

Diagnostic and Predictive Utility of Peritoneal tumor DNA in Gastroesophageal Cancer: A prospective multicenter study

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BACKGROUND

Gastric and gastroesophageal adenocarcinomas (G/GEC) frequently metastasize to the peritoneum. However, PET/CT imaging and peritoneal cytology have limited sensitivity for detecting peritoneal metastases. Circulating tumor DNA (ctDNA) correlates poorly with peritoneal disease, however peritoneal tumor DNA (ptDNA) may detect early peritoneal metastatic disease. We developed a tumor-informed whole-genome sequencing (WGS) platform to detect ptDNA and determine:

- (i) Its accuracy in diagnosing peritoneal metastases
- (ii) Its ability to predict survival in G/GEC treated with curative intent

METHODS

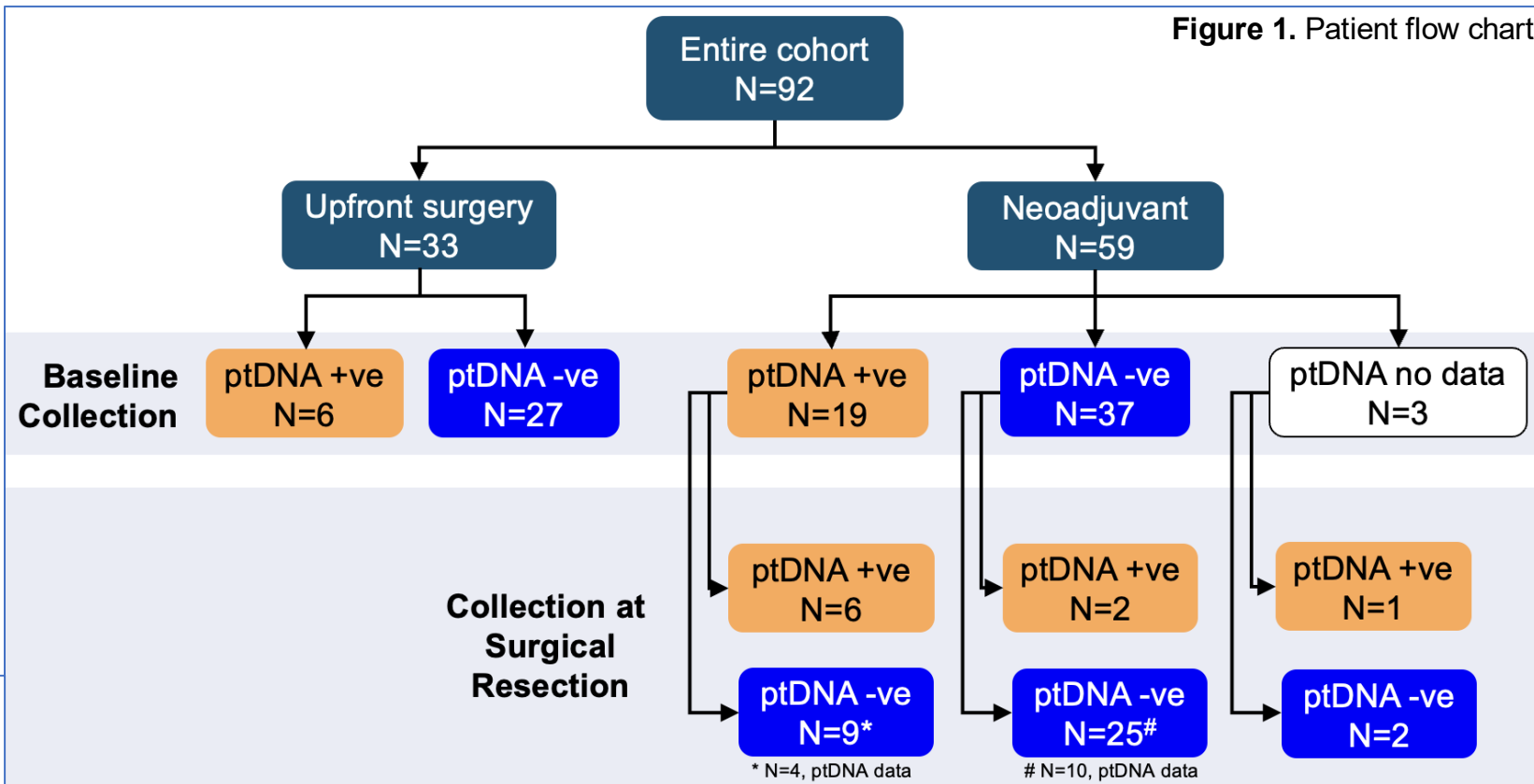
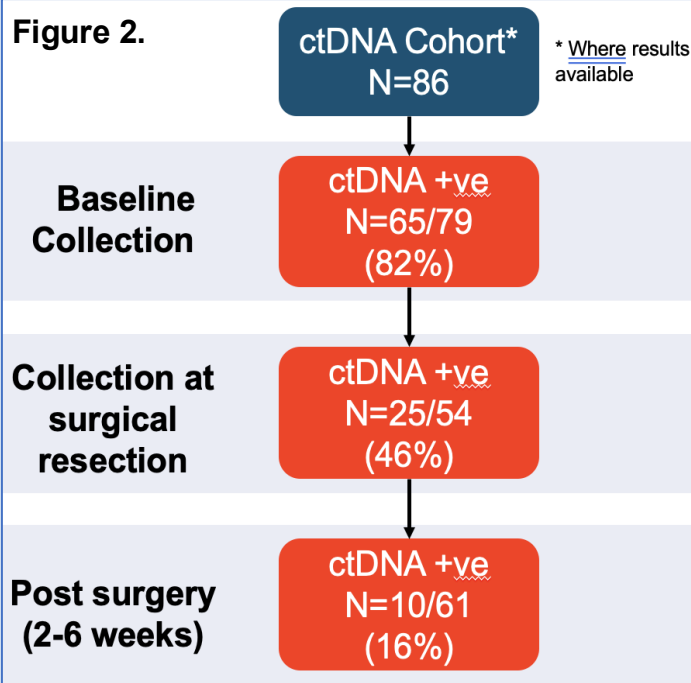
- Prospective nine-center Australian cohort study enrolling curative-intent G/GEC patients (upfront surgery, perioperative FLOT or neoadjuvant CROSS/nivolumab) with tumor biopsies, blood, and peritoneal lavage collected at baseline staging laparoscopy, and/or at surgical resection.
- Tumor-informed WGS detected ctDNA and ptDNA, with associations to RFS, peritoneal-RFS, non-peritoneal RFS and OS evaluated using multivariate Cox regression.
- Diagnostic accuracy of ptDNA for peritoneal metastases was assessed by comparing true-negative patients (>2 years disease-free post surgery alone) with an independently enrolled true-positive cohort (macroscopic/cytology-positive peritoneal disease).

