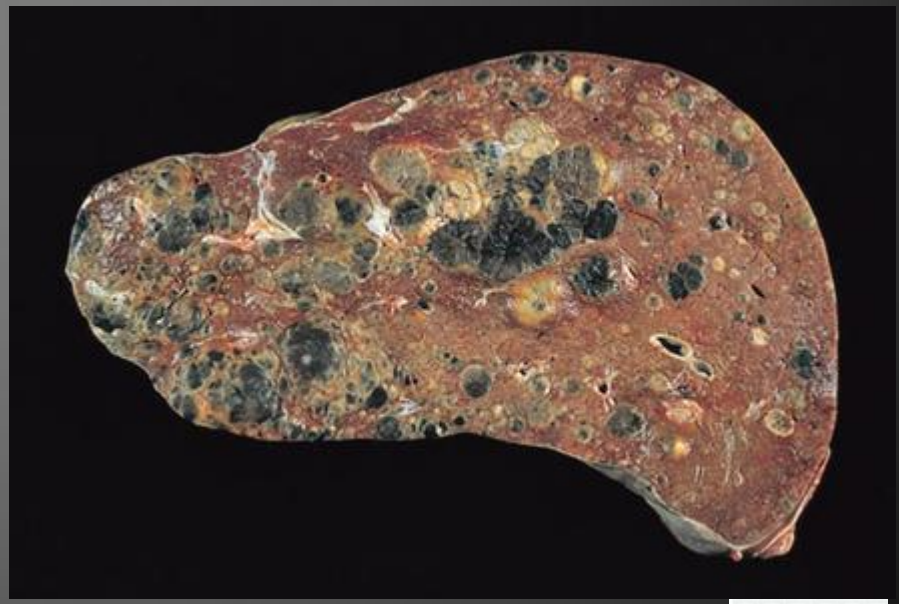
Factors influencing survival after surgical resection.

Prognostic factor	Influence on prognosis		
	Positive	Negative	No influence
1. *Features of primary BC*			
Anatomic site			27
Surgical procedure			27,31,35
Stage (TN-stage)			20–22,24,27,31,35,36
Histology:grade/differentiation			27,31,35,36
Presence of hormone receptors		36	27,31
2. *Features of BCLM*			
Interval between BC and BCLM	20,22,37		21,24,26,27,31,35,36
Number and size		36	20–22,24,26,27,31,35
Presence of hormone receptors	24	36	20,26,31,35
Invasion of liver vasculature			35
3. *Extrahepatic factors*			
Patient age (high vs. low)	36		24,26,27,31,35
Presence of extrahepatic disease		27,35	20,21,31
Presence of hilar gland metastases			20,27,31
Presence of abdominal gland metastases			21
4. *Therapeutic factors*			
R0-resection	18,31,35		24
Type of resection (minor vs. major)	36		20,22,26,27,31
Repeat hepatectomy	31		
Response to preoperative chemotherapy	31		22,26
Blood or plasma transfusion			36

Numbers correspond to reference list.

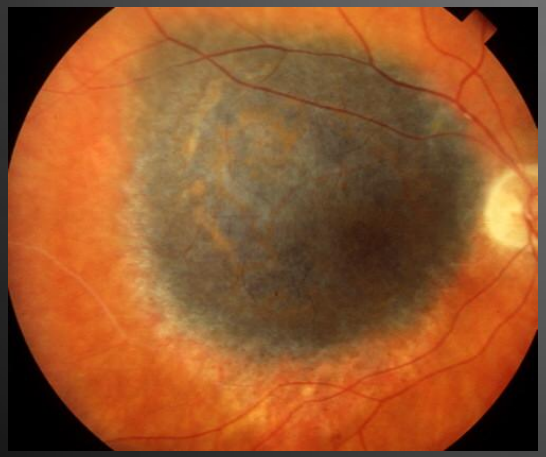
Melanoma Liver Metastases (MLM)





Malignant Melanoma (MM)

- 70 000 cases per year in USA
- 95% cutaneous
  - 10% - 20% of pts with metastatic MM develop liver metastases
- 5% ocular
  - Liver metastases develop in 13% - 21%
  - 95% of pts with metastatic MM develop liver metastases
  - Liver is sole site of metastases in 60% - 80%
  - Often long delay before appearance of MLM
- Multiple liver metastases typical
- Median survival of 4-6 months in metastatic MM



