

Supplementary material for A New Clinically-Based Staging System for Perihilar Cholangiocarcinoma

Supplementary Table 1. Association between initial treatment type and survival of pCCA patients*

	Unadjusted HR (95% CI)	<i>P</i>	Adjusted HR [†] (95% CI)	<i>P</i>
Best supportive care	9.98 (5.34-18.67)	<0.0001	3.02 (1.25-7.33)	0.0144
Palliative biliary drainage	6.53 (4.58-9.31)	<0.0001	3.23 (1.97-5.29)	<0.0001
Resection	2.13 (1.44-3.16)	0.0002	2.20 (1.35-3.58)	0.0015
Transplantation	1.00 (reference)		1.00 (reference)	

*The models included 342 patients who had complete data on all variables.

†Adjusted for age, gender, ethnicity, cirrhosis, primary sclerosing cholangitis, ECOG performance status, maximum tumor size, tumor number, vascular encasement, lymph node metastasis, peritoneal (or other organ) metastasis, and CA 19-9 >1000 U/mL

HR=Hazard ratio

Supplementary Table 2. Association between variables at the time of pCCA diagnosis and survival of pCCA patients within treatment stratified Cox proportional hazard models*

Variables	Unadjusted HR	95% CI	<i>P</i>	Adjusted HR	95% CI	<i>P</i>
Age per 10 years	1.04	0.95-1.15	0.38	1.22	1.07-1.40	0.0037
Female	1.09	0.86-1.38	0.49	1.29	0.97-1.70	0.0773
White	0.94	0.51-1.73	0.84	0.78	0.39-1.54	0.48
Cirrhosis	1.48	0.91-2.42	0.11	1.23	0.69-2.17	0.48
PSC	0.84	0.63-1.14	0.26	1.42	0.93-2.15	0.10
ECOG			<0.0001			<0.0001
0	1.00	reference		1.00	reference	
1-2	1.72	1.34-2.21	<0.0001	1.61	1.21-2.14	0.0012
3-4	9.00	5.10-15.88	<0.0001	10.60	5.11-21.98	<0.0001
Maximum tumor size [†]	1.12	1.05-1.19	0.0006	1.23	1.07-1.41	0.0029
Tumor number			0.0295			0.13
Non-identified	1.00	reference		1.00	reference	
Single	1.20	0.93-1.56	0.17	0.65	0.38-1.09	0.10
Multiple (≥ 2)	1.68	1.14-2.47	0.0084	0.84	0.38-1.83	0.65
Vascular encasement	1.26	0.99-1.60	0.0596	1.27	0.95-1.70	0.11

Variables	Unadjusted HR	95% CI	<i>P</i>	Adjusted HR	95% CI	<i>P</i>
Lymph node metastasis			0.52			0.13
None	1.00	reference		1.00	reference	
Hilar	0.89	0.54-1.45	0.63	0.68	0.38-1.20	0.18
Distant	1.18	0.84-1.66	0.35	1.34	0.85-2.09	0.21
Peritoneal (or other organ) metastasis	2.73	1.90-3.95	<0.0001	3.01	1.84-4.93	<0.0001
CA 19-9 >1000 U/mL	2.01	1.52-2.66	<0.0001	1.80	1.32-2.46	0.0002

*The models included 342 patients who had complete data on all variables.

†Based on the spline function analysis (i.e. a spline curve of size vs. hazard ratio of the entire cohort), there was no evidence for a further increase in risk of death beyond a tumor size of 6 cm (Supplementary Figure 2). Once a linear size effect from 0 to 6 cm was accounted for, there was no further significant effect of size ($P = 0.17$). A tumor size >6 cm was therefore coded as 6 cm.

HR=Hazard ratio

Supplementary Table 3. Kaplan-Meier estimate of median survival and survival rate of pCCA patients in the transplantation group classified by the proposed staging system (n=92)

Stage	Number of death/total	Median survival (months)	1-year Kaplan- Meier estimate (95% CI)	5-year Kaplan- Meier estimate (95% CI)	Univariate HR (95% CI)	<i>P</i>
I	7/33	Not reached	97.0% (91.3-100.0)	77.9% (64.6-93.8)	1.00 (reference)	<0.0001
II	22/40	52.1	76.5% (64.2-91.2)	44.1% (30.7-63.3)	3.58 (1.53-8.40)	0.0033
III	16/19	15.5	55.7% (36.9-84.1)	6.2% (0.9-41.1)	11.01 (4.43-27.38)	<0.0001
IV	0/0	-	-	-	-	-

Supplementary Table 4. Kaplan-Meier estimate of median survival and survival rate of pCCA patients in the resection group classified by the proposed staging system (n=74)*

Stage	Number of death/total	Median survival (months)	1-year Kaplan- Meier estimate (95% CI)	5-year Kaplan- Meier estimate (95% CI)	Univariate HR (95% CI)	<i>P</i>
I	24/32	35.2	78.0% (64.8-93.8)	19.3% (7.9-42.9)	1.00 (reference)	0.41
II	18/26	20.2	70.8% (54.8-91.6)	22.1% (9.6-50.8)	1.07 (0.58-1.98)	0.83
III	11/16	9.7	47.4% (27.8-80.8)	16.2% (3.4-78.7)	1.62 (0.78-3.33)	0.19
IV	0/0	-	-	-	-	-

*The analysis included 74 patients who had complete data for both the proposed staging system and the TNM staging system.

