

Liver resection in patients (pts) treated with 1st line chemotherapy (CT) for metastatic colorectal cancer (mCRC) from Japanese cross-sectional and cohort study (EMERaLD study)



Evaluation of first-line treatment for Metastatic colorectal cancer, Especially Resection of liver metastasis and Long survival, in Japanese Database

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Background

An observational cohort study plays a crucial role to understand the current status of clinical practice and can be utilized as database for multi-purpose outcome research. We planned and conducted a large cohort study to establish database available including treatments for mCRC in Japan (EMERaLD study).

Complete resection of metastatic diseases can only result in cure with mCRC. EMERaLD study evaluated the 6-month efficacy and safety data on 1,005 pts. We performed a subgroup analysis focused on 362 pts with liver limited disease on this data.

EMERaLD study design

UMIN-CTR UMIN000006392

mCRC, previously untreated, database

n=1,005

registration period : Oct, 2010 - Sep, 2011

Key data inclusion criteria

1. With first line CT including oxaliplatin and bevacizumab for mCRC
2. Treatment-Initiated after January, 2010
3. Radiologically assessed during first line CT
4. Monitored by laboratory test and symptom check during first line CT
5. Able to provide observation data to this study

6 months follow-up data cut-off : Mar, 2012

- pts characteristics
- chemo (6 months follow-up)
- liver resection
- response to chemo
- 6-month PFS

2 years follow-up data cut-off : Sep, 2013

- PFS
- RFS after liver resection
- post-progression treatment
- 2-year OS

Primary endpoints

Overall survival, Liver resection rate, R0 liver resection rate

Secondary endpoints

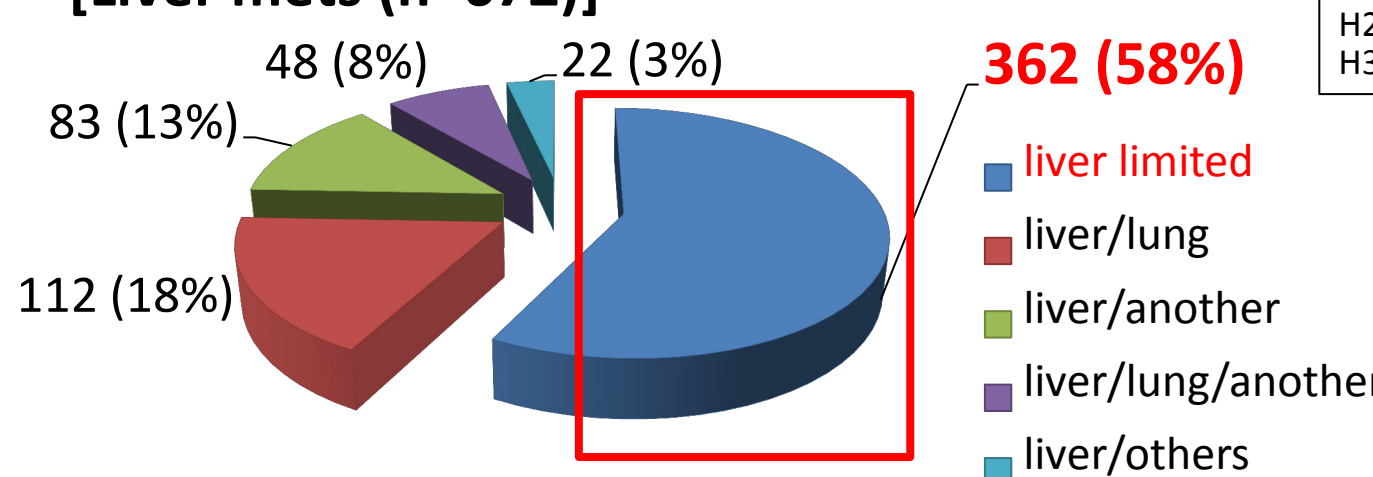
Response rate, Progression-free survival, Safety, Sub-group analysis by regimens, KRAS status, etc

Liver metastases

672 pts had liver mets among 1,005 pts.

362 pts had liver limited.

