

**Table S1. Clinicopathologic features of PDAC patients enrolled for analyses.**

	<b>Surgery Alone Group</b>	<b>Neoadjuvant Treatment Group</b>
<b>Total</b>	380	136
<b>Age</b>		
≤60	179(47.1%)	73(53.7%)
>60	201(52.9%)	63(46.3%)
<b>Gender</b>		
Male	216(56.8%)	70(51.5%)
Female	164(43.2%)	66(48.5%)
<b>TNM Stage</b>		
I	108(28.4%)	33(24.3%)
II	149(39.2%)	54(39.7%)
III	119(31.3%)	47(34.6%)
Unknown	4(1.1%)	2(1.5%)
<b>T</b>		
T1/T2	199(52.4%)	78(57.4%)
T3	181(47.6%)	56(41.2%)
Unknown	0(1.1%)	2(1.5%)
<b>N</b>		
N0	184(48.4%)	65(47.8%)
N1/N2	196(51.6%)	69(50.7%)
Unknown	0(0.0%)	2(1.5%)
<b>Grade</b>		
G1/2	221(58.2%)	83(61.0%)
G3	159(41.8%)	50(36.8%)
Unknown	0(0.0%)	3(2.2%)
<b>Tumor Location</b>		
Head	199(52.4%)	49(36.0%)
Body/Tail	171(45.0%)	86(63.2%)
Unknown	10(2.6%)	1(0.7%)
<b>Nerve Invasion</b>		
No	75(19.7%)	10(7.4%)
Yes	301(79.2%)	125(91.9%)
Unknown	4(1.1%)	1(0.7%)
<b>Vascular Invasion</b>		
No	286(75.3%)	84(61.8%)
Yes	81(21.3%)	51(37.5%)
Unknown	13(3.4%)	1(0.7%)

TNM stage: tumor-node-metastasis staging system (AJCC 8<sup>th</sup> edition); presented as number (percentage).

**Table S2. Detailed information of antibodies used in mIHC analyses.**

<b>Antibody</b>	<b>Source</b>	<b>Antigen retrieval condition</b>	<b>Concentration</b>
CD4	Abcam(ab133616)	pH 9.0	1/200
CD8	Abcam(ab178089)	pH 9.0	1/100
CD20	Abcam(ab64088)	pH 6.0	1/100
CD21	Abcam(ab227668)	pH 6.0	1/100
CD23	Abcam(ab254162)	pH 9.0	1/100
FOXP3	Cell Signaling(98377s)	pH 9.0	1/100
CD68	Abcam(ab955)	pH 9.0	1/1000
CD11c	Abcam(ab52632)	pH 9.0	1/200
CD15	Abcam(ab241552)	pH 6.0	1/100
CD45RO	Abcam(ab23)	pH 6.0	1/100
CD69	Abcam(ab233396)	pH 9.0	1/500
CD30	Abcam(ab134080)	pH 9.0	1/1000
HLA-DR	Abcam(ab20181)	pH 6.0	1/100
CD25	Abcam(ab128955)	pH 9.0	1/100
CD28	Abcam(ab243228)	pH 9.0	1/1000
CD80	Abcam(ab134120)	pH 9.0	1/1000
CD86	Abcam(ab239075)	pH 9.0	1/100
OX40	Abcam(ab229021)	pH 9.0	1/1000
OX40L	Cell Signaling(59036)	pH 9.0	1/200
CTLA-4	Abcam(ab237712)	pH 9.0	1/500
PD-1	Abcam(ab52587)	pH 6.0	1/50
TIM-3	Abcam(ab241332)	pH 9.0	1/1000
LAG-3	Abcam(ab209236)	pH 9.0	1/1000

**Table S3. Clinicopathologic features of PDAC patients in the external validation cohort.**

	External validation cohort	Chi-Square test P-value (versus the SA group)
<b>Total</b>	123	
<b>Age</b>		
≤60	56(45.5%)	0.761
>60	67(54.5%)	
<b>Gender</b>		
Male	82(66.7%)	0.054
Female	41(33.3%)	
<b>TNM Stage</b>		
I	42(34.1%)	0.055
II	56(45.5%)	
III	25(20.3%)	
<b>T</b>		
T1/T2	71(57.7%)	0.300
T3/T4	52(42.3%)	
<b>N</b>		
N0	73(59.3%)	0.035
N1/N2	50(40.7%)	
<b>Grade</b>		
G1/2	73(59.3%)	0.816
G3	50(40.7%)	
<b>Tumor Location</b>		
Head	68(55.3%)	0.772
Body/Tail	55(44.7%)	
<b>Nerve Invasion</b>		
No	12(9.8%)	0.012
Yes	109(88.6%)	
Unknown	2(1.6%)	
<b>Vascular Invasion</b>		
No	98(79.7%)	0.175
Yes	19(15.4%)	
Unknown	6(4.9%)	