Clinico-pathological characteristics	ptDNA NEGATIVE (n=64)	ptDNA POSITIVE (n=28)	p-value
Age, years, median (range)	69 (38-88)	68 (59-77)	0.59
Male sex, n (%)	47 (73%)	20 (71%)	1.00
Charlson Comorbidity Index, median (IQR)	3 (2-4)	3 (2-4)	0.15
Neoadjuvant therapy, yes, n (%)	37 (58%)	22 (79%)	0.10
Chemoradiation	9 (14%)	3 (11%)	
Chemotherapy	28 (44%)	19 (68%)	
None	27 (42%)	6 (21%)	
cT-stage, n (%)			0.007
cT1	13 (20%)	0 (0%)	
cT2-3	47 (73%)	23 (82%)	
cT4	4 (6%)	5 (18%)	
cN-stage, n (%)			0.065
cN0	42 (66%)	12 (43%)	
cN+	22 (34%)	16 (57%)	
(y)pT-stage, n (%)			<0.001
(y)pT0	4 (6%)	4 (14%)	
(y)pT1	26 (41%)	0 (0%)	
(y)pT2	9 (14%)	4 (14%)	
(y)pT3	19 (30%)	10 (36%)	
(y)pT4	6 (9%)	10 (36%)	
(y)pN-stage, n (%)			0.85
(y)pN0	34 (53%)	13 (46%)	
(y)pN+	30 (47%)	15 (54%)	

Table 1. Clinico-pathological features according to ptDNA status.

