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MRI Detection of Intratumoral Fat in Colorectal Liver Metastases after Preoperative Chemotherapy

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Introduction

- Curative liver resection is the most effective treatment for colorectal liver metastasis (CLM).

Ann Surg 247: 125-135, 2008.

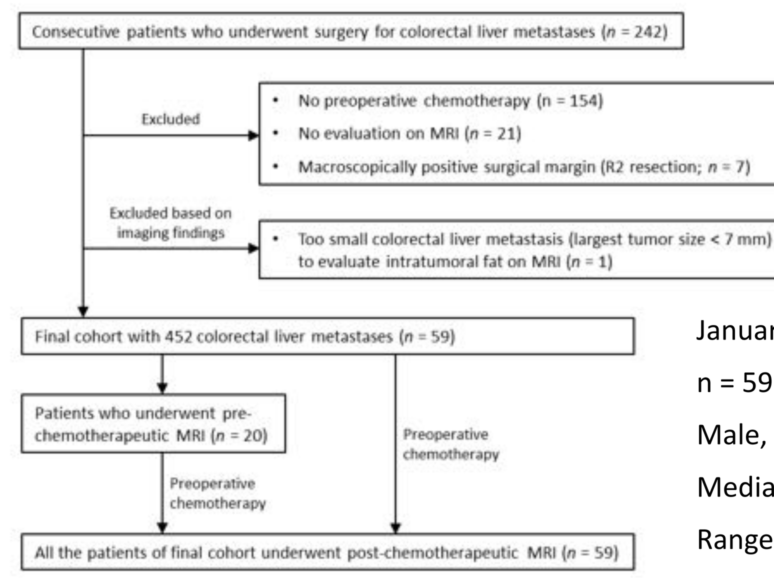
- More effective predictors of response to chemotherapy are required.
- We have occasionally observed intratumoral fat deposition in CLMs after preoperative chemotherapy on dual-echo gradient-recalled echo (GRE) MRI.

Purpose

- To investigate the incidence and clinical significance of fat deposition in CLMs after preoperative chemotherapy by dual-echo GRE MRI.

Materials and Methods; Patients

- Patients who underwent preoperative MRI and curative surgery for CLM after preoperative chemotherapy.



January 2008–June 2014
n = 59
Male, 34; Female, 26
Median age, 62 years
Range, 28–79 years

Imaging Analysis

- Dual-echo T1-weighted GRE MR images were acquired for all patients.
- Two radiologists (5 and 6 years of experience in abdominal imaging).
- Intratumoral fat deposition in CLMs, number and maximum diameter of CLMs, presence/absence of fatty liver, presence/absence of intratumoral calcification, and response to chemotherapy according to RECIST version 1.1 and morphologic response criteria were assessed on CT and/or MRI.

Eur J Cancer 45: 228-247, 2009.
Jama 302: 2338-2344, 2009.

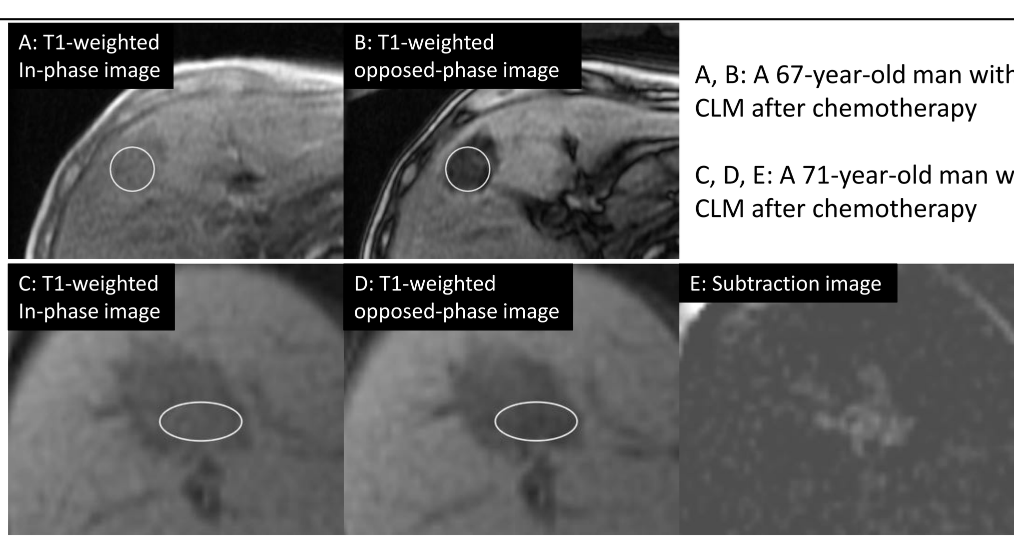
Evaluation of intratumoral fat deposition