**Table S4. Clinicopathologic features of PDAC patients with intratumoral TLSs in the SA and NAT group.**

	SA group			Chi-square test P-value	NAT group			Chi-square test P-value
	TLS (+)	TLS (-)	Total		TLS (+)	TLS (-)	Total	
<b>Number</b>	<b>80(21.1%)</b>	<b>300(78.9%)</b>	<b>380</b>		<b>21(15.4%)</b>	<b>115(84.6%)</b>	<b>136</b>	
<b>Age</b>				0.353				0.897
≤60	34(8.9%)	145(38.2%)	179		11(8.1%)	62(45.6%)	73	
>60	46(12.1%)	155(40.8%)	201		10(7.4%)	53(39.0%)	63	
<b>Gender</b>				0.894				0.928
Male	46(12.1%)	170(44.7%)	216		11(8.1%)	59(43.4%)	70	
Female	34(8.9%)	130(34.2%)	164		10(7.4%)	56(41.2%)	66	
<b>TNM Stage</b>				0.688				0.689
I	26(6.8%)	82(21.6%)	108		7(5.1%)	26(19.1%)	33	
II	32(8.4%)	117(30.8%)	149		7(5.1%)	47(34.6%)	54	
III	21(5.5%)	98(25.8%)	119		7(5.1%)	40(29.4%)	47	
Unknown	1(0.3%)	3(0.8%)	4		0(0.0%)	2(1.5%)	2	
<b>T</b>				0.079				0.697
T1/T2	49(12.9%)	150(39.5%)	199		11(8.1%)	67(49.3%)	78	
T3	31(8.2%)	150(39.5%)	181		10(7.4%)	46(33.8%)	56	
Unknown	0(0.0%)	0(0.0%)	0		0(0.0%)	2(1.5%)	2	
<b>N</b>				0.947				0.770
N0	39(10.3%)	145(38.2%)	184		11(8.1%)	54(39.7%)	65	
N1/N2	41(10.8%)	155(40.8%)	196		10(7.4%)	59(43.4%)	69	
Unknown	0(0.0%)	0(0.0%)	0		0(0.0%)	2(1.5%)	2	
<b>Grade</b>				0.308				0.755
G1/2	51(13.4%)	170(44.7%)	221		13(9.6%)	70(51.5%)	83	
G3	29(7.6%)	130(34.2%)	159		8(5.9%)	42(30.9%)	50	
Unknown	0(0.0%)	0(0.0%)	0		0(0.0%)	3(2.2%)	3	
<b>Tumor Location</b>				0.224				0.660
Head	45(11.8%)	154(40.5%)	199		6(4.4%)	43(31.6%)	49	
Body/Tail	35(9.2%)	136(35.8%)	171		15(11.0%)	71(52.2%)	86	
Unknown	0(0.0%)	10(2.6%)	10		0(0.0%)	1(0.7%)	1	
<b>Nerve Invasion</b>				0.163				0.335
No	21(5.5%)	54(14.2%)	75		0(0.0%)	10(7.4%)	10	
Yes	59(15.5%)	242(63.7%)	301		21(15.4%)	104(76.5%)	125	
Unknown	0(0.0%)	4(1.1%)	4		0(0.0%)	1(0.7%)	1	
<b>Vascular Invasion</b>				0.514				0.578
No	62(16.3%)	224(58.9%)	286		13(9.6%)	71(52.2%)	84	
Yes	17(4.5%)	64(16.8%)	81		8(5.9%)	43(31.6%)	51	
Unknown	1(0.3%)	12(3.2%)	13		0(0.0%)	1(0.7%)	1	
<b>Therapy</b>								0.143

