

Supplementary material 1: Univariate survival analysis (A: Training cohort; B: Internal validation; C: Whole ENS-CCA series; D: External Validation cohort (SEER)), exploring impact of staging systems on OS

AJCC: American Joint Committee on Cancer (AJCC); mAJCC: modified staging system; HR: Hazard Ratio; CI: confidence interval; ENS-CCA: European Network for the Study of Cholangiocarcinoma; SEER: Surveillance, Epidemiology, and End Results; OS: overall survival; %: percentage; N: number; mts: metastases; Ref: reference; n/a: not applicable

A: Training cohort (ENS-CCA) (N=141)		N	%	Median OS (95% CI)		Log-Rank p-value	Univariate Cox Regression HR (95% CI)	P-value
AJCC v.7	Stage I-III (including T2bN0M0; liver satellite lesions)	43	30.50	10.97	(6.96-16.95)	0.0125	1 (Ref)	n/a
	Stage IVa (including T2bN1M0)	28	19.86	15.01	(6.04-19.05)		1.04 (0.64-1.71)	0.867
	Stage IVb (distant mts)	70	49.65	7.03	(4.01-10.97)		1.69 (1.13-2.53)	0.011
mAJCC v.7	Group A: Stage I-III (excluding T2bN0M0)	13	9.22	15.01	(5.94-26.04)	0.0269	1 (Ref)	n/a
	Group B: Stage IVa (excluding T2bN1M0)	20	14.18	14.97	(4.01-22.99)		1.23 (0.57-2.63)	0.592

	Group C: Stage T2bN0/1M0: liver mts	38	26.95	9.98 (5.94-16.06)		1.30 (0.65-2.64)	0.460
	Group D: Stage IVb	70	49.65	7.03 (4.01-10.97)		2.03 (1.04-3.96)	0.037
mAJCC v.7	Group A: Stage I-III (<u>excluding</u> T2bN0M0)	13	9.22	15.01 (5.94-26.04)	0.0269	0.77 (0.38-1.55)	0.460
	Group B: Stage IVa (<u>excluding</u> T2bN1M0)	20	14.18	14.97 (4.01-22.99)		0.94 (0.54-1.64)	0.838
	Group C: Stage T2bN0/1M0: liver mts	38	26.95	9.98 (5.94-16.06)		1 (Ref)	n/a
	Group D: Stage IVb	70	49.65	7.03 (4.01-10.97)		1.56 (1.03-2.35)	0.034

B: Internal validation cohort (ENSCCA) (N=433)		N	%	Median OS (95% CI)	Log-Rank p-value	Univariate Cox Regression HR (95% CI)	P-value
AJCC v.7	Stage I-III (including T2bN0M0; liver satellite lesions)	224	51.73	32.51 (26.73-38.95)	<0.001	1 (Ref)	n/a
	Stage IVa (including T2bN1M0)	100	23.09	11.92 (9.26-16.68)		2.49 (1.85-3.36)	<0.001
	Stage IVb (distant mts)	109	25.17	9.26 (5.94-11.36)		3.23 (2.42-4.29)	<0.001
mAJCC v.7	Group A: Stage I-III (excluding T2bN0M0)	179	41.34	36.95 (28.24-47.06)	<0.001	1 (Ref)	n/a
	Group B: Stage IVa (excluding T2bN1M0)	69	15.94	14.22 (10.34-26.69)		2.38 (1.65-3.43)	<0.001
	Group C: Stage T2bN0/1M0: liver mts	76	17.55	11.82 (7.16-16.72)		3.25 (2.29-4.59)	<0.001
	Group D: Stage IVb	109	25.17	9.26 (5.94-11.36)		3.89 (2.85-5.30)	<0.001
mAJ	Group A: Stage I-III (excluding T2bN0M0)	179	41.34	36.95 (28.24-47.06)	<0.001	0.31 (0.22-0.44)	<0.001

	Group B: Stage IVa (excluding T2bN1M0)	69	15.94	14.22 (10.34- 26.69)		0.73 (0.49-1.08)	0.114
	Group C: Stage T2bN0/1M0: liver mts	76	17.55	11.82 (7.16- 16.72)		1 (Ref)	n/a
	Group D: Stage IVb	109	25.17	9.26 (5.94- 11.36)		1.19 (0.86-1.67)	0.290