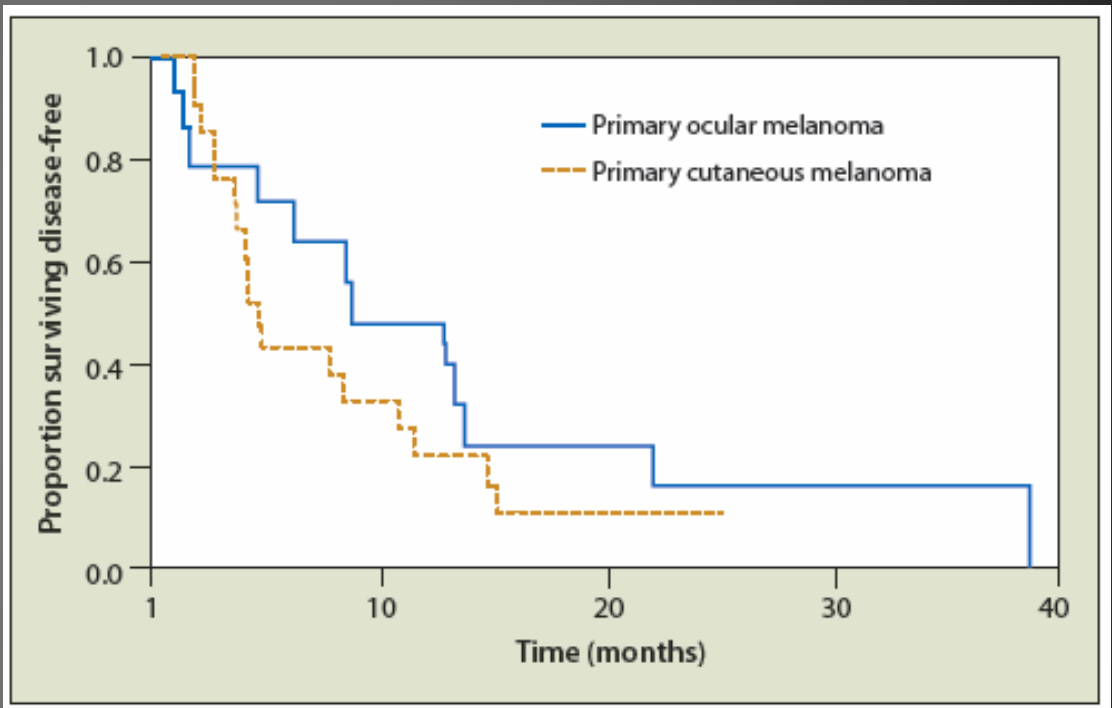


Figure 1: Disease-Free Survival in Patients With Primary Ocular or Primary Cutaneous Melanoma—Despite similar recurrence rates for patients with primary ocular melanoma (n = 12; 75.0%) and patients with primary cutaneous melanoma (n = 18; 75.0%; $P = .9$), those with a primary ocular melanoma tended to have a longer disease-free survival (8.8 months) than did those with a primary cutaneous melanoma (4.7 months; $P = .3$). Adapted from Pawlek et al.[25]

Management of metastatic MM

- Interferon
- Immunotherapy
- Chemotherapy (response rate < 20%)

  dacarbazine, temozolomide, interleukin-2, paclitaxel, cisplatin, and carboplatin
- Targeted agents

  vemurafenib and ipilimumab
- Surgery

  No controlled data

Role of liver resection for MLM

John Wayne Cancer Centre

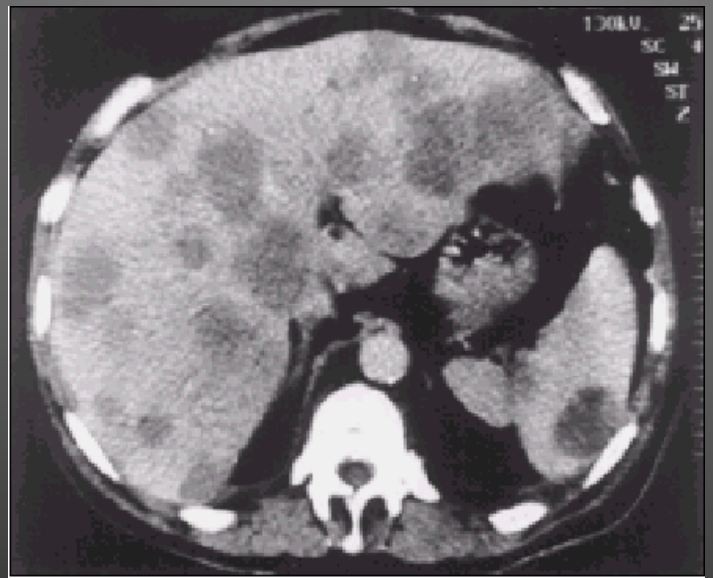
- 1750 pts with MLM
- 34 (2%) considered for resection
- 24 (1.4%) underwent resection
- Median overall survival 38 months in resected cases
- Median overall survival 4 months in unresected cases

