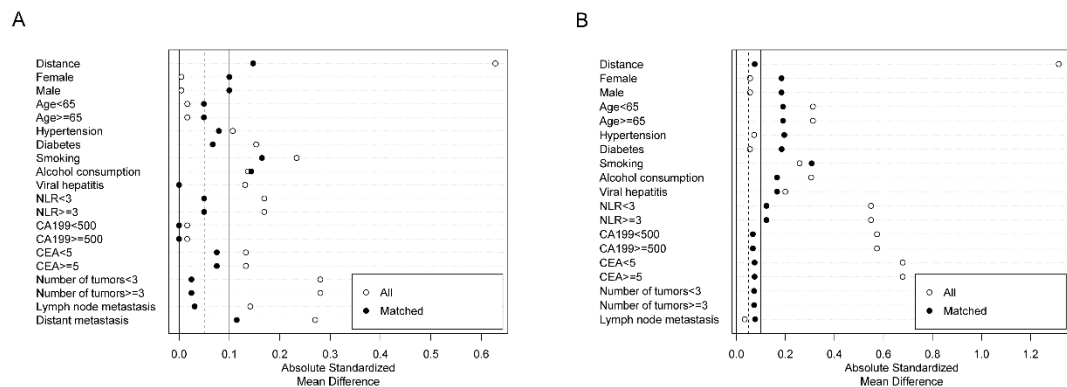


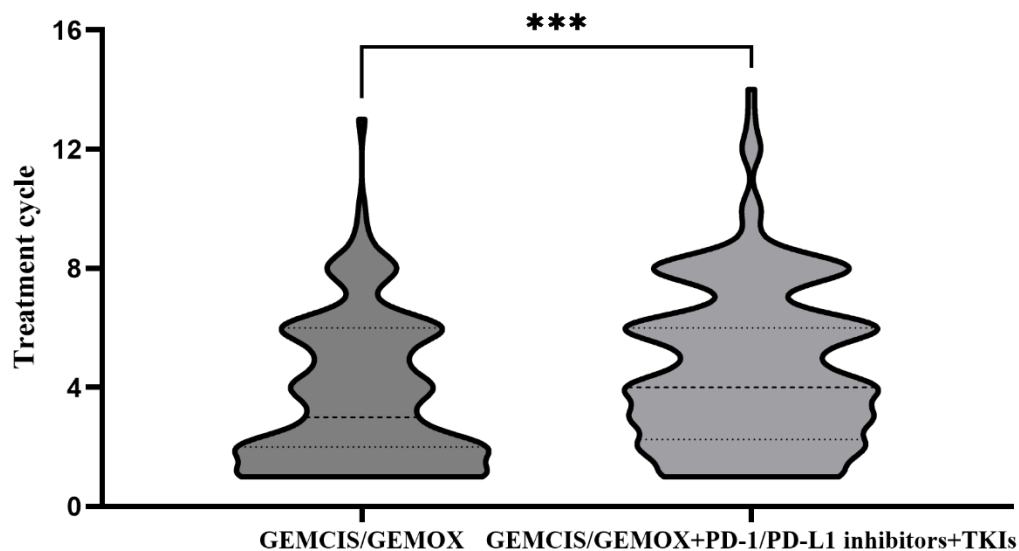
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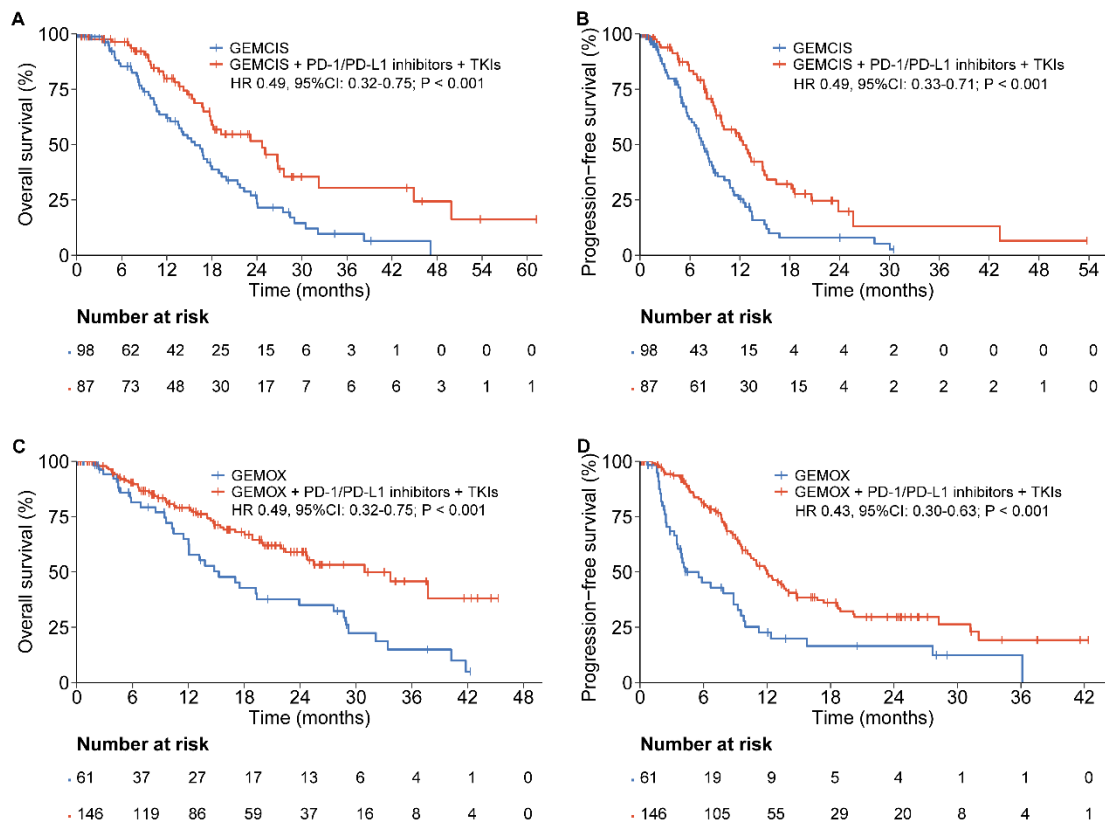
Figure and illustrations:



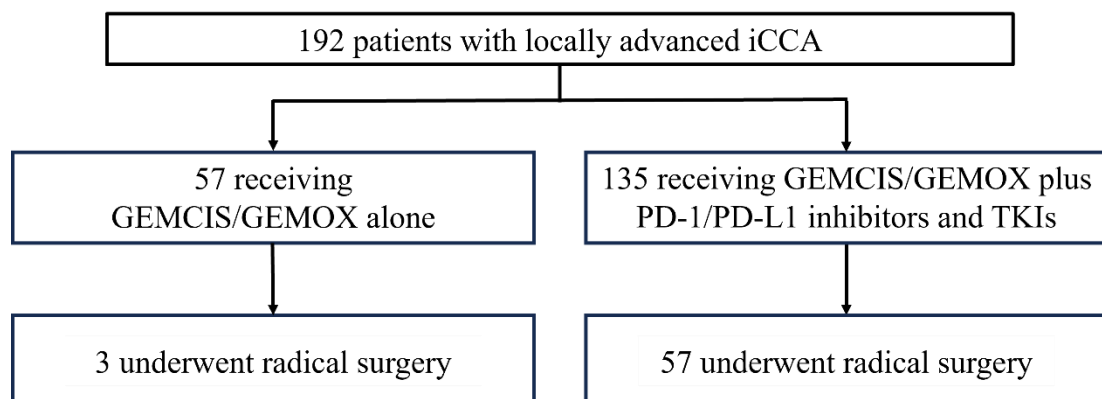
Supplementary Figure 1. Absolute Standardized Mean Differences after PSM. A: PSM between GEMCIS/GEMOX and GEMCIS/GEMOX plus PD-1/PD-L1 inhibitors and TKIs; B: PSM between surgery and non-surgery. CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; GEMCIS, gemcitabine and cisplatin; GEMOX, gemcitabine and oxaliplatin; NLR, neutrophil-to-lymphocyte ratio; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; PSM, propensity score matching; TKIs, tyrosine kinase inhibitors.