ptDNA RESULTS

- ptDNA was detected in 28 of 92 (30.4%, **Figure 1**) consecutive non-metastatic patients and significantly correlated with advanced cT and (y)pT stage (**Table 1**).
- At a median follow-up of 17 months, there were 12 (13%) peritoneal and 10 (11%) non-peritoneal recurrences. ptDNA-positivity independently predicted poorer peritoneal-RFS, RFS and OS, but not non-peritoneal RFS (**Figure 3**).
- Nine patients converted from ptDNA-positive to ptDNA-negative post neoadjuvant treatment (**Figure 1**).
- Patients who were ptDNA-positive at baseline and remained positive post-neoadjuvant therapy had markedly worse peritoneal-RFS (3/6 recurred), whereas 0/25 persistently ptDNA negative patients experienced peritoneal recurrence.
- Diagnostic accuracy of ptDNA was validated in 10 true negative and 12 true positive patients. In this cohort, ptDNA achieved 100% sensitivity, specificity, positive and negative predictive values (95% CI 75.8-100%) for detecting peritoneal metastases (**Table 2**).



ctDNA RESULTS

- ctDNA results are available in 86 of 92 patients (93%, **Figure 2**).
- Baseline ctDNA status did not correlate with peritoneal nor non-peritoneal RFS (**Figure 5**).
- In patients who received neoadjuvant therapy, ctDNA-positivity at time of surgery predicted non-peritoneal RFS but not peritoneal RFS (**Figure 6**).
- Post-surgery ctDNA-positivity independently predicted poorer RFS and OS (data not shown).

CONCLUSION

Tumor-informed WGS-based ptDNA accurately diagnoses peritoneal disease and predicts peritoneal recurrence post curative-intent treatment for gastric and gastroesophageal adenocarcinomas.

ctDNA status accurately predicts for non-peritoneal recurrence, but does not predict peritoneal recurrence.

ptDNA and ctDNA provides complementary information and shows strong potential to personalize clinical management and guide future intraperitoneal strategies.

