

New Preoperative CT Staging of Intrahepatic Cholangiocarcinoma: Impact of Up-staging of Tumor Multiplicity on Survival Outcomes

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Background

- **Tumor multiplicity** has been emphasized as an indicator of **advanced-stage** cancer rather than early-stage (i.e., T2, as defined by the eighth edition AJCC) cancer.
- There has been considerable debate as to whether multiple tumors should be considered as **metastatic or locally advanced** disease.
 - One of the reasons for this controversy is that the 2 categories of multiple tumors, that is, **satellitosis or multifocal tumors**, have been both defined as intrahepatic metastasis in the previous study.
 - **Identification of suitable candidates for surgery** remains crucial in patients with multiple intrahepatic tumors, and **subdividing the multiple tumors category** in cancer staging may have prognostic significance when planning curative surgical treatment.

Background / Aim

- The current eighth edition AJCC staging system is based on postoperative pathology and may be suboptimal in the **preoperative setting**.
 - CT is the primary imaging modality for preoperative staging of intrahepatic and extrahepatic diseases.
- We aimed to develop and validate a **preoperative CT staging system** for iCCA adapted from the eighth edition AJCC staging system in a multi-institutional cohort from South Korea, focusing on **tumor multiplicity**.

Patients

Partial hepatectomy for mass-forming iCCA
at six participating institutions
from Jan 2009 through Dec 2015 (n = 418)

Partial hepatectomy for mass-forming iCCA
at one institution
from Jan 2016 through May 2020 (n = 83)

- Exclusion (n = 99)
- Radiologically invisible tumor (n = 1)
 - No preoperative CT (n = 23)
 - Suboptimal quality of CT (n = 22)
 - Previous surgery for iCCA (n = 2)
 - Perioperative mortality (n = 4)
 - Palliative surgery (n = 36)
 - R2 resection (n = 11)

- Exclusion (n = 23)
- Radiologically invisible tumor (n = 2)
 - No preoperative CT (n = 4)
 - Unenhanced CT only (n = 1)
 - Preoperative treatment for iCCA (n = 8)
 - Preoperative portal vein embolization (n = 4)
 - Palliative surgery (n = 3)
 - Follow-up loss (n = 1)

Development cohort (n = 319)
Adequate preoperative CT and
R0 or R1 resection for mass-forming iCCA

Temporal validation cohort (n = 60)
Adequate preoperative CT and
R0 or R1 resection for mass-forming iCCA

Cox regression analysis of preoperative CT parameters for OS

Cox proportional hazards regression was performed to identify independent staging predictors of OS, and the staging system was modified accordingly.

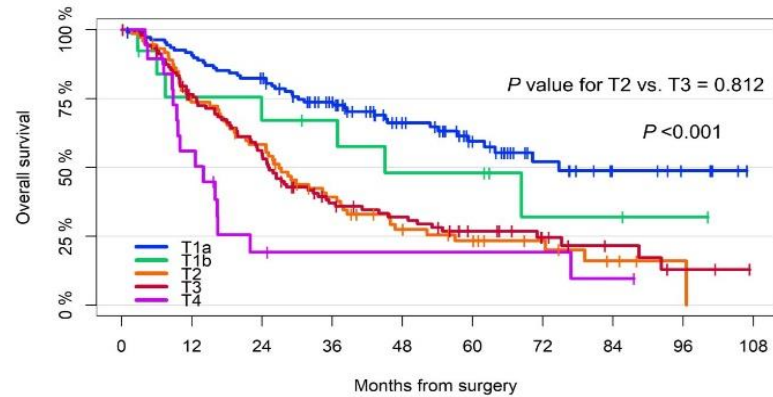
Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
AJCC staging parameters				
Solitary tumor ≤5 cm without vascular invasion (T1a)	1 (Reference)		1 (Reference)	
Solitary tumor >5 cm (T1b)	1.66 (0.75–3.71)	0.213	1.49 (0.67–3.35)	0.331
Intrahepatic vascular invasion or multiple tumors (T2)	2.90 (1.93–4.35)	<0.001	2.55 (1.68–3.89)	<0.001
Visceral peritoneal perforation (T3)	2.74 (1.87–4.02)	<0.001	2.40 (1.61–3.59)	<0.001
Local extrahepatic structure invasion (T4)	5.23 (2.87–9.53)	<0.001	4.40 (2.37–8.16)	<0.001
Lymph node metastasis (N1)	2.08 (1.55–2.80)	<0.001	1.46 (1.07–2.00)	0.017
Modified staging parameters				
Solitary tumor	1 (Reference)		1 (Reference)	
Intrahepatic vascular invasion	2.16 (1.40–3.34)	0.001	1.98 (1.27–3.09)	0.003
Visceral peritoneal perforation	2.16 (1.44–3.22)	<0.001	2.00 (1.32–3.01)	0.001
Satellitosis	3.55 (2.21–5.70)	<0.001	3.03 (1.84–5.00)	<0.001
Multifocal tumors	4.55 (2.69–7.68)	<0.001	3.92 (2.27–6.77)	<0.001
Local extrahepatic structure invasion	4.88 (2.71–8.77)	<0.001	4.24 (2.32–7.77)	<0.001
Lymph node metastasis	2.08 (1.55–2.80)	<0.001	1.39 (1.01–1.91)	0.045