[Liver mets (n=672)]



Pts characteristics (n=362)

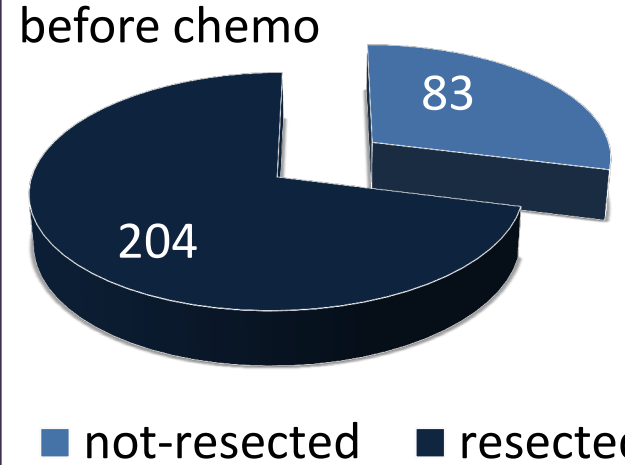
Gender	Male	245 (67.7%)
	Female	117 (32.3%)
Age (yrs)	Median	64
	Range	27-85
ECOG PS	0	306 (84.5%)
	1	51 (14.1%)
	2	4 (1.1%)
	≥ 3	1 (0.3%)
CEA (ng/mL)	Median	29.6
	Range	0.4-29,600
Comorbidity	Without	218 (60.2%)
	With	125 (34.5%)
	Unknown	19 (5.2%)
Chemo regimens	FOLFOX+BV	146 (40.3%)
	XELOX+BV	207 (57.2%)
	Other oxali. +BV	9 (2.5%)
KRAS mutation	Wild type	113 (31.2%)
	Mutant	82 (22.7%)
	Unknown	167 (46.1%)

Primary disease

Primary site	Colon	205 (56.6%)
	Rectum	154 (42.5%)
	Colon and rectum	3 (0.8%)
Synchronous/Metachronous	Synchronous	287 (79.3%)
	Metachronous	75 (20.7%)

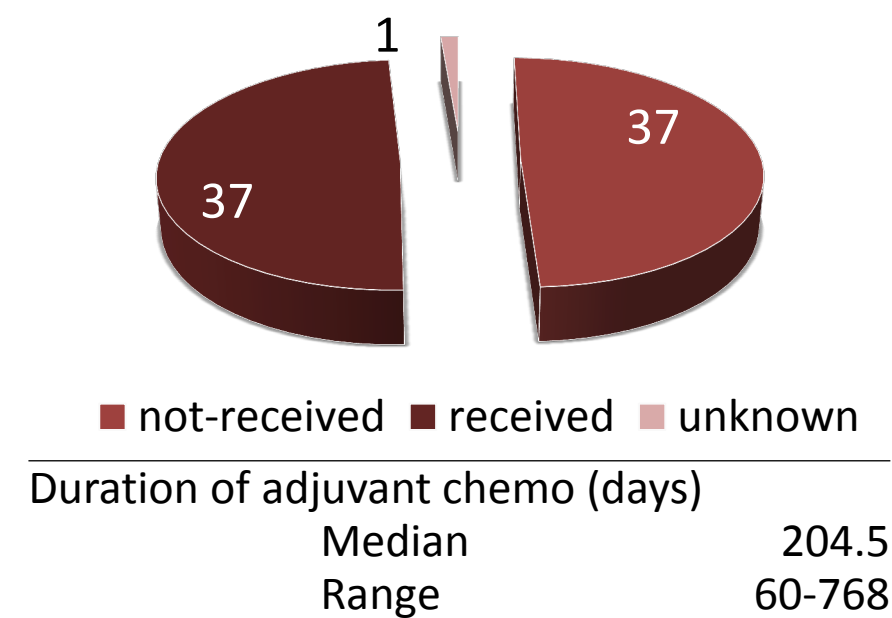
[Synchronous (n=287)]

primary resection before chemo



[Metachronous (n=75)]