Published series on resection of MLM

Table 1 Data Review of Modern Liver Metastectomy Series for Uveal Melanoma

Study	Uveal Melanoma	Metastatic Disease	Liver-Only Metastasis	Patients with ≤ 4 Mets	Major/Minor Hepatectomy	RO/R1/R2 Resection	Median Survival Following Liver Metastasectomy—(R0/R1/R2/No Surgery)
Mariani et al[27]	3873	798	255	76	77/178	76/22/157	27/17/11/8 months
Frenkel et al[28]	558	74	35	14	15/20	13/22[a]	65.6/16.6 months[a]
Rivoire et al[26]	602	63	54	11	7/21	14/NR/14	16/NR/14/11 months

[a]Combined R1 and R2 resection data analysis.
NR = not reported.



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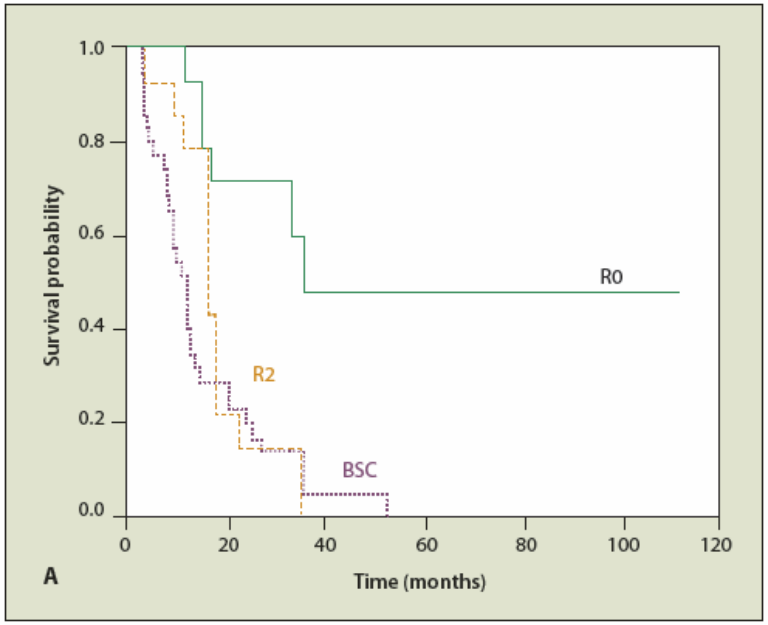


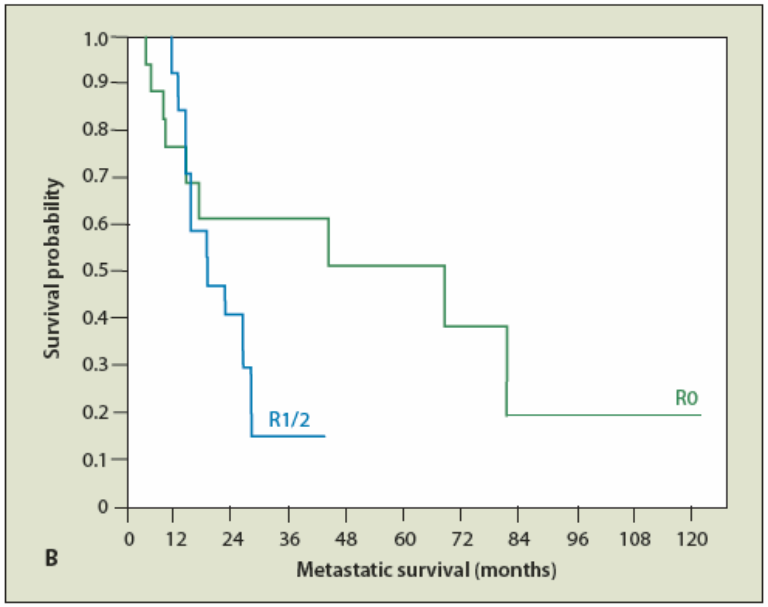


Figure 2: Survival According to Treatment of Uveal Melanoma–Associated Liver Metastases—(A) Adapted from Rivoire et al.[26] BSC = best supportive care. (B) Adapted from Frenkel et al.[28]