Supplementary Table 5. Kaplan-Meier estimate of median survival and survival rate of pCCA patients in the palliative biliary drainage group classified by the proposed staging system (n=218)*

Stage	Number of death/total	Median survival (months)	6-month Kaplan- Meier estimate (95% CI)	1-year Kaplan- Meier estimate (95% CI)	Univariate HR (95% CI)	<i>P</i>
I	8/11	20.8	100%	88.9% (70.6-100)	1.00 (reference)	<0.0001
II	22/34	12.4	81.7% (68.4-97.6)	57.8% (41.0-80.5)	1.82 (0.81-4.11)	0.15
III	92/119	7.7	57.7% (48.8-68.2)	32.4% (24.3-43.2)	2.87 (1.38-5.99)	0.0049
IV	47/54	3.0	24.1% (14.4-40.1)	8.8% (3.4-22.3)	7.70 (3.52-16.82)	<0.0001

*The analysis included 218 patients who had complete data for both the proposed staging system and the TNM staging system.

Supplementary Table 6. Kaplan-Meier estimate of median survival and survival rate of pCCA patients in the best supportive care group classified by the proposed staging system (n=15)

Stage	Number of death/total	Median survival (months)	3-month Kaplan- Meier estimate (95% CI)	6-month Kaplan- Meier estimate (95% CI)	1-year Kaplan- Meier estimate (95% CI)	Univariate HR (95% CI)	<i>P</i>
I	0/0	-	-	-	-	-	-
II	0/1	-	100.0%	-	-	0.00 (0.00-0.67)	0.0245
III	10/10	6.1	100.0%	50.0% (26.9-92.9)	20.0% (5.8-69.1)	0.04 (0.01-0.42)	0.0063
IV	4/4	1.0	25.0% (4.6-100)	-	-	1.00 (reference)	0.0241

Supplementary Table 7. Kaplan-Meier estimate of median survival and survival rate of pCCA patients in the transplantation group classified by the radiologic TNM staging system (n=92)

Stage	Number of death/total	Median survival (months)	1-year Kaplan- Meier estimate (95% CI)	5-year Kaplan- Meier estimate (95% CI)	Univariate HR (95% CI)	<i>P</i>
I/II	13/43	Not reached	88.2% (78.9-98.5)	70.4% (57.2-86.0)	1.00 (reference)	0.0041
III	3/4	15.5	75.0% (42.6-100.0)	25.0% (4.6-100.0)	4.06 (1.15-14.35)	0.0293
IV	29/45	31.1	72.2% (60.0-86.9)	31.9% (20.5-49.6)	2.84 (1.47-5.47)	0.0018

Supplementary Table 8. Kaplan-Meier estimate of median survival and survival rate of pCCA patients in the resection group classified by the radiologic TNM staging system (n=74)*

Stage	Number of death/total	Median survival (months)	1-year Kaplan- Meier estimate (95% CI)	5-year Kaplan- Meier estimate (95% CI)	Univariate HR (95% CI)	<i>P</i>
I/II	17/55	25.3	67.2% (56.1-80.5)	20.8% (11.5-36.4)	1.00 (reference)	0.36
III	4/17	29.2	72.2% (54.2-96.2)	18.4% (5.6-60.9)	1.13 (0.60-2.12)	0.71
IV	0/2	8.7	50.0% (12.5-100.0)	-	2.82 (0.66-12.01)	0.16

*The analysis included 74 patients who had complete data for both the proposed staging system and the TNM staging system.