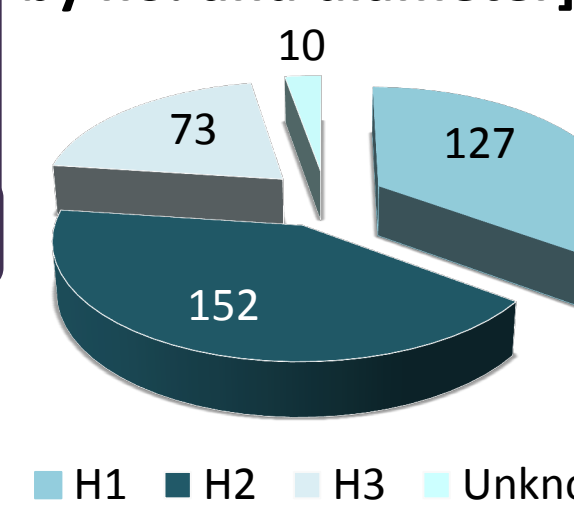
adjuvant chemo after primary resection



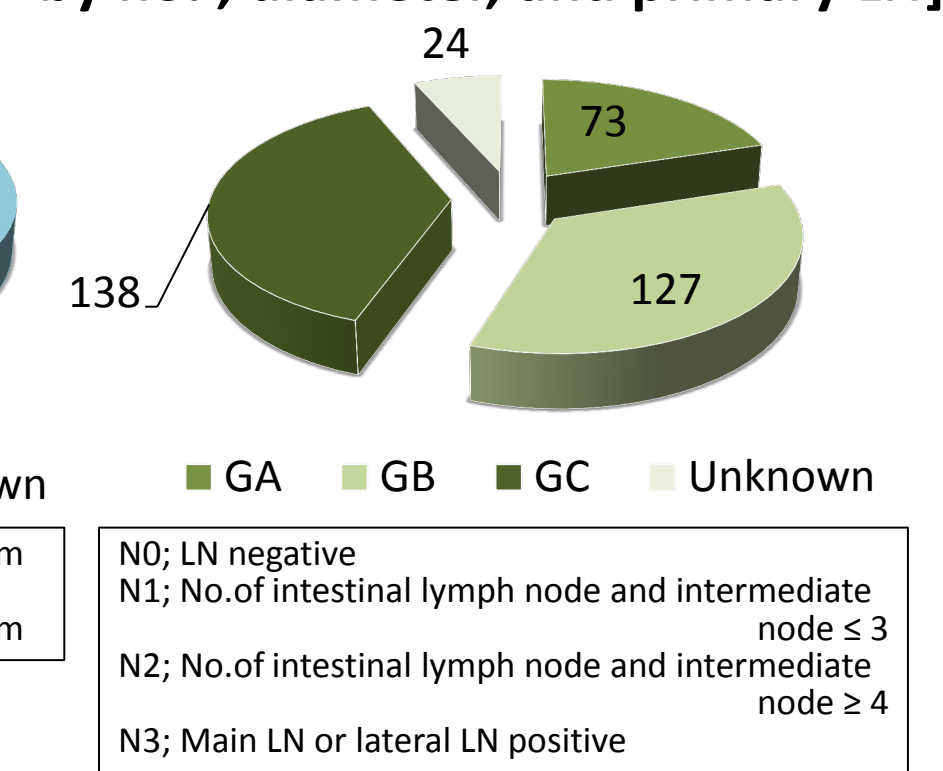
Liver Metastases

No.	Median	5
	1-4	164 (45.3%)
	5 ≤	191 (52.8%)
	unknown	7 (1.9%)
Max. diameter (cm)	Median	3.5
	Range	0.25-23
Vascular invasion	No	280 (77.3%)
	Yes	63 (17.3%)
	hepatic vein	46
	hepatic artery	12
	portal vein	20
	biliary duct	9
	Unknown	19 (5.2%)

[Category by no. and diameter]



[Category by no., diameter, and primary LN]



*Japanese Classification of Colorectal Carcinoma, Second English Edition

Results

Liver resection (n=362)