Factors predicting improved outcome

- R0 resection
- Age < 70
- Number of metastases < 4
- Disease-free interval from primary tumour diagnosis > 24 months

Sarcoma Liver Metastases (SLM)

Metastatic Sarcoma

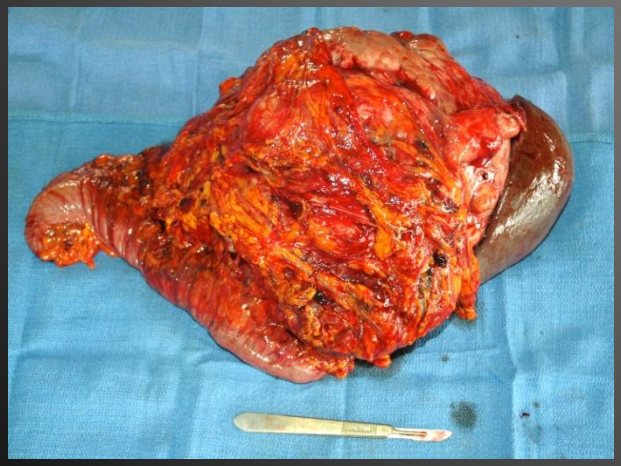
- 25% of pts with sarcoma develop SLM
  - 16% for retroperitoneal sarcoma
  - 62% for visceral sarcoma
- Significant difference in survival for CD117 (c-kit) tumours (GIST)
  - CD117 positive 80% 5-year survival
  - CD117 negative 33% - 50% 5-year survival
  - Imatinib is the likely reason for improved survival

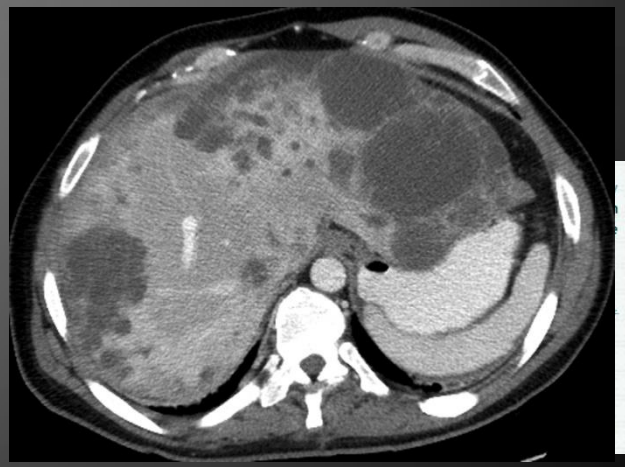
Published series of resection of SLM

TABLE 3. Outcomes From a Review of the Literature With 6 Reports of Curative Hepatic Resection for Sarcoma Liver Metastases