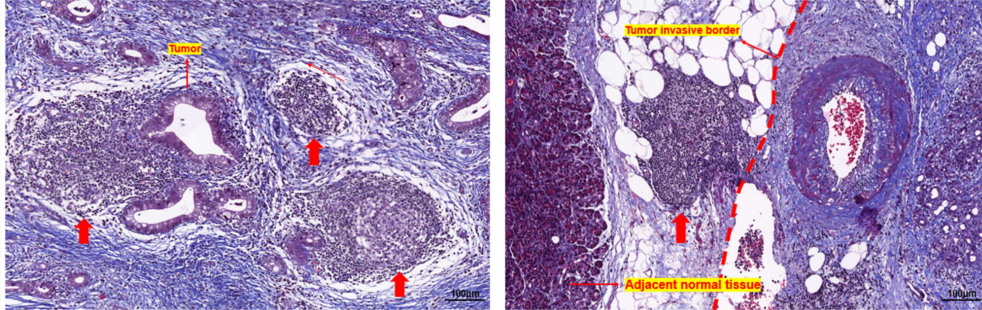
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AG	12(8.8%)	75(55.1%)	87
GS	6(4.4%)	16(11.8%)	22
GEMOX	1(0.7%)	20(14.7%)	21
FOLFIRINOX	2(1.5%)	3(2.2%)	5
Other	0(0.0%)	1(0.7%)	1

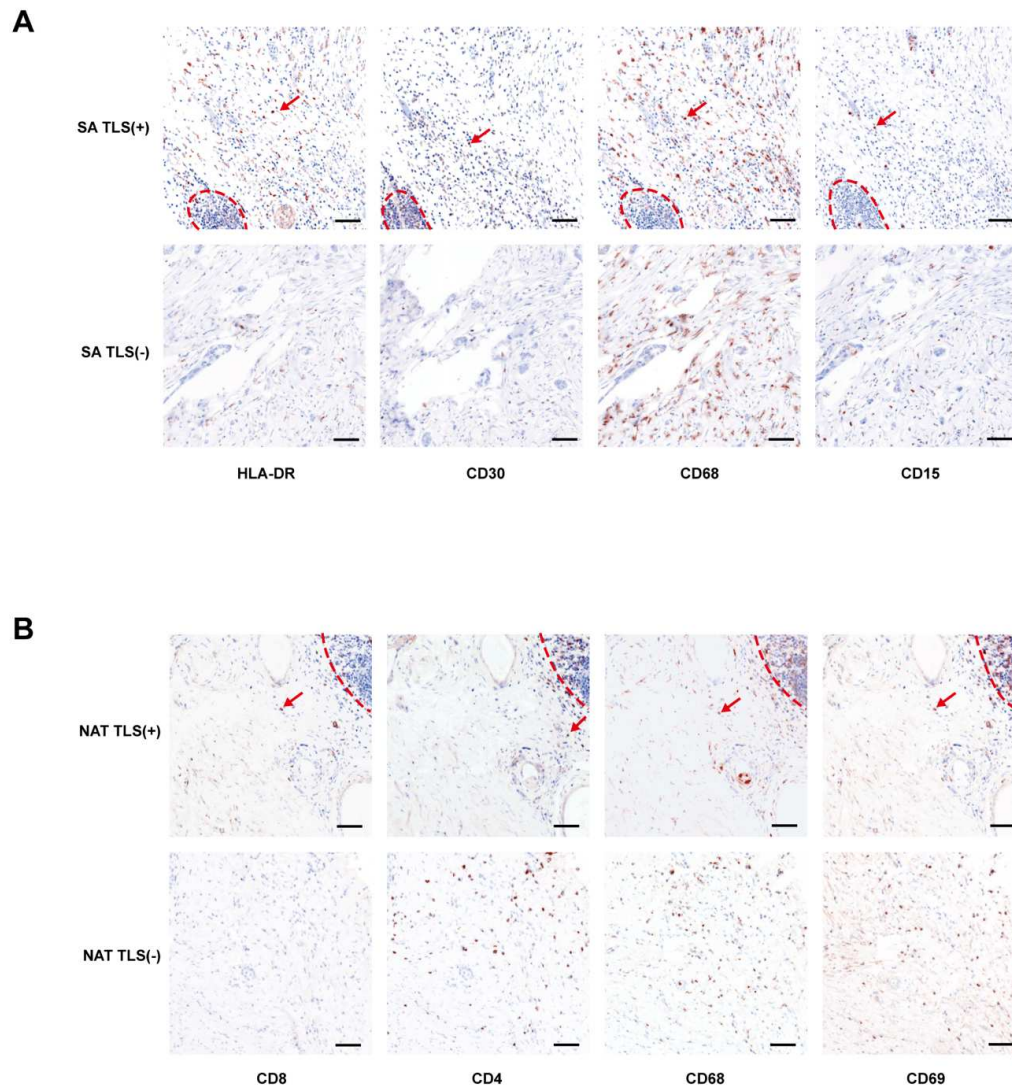
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TNM stage: tumor-node-metastasis staging system (AJCC 8<sup>th</sup> edition); T: primary tumor, N: regional lymph node, M: distant metastasis.