C: Whole ENS-CCA series (N=574)		N	%	Median OS (95% CI)		Log-Rank p-value	Univariate Cox Regression HR (95% CI)	P-value
AJCC v.7	Stage I-III (<u>including</u> T2bN0M0; liver satellite lesions)	267	46.52	26.96	(22.89-32.51)	<0.001	1 (Ref)	n/a
	Stage IVa (<u>including</u> T2bN1M0)	128	22.30	13.01	(9.79-16.06)		2.16 (1.67-2.78)	<0.001
	Stage IVb (distant mts)	179	31.18	8.44	(5.94-10.25)		3.06 (2.43-3.86)	<0.001
mAJCC v.7	Group A: Stage I-III (<u>excluding</u> T2bN0M0)	192	33.45	34.09	(27.32-41.84)	<0.001	1 (Ref)	n/a
	Group B: Stage IVa (<u>excluding</u> T2bN1M0)	89	15.51	14.98	(11.63-21.74)		2.42 (1.76-3.33)	<0.001
	Group C: Stage T2bN0/1M0: liver mts	114	19.86	10.97	(7.45-15.99)		3.10 (2.30-4.18)	<0.001
	Group D: Stage IVb	179	31.18	8.44	(5.94-10.25)		4.11 (3.14-5.37)	<0.001

mAJCC v.7	Group A: Stage I-III (excluding T2bN0M0)	192	33.45	34.09 (27.32-41.84)	<0.001	0.32 (0.24-0.43)	<0.001
	Group B: Stage IVa (excluding T2bN1M0)	89	15.51	14.98 (11.63-21.74)		0.78 (0.57-1.07)	0.122
	Group C: Stage T2bN0/1M0: liver mts	114	19.86	10.97 (7.45-15.99)		1 (Ref)	n/a
	Group D: Stage IVb	179	31.18	8.44 (5.94-10.25)		1.32 (1.02-1.71)	0.032

D : External validation cohort (SEER) (N=4,171)		N	%	Median OS (95% CI)	Log-Rank p-value	Univariate Cox Regression HR (95% CI)	P-value
AJCC v.7	Stage I-III (including T2bN0M0; liver satellite lesions)	1,813	43.47	16 (14-17)	<0.001	1 (Ref)	n/a
	Stage IVa (including T2bN1M0)	676	16.21	12 (11-14)		1.39 (1.26-1.55)	<0.001
	Stage IVb (distant mts)	1,682	40.33	6 (6-7)		2.21 (2.04-2.39)	<0.001
mAJCC v.7	Group A: Stage I-III (excluding T2bN0M0)	1,255	30.09	19 (17-21)	<0.001	1 (Ref)	n/a
	Group B: Stage IVa (excluding T2bN1M0)	512	12.28	13 (11-14)		1.60 (1.42-1.81)	<0.001
	Group C: Stage T2bN0/1M0: liver mts	722	17.31	10 (9-11)		1.88 (1.68-2.09)	<0.001
	Group D: Stage IVb	1,682	40.33	6 (6-7)		2.66 (2.42-2.92)	<0.001
mAJ	Group A: Stage I-III (excluding T2bN0M0)	1,255	30.09	19 (17-21)	<0.001	0.53 (0.48-0.59)	<0.001

	Group B: Stage IVa (excluding T2bN1M0)	512	12.28	13 (11-14)		0.85 (0.75-0.97)	0.017
	Group C: Stage T2bN0/1M0: liver mts	722	17.31	10 (9-11)		1 (Ref)	n/a
	Group D: Stage IVb	1,682	40.33	6 (6-7)		1.42 (1.28-1.57)	<0.001

Supplementary material 2: Stepwise Cox Regression analysis in the training (overall survival)

AJCC: American Joint Committee on Cancer (AJCC); mAJCC: modified staging system; ECOG-PS: Eastern Cooperative Oncology Group performance status HR: Hazard Ratio; CI: confidence interval.

Stepwise Cox Regression		Training cohort (n=122)	
Overall Survival		HR (95% CI)	P-value
Gender	Male (vs Female)	0.91 (0.61-1.36)	0.650
Age (years)	Continuous variable	1.01 (0.99-1.03)	0.135
Ethnicity	Continuous variable	0.84 (0.59-1.19)	0.338
Obesity	Yes (vs No)	0.56 (0.34-0.91)	0.018
Diabetes	Yes (vs No)	1.59 (0.97-2.62)	0.064
ECOG-PS	Continuous variable	1.89 (1.51-2.39)	<0.001
Surgery	Yes (vs No)	0.53 (1.82-1.55)	0.249
Stage (mAJCC v.7)	Continuous variable	1.37 (1.10-1.69)	0.004

Supplementary material 3: Multivariable Cox Regression analysis in the training and internal validation cohorts (overall survival)

AJCC: American Joint Committee on Cancer (AJCC); mAJCC: modified staging system; ECOG-PS: Eastern Cooperative Oncology Group performance status; HR: Hazard Ratio; CI: confidence interval; OS: overall survival; n/a: not applicable; Ref: reference; vs: versus.