Supplementary Figure 2. Violin Plot of Treatment Cycles.



Supplementary Figure 3. Subgroup Analyses of Survival Outcomes by Chemotherapy Regimen. A, B: Kaplan-Meier curve estimates of OS and PFS between GEMCIS and GEMCIS plus PD-1/PD-L1 inhibitors and TKIs; C, D: Kaplan-Meier curve estimates of OS and PFS between GEMOX and GEMOX plus PD-1/PD-L1 inhibitors and TKIs. GEMCIS, gemcitabine and cisplatin; GEMOX, gemcitabine and oxaliplatin; OS, overall survival; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; PFS, progression-free survival; TKIs, tyrosine kinase inhibitors.



Supplementary Figure 4. Flowchart for the Study of Locally Advanced Disease. GEMCIS, gemcitabine and cisplatin; GEMOX, gemcitabine and oxaliplatin; PD-1/PD-

L1, programmed cell death protein 1/programmed death-ligand 1; TKIs, tyrosine kinase inhibitors.

Supplementary Table 1. Patient Enrollment by Participating Institutions

Institution	Time of diagnosis	No. of patients
The Second Affiliated Hospital Zhejiang University School of Medicine	2016.01-2024.12	107
Zhejiang Cancer Hospital	2016.01-2024.12	65
The First Affiliated Hospital of Zhengzhou University	2019.01-2024.12	37
Cancer Hospital Chinese Academy of Medical Science	2019.01-2024.12	18
Peking Union Medical College Hospital	2019.01-2024.12	10
The First Hospital of Jiaxing	2019.01-2024.12	6
The First Affiliated Hospital of Wenzhou Medical University	2021.01-2024.12	6
Huzhou Central Hospital	2021.01-2024.12	5
China-Japan Friendship Hospital	2021.01-2024.12	4
The Fourth Affiliated Hospital, Zhejiang University School of Medicine	2021.01-2024.12	3
Xinjiang Medical University Affiliated Tumor Hospital	2021.01-2024.12	2
Shangrao People’s Hospital	2021.01-2024.12	2

Supplementary Table 2. Baseline Demographics and Clinical Characteristics (Full Cohort Analysis)

Characteristics	Full cohort (N=392)	GEMCIS/GEMOX (N=159)	GEMCIS/GEMOX+ PD-1/PD-L1 inhibitors+ TKIs (N=233)	<i>P</i>
Age, years	62 (55-68)	62 (55-68)	62 (55-69)	0.573
<65	231 (59)	91 (57)	140 (60)	
≥ 65	161 (41)	68 (43)	93 (40)	
Gender				0.462
Male	233 (59)	91 (57)	142 (61)	
Female	159 (41)	68 (43)	91 (39)	
Hypertension				0.986
No	271 (69)	110(69)	161 (69)	
Yes	121 (31)	49 (31)	72 (31)	
Diabetes				0.098
No	339 (86)	143 (90)	196 (84)	
Yes	53 (14)	16 (10)	37 (16)	
Smoking				0.743
No	287 (73)	115 (72)	172 (74)	
Yes	105 (27)	44 (28)	61 (26)	
Alcohol consumption				0.946
No	299 (76)	121 (76)	178 (76)	
Yes	93 (24)	38 (24)	55 (24)	
Viral hepatitis				0.128
No	306 (78)	118 (74)	188 (81)	
Yes	86 (22)	41 (26)	45 (19)	
NLR				0.086
< 3	138 (35)	48 (30)	90 (39)	
≥ 3	254 (65)	111 (70)	143 (61)	
CA 19-9, U/mL				0.900
< 500	219 (56)	87 (55)	132 (57)	
≥ 500	166 (42)	67 (42)	99 (42)	
NA	7 (2)	5 (3)	2 (1)	
CEA, ng/mL				0.246
< 5	216 (55)	81 (51)	135 (58)	
≥ 5	166 (42)	72 (45)	94 (40)	
NA	10 (3)	6 (4)	4 (2)	
Number of tumors				0.045*