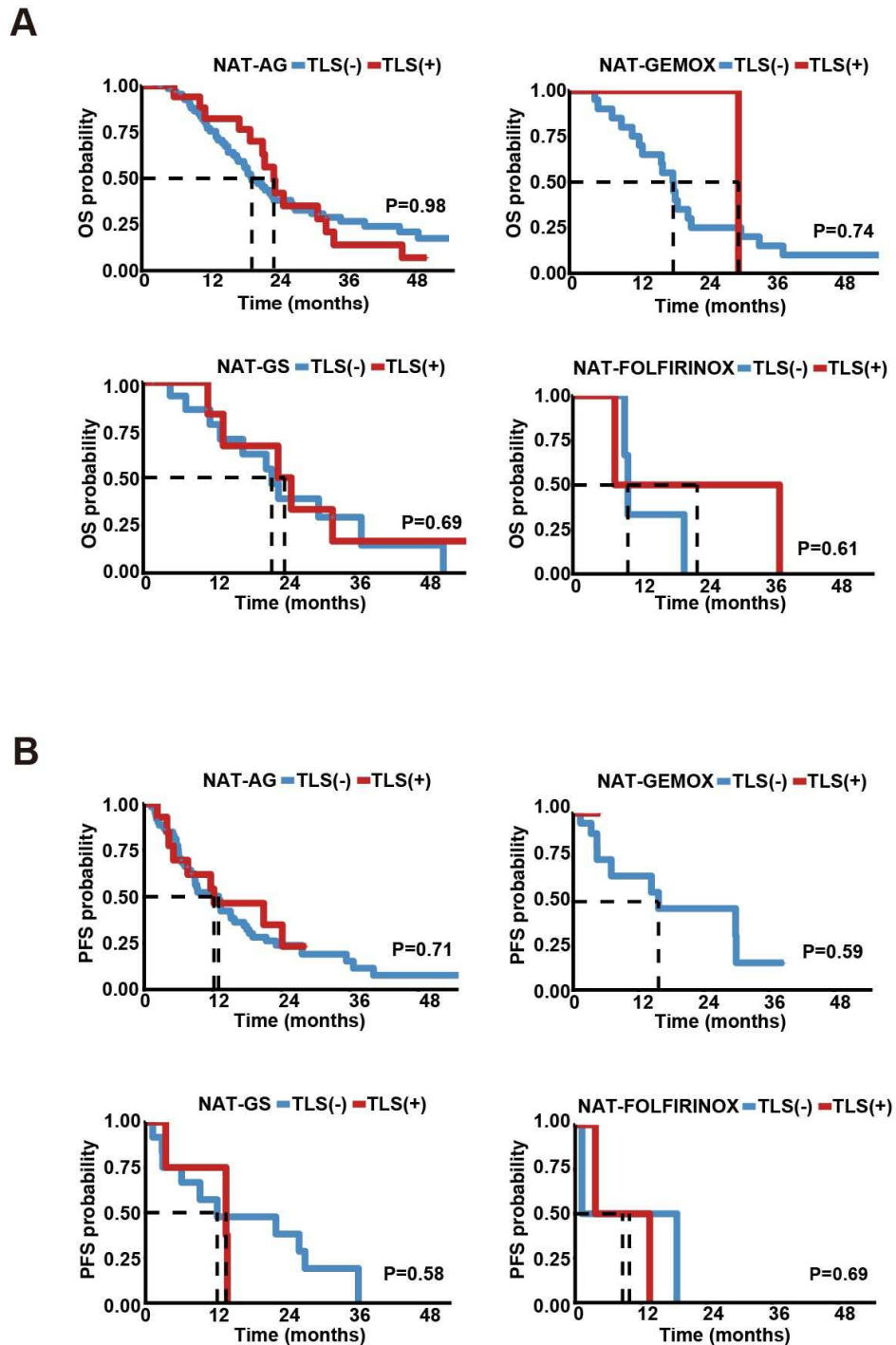
**Figure S1.** Representative H&E staining images of intratumoural (left) and peritumoural (right) TLS in PDAC; TLSs are indicated by red arrows.



**Figure S2.** Representative brightfield mIHC images comparing infiltration levels of several other immune cells; TLSs are circled with dotted red lines; red arrows indicate the examples of positively stained cells; scale bar: 100  $\mu$ m.