- Qualitative evaluation by subtraction of opposed-phase from in-phase images.
- Quantitative evaluation by calculating fat signal fraction (FSF).

$$FSF = \frac{SI_{IP} - SI_{OP}}{2(SI_{IP})} \times 100$$

SI_{IP} and SI_{OP} are the signal intensities of the lesion in in-phase and opposed-phase images, respectively.

Radiology 153: 189-194, 1984.
J Magn Reson Imaging 34: spcone, 2011.



A, B: A 67-year-old man with CLM after chemotherapy

C, D, E: A 71-year-old man with CLM after chemotherapy

- An elliptical region of interest (ROI) for determining signal intensities was drawn as large as possible to cover the region with fat deposition (Fig. A, B).
- In case of focal or heterogeneous intratumoral fat deposition, the ROI was drawn focally to cover only the region with fat deposition (Fig. C, D).
- Qualitative intratumoral fat deposition was determined using subtraction image (Fig. E).
- FSF was measured for all lesions having intratumoral fat, in which the highest value in each patient was used for analysis.
- SI_{IP} and SI_{OP} were measured three times, and the average values were used for analysis.

Clinical Factors

- Age, sex, BMI, OS, and RFS.
- Primary site of tumor, primary tumor nodal status, extrahepatic disease, DFI, No. of chemotherapy cycles, and presence or absence of adjuvant chemotherapy.
- Preoperative serological data (serum cholesterol, triglyceride, HbA1c, CEA, and CA19-9).

Histological Analysis

- Specimens of CLMs from patients who did not undergo chemotherapy between final MRI and hepatectomy (56 of 59 patients).
- The lesions were classified into groups separated by 5% based on tumor viability.

J Clin Oncol 26: 5344-5351, 2008.

Statistical Analysis

- Fisher's exact test, Spearman's rank correlation analysis, log-rank test, Cox proportional hazard model , multivariate logistic regression analysis, Cohen's coefficient kappa, Kendall's coefficients of concordance and Ebel's intraclass correlation coefficients.
- Multivariate analysis with stepwise backward selection and preceding backward elimination of variables identified as relatively significant ($p < .15$) upon univariate analysis.

Note—BMI = body mass index; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; DFI = disease-free interval from diagnosis of primary tumor to diagnosis of liver metastasis; OS = overall survival; RFS = recurrence-free survival.

Results
Patient Characteristics

Characteristics	Values
Median age, years [range]	62 [28–79]
Sex, No. [%]	
Male/female	33/26 [56/44]
Primary tumor, No. [%]	
Rectum/colon	15/44 [25/75]
Histopathological types of primary tumors, No. [%]*	
Well-differentiated adenocarcinoma	20 [34]
Moderately differentiated adenocarcinoma	33 [56]
Mucinous adenocarcinoma	3 [5]
Papillary adenocarcinoma	1 [2]
Not available	2 [3]
Primary tumor nodal status, No. [%]	
Positive/negative	44/15 [75/25]
Extrahepatic disease, No. [%]	
Present/absent	12/47 [20/80]
DFI, year, No. [%]	
< 1/≥ 1	38/21 [64/36]
Median number of CLMs, No. [range]	4 [1–39]
Median largest tumor size before surgery, cm [range]	2.6 [0.7–7]
Fluorouracil-based chemotherapy regimen, No. [%]	
Oxaliplatin	37 [63]
Irinotecan	8 [13]
Oxaliplatin + irinotecan	1 [2]
Neither oxaliplatin nor irinotecan	1 [2]
Two or more regimens	12 [20]
Bevacizumab, No. [%]†	
Yes/no	32/27 [54/46]
Cetuximab or panitumumab, No. [%]†	
Yes/no	27/32 [46/54]
Median no. of chemotherapy cycles before surgery, No. [range]	8 [4–56]
Postoperative adjuvant chemotherapy, No. [%]	
Yes/no	24/35 [41/59]
Surgical margin, No. [%]	
R0/R1	42/17 [71/29]