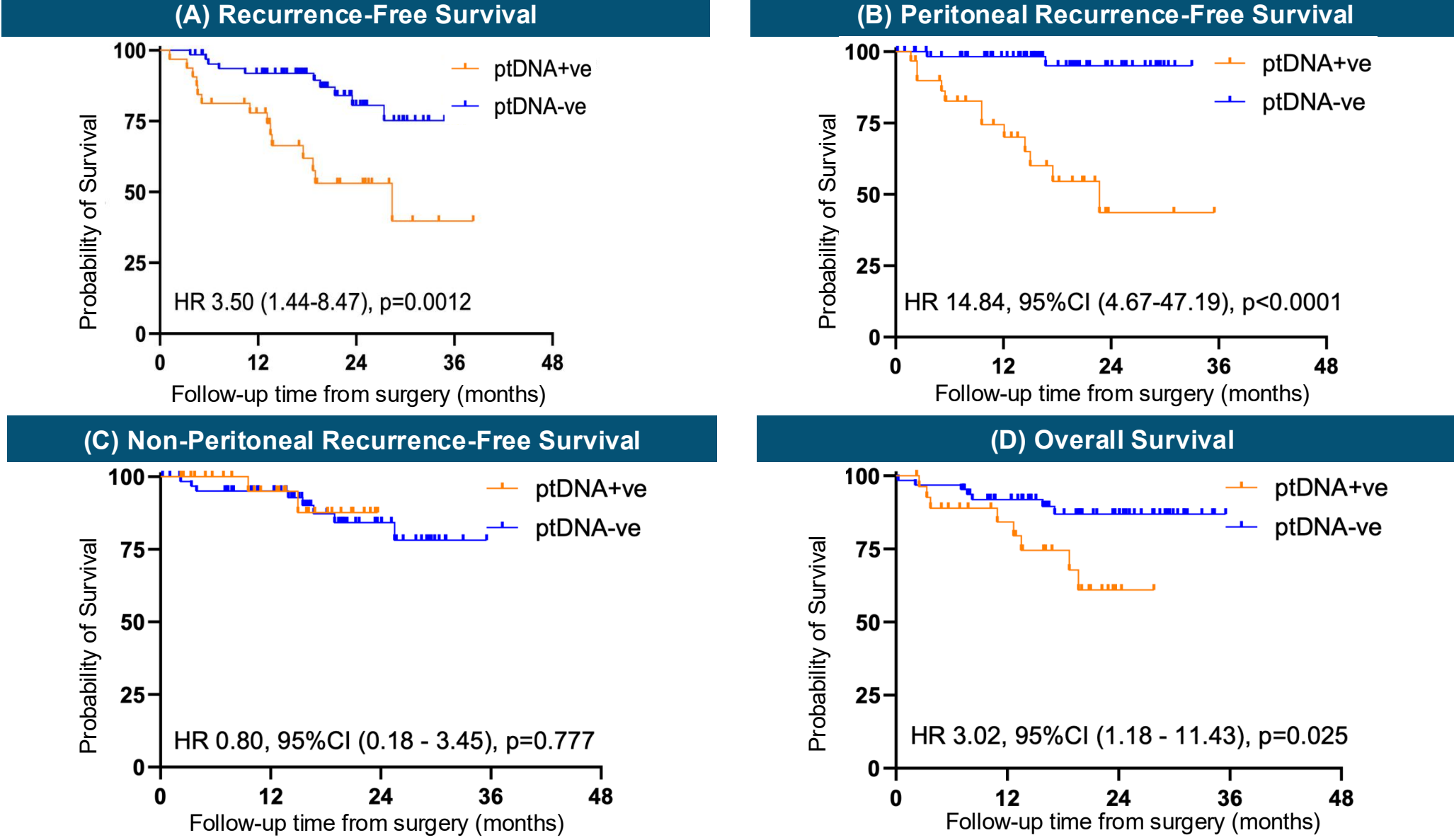
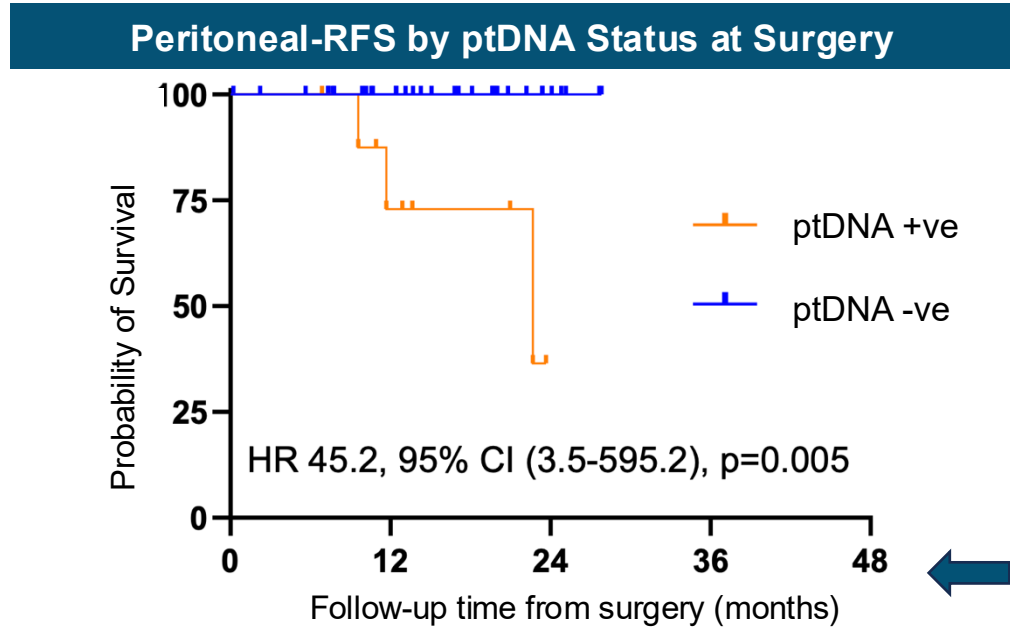


Figure 3. (A) Recurrence-free survival, (B) Peritoneal-specific recurrence-free survival, (C) Non-peritoneal recurrence-free survival, and (D) Overall survival according to ptDNA status at baseline and/or at surgery



Diagnostic Performance	Value	95% CI
Sensitivity	100%	0.76-1.00
Specificity	100%	0.72-1.00
Positive Predictive Value	100%	0.76-1.00
Negative Predictive Value	100%	0.72-1.00

Table 2. Diagnostic performance of ptDNA

Figure 4. For patients who received neoadjuvant therapy, peritoneal-specific recurrence-free survival according to ptDNA status at surgery