< 3	204 (52)	73 (46)	131 (56)	
≥ 3	188 (48)	86 (54)	102 (44)	
Lymph node metastasis^a				0.888
No	80 (20)	33 (21)	47 (20)	
Yes	312 (80)	126 (79)	186 (80)	
Distant metastasis^b				0.005*
No	268 (68)	96 (60)	172 (74)	
Yes	124 (32)	63 (40)	61 (26)	

Data are median (IQR) or n (%).

CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; GEMCIS, gemcitabine and cisplatin; GEMOX, gemcitabine and oxaliplatin; NA, not available; NLR, neutrophil-to-lymphocyte ratio; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; PSM, propensity score matching; TKIs, tyrosine kinase inhibitors.

^a Regional or distant lymph node metastasis.

^b Including metastases to other sites such as the peritoneum, lungs, and bones, while excluding lymph nodes and intrahepatic metastases.

*P<0.05.

Supplementary Table 3. Baseline Demographics and Clinical Characteristics (Primary Analysis)

Characteristics	N=265
Age, years	62 (55-68)
<65	152 (57)
≥ 65	113 (43)
Gender	
Male	160 (60)
Female	105 (40)
Hypertension	
No	187 (71)
Yes	78 (29)
Diabetes	
No	228 (86)
Yes	37 (14)
Smoking	
No	184 (69)
Yes	81 (31)
Alcohol consumption	
No	197 (74)
Yes	68 (26)
Viral hepatitis	
No	208 (78)
Yes	57 (22)
NLR	
< 3	99 (37)
≥ 3	166 (63)
CA 19-9, U/mL	
< 500	158 (60)
≥ 500	107 (40)
CEA, ng/mL	
< 5	156 (59)
≥ 5	109 (41)
Number of tumors	
< 3	139 (52)
≥ 3	126 (48)
Lymph node metastasis^a	
No	46 (17)

Yes	219 (83)
Distant metastasis^β	
No	192 (72)
Yes	73 (28)

Data are median (IQR) or n (%).

CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; NLR, neutrophil-to-lymphocyte ratio.

^α Regional or distant lymph node metastasis.

^β Including metastases to other sites such as the peritoneum, lungs, and bones, while excluding lymph nodes and intrahepatic metastases.

Supplementary Table 4. Treatment Cycles, Best Objective Response, and Survival Outcomes in Patients Treated with GEMCIS/GEMOX Alone or in Combination with PD-1/PD-L1 Inhibitors and TKIs (Full Cohort Analysis).

	GEMCIS/GEMOX (N=159)	GEMCIS/GEMOX+ PD-1/PD-L1 inhibitors + TKIs (N=233)
Treatment cycle	3 (2-6)	4 (3-6)
<i>Response</i>		
CR	0	0
PR	17 (16)	85 (43)
SD	60 (56)	103 (52)
PD	30 (28)	10 (5)
NA	52 (33)	35 (15)
ORR	17 (16)	85 (43)
DCR	77 (72)	188 (95)
<i>Overall survival</i>		
Median OS	15.3 (12.6-17.9)	26.7 (21.3-32.2)
1-year OS	68	80
2-year OS	33	57
3-year OS	14	41
<i>Progression-free survival</i>		
Median PFS	7.0 (5.4-8.6)	12.2 (10.7-13.7)
1-year PFS	35	54
2-year PFS	17	28
3-year PFS	8	15

Data are median (IQR) or n (%).

CR, complete response; DCR, disease control rate; GEMCIS, gemcitabine and cisplatin; GEMOX, gemcitabine and oxaliplatin; NA, not available; ORR, objective response rate; OS, overall survival; PD, progression disease; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; PFS, progression-free survival; PR, partial response; PSM, propensity score matching; SD, stable disease; TKIs, tyrosine kinase inhibitors.

Supplementary Table 5. Univariable and Multivariable Analyses for Overall Survival and Progression-Free Survival after PSM.