Note—CLMs = colorectal liver metastases; DFI = disease-free interval from diagnosis of primary tumor to diagnosis of liver metastasis; R0 = microscopically negative surgical margin; R1 = microscopically positive surgical margin.
*Six patients (10%) had metachronously received bevacizumab and either cetuximab or panitumumab

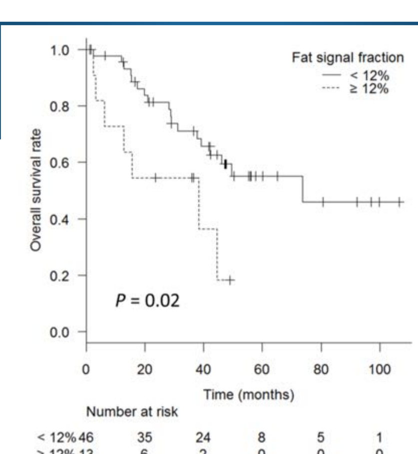
- n = 59
- The median follow-up period was 36.6 months. (range, 1.1–106.6 months)
- 25 deaths (42%) occurred.
- 2 patients (3%) died within 90 days of surgery.
- 44 (75%) tumor recurrence occurred.
- All Chemotherapy were Fluorouracil-based.
- Extrahepatic lesions were radically resected during or after hepatectomy

Results; Intratumoral Fat Before and After Chemotherapy

- Intratumoral fat deposition was qualitatively detected in 32 (32/59; 54%) patients after chemotherapy.
- In 20 patients with pre-chemotherapeutic MRI,
  0 (0/20; 0%) patients before chemotherapy with intratumoral fat
  9 (9/20; 47%) patients after chemotherapy with intratumoral fat.

Relationship Between Fat Signal Fraction and Overall Survival

- Poorer OS among patients with tumor FSF values ≥ 12% (log-rank test).
- This cutoff value was determined to minimize the p value.



Preoperative Predictors of Overall Survival
by Cox Proportional Hazard Model

Factor		No. of Patients	5-Year OS (%)	Median OS (months)	Univariate Analysis P	HR	95% CI	Multivariate Analysis P	HR	95% CI
Age, years	≥ 65	27	33.7	44.4	0.10	1.96	0.88–4.37	0.02	2.81	1.18-6.71
	< 65	32	61.8	NA						
Sex	Male	33	49.1	49.5	0.49	0.76	0.35–1.67			
	Female	26	48.7	46.2						
Primary site of tumor	Rectum	15	46.3	42.2	0.75	0.86	0.34–2.17			
	Colon	44	49.1	49.5						
Primary tumor nodal status	Positive	44	54.5	73.7	0.13	0.51	0.22–1.20	Eliminated§		
	Negative	15	NA	39.1						
Extrahepatic disease	Present	12	41.7	35.1	0.30	1.59	0.66-3.81			
	Absent	47	51.8	73.7						
DFI, year	< 1	37	51.0	73.7	0.58	0.80	0.35–1.81			
	≥ 1	22	48.6	49.5						
No. of CLMs	≥ 5	29	27.7	28.9	0.002	3.84	1.63–9.01	0.0003	5.77	2.22–14.99
	< 5	30	69.6	NA						
Largest tumor size before surgery, cm	≥ 5	13	36.4	12.8	0.02	2.79	1.16–6.72	Eliminated§		
	< 5	46	52.1	73.7						
Bevacizumab	Yes	32	57.9	73.7	0.60	0.81	0.37–1.78			
	No	27	37.8	44.4						
Cetuximab or panitumumab	Yes	27	NA	NA	0.10	1.99	0.88–4.50	Eliminated§		
	No	32	58.3	73.7						
No. of chemotherapy cycles	≥ 5	48	49.7	49.5	0.32	0.63	0.25–1.57			
	< 5	11	46.0	39.1						

