Practical Evaluation of Tumor Number-Volume Distribution Predicts Liver-specific Progression-free Survival after Surgery for Neuroendocrine Tumor Liver Metastases

Yosuke Kasai[1, 2], Kenzo Hirose[1, 2], Carlos U. Corvera[1, 2], Grace E. Kim[2, 3], Brandon E. Shih[2], Robert S. Warren[1, 2], Emily K. Bergsland[2, 4], Eric K. Nakakura[1, 2]
Department of [1]Surgery, [3]Pathology, and [4]Medicine, University of California, San Francisco, [2]UCSF Helen Diller Family Comprehensive Cancer Center

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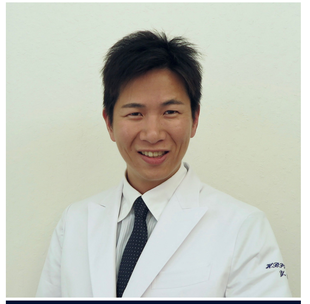
Abstract

Background. Previous reports have ascribed improved outcomes to tumor debulking for patients with neuroendocrine tumor liver metastases (NELM), but the methods used to assess the extent of tumor debulking are ill-defined. We propose a simple and practical method to evaluate the tumor volume that reliably predicts liver-specific progression-free survival (LSPFS).

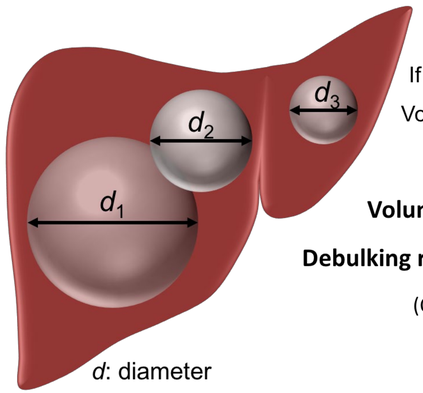
Methods. Seventy patients who underwent surgery for NELM were analyzed. Individual liver tumor diameter ≥ 1 cm was measured on preoperative imaging, and the index of the total liver tumor volume was calculated by the sum of the cube of the individual tumor diameter. Debulking extent was assessed by comparing preoperative and postoperative imaging for the individual tumor.

Results. A median of 2 tumors (range 1-28) were removed, mainly using a parenchyma-sparing technique (69%). Forty-five patients (64%) underwent 100% debulking. The median overall survival was not reached with a median follow-up of 23.1 months. The median LSPFS was 10.5 months. In multivariate analysis, tumor number ≥ 4 (HR: 6.79, 95% CI: 2.15-22.7) and tumor volume index ≥ 40 cm^3 (HR: 2.52, 95% CI: 1.08-6.25) were independent prognostic factors for LSPFS. When tumor number-volume distribution was categorized into low-distribution (tumor number ≤ 3 and tumor volume index < 40 cm^3), high-distribution (tumor number ≥ 4 and tumor volume index ≥ 40 cm^3), and intermediate-distribution (the others), LSPFS significantly differed based on the tumor number-volume distribution (median 33.8, 4.2, and 16.0 months, respectively).

Conclusion. Tumor number-volume distribution calculated by our simple and practical method predicts LSPFS after debulking surgery for NELM.