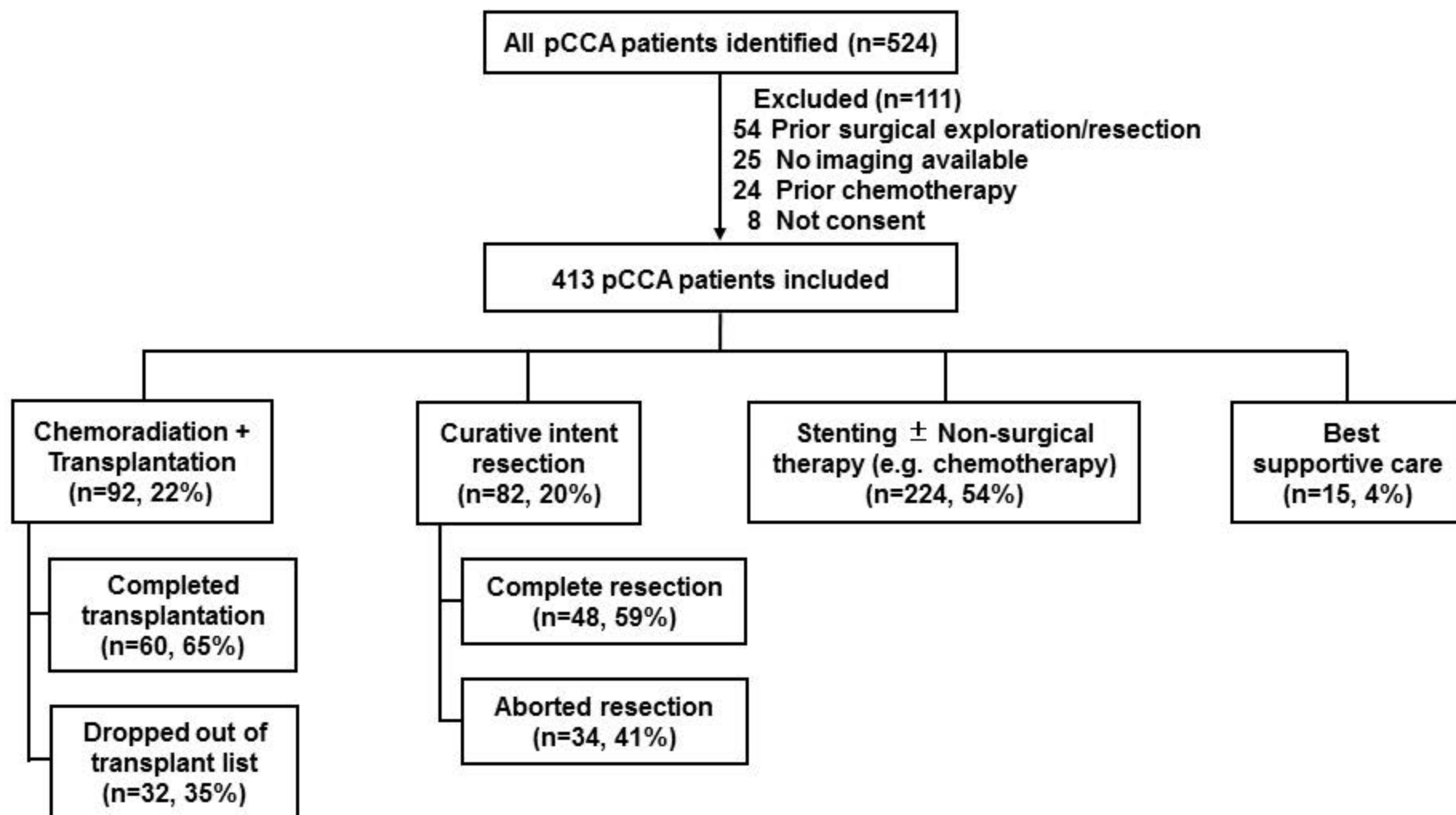
Supplementary Table 9. Kaplan-Meier estimate of median survival and survival rate of pCCA patients in the palliative biliary drainage group classified by the radiologic TNM staging system (n=218)*

Stage	Number of death/total	Median survival (months)	6-month Kaplan- Meier estimate (95% CI)	1-year Kaplan- Meier estimate (95% CI)	Univariate HR (95% CI)	<i>P</i>
I/II	18/23	7.7	65.9% (48.2-90.1)	44.3% (26.8-73.2)	1.00 (reference)	0.50
III	21/23	9.5	54.5% (37.3-79.9)	40.9% (24.8-67.6)	1.34 (0.69-2.63)	0.39
IV	135/178	6.4	53.1% (45.6-61.8)	29.8% (23.1-38.4)	1.38 (0.81-2.35)	0.24

*The analysis included 218 patients who had complete data for both the proposed staging system and the TNM staging system.

Supplementary Table 10. Kaplan-Meier estimate of median survival and survival rate of pCCA patients in the best supportive care group classified by the radiologic TNM staging system (n=15)

Stage	Number of death/total	Median survival (months)	3-month Kaplan- Meier estimate (95% CI)	6-month Kaplan- Meier estimate (95% CI)	1-year Kaplan- Meier estimate (95% CI)	Univariate HR (95% CI)	<i>P</i>
I/II	0/0	-	-	-	-	-	-
III	2/2	3.1	100%	50.0% (12.5-100.0)	50.0% (12.5-100.0)	1.00 (reference)	
IV	12/13	5.6	76.9% (57.1-100.0)	35.2% (16.3-76.1)	8.8% (1.4-56.7)	1.34 (0.28-6.39)	0.71



Supplemental Figure 2