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Factor		No. of Patients	5-Year OS (%)	Median OS (months)	Univariate Analysis P	HR	95% CI	Multivariate Analysis P	HR	95% CI
Presurgical serum CEA level, ng/mL	> 30	17	42.9	35.6	0.19	1.72	0.76–3.91			
	≤ 30	42	51.4	73.7						
RECIST 1.1 response*	PD or SD	22	37.6	42.2	0.12	1.92	0.85–4.38	0.049	2.41	1.00–5.80
	PR	32	59.3	NA						
Morphological response†	Group 3	32	36.0	39.1	0.13	1.89	0.83–4.29	Eliminated§		
	Group 1 or 2	26	63.4	73.7						
Magnetic field strength, tesla	3.0	21	NA	39.1	0.62	1.26	0.51–3.10			
	1.5	38	51.5	73.7						
Intratumoral fat in CLM (qualitative)‡	Present	32	42.5	42.2	0.35	1.47	0.66–3.26	Eliminated§		
	Absent	27	54.8	73.7						
Fat signal fraction of CLM, %‡	≥ 12	13	NA	38.4	0.03	2.77	1.13–6.80	0.01	3.70	1.34–10.20
	< 12	46	55.1	73.7						
Pattern of fat deposition in CLM‡	Focal	9	15.6	38.4	0.06	2.48	0.98–6.26	Eliminated§		
	Diffuse or no fat	50	55.1	73.7						

Note—CEA = carcinoembryonic antigen; CI = confidence interval; CLMs = colorectal liver metastases; DFI = disease-free interval from diagnosis of primary tumor to diagnosis of liver metastasis; HR = hazard ratio; NA = not available; OS = overall survival; PD = progressive disease; PR = partial response; RECIST = response evaluation criteria in solid tumors; SD = stable disease.
*Response was not assessable in 5 patients because of lack of pre-chemotherapeutic computed tomography data.
†Group 3, heterogeneous attenuation and a thick, poorly defined tumor–liver interface; group 1, homogeneous hypoattenuation, with a thin, sharply defined tumor–liver interface; group 2, morphological response that could not be classified as either group 3 or 1.
‡Intratumoral fat (qualitative), fat signal fraction, and pattern of fat deposition in CLM were separately evaluated by multivariate analysis.
§These items were eliminated upon multivariate analysis using a Cox proportional hazards model with stepwise backward selection.

Independent Predictors of Poor Overall Survival
by Cox Proportional Hazard Model

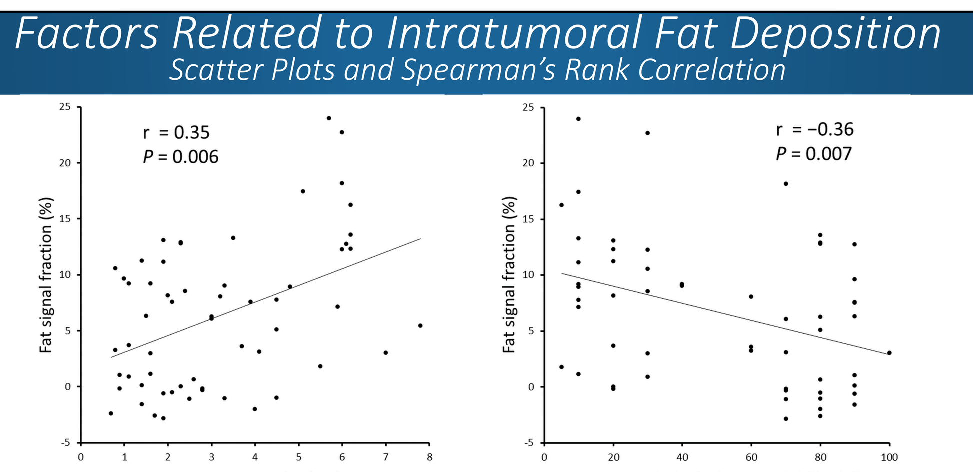
- Metastases ≥ 5 (HR, 5.77; 95% CI, 2.22–14.99; p = .0003)
- FSF ≥ 12% (HR, 3.70; 95% CI, 1.34–10.20; p = .001)
- Age ≥ 65 years (HR, 2.81; 95% CI, 1.18–6.71; p = .02)
- PD or SD by RECIST ver. 1.1 (HR, 2.41; 95% CI, 1.00–5.80; p = .049)