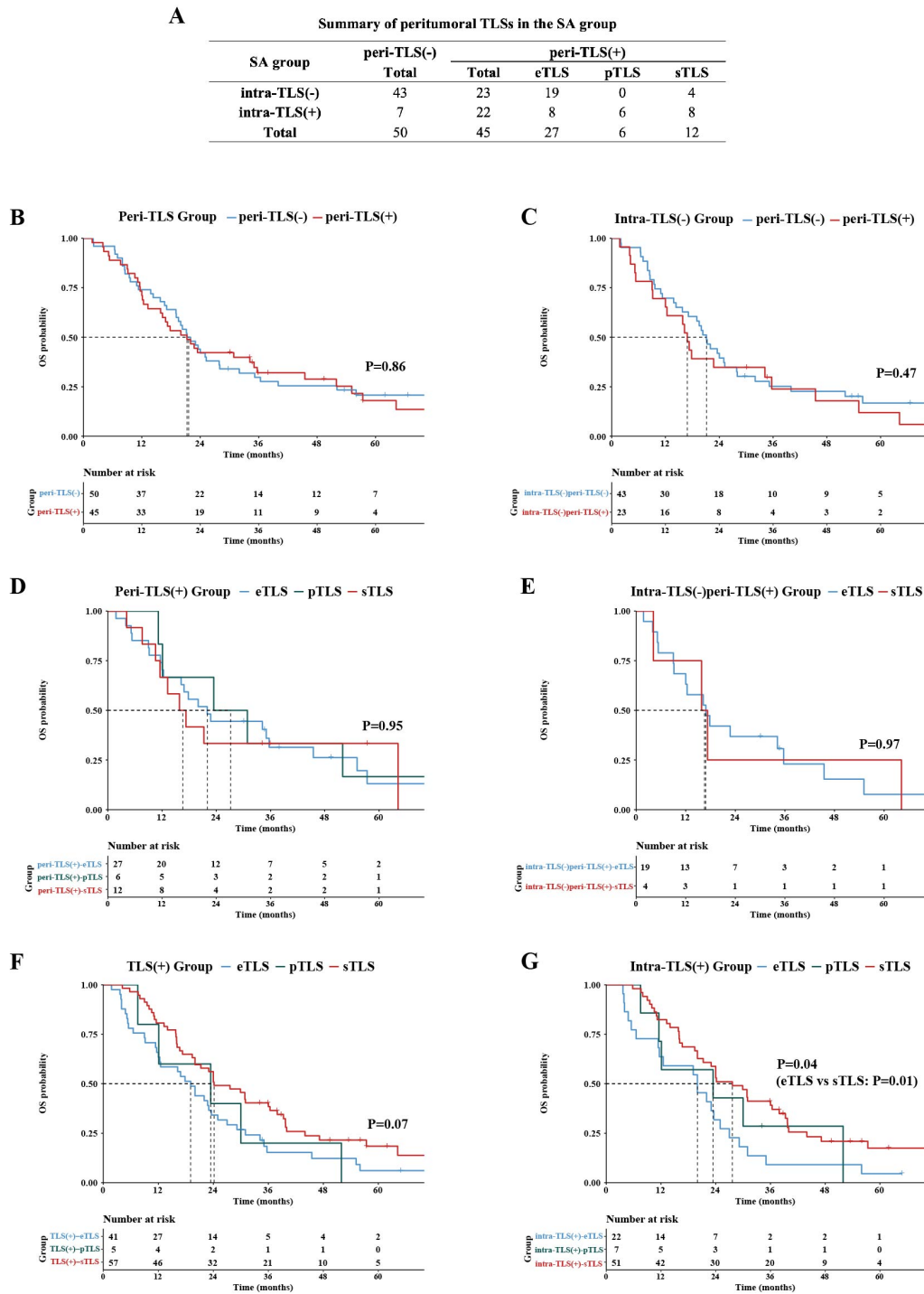


**Figure S3.** Kaplan–Meier curves comparing OS and PFS probabilities between TLS (+) and TLS (-) patients receiving different NAT therapies.