Metastasectomy	91 (25.1%)
Liver resection	88 (24.3%)
R0 liver resection	77 (21.3%)
R1 liver resection	7
R2 liver resection	2
RX	2
LN resection	4 (1.1%)
Primary resection	17 (4.7%)
Local recurrence resection	2 (0.6%)
Others	2 (0.6%)

[subgroup analysis by H 1/2/3]

Liver resection	88
H1 (n=127)	51 (40.2%)
H2 (n=152)	28 (18.4%)
H3 (n=73)	7 (9.6%)
Unknown (n=10)	2 (2.0%)
R0 liver resection	77
H1 (n=127)	46 (36.2%)
H2 (n=152)	24 (15.8%)
H3 (n=73)	5 (6.8%)
Unknown (n=10)	2 (2.0%)

[Preoperative chemo (n=88)]

Duration of chemotherapy (days)	Median	137
	Range	71-220
Interval between last chemo and ope (days)	Median	37
	Range	10-104
Interval between last BV and ope (days)	Median	52
	Range	20-133

[Operative details (n=88)]

Preoperative no. of mets	Median	2.5
Preoperative max. diameter of mets (cm)	Median	2
	Range	0-10
Operative procedure	Resection	79 (89.8%)
	Resection + RFA	8 (9.1%)
	RFA	1 (1.1%)
Resected no. of mets	Median	3
Blood loss	Median	591.5
	Range	0-4,579
Perioperative complications	No	70 (79.5%)
	Yes	18 (20.5%)
	Fever	4
	Wound infection	2
	Shock	2
	Others	12
Postoperative hospital days (days)	Median	15
	Range	7-84

Univariate analysis

Univariate analysis	Odds	95%CI	P-value
Gender (male/female)	1.370	0.805 2.331	0.2457
Age (< 75 yrs/75 yrs ≤)	1.379	0.697 2.730	0.3561
CEA	0.999	0.998 1.000	0.0413
Comorbidity (without/with)	0.756	0.455 1.256	0.2796
Regimens (FOLFOX+BV/XELOX+BV)	0.940	0.574 1.539	0.3510
Regimens (FOLFOX+BV/Others)	2.522	0.305 20.870	0.3707
KRAS mutation (wild/mutant)	0.627	0.310 1.268	0.7190
KRAS mutation (wild/unknown)	0.487	0.268 0.882	0.0494
Primary site (colon/rectum)	0.985	0.606 1.600	0.9504
Synch./metach. (synch./metach.)	0.854	0.478 1.524	0.5932
Primary resection (not/resected)	0.622	0.335 1.157	0.1337
Primary LN (negative/positive)	1.334	0.791 2.249	0.2792
No. of liver mets	0.839	0.780 0.902	<.0001
No. of liver mets (1-4/5 ≤)	4.453	2.620 7.570	<.0001
Max. diameter of liver mets	0.991	0.983 0.999	0.0348
Max. diameter of liver mets (≤ 5/5 <)	1.832	1.038 3.232	0.0366
Vascular invasion of liver mets (no/yes)	2.116	0.995 4.499	0.0515
Portal vein invasion of liver mets (no/yes)	3.022	0.687 13.290	0.1432
Hepatic vein invasion of liver mets (no/yes)	1.610	0.721 3.596	0.2452
Chemo response (responded/not)	2.838	1.647 4.893	0.0002

Multivariate analysis

Multivariate analysis	Odds	95%CI	P-value
Age (< 75 yrs/75 yrs ≤)	1.778	0.835 3.787	0.1355
No. of liver mets	0.819	0.757 0.885	<.0001
Chemo response (responded/not)	3.405	1.895 6.119	<.0001

[subgroup analysis by no. of liver mets]

Liver resection	88
< 6 (n=193)	72 (37.3%)
6 ≤ (n=151)	15 (9.9%)
NA (n=18)	1 (5.6%)
R0 liver resection	77
< 6 (n=193)	64 (33.1%)
6 ≤ (n=151)	12 (7.9%)
NA (n=18)	1 (5.6%)

*A cut-off value of 6 was calculated by the Receiver Operating Characteristic analysis.