Independent Predictors of Poor Recurrence-Free Survival
by Cox Proportional Hazard Model

- Metastases ≥ 5 (HR, 5.25; 95% CI, 2.52–10.93; p < .0001)
- Age ≥ 65 years (HR, 3.194; 95% CI, 1.57–6.49; p = .001)
- PD or SD by RECIST ver. 1.1 (HR, 2.07; 95% CI, 1.04–4.12; p = .04)
- Morphologic response group 3 (HR, 1.97; 95% CI, 1.01–3.86; p = .04)
- FSF ≥ 12% was not significant predictors of poor RFS

Note—CI = confidence interval; HR = hazard ratio; PD = progressive disease; SD = stable disease

Factors Related to Intratumoral Fat Deposition
Scatter Plots and Spearman's Rank Correlation



- Intratumoral fat deposition tended to be observed in larger and less viable CLMs but their correlations were weak.

Independent Predictors of Fat Signal Fraction ≥ 12%
by Multivariate Logistic Regression Analysis

- Tumor calcification (odds ratio [OR], 17.40; 95% CI, 2.13–143.00; p = .008)
- Tumor size ≥ 5 cm (OR, 17.00; 95% CI, 2.38–121.00; p = .005)
- Cetuximab or panitumumab usage (OR, 8.87; 95% CI, 1.10–71.20; p = .04)

Discussion
Where Do Lipid Signals Come From?

- In MRI, lipid resonance arises from relatively non-restricted molecules, the so-called mobile lipids.

Trends Biochem Sci 25: 357-362, 2000.

X Cell membrane bilayers
△ Membrane microdomains
○ Intracellular lipid body

- The speculated mechanisms by which lipid signals appear in the tumor on MR spectroscopy (MRS) include chemotherapeutic effect, tumor necrosis, apoptosis, hypoxia, mitochondrial damage in tumor cells, macrophage-mediated phagocytosis, and/or exposure of fibroblasts to environmental stress based.

NMR Biomed 24: 592-611, 2011.
Cancer Res 62: 1394-1400, 2002.
Cell Death Differ 8: 219-224, 2001.
Magn Reson Imaging 30: 848-853, 2012.
Exp Gerontol 31: 669-686, 1996.
J Cell Sci 125: 3485-3493, 2012.

Why Intratumoral Fat Deposition Is a Poor Prognostic Factor?

- Several studies based on MRS reported intratumoral lipid in various tumors as an early indicator of chemotherapy response.

NMR Biomed 24: 592-611, 2011.

- However, in the present study, intratumoral lipid was a possible poor long-term prognostic factor.

Our Hypothesis:

1. Total tumor volume might affect prognosis, as suggested by our findings of strong correlation between higher degree of intratumoral fat deposition and larger tumor size.
2. Presence of hypoxic cancer cells might affect prognosis, because hypoxia is thought to be a major cause of failure in cancer treatment; it is also speculated that hypoxia causes lipid accumulation in tumor cells.

J Cell Sci 125: 3485-3493, 2012.
Anticancer Res 10: 613-622, 1990.
Cancer Manag Res 7: 253-264, 2015.

Limitations

- A retrospective study including a limited number of patients and relatively large number of parameters were evaluated.
- The chemotherapy regimens were not uniform.
- Patients who did not undergo CLM resection were not included.
- Special fat staining was not performed during histological analysis.
- Fat signal fraction may be biased because of many confounding factors including magnetic field strength, T1 bias, T2 relaxation, T2* decay, spectral complexity of the fat spectrum, J-coupling, noise bias, and eddy currents, which Dual-echo gradient-recalled MRI cannot correct.

➢ To increase generalizability, further studies using a less biased technique such as chemical shift-encoded MRI or MR spectroscopy are needed.

Conclusions

- Intratumoral fat deposition was frequently identified in CLMs on MR images acquired after preoperative chemotherapy.
- The present findings demonstrated the possibility of a correlation between MRI detection of intratumoral fat in CLMs after preoperative chemotherapy and poor long-term prognosis.
- However, since the true clinical significance of this relationship was not clarified in this study, further studies are required.