Characteristics	Univariable analysis			Multivariable analysis		
	HR	95%CI	P	HR	95%CI	P
<i>OS analyses</i>						
Age, years (≥ 65 vs <65)	0.95	0.65-1.39	0.787			
Gender (Male vs Female)	1.21	0.83-1.78	0.325			
Hypertension (Yes vs No)	1.08	0.72-1.61	0.711			
Diabetes (Yes vs No)	0.79	0.44-1.41	0.424			
Smoking (Yes vs No)	1.67	1.14-2.43	0.008*	1.58	1.08-2.32	0.017*
Alcohol consumption (Yes vs No)	1.71	1.16-2.53	0.007*			
Viral hepatitis (Yes vs No)	1.18	0.78-1.83	0.467			
NLR (≥ 3 vs <3)	1.21	0.81-1.80	0.363			
CA19-9, U/mL (≥ 500 vs <500)	2.14	1.47-3.12	<0.001*	2.28	1.56-3.34	<0.001*
CEA, ng/mL (≥ 5 vs <5)	1.87	1.29-2.73	0.001*			
Number of tumors (≥ 3 vs <3)	1.26	0.86-1.84	0.232			
Lymph node metastasis (Yes vs No)	0.91	0.55-1.51	0.718			
Distant metastasis (Yes vs No)	1.34	0.90-1.99	0.147			
Treatment regimen (GEMCIS/GEMOX plus PD-1/PD-L1 inhibitors and TKIs vs GEMCIS/GEMOX alone)	0.56	0.38-0.83	0.004*	0.54	0.36-0.80	0.002*
<i>PFS analyses</i>						
Age, years (≥ 65 vs <65)	0.59	0.41-0.85	0.005*	0.51	0.35-0.75	<0.001*
Gender (Male vs Female)	1.29	0.89-1.87	0.177			
Hypertension (Yes vs No)	0.90	0.62-1.32	0.603			
Diabetes (Yes vs No)	0.81	0.48-1.37	0.427			
Smoking (Yes vs No)	1.63	1.14-2.35	0.008*	1.48	1.03-2.14	0.034*

Alcohol consumption (Yes vs No)	1.63	1.12-2.36	0.010*			
Viral hepatitis (Yes vs No)	1.04	0.69-1.59	0.841			
NLR (≥ 3 vs <3)	1.16	0.80-1.70	0.437			
CA19-9, U/mL (≥ 500 vs <500)	1.40	0.97-2.01	0.070			
CEA, ng/mL (≥ 5 vs <5)	1.47	1.03-2.10	0.035*	1.61	1.10-2.37	0.014*
Number of tumors (≥ 3 vs <3)	1.32	0.92-1.90	0.136			
Lymph node metastasis (Yes vs No)	1.15	0.70-1.90	0.585			
Distant metastasis (Yes vs No)	1.29	0.88-1.90	0.198			
Treatment regimen (GEMCIS/GEMOX plus PD-1/PD-L1 inhibitors and TKIs vs GEMCIS/GEMOX)	0.46	0.32-0.67	<0.001*	0.49	0.34-0.71	<0.001*

CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; GEMCIS, gemcitabine and cisplatin; GEMOX, gemcitabine and oxaliplatin; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; PFS, progression-free survival; PSM, propensity score matching; TKIs, tyrosine kinase inhibitors.

* $P < 0.05$.

Supplementary Table 6. Summary of Adverse Events in Patients Treated with GEMCIS/GEMOX plus PD-1/PD-L1 Inhibitors and TKIs Compared to Those Treated with GEMCIS/GEMOX Alone (Full Cohort Analysis).