Yosuke Kasai, MD, PhD



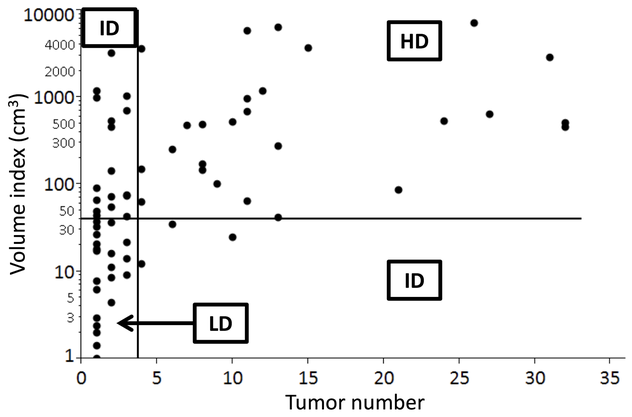
If tumors were complete spheres,

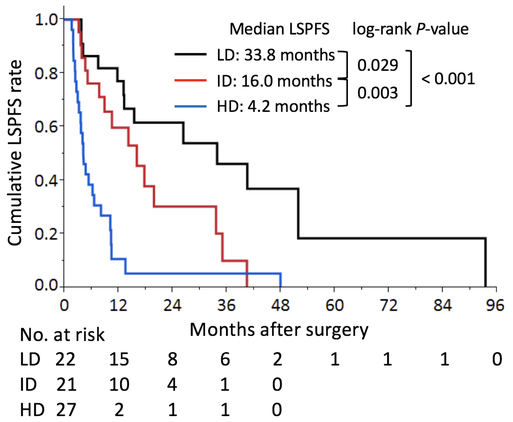
Volume = π/6 ($d_1^3 + d_2^3 + \ldots + d_n^3$)

Volume index (VI) = $d_1^3 + d_2^3 + \ldots + d_n^3$

Debulking rate (%) = 100 – 100 x (Post VI)/(Pre VI)

(Only tumors ≥ 1 cm were counted)





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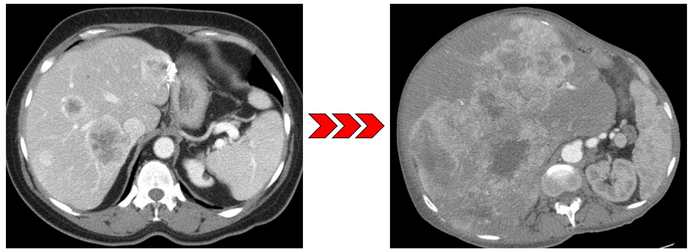
Introduction

40% of NET patients develop liver metastasis (**NELM**).
Modlin, et al. Cancer 2003



NELM is the **strongest prognosticator** of NET (5-y survival 13-54%)
Frilling, et al. Lancet Oncol 2014

"**Debulking**" or "**Cytoreduction**" **Surgery** of NELM has been associated with **survival and symptomatic benefits**.

- 1990 McEntee, et al. Surgery
  - Curative resection prolonged survival and **cytoreductive surgery** relieve symptoms of NELM.
- 2003 Sarmiento, et al. J Am Coll Surg
  - **≥ 90% debulking** prolonged survival and achieved symptom control of NELM.
- 2014 Graff-Baker, Pommier, et al. Surgery
  - Debulking threshold of **≥ 70%** maintained favorable prognoses of NELM with intestinal origin.
- 2016 Maxwell, Howe, et al. Surgery
  - **≥ 70% debulking** with parenchyma-sparing technique resulted in favorable prognoses.
- 2018 Morgan, Pommier, et al. Surgery
  - Debulking threshold of **≥ 70%** maintained favorable prognoses of NELM with pancreatic origin.

How to Assess
Tumor Volume or
Debulking Rate

Not specified or based on surgeon's judgement
Reproducible?
Objective?

Objective

To develop a **simple** and **practical** preoperative assessment of tumor burden that predicts outcome after debulking surgery for NELM

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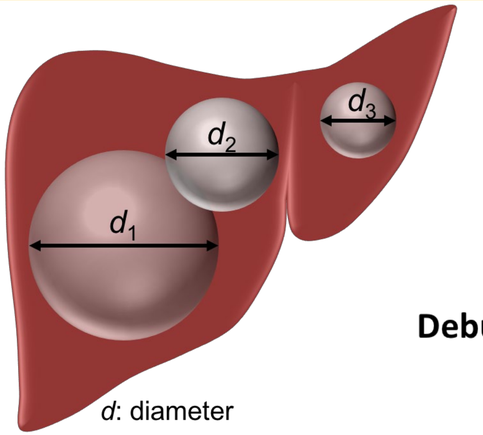
Methods

70 patients

Surgical cases for NELM between 2007 and 2017

Excluding:

- ✓Intended for only tissue sampling
- ✓No LM ≥ 1 cm detectable on baseline imaging
- ✓Baseline or postoperative imaging unavailable
- ✓Mixed neuroendocrine-non-endocrine neoplasm (MiNEN)



d: diameter

If tumors were complete spheres,

Volume = π/6 ($d_1^3 + d_2^3 + \ldots + d_n^3$)