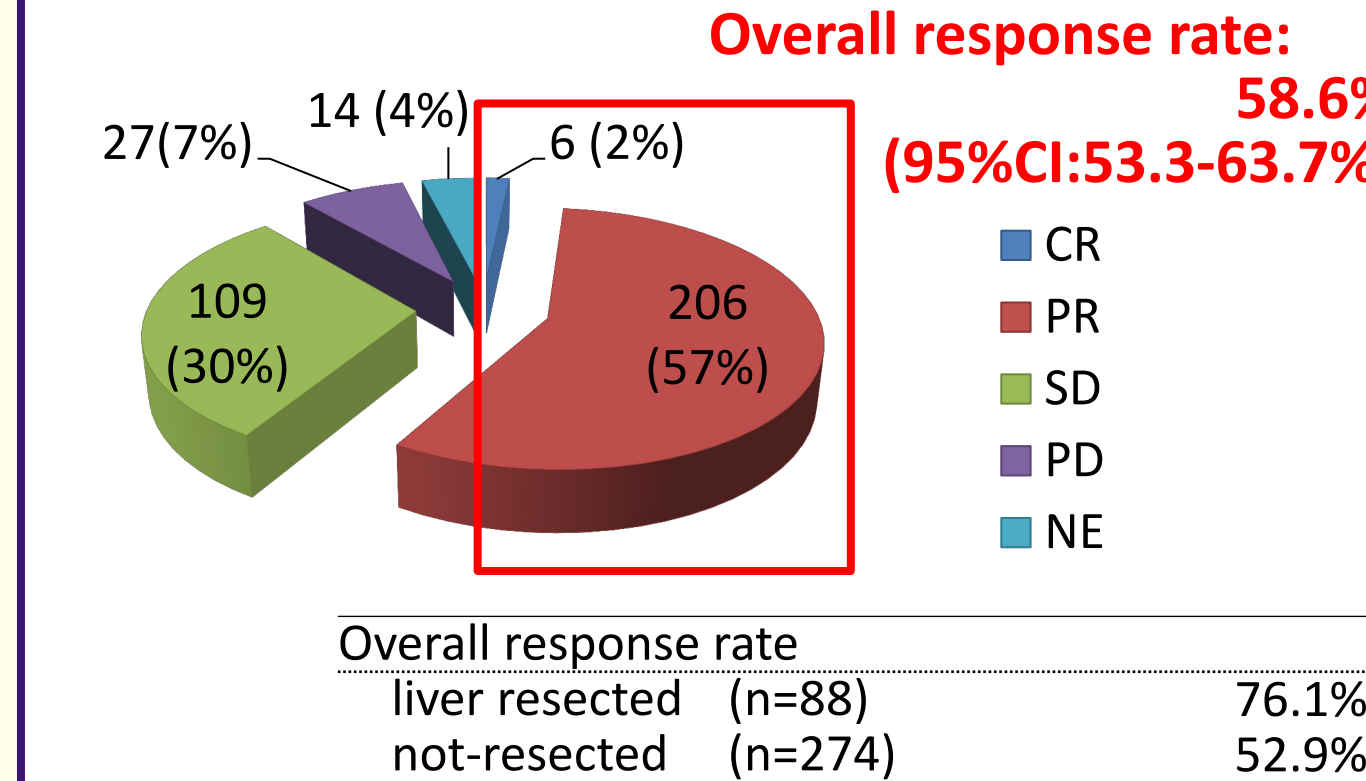
[subgroup analysis by chemo response]

Liver resection	88
responded (n=212)	67 (31.6%)
not-responded (n=150)	21 (14.0%)
R0 liver resection	77
responded (n=212)	58 (27.4%)
not-responded (n=150)	19 (12.7%)