	GEMCIS/GEMOX (N=126)			GEMCIS/GEMOX + PD-1/PD-L1 inhibitors + TKIs (N=212)		
	Grade 1-2	Grade 3-4	Any grade	Grade 1-2	Grade 3-4	Any grade
Leukopenia	32 (25)	7 (6)	39 (31)	93 (44)	10 (5)	103 (49)
Neutropenia	28 (22)	13 (10)	41 (33)	79 (37)	20 (9)	99 (47)
Thrombocytopenia	26 (21)	21 (17)	47 (37)	62 (29)	32 (15)	94 (44)
Anemia	77 (61)	7 (6)	84 (67)	135 (64)	16 (8)	151 (71)
ALT/AST increased	34 (27)	2 (2)	36 (29)	65 (31)	8 (4)	73 (34)
Blood bilirubin increased	12 (10)	4 (3)	16 (13)	33 (16)	7 (3)	40 (19)
Blood creatinine increased	9 (7)	0	9 (7)	32 (15)	1 (<1)	33 (16)
Hypoalbuminaemia	42 (33)	0	42 (33)	54 (25)	3 (1)	57 (27)
Total	101 (80)	35 (28)	104 (83)	179 (84)	62 (29)	180 (85)

Data are n (%).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GEMCIS, gemcitabine and cisplatin; GEMOX, gemcitabine and oxaliplatin; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; PSM, propensity score matching; TKIs, tyrosine kinase inhibitors.

Supplementary Table 7. Treatment details

Initial treatment regimen	Number of patients
GEMCIS	54
GEMOX	34
GEMOX + Adebrelimab + Anlotinib	1
GEMOX + Atezolizumab + Apatinib	1
GEMOX + Durvalumab + Lenvatinib	1
GEMOX + Durvalumab + Surufatinib	1
GEMOX + Envafohimab + Anlotinib	1
GEMOX + Envafohimab + Lenvatinib	5
GEMOX + Camrelizumab + Lenvatinib	3
GEMOX + Camrelizumab + Donafenib	1
GEMOX + Camrelizumab + Surufatinib	1
GEMOX + Pembrolizumab + Lenvatinib	7
GEMOX + Pembrolizumab + Surufatinib	2
GEMOX + Penpulimab + Anlotinib	4
GEMOX + Serplulimab + Lenvatinib	2
GEMOX + Toripalimab + Anlotinib	2
GEMOX + Toripalimab + Donafenib	3
GEMOX + Toripalimab + Lenvatinib	22
GEMOX + Toripalimab + Surufatinib	3
GEMOX + Tislelizumab + Anlotinib	1
GEMOX + Tislelizumab + Donafenib	3
GEMOX + Tislelizumab + Lenvatinib	29
GEMOX + Tislelizumab + Surufatinib	2
GEMOX + Sintilimab + Anlotinib	1
GEMOX + Sintilimab + Donafenib	2
GEMOX + Sintilimab + Lenvatinib	11
GEMOX + Sintilimab + Surufatinib	1
GEMCIS + Adebrelimab + Anlotinib	1
GEMCIS + Adebrelimab + Fruquintinib	1
GEMCIS + Durvalumab + Lenvatinib	4
GEMCIS + Durvalumab + Surufatinib	1
GEMCIS + Envafohimab + Lenvatinib	2
GEMCIS + Camrelizumab + Lenvatinib	1
GEMCIS + Pembrolizumab + Fruquintinib	1
GEMCIS + Pembrolizumab + Lenvatinib	6

GEMCIS + Serplulimab + Lenvatinib	1
GEMCIS + Toripalimab + Fruquintinib	1
GEMCIS + Toripalimab + Lenvatinib	1
GEMCIS + Tislelizumab + Anlotinib	2
GEMCIS + Tislelizumab + Donafenib	1
GEMCIS + Tislelizumab + Lenvatinib	32
GEMCIS + Sintilimab + Anlotinib	6
GEMCIS + Sintilimab + Lenvatinib	6
GEMCIS + PD-1 inhibitors + Lenvatinib	47
GEMCIS + PD-L1 inhibitors + Lenvatinib	6
GEMOX + PD-1 inhibitors + Lenvatinib	74
GEMOX + PD-L1 inhibitors + Lenvatinib	6

GEMCIS, gemcitabine and cisplatin; GEMOX, gemcitabine and oxaliplatin; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Supplementary Table 8. Surgical Characteristics of Patients with Locally Advanced Disease.