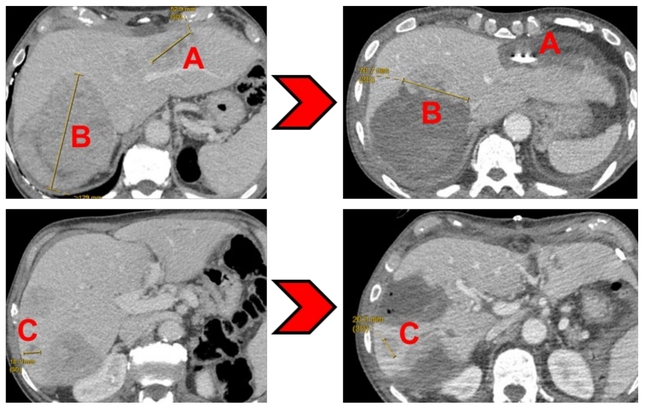
Volume index (VI) = $d_1^3 + d_2^3 + \ldots + d_n^3$

Debulking rate (%) = 100 – 100 x (Post VI)/(Pre VI)

(Only tumors ≥ 1 cm were counted)

Example case

Baseline Post-ope



Tumor A was completely resected/ablated:
5.3 cm → 0 cm

Tumor B was partially resected/ablated:
12.9 cm → 7.1 cm (postoperative diameter)

Tumor C was untreated with/without tumor growth:
1.8 cm → **1.8** cm (**BASELINE diameter**)

VI: $5.3^3 + 12.9^3 + 1.8^3 \rightarrow 0^3 + 7.1^3 + 1.8^3$
Debulking rate = 84.4%

Outcome

Liver-specific Progression-free Survival (LSPFS)

Progression was defined as partly modified RECIST1.1:

- ✓Sum of intrahepatic tumor diameters increases ≥ 20% and 5 mm from the minimum value (just postoperative status).
- ✓New intrahepatic lesion (≥ 1 cm) emerges.

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Result 1

Table 1. Patients demographics (*Grade was unknown in 12 patients)

Variables	70 patients
Age	56.5 (49-65.3)
Gender Male/Female	36 (51%)/34 (49%)
Primary origin Small intestine/Pancreas/Other	37 (53%)/23 (33%)/10 (14%)
Carcinoid syndrome/Gastrinoma/Insulinoma/VIPoma /Glucagonoma/Non-functional	19 (27%)/5 (7%)/2 (3%)/2 (3%) /1 (1%)/41 (59%)
*WHO2017 Grade 1/2/3	18 (31%)/36 (62%)/4 (7%)
Previous history of liver resection	9 (13%)
Tumor number	3 (1-10)
Maximum tumor diameter (cm)	3.8 (2.5-7.0)
Volume index (cm^3)	72.5 (20.0-520.4)
Lymph node metastasis	52 (74%)
Extrahepatic distant metastasis	15 (21%)
Concurrent resection of the primary tumor	26 (37%)
Hemihepatectomy/monosectionectomy/ parenchyma-sparing resection	12 (17%)/10 (14%)/48 (69%)
Addition of ablation	34 (49%)

Fig. 1. A scatter plot of preoperative and postoperative volume index sorted by the extent of tumor debulking. Note that the horizontal axis and the upper part of the vertical axis is converted to logarithm.

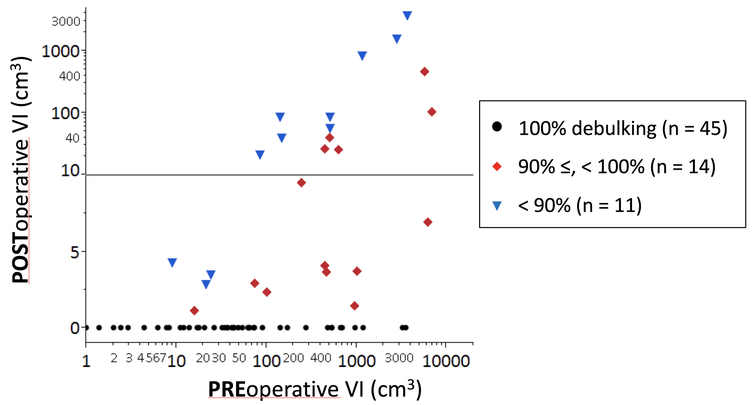


Fig. 2. Long-term outcomes. **(A)** The median OS time was not reached with a median follow-up of 23.1 months. **(B)** The median LSPFS time was 10.5 months (95% confidence interval: 6.5-16.9).