Multivariable Cox Regression		Training cohort (n=122)		Internal validation cohort (n=413)	
		Multivariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Obesity	Yes (vs No)	0.59 (0.37-0.94)	0.026	0.92 (0.67-1.27)	0.614
ECOG-PS	Continuous variable	1.98 (1.57-2.50)	<0.001	1.56 (1.34-1.80)	<0.001
mAJCC v.7	Group A: Stage I-III (excluding T2bN0M0)	1 (Ref)	n/a	1 (Ref)	n/a
	Group B: Stage IVa (excluding T2bN1M0)	2.53 (1.18-5.42)	0.295	2.37 (1.63-3.44)	<0.001
	Group C: Stage T2bN0/1M0: liver metastases	2.53 (1.18-5.42)	0.017	2.93 (2.04-4.19)	<0.001
	Group D: Stage IVb	2.74 (1.37-5.46)	0.004	3.46 (2.49-4.81)	<0.001

Multivariable Cox Regression Overall Survival		Training cohort (n=122)		Internal validation cohort (n=413)	
		Multivariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Obesity	Yes (vs No)	0.59 (0.37-0.94)	0.026	0.92 (0.67-1.27)	0.614
ECOG-PS	Continuous variable	1.98 (1.57-2.50)	<0.001	1.56 (1.34-1.80)	<0.001
mAJCC v.7	Group A: Stage I-III (excluding T2bN0M0)	0.39 (0.18-0.85)	0.017	0.34 (0.24-0.49)	<0.001
	Group B: Stage IVa (excluding T2bN1M0)	0.60 (0.33-1.12)	0.109	0.81 (0.55-1.20)	0.297
	Group C: Stage T2bN0/1M0: liver metastases	1 (Ref)	n/a	1 (Ref)	n/a
	Group D: Stage IVb	1.08 (0.69-1.71)	0.737	1.18 (0.84-1.67)	0.341

Supplementary material 4: Sensitivity analysis: Multivariable Cox Regression analysis whole cohort (overall survival)

AJCC: American Joint Committee on Cancer (AJCC); mAJCC: modified staging system; HR: Hazard Ratio; CI: confidence interval; ; OS: overall survival; n/a: not applicable; Ref: reference; vs: versus.

Multivariable Cox Regression		Whole ENS-CCA cohort (n=535)	
Overall Survival (Sensitivity analysis)		Multivariable HR (95% CI)	P-value
Obesity	Yes (vs No)	0.83 (0.64-1.07)	0.158
ECOG-PS	Continuous variable	1.68 (1.49-1.89)	<0.001
mAJCC v.7	Group A: Stage I-III (excluding T2bN0M0)	1 (Ref)	n/a
	Group B: Stage IVa (including T2bN1M0)	2.57 (1.91-3.46)	<0.001
	Group C: Stage T2bN0M0: liver metastases	2.51 (1.76-3.56)	<0.001
	Group D: Stage IVb	3.38 (2.55-4.47)	<0.001
Multivariable Cox Regression		Whole ENS-CCA cohort (n=535)	

Overall Survival (Sensitivity analysis)		Multivariable HR (95% CI)	P-value
Obesity	Yes (vs No)	0.83 (0.64-1.07)	0.158
ECOG-PS	Continuous variable	1.68 (1.49-1.89)	<0.001
mAJCC v.7	Group A: Stage I-III (excluding T2bN0M0)	0.39 (0.28-0.57)	<0.001
	Group B: Stage IVa (including T2bN1M0)	1.03 (0.73-1.44)	0.880
	Group C: Stage T2bN0M0: liver metastases	1 (Ref)	n/a
	Group D: Stage IVb	1.35 (0.98-1.86)	0.068

Supplementary material 5: Surveillance, Epidemiology, and End Results (SEER) cohort (external validation)

‰: percentage; AJCC: American Joint Committee on Cancer; mAJCC: modified staging system; CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group performance status; N: number; SEER: Surveillance, Epidemiology and End Results

SEER cohort (N=4,171)			
Patient characteristics		N	%
Gender	Female	2055	49.27
	Male	2116	50.73
Age (years)	Median (range)	67 (14-99)	
Ethnicity	Caucasian	3,268	78.35
	Black	337	8.08
	Other	559	13.40
	Not reported	7	0.17
Obesity	Yes	Not reported	
Diabetes mellitus	Yes	Not reported	
ECOG-PS	Not reported	Not reported	
Staging classification		N	%

AJCC v.7	Stage I	783	18.77
	Stage II	804	19.28
	Stage III	226	5.42
	Stage IVa	676	16.21
	Stage IVb	1,682	40.33
mAJCC v.7	Group A (AJCC v.7 stage I)	783	18.77
	Group A (AJCC v.7 stage II; excluding T2bN0)	246	5.90
	Group A (AJCC v.7 stage III)	226	5.42

	Group B (AJCC v.7 stage IVa; excluding T2bN1)	512	12.28
	Group C (Liver metastases; AJCC v.7 T2bN0/N1)	772	17.31
	Group D (AJCC v.7 stage IVb)	1,682	40.33
Outcome		N	%
Status at the end of follow-up	Alive	737	17.67
	Dead	3,434	82.33
Overall survival (months)	Median (95% CI)	10 (9-10)	