ABSTRACT #: 708

Selecting Patients with Stage II or III Colorectal Cancer for 5-Fluorouracil-based Adjuvant Chemotherapy Using Proteomic Analysis

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BACKGROUND

- 5-fluorouracil (5-FU) is widely used to treat high-risk stage II and III colorectal cancer (CRC). Even in combination with oxaliplatin, about 15% of stage II patients and 30% of stage III patients relapse within 48 months [1]. Identifying biomarkers of response to 5-FU can improve patient selection for chemotherapy.
- 5-FU requires biochemical conversions to mediate cytotoxicity. This process involves enzymes such as thymidine phosphorylase (TYMP) and uridine-cytidine kinase 2 (UCK2).
- Mass spectrometry-based targeted proteomic analysis objectively quantitates candidate protein biomarkers in formalin-fixed, paraffin-embedded (FFPE) tumor samples.
- Protein expression levels of TYMP were associated with overall survival in a retrospective analysis of gastric cancer patients who received 5-FU-based chemotherapy [2].
- We hypothesized that protein biomarkers associated with 5-FU metabolism predict survival in stage II/III CRC patients treated with 5-FU.

METHODS

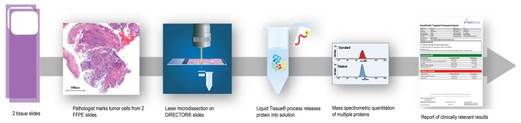

Figure 1. In archived clinical samples of stage II/III CRC (n=128), 66 proteins were quantitated with mass spectrometry. Protein expression cutoffs were derived via Cox proportional hazard modeling and Monte-Carlo 2-fold cross-validation. Patients were dichotomized by UCK2 and TYMP protein expression level. Survival curves were compared using the Mantel-Cox log-rank test.

RESULTS

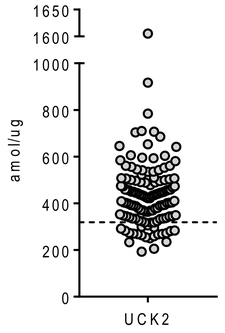

Figure 2. Distribution of UCK2 protein expression in stage II/III CRC (n=128). The dashed line denotes the cutoff of 319 attomoles per microgram (amol/ug).

Stage II/III CRC: 5-FU-treated patients with high UCK2 expression had longer RFS and OS

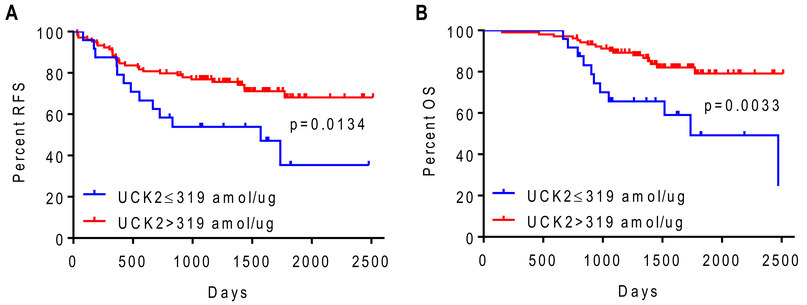

Figure 3. (A) Among stage II/III CRC patients receiving 5-FU (n=128), those with UCK2>319 amol/ug (n=104) had longer relapse-free survival (RFS) compared with patients with lower UCK2 expression (hazard ratio [HR]: 0.45; p=0.0134; median RFS [mRFS] not reached vs. 1571 days). **(B)** High UCK2 expression was similarly associated with superior overall survival (OS) (HR: 0.33; p=0.0033; median OS [mOS] not reached vs. 1736 days). The associations between UCK2 level and survival remained significant in bivariate Cox models after adjusting for clinical covariates, except for differentiation status.

Stage III CRC: 5-FU-treated patients with high UCK2 expression had longer RFS and OS

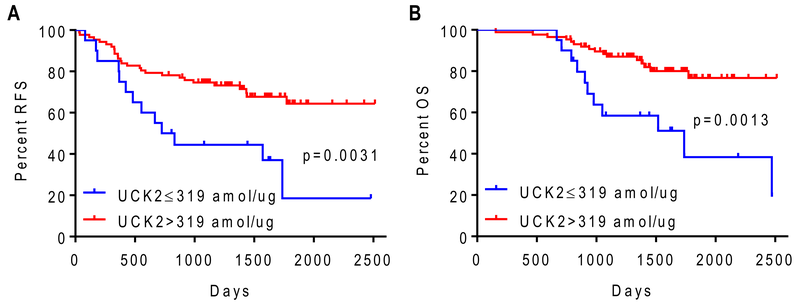

Figure 4. (A) Among stage III CRC patients receiving 5-FU (n=107), those with UCK2>319 amol/ug (n=87) had longer RFS compared with patients with lower UCK2 expression (HR: 0.38; p=0.0031; mRFS not reached vs. 778 days). **(B)** High UCK2 expression was similarly associated with longer OS (HR: 0.3; p=0.0013; mOS not reached vs. 1736 days).

Stage II/III CRC: 5-FU-treated patients with high levels of TYMP and UCK2 had longer RFS and OS

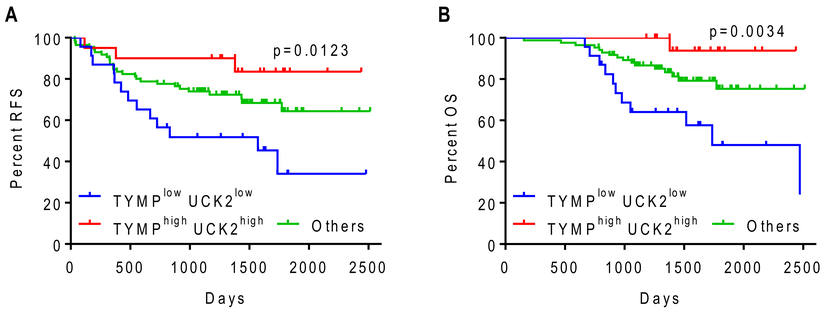

Figure 5. (A) Patients with high levels of both TYMP and UCK2 (n=20) had longer RFS than patients with low TYMP and UCK2 expression (n=23; mRFS not reached vs. 1571 days) and others (n=85). **(B)** High levels of TYMP and UCK2 were similarly associated with longer OS than low levels of TYMP and UCK2 (mOS not reached vs. 1736 days). The p values were calculated with ANOVA.

CONCLUSIONS

- Stage II/III CRC patients with high intratumoral expression of UCK2 (>319 amol/ug) derived significantly more survival benefit from 5-FU-based chemotherapy, compared with low UCK2 expressors. The association between UCK2 level and survival remains statistically significant in the stage III subgroup.
- Stage II/III CRC patients with a signature of high TYMP and high UCK2 expression gained the largest survival benefit from 5-FU.
- Quantitative targeted proteomics represents an objective and robust approach to identifying likely responders to 5-FU-based chemotherapy.

FUTURE DIRECTION

- Studies are underway to validate UCK2 and TYMP as predictive biomarkers for 5-FU-based chemotherapy.

REFERENCE

[1] *J Clin Oncol*. 2009; 27(19):3109-16. [2] *Annals of Oncology*. 2017; 28 (suppl_5): v22-v42.