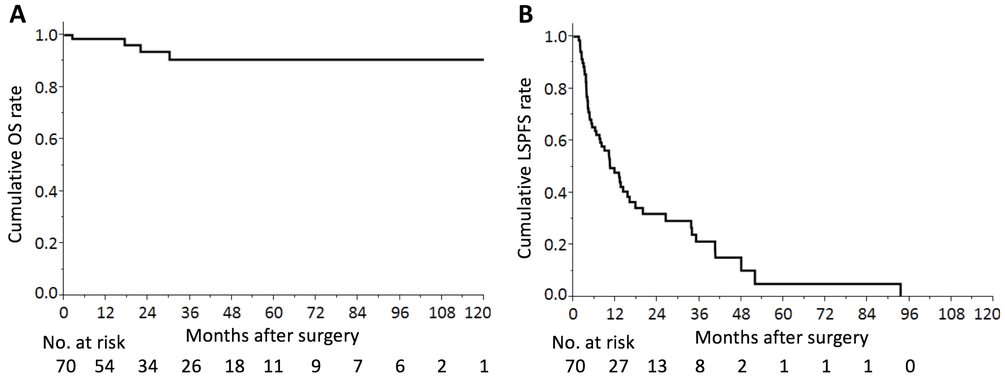
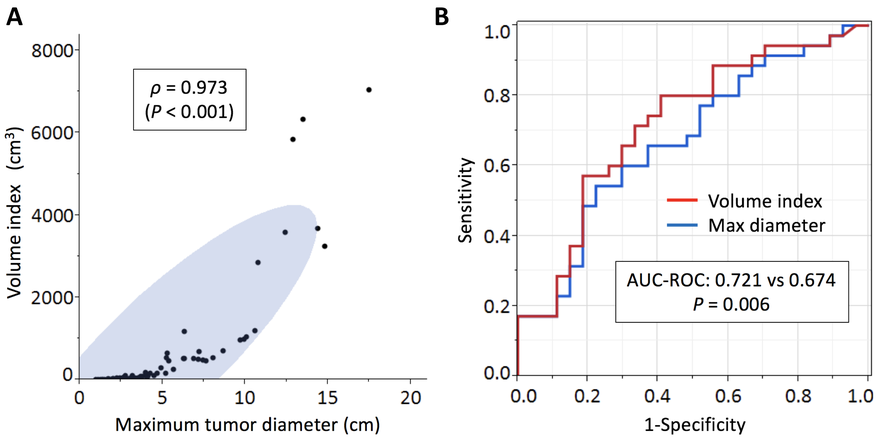


Fig. 3. (A) Correlation between the maximum tumor diameter and the volume index. **(B)** Prediction capability for early progression within 12 months of the volume index was superior to that of the maximum tumor.



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Result 2

Table 2. Cox-proportional hazard model for LSPFS

		Univariate analysis			Multivariate analysis		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Primary origin	SI vs Panc	0.63	0.33-1.19	0.148			
	SI vs Other	0.63	0.28-1.59	0.302			
	Panc vs Other	1.00	0.43-2.58	0.999			
Functional	Yes vs No	1.64	0.93-2.88	0.087			
WHO2017-Grade	G2 vs G1	**2.44**	**1.16-5.79**	**0.018**	2.13	0.96-5.28	0.063
	G3 vs G1	**41.1**	**7.38-203**	**< 0.001**	**16.6**	**2.85-86.5**	**0.003**
	G3 vs G2	**16.9**	**3.34-71.7**	**0.002**	**7.76**	**1.51-34.0**	**0.017**
Tumor number	≥ 4 vs ≤ 3	**3.82**	**2.14-6.89**	**< 0.001**	**6.79**	**2.15-22.7**	**0.001**
Maximum tumor diameter (cm)	> 4.5 vs ≤ 4.5	**1.94**	**1.10-3.40**	**0.023**			
Volume index (cm^3)	≥ 40 vs < 40	**3.01**	**1.63-5.87**	**< 0.001**	**2.52**	**1.08-6.25**	**0.032**
Lymph node metastasis	Present vs Absent	0.67	0.37-1.28	0.214			
Extrahepatic distant metastasis	Present vs Absent	1.27	0.62-2.41	0.492			
Debulking rate	100% vs < 100%	**0.29**	**0.16-0.53**	**< 0.001**	1.02	0.42-2.41	0.962

Fig. 5. LSPFS stratified by tumor number-volume distribution. The median LSPFS times (95% confidence intervals) were 33.8 (13.1-93.4) months, 16.0 (7.7-33.6) months, and 4.2 (2.9-6.5) months for LD, ID, and HD groups, respectively.