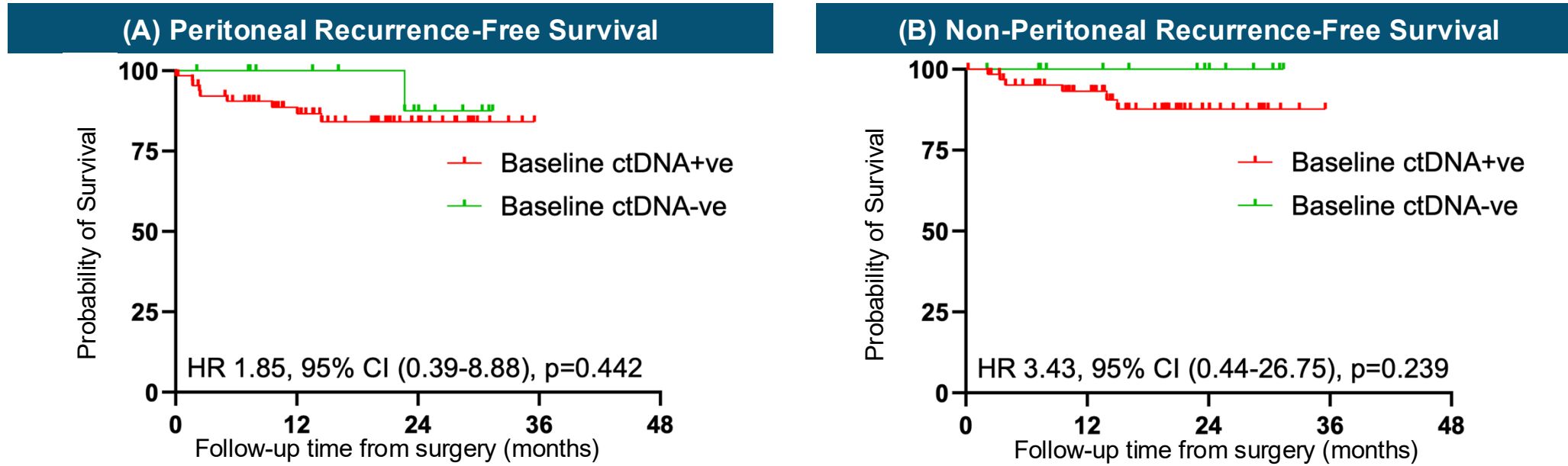


Figure 5. (A) Peritoneal RFS and (B) Non-peritoneal RFS according to baseline ctDNA status

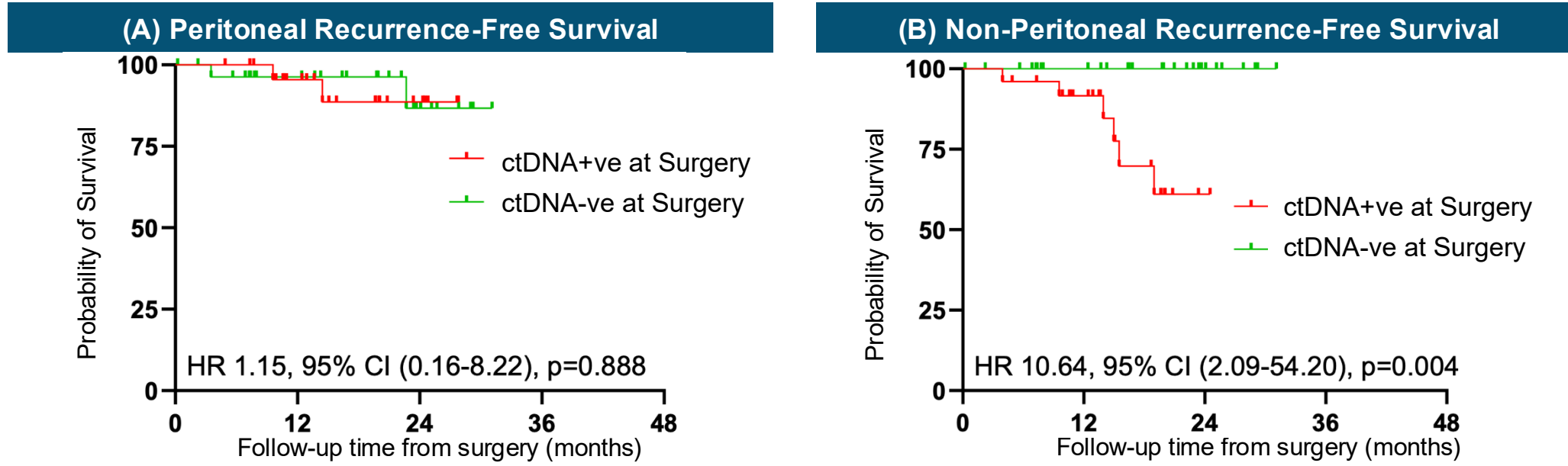


Figure 6. (A) Peritoneal RFS and (B) Non-peritoneal RFS according to surgical ctDNA status for patients who received neoadjuvant therapy

