

Prognostic Value of Preoperative Circulating Tumor DNA in Non-Small Cell Lung Cancer:

A Systematic Review and Meta-analysis

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Table S1. Definition of endpoints for studies included in the meta-analysis

Author	Year	Endpoint definitions
Peng M	2020	RFS: defined as the length of time after surgery that the patient survives without any signs or symptoms of lung cancer. OS: defined as the length of time from the date of diagnosis until death.
Qiu B	2021	RFS: measured from the date of surgery to the verified first radiographic recurrence (local or distant).
Tan A	2021	NA
Waldeck S	2022	PFS: defined as time from blood sample collection to any of the following: disease progression as defined by RECIST 1.1-based radiographic assessment, death from any cause or last follow-up visit. OS: considered as secondary endpoint and was defined as the time from blood sample collection to death from any cause or last follow up.
Xia L	2022	RFS: defined as the time interval from the surgery to the first verified recurrence (local or distant) or death for any cause.
Gale, D	2022	RFS: measured from the date of surgery to the events either recurrence of the first primary tumour, or death if not preceded by a second primary tumour OS: measured from the date of surgery to the death for any cause
Li, N	2022	RFS: measured from the date of surgery to the first documented radiologic recurrence/metastasis as a result of NSCLC OS: measured from the date of surgery to the death as a result of NSCLC
Yue, D	2022	RFS: defined as the time between the date of surgery and the date when local recurrence or distant relapses were diagnosed
Provencio, M	2022	OS: defined as the time from the start of neoadjuvant treatment to death from any cause. PFS: defined as the time between the start of neoadjuvant treatment and disease progression
Zhang, JT	2022	DFS: measured from the day of definitive surgery to the first radiographic recurrence or death.
Chen, KZ	2022	OS: estimated from the date of surgical resection until death of any cause or the date of the last follow-up DFS: defined as the time from the day of surgery until the first event (relapse or metastasis) or last follow-up

Table S3. Univariate regression analysis

RFS: Pre-surgery ctDNA presence in patients.

Study	HR	95%CI
TAN A 2021	5.46	1.21-24.62
Zhang JT 2022	4.85	2.63-8.94
Waldeck S 2022	2.00	0.41-9.78
Yue D 2022	7.41	0.91-60.28
Xia L 2022	4.19	2.61-6.72
Peng M 2020	3.72	1.61-8.60
Qiu B 2021	2.58	1.00-6.67
Li N 2022	2.44	1.12-5.32
Gale D 2022	3.08	1.39-6.82
Chen KZ 2022	2.79	1.13-6.88
Overall (Fixed effects)	3.62	2.80-4.67
Overall (Random effects)	3.62	2.80-4.67
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.88$		

OS: Pre-surgery ctDNA presence in patients.

Study	HR	95%CI
Waldeck S 2022	3.01	0.31-29.32
Peng M 2020	4.91	1.68-14.37
Li N 2022	5.54	1.01-30.38
Gale D 2022	2.76	1.14-6.68
Chen KZ 2022	2.10	0.80-5.52
Overall (Fixed effects)	3.12	1.86-5.23
Overall (Random effects)	3.12	1.86-5.23
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.76$		

RFS: Pre-surgery ctDNA presence in LUAD patients.

Study	HR	95%CI
Xia L 2022	6.02	3.42-10.59
Peng M 2020	3.44	1.33-8.90
Qiu B 2021	3.61	1.31-9.95
Li N 2022	3.16	1.12-8.91
Gale D 2022	3.99	1.56-10.22
Chen KZ 2022	3.08	1.11-8.54
Overall (Fixed effects)	4.27	3.02-6.05
Overall (Random effects)	4.27	3.02-6.05
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.78$		

OS: Pre-surgery ctDNA presence in LUAD patients.

Study	HR	95%CI
Peng M 2020	4.68	1.43-15.29
Li N 2022	7.48	0.67-83.24
Gale D 2022	3.63	1.31-10.06
Chen KZ 2022	2.26	0.75-6.82
Overall (Fixed effects)	3.52	1.91-6.49
Overall (Random effects)	3.52	1.91-6.49
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.75$		

RFS: Pre-surgery ctDNA presence in non-LUAD patients.

Study	HR	95%CI
Waldeck S 2022	1.16	0.13-10.20
Xia L 2022	1.35	0.44-4.15
Li N 2022	1.29	0.39-4.26
Chen KZ 2022	1.07	0.15-7.76
Overall (Fixed effects)	1.27	0.62-2.59
Overall (Random effects)	1.27	0.62-2.59
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$		

OS: Pre-surgery ctDNA presence in non-LUAD patients.

Study	HR	95%CI
Waldeck S 2022	2.54	0.26-24.81
Li N 2022	2.91	0.26-32.37
Chen KZ 2022	1.07	0.15-7.76
Overall (Fixed effects)	1.85	0.52-6.59
Overall (Random effects)	1.85	0.52-6.59
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.78$		

RFS: Pre-surgery ctDNA presence in stage I-II patients.

Study	HR	95%CI
Xia L 2022	5.00	2.85-8.78
Peng M 2020	2.69	1.03-7.02
Qiu B 2021	2.60	0.55-12.28
Li N 2022	1.62	0.51-5.17
Gale D 2022	3.17	1.29-7.78
Chen KZ 2022	2.79	1.13-6.88
Overall (Fixed effects)	3.39	2.37-4.84
Overall (Random effects)	3.30	2.24-4.85
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0238$, $p = 0.56$		

OS: Pre-surgery ctDNA presence in stage I-II patients.