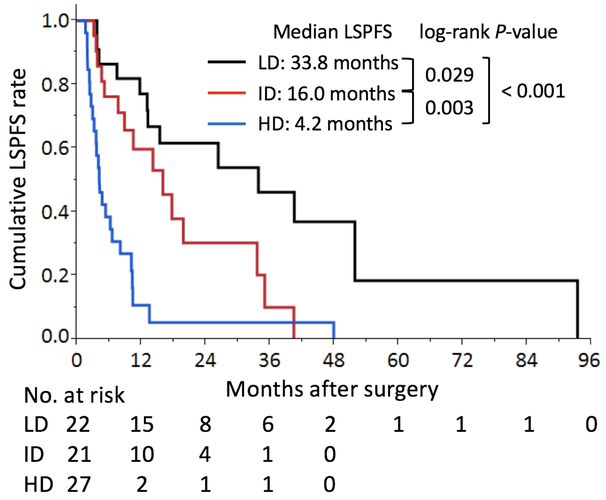
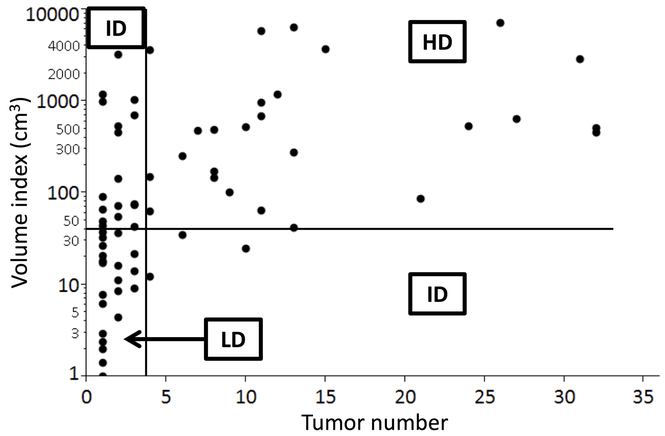
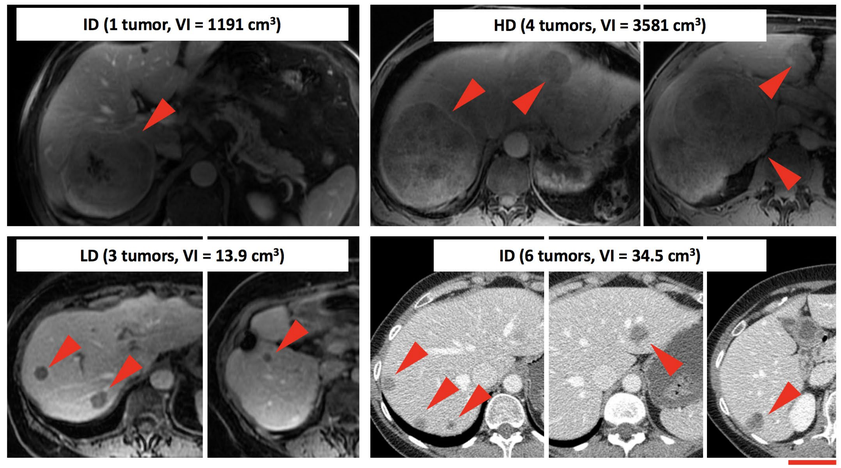


Fig. 4. (A) A scatter plot of tumor number-volume distribution. LD: low-distribution (tumor number ≤ 3, VI < 40 cm^3, 22 patients), ID: intermediate-distribution (other than LD and HD, 21 patients), HD: high-distribution (tumor number ≥ 4, VI ≥ 40 cm^3, 27 patients). **(B)** The representative preoperative image of each distribution.

A



B



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Conclusion

Tumor number-volume distribution calculated by our simple and practical method predicts LSPFS after debulking surgery for NELM.

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