Definition of the staging systems

AJCC 8th staging				Modified staging			
<i>T staging</i>							
T1a: solitary tumor ≤5 cm without vascular invasion				T1: solitary tumor without vascular invasion			
T1b: solitary tumor >5 cm without vascular invasion							
T2: solitary tumor with intrahepatic vascular invasion or multiple tumors with or without vascular invasion				T2: solitary tumor with intrahepatic vascular invasion or visceral peritoneal perforation			
T3: tumor perforating the visceral peritoneum				T3a: the presence of satellitosis			
				T3b: the presence of multifocal tumors			
T4: tumor involving local extrahepatic structures by direct invasion				T4: tumor involving local extrahepatic structures by direct invasion			
<i>TNM staging</i>							
T	N	M	Stage	T	N	M	Stage
T1a	N0	M0	IA	T1	N0	M0	I
T1b	N0	M0	IB	T2	N0	M0	II
T2	N0	M0	II	T3a	N0	M0	IIIA
T3	N0	M0	IIIA	T3b	N0	M0	IIIB
T4	N0	M0	IIIB	T4	N0	M0	IIIC
Any T	N1	M0	IIIB	Any T	N1	M0	IIIC

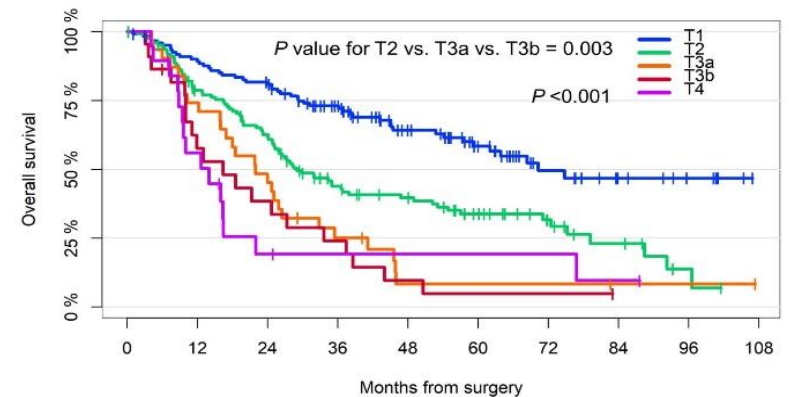
Overall Survival – development cohort

- Our modified system provided better stratification of OS probabilities than the current system using preoperative CT staging.
 - AJCC T2 and T3 did not discriminate the survival curves on preoperative CT (log-rank P for T2 vs. T3 = .81; 5-year OS, 23.4% vs. 26.8%), but modified T2 gave better OS outcomes than modified T3a or T3b (log-rank P for T2 vs. T3a vs. T3b = .003; 5-year OS, 33.8% vs. 8.4% vs. 4.8%).
 - The Kaplan-Meier curves using TNM staging showed better stratification of stages II and III using the modified system (log-rank P for II vs. III; AJCC, P = .74; modified system, P = .003).