	GEMCIS/GEMOX (N=57)	GEMCIS/GEMOX + PD-1/PD-L1 Inhibitors + TKIs (N=135)
<i>Surgery</i>	3 (5)	57 (42)
PR	2 (67)	36 (63)
SD	1 (33)	21 (37)
PD	0	0
<i>Adjuvant therapy</i>	3 (100)	37 (65)
Chemotherapy	2 (67)	6 (16)
PD-1/PD-L1 inhibitors	1 (33)	2 (8)
Chemotherapy + PD-1/PD-L1 inhibitors	0	11 (30)
PD-1/PD-L1 inhibitors + TKIs	0	5 (14)
Chemotherapy + PD-1/PD-L1 inhibitors + TKIs	0	9 (24)
Other therapy	0	4 (11)

Data are n (%).

GEMCIS, gemcitabine and cisplatin; GEMOX, gemcitabine and oxaliplatin; PD, progression disease; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; PR, partial response; SD, stable disease; TKIs, tyrosine kinase inhibitors.

Supplementary Table 9. Baseline Demographics and Clinical Characteristics of Locally Advanced ICC Patients with Surgery or Not Following GEMCIS/GEMOX plus PD-1/PD-L1 Inhibitors and TKIs.

Characteristics	Before PSM			After PSM		
	Non-surgery (N=78)	Surgery (N=57)	<i>P</i>	Non-surgery (N=33)	Surgery (N=33)	<i>P</i>
Age, years	64 (55-70)	61 (55-67)	0.084	62 (56-70)	61 (56-66)	0.453
<65	39 (50)	37 (65)		18 (55)	21 (64)	
≥ 65	39 (50)	20 (35)		15 (45)	12 (36)	
Gender			0.749			0.447
Male	43 (55)	33 (58)		22 (67)	19 (58)	
Female	35 (45)	24 (42)		11 (33)	14 (42)	
Hypertension			0.672			0.428
No	56 (72)	39 (68)		21 (64)	24 (73)	
Yes	22 (28)	18 (32)		12 (36)	9 (27)	
Diabetes			0.758			0.523
No	67 (86)	50 (88)		26 (79)	28 (85)	
Yes	11 (14)	7 (12)		7 (21)	5 (15)	
Smoking			0.178			0.251
No	55 (71)	46 (81)		23 (70)	27 (82)	
Yes	23 (29)	11 (19)		10 (30)	6 (18)	
Alcohol consumption			0.124			0.566
No	57 (73)	48 (84)		24 (73)	26 (79)	
Yes	21 (27)	9 (16)		9 (27)	7 (21)	
Viral hepatitis			0.296			0.733
No	60 (77)	48 (84)		29 (88)	27 (82)	

Yes	18 (23)	9 (16)		4 (12)	6 (18)	
NLR			0.002*			0.621
< 3	24 (31)	33 (58)		14 (42)	16 (48)	
≥ 3	54 (69)	24 (42)		19 (58)	17 (52)	
CA 19-9, U/mL			0.003*			0.802
< 500	36 (46)	41 (72)		20 (61)	19 (58)	
≥ 500	42 (54)	16 (28)		13 (39)	14 (42)	
CEA, ng/mL			0.001*			0.796
< 5	40 (51)	45 (79)		21 (64)	22 (64)	
≥ 5	38 (49)	12 (21)		12 (36)	11 (36)	
Number of tumors			<0.001			0.796
< 3	35 (45)	44 (77)		21 (64)	22 (64)	
≥ 3	43 (55)	13 (23)		12 (36)	11 (36)	
Lymph node metastasis^a			0.842			0.757
No	14 (18)	11 (19)		6 (18)	7 (21)	
Yes	64 (82)	46 (81)		27 (82)	26 (79)	

Data are median (IQR) or n (%).

CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; GEMCIS, gemcitabine and cisplatin; GEMOX, gemcitabine and oxaliplatin; NLR, neutrophil-to-lymphocyte ratio; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; PSM, propensity score matching; TKIs, tyrosine kinase inhibitors.

^a Regional or distant lymph node metastasis.

*P<0.05.