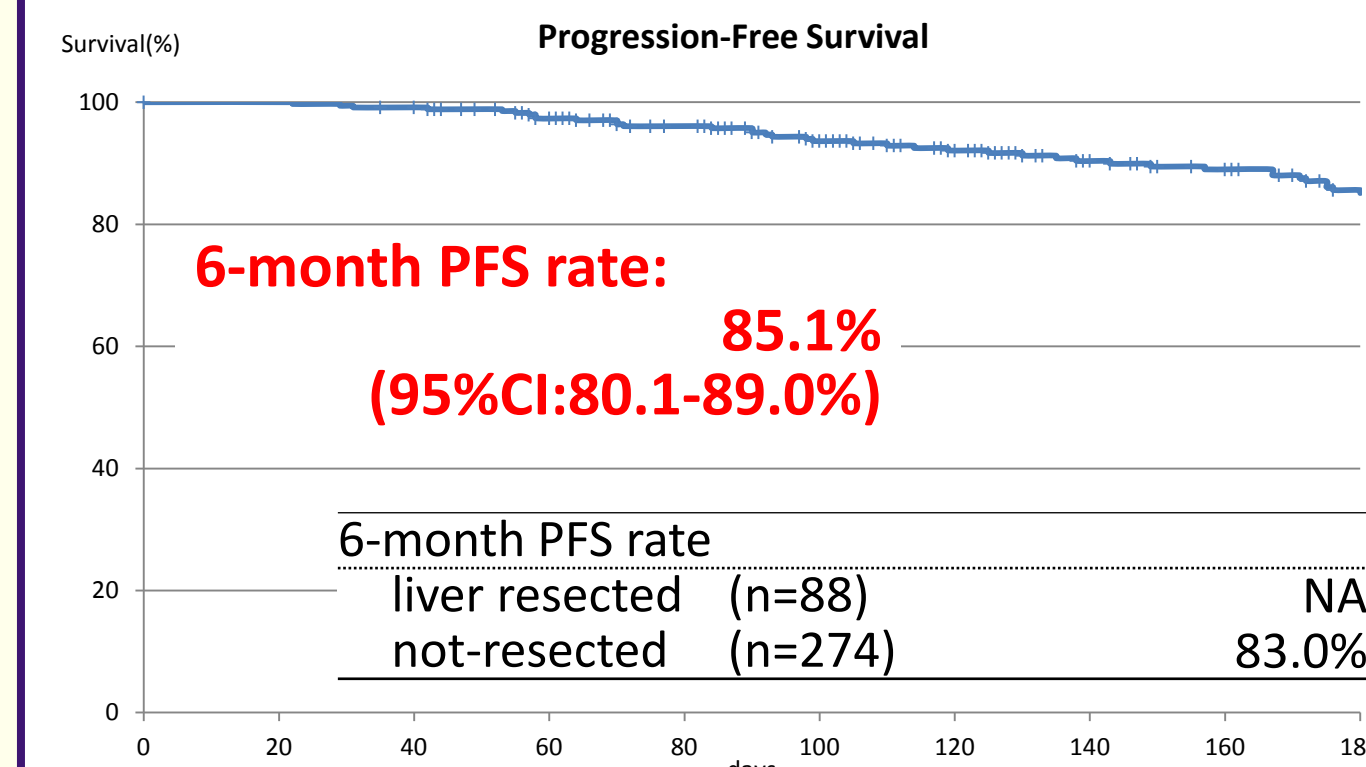
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6-month response (n=362)



6-month PFS (n=362)



Summary

- ✓ 362 pts had liver limited disease among 1,005 pts.
- ✓ 88 pts (24.3%) received liver resection followed by 1st line chemo at 6 months. 77 pts (21.3%) had R0 liver resection.
- ✓ As a result of multivariate analysis, the following variables at baseline were associated to liver resection; no. of liver mets and response to 1st line chemo.
- ✓ For the number of liver mets, the Receiver Operating Characteristic analysis identified a cut-off value of 6 (1-5/≥6) to distinguish between pts with or without liver resection.

Conclusion

- ✓ Liver resection rate was not different from previous reports.
 - ✓ Observational cohort reported higher liver resection rate, which might result from including cohort received neo-adjuvant chemo.
- Liver resection rate followed by oxaliplatin-based chemo with BV for pts with liver limited disease
- | | | |
|-------------|---------|------------------|
| First-BEAT* | (n=350) | 20.3% (RO:15.4%) |
| NO16966* | (n=211) | (RO:12.3%) |
| EMERaLD | (n=362) | 24.3% (RO:21.3%) |
- *Okines et al. Br J Cancer 2009.

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