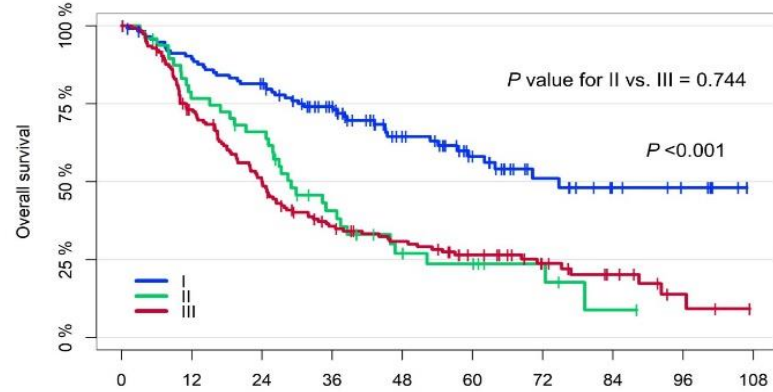
	0	12	24	36	48	60	72	84	96	108
T1a:	109	99	88	68	45	30	16	9	6	0
T1b:	14	9	8	7	5	5	2	2	1	0
T2:	73	53	41	25	15	11	7	3	1	0
T3:	104	75	55	31	25	15	9	5	2	0
T4:	19	10	3	2	2	2	2	1	0	0

(a)



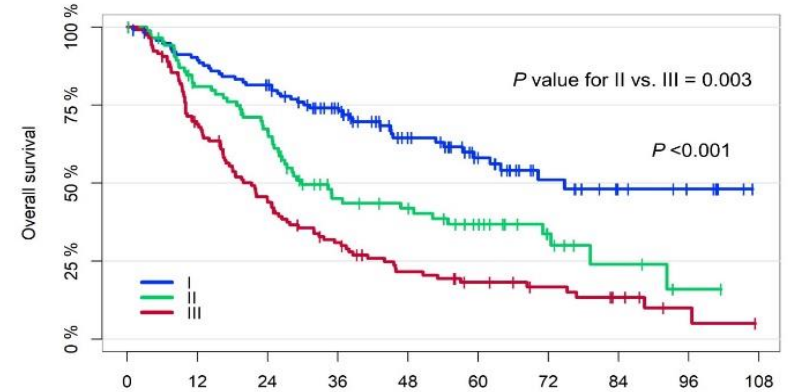
	0	12	24	36	48	60	72	84	96	108
T1:	123	108	96	75	50	35	18	11	7	0
T2:	124	93	73	44	36	23	13	7	2	0
T3a:	31	23	15	7	2	2	2	1	1	0
T3b:	22	12	8	5	2	1	1	0	0	0
T4:	19	10	3	2	2	2	2	1	0	0

(b)



	0	12	24	36	48	60	72	84	96	108
I:	116	102	91	71	46	31	17	10	7	0
II:	48	36	30	16	9	7	4	1	0	0
III:	155	108	74	46	37	25	15	9	3	0

(c)



	0	12	24	36	48	60	72	84	96	108
I:	116	102	91	71	46	31	17	10	7	0
II:	86	66	54	30	26	18	9	4	1	0
III:	117	78	50	32	20	14	10	6	2	0

(d)

Kaplan-Meier curves for predicting OS in the development cohort with preoperative CT staging

using (A) AJCC T staging, (B) modified T staging, (C) AJCC TNM staging, and (D) modified TNM staging.

Overall Survival – validation cohort

- Our modified system, but not the current system, showed statistically significant differences in the survival probability on preoperative CT in the validation cohort (log-rank $P = .03$; log-rank P for T2 vs. T3a vs. T3b = .04).
- The **Harrell C-indexes** of the modified system were comparable to those of the current system for predicting OS preoperatively in the development cohort and in the validation cohort.

	AJCC 8th staging	Modified staging	P value
Development cohort			
T	0.626 (0.585, 0.666)	0.647 (0.608, 0.686)	0.061
TNM (3-tier)	0.614 (0.575, 0.654)	0.636 (0.596, 0.675)	0.069
Validation cohort			
T	0.662 (0.482, 0.842)	0.745 (0.590, 0.899)	0.248
TNM (3-tier)	0.719 (0.610, 0.829)	0.739 (0.592, 0.886)	0.737

Conclusion

- Our new, modified preoperative CT staging system, which **upstages and subdivides tumor multiplicity**, can improve prognostic discrimination in patients with iCCA.
- This new staging system may be more useful than the current eighth edition AJCC staging system to guide management and prediction of prognosis **in the preoperative setting**.