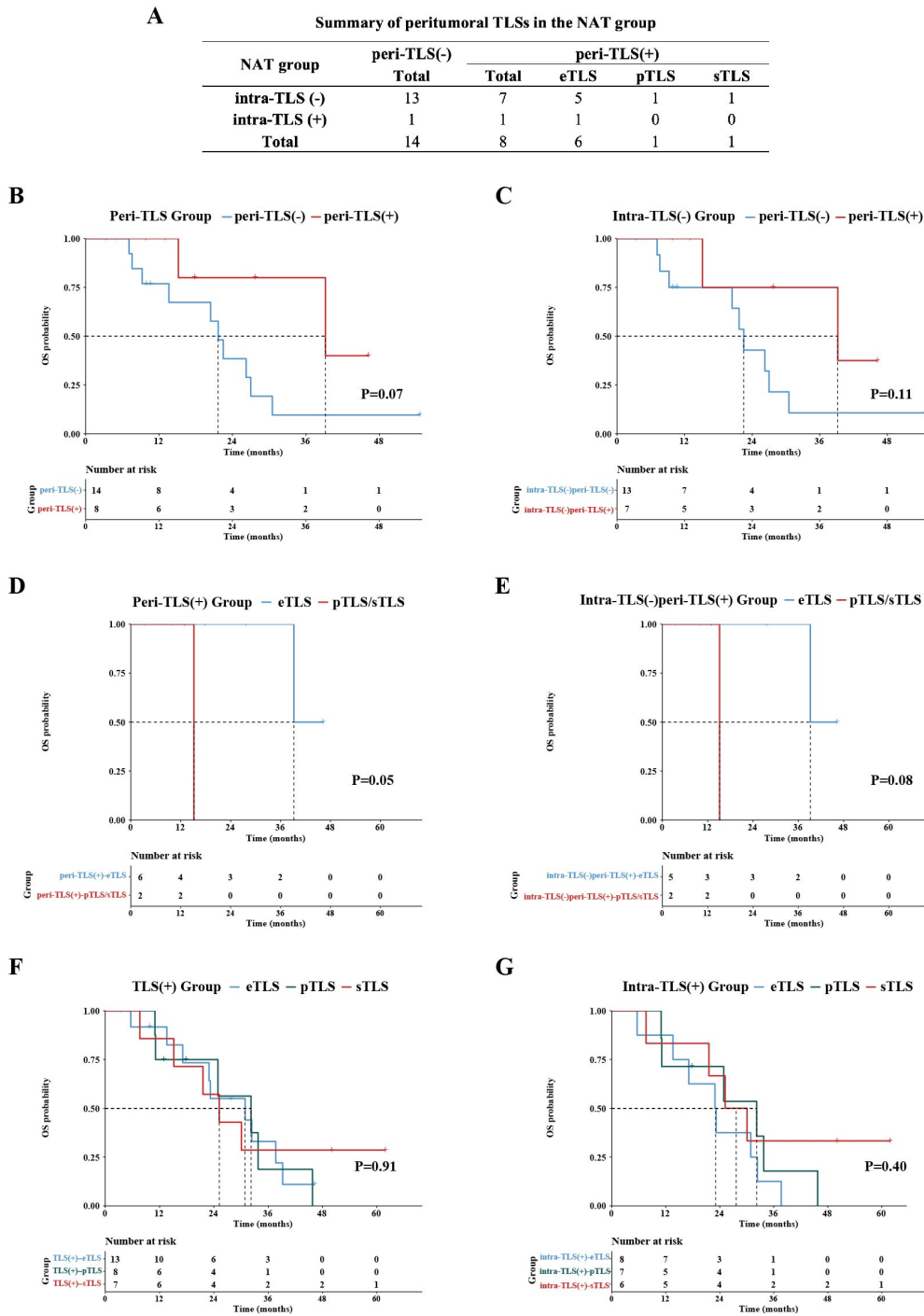




**Figure S4.** Frequency and prognostic value of TLS location and maturation in the SA cohort; peri-TLS: peritumoural TLS, intra-TLS: intratumoural TLS; eTLS group: eTLS(+) pTLS(-) sTLS(-) samples, pTLS group: pTLS(+) sTLS(-) samples, sTLS group: sTLS(+) samples.



**Figure S5.** Frequency and prognostic value of TLS location and maturation in the NAT cohort; peri-TLS: peritumoural TLS, intra-TLS: intratumoural TLS; eTLS group: eTLS(+) pTLS(-) sTLS(-) samples, pTLS group: pTLS(+) sTLS(-) samples, sTLS group: sTLS(+) samples.



**Figure S6.** Representative mIHC images showing the expression levels of activation markers, costimulation molecules and inhibitory molecules within intratumoral TLSs in the SA and NAT group; TLSs are circled with dotted white lines; scale bar: 50  $\mu$ m.