Study	HR	95%CI
Peng M 2020	3.75	1.03-13.65
Li N 2022	2.32	0.21-25.59
Gale D 2022	2.69	0.96-7.58
Chen KZ 2022	2.1	0.80-5.52
Overall (Fixed effects)	2.60	1.43-4.74
Overall (Random effects)	2.60	1.43-4.74
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.92$		

RFS: Pre-surgery ctDNA presence in stage III patients.

Study	HR	95%CI
Xia L 2022	1.60	0.66-3.88
Peng M 2020	5.83	0.75-45.43
Qiu B 2021	2.13	0.63-7.20
Li N 2022	1.23	0.39-3.87
Gale D 2022	0.85	0.14-5.20
Overall (Fixed effects)	1.65	0.95-2.88
Overall (Random effects)	1.65	0.95-2.88
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.66$		

OS: Pre-surgery ctDNA presence in stage III patients.

Study	HR	95%CI
Peng M 2020	5.27	0.65-42.72
Gale D 2022	1.06	0.17-6.53
Overall (Fixed effects)	2.11	0.54-8.34
Overall (Random effects)	2.17	0.45-10.34
Heterogeneity: $I^2 = 22\%$, $\tau^2 = 0.2855$, $p = 0.26$		

RFS: Pre-surgery ctDNA presence in patients (postoperative AT).

Study	HR	95%CI
Xia L 2022	0.35	0.17-0.73
Qiu B 2021	0.49	0.22-1.10
Gale D 2022	0.67	0.19-2.36
Overall (Fixed effects)	0.44	0.27-0.72
Overall (Random effects)	0.44	0.27-0.72
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.64$		

RFS: Pre-surgery ctDNA not presence in patients (postoperative AT).

Study	HR	95%CI
Xia L 2022	3.58	1.88-6.82
Qiu B 2021	0.61	0.07-5.46
Gale D 2022	11.82	1.23-113.64
Waldeck S 2022	0.57	0.12-2.61
Overall (Fixed effects)	2.70	1.55-4.70
Overall (Random effects)	1.98	0.56-7.05
Heterogeneity: $I^2 = 63\%$, $\tau^2 = 1.0053$, $p = 0.04$		

***RFS: relapse-free survival. OS: overall survival. AT: adjuvant therapy**

Table S4. Multivariate regression analysis

RFS: Pre-surgery ctDNA presence in patients.

Study	HR	95%CI
Xia L 2022	2.6	1.31-5.15
Peng M 2020	3.46	1.37-8.71
Qiu B 2021	3.03	1.04-8.82
Li N 2022	1.33	0.58-3.07
Gale D 2022	2.22	0.9-5.48
Provencio M 2022	3.85	1.08-13.73
Overall (Fixed effects)	2.45	1.70-3.53
Overall (Random effects)	2.45	1.70-3.53
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.65$		

RFS: Pre-surgery ctDNA presence in LUAD patients.

Study	HR	95%CI
Xia L 2022	3.45	1.66-7.18

RFS: Pre-surgery ctDNA presence in non-LUAD patients.

Study	HR	95%CI
NA	NA	NA

RFS: Pre-surgery ctDNA presence in stage I-II patients.

Study	HR	95%CI
Xia L 2022	3.49	1.54-7.92
Peng M 2020	2.08	0.77-5.62
Gale D 2022	4.64	1.69-12.72
Overall (Fixed effects)	3.25	1.90-5.56
Overall (Random effects)	3.25	1.90-5.56
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.53$		

OS: Pre-surgery ctDNA presence in patients.

Study	HR	95%CI
Peng M 2020	3.39	1.28-8.97
Gale D 2022	1.75	0.68-4.53
Provencio M 2022	23	1.84-287.72
Overall (Fixed effects)	2.81	1.46-5.42
Overall (Random effects)	3.03	1.31-7.00
Heterogeneity: $I^2 = 47\%$, $\tau^2 = 0.1644$, $p = 0.15$		

OS: Pre-surgery ctDNA presence in LUAD patients.

Study	HR	95%CI
NA	NA	NA

OS: Pre-surgery ctDNA presence in non-LUAD patients.

Study	HR	95%CI
NA	NA	NA

OS: Pre-surgery ctDNA presence in stage I-II patients.

Study	HR	95%CI
NA	NA	NA

RFS: Pre-surgery ctDNA presence in stage III patients.

Study	HR	95%CI
Xia L 2022	1.19	0.46-3.09
Qiu B 2021	3.1	0.87-11.06
Overall (Fixed effects)	1.68	0.78-3.60
Overall (Random effects)	1.74	0.70-4.37
Heterogeneity: $I^2 = 28\%$, $\tau^2 = 0.1300$, $p = 0.24$		

OS: Pre-surgery ctDNA presence in stage III patients.

Study	HR	95%CI
NA	NA	NA

RFS: Pre-surgery ctDNA presence in patients (postoperative AT).

Study	HR	95%CI
Xia L 2022	0.24	0.1-0.58
Qiu B 2021	0.47	0.2-1.11
Overall (Fixed effects)	0.34	0.18-0.63
Overall (Random effects)	0.34	0.18-0.65
Heterogeneity: $I^2 = 13\%$, $\tau^2 = 0.0297$, $p = 0.28$		

RFS: Pre-surgery ctDNA not presence in patients (postoperative AT).

Study	HR	95%CI
Xia L 2022	1.89	0.75-4.74

***RFS: relapse-free survival. OS: overall survival. AT: adjuvant therapy**