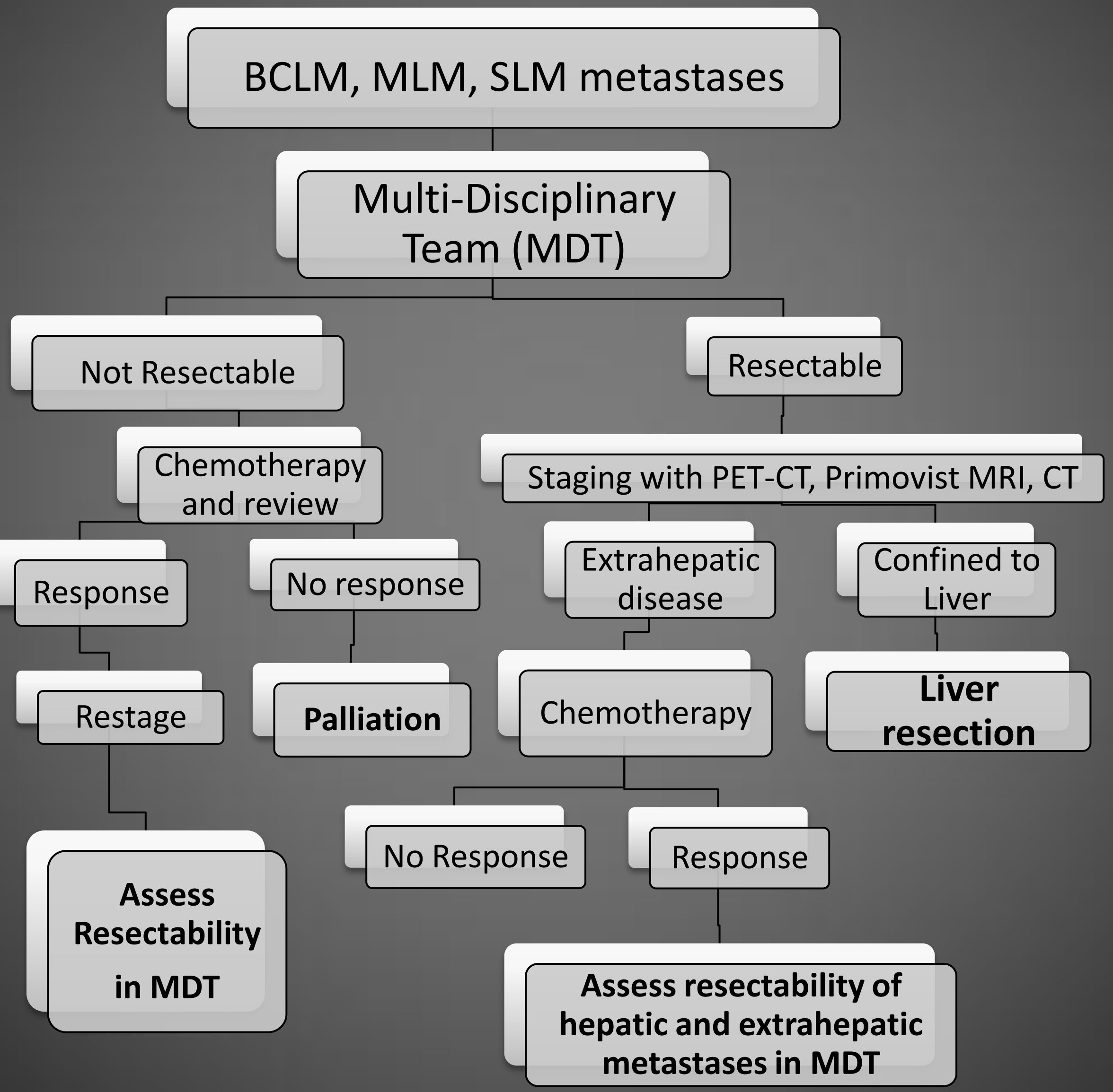
Author	Year Published	Patients (n)	Majority of Primary Tumor Type	Median Overall Survival (mo)	5-Year Survival (%)	Median Disease-Free Survival (mo)	Prognostic Factors
Rehders et al[11]	2009	27	Leiomyosarcoma and GIST	44	49	23	Disease-free interval >24 mo, repeat metastasectomy
Pawlik et al[10]	2006	66	Leiomyosarcoma and GIST	47	27	21% at 3 yr	Size of metastasis ≤3 cm
Nunobe et al[9]	2005	18	GIST	36	34	14	None
Shima et al[12]	2003	10	GIST	39	NR	22% at 2 yr	None
DeMatteo et al[6]	2001	56	Leiomyosarcoma and GIST	58	30	32	Metachronous presentation, surgery with ≥ lobectomy, time to liver metastasis >2 yr
Lang et al[8]	2000	26	Leiomyosarcoma	40	33	NR	NR
Jaques et al[7]	1995	14	Leiomyosarcoma	30	NR	NR	None

NR indicates not reported.





Approach to breast, melanoma and sarcoma LM



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Conclusions

- No controlled data on resection of breast, melanoma and sarcoma liver metastases
- Resection of these liver metastases appears to confer survival benefit
- Surgery is however one of many treatment options in multimodal therapy
- Patient selection in the setting of a MDT is vital