Whole-transcriptome profiling of biopsies from unresectable intrahepatic cholangiocarcinoma (iCCA) reveals a prognostic signature with treatment implications.

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INTRODUCTION

Transcriptome profiling provides useful insights for therapeutics. However, only data for resected disease are available to date, limiting the clinical implications for advanced iCCA. To mitigate the challenge of achieving sufficient statistical power in a rare cancer type, we identified a clinically homogenous cohort of advanced iCCA patients that displayed significantly different survival on first-line chemotherapy: rapid progressors (RP; survival ≤ 6m) and long survivors (LS; survival ≥ 23m). Here, we applied transcriptome profiling to derive a prognostic signature from RP and LS patients.

AIMS

- To determine the feasibility of transcriptome profiling in advanced iCCA patient biopsies;
- To characterize the molecular basis of RP and LS patients with discordant response to chemotherapy;
- To evaluate the biological and prognostic implications of a RP-LS signature in resected iCCA.

METHODS

- RP and LS were defined according to overall survival (OS): RP ≤ 6 months, LS ≥23 months.
- mRNA expression profiling was performed with TempO-Seq targeted-sequencing technology on pretreatment liver biopsies.
- The RP-LS signature was established from differentially expressed genes (DEGs; fold-change≥2, p<0.05).
- The RP-LS signature was evaluated in 401 resected patients (1-4), including survival analyses (Kaplan-Meier, Cox proportional hazards), as well as genomic analyses.
- A pancreatic cancer transcriptomic predictor of gemcitabine sensitivity was evaluated using GemPred (5).
- Potential responsiveness of tumors to checkpoint inhibitors was predicted using the TIDE metric (6).

CONCLUSIONS

We showed the feasibility of whole-transcriptome profiling of biopsies from advanced iCCA and identified a gene-signature with prognostic implications, including predicted benefit from chemotherapy and immunotherapy. This signature was recapitulated in resected cases even though classified early stages as mainly at good prognosis. On the bases of this signature, it is possible to speculate that patients rapidly progressing on chemotherapy may benefit from immunotherapy checkpoint inhibitors.

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RESULTS

RP and LS iCCA patients significantly differ in response to chemotherapy & display distinct transcriptomic profiles

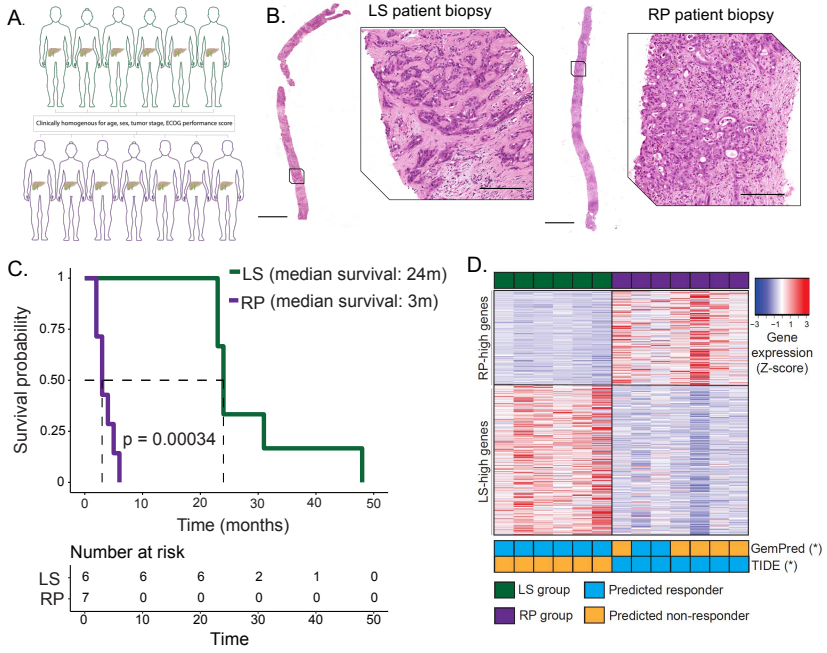

Figure 1: (A) Overview of RP and LS advanced iCCA patients. Both groups are clinically matched for age, sex, tumor stage, ECOG performance score and first-line chemotherapy; however, RP and LS patients significantly differed in survival on first-line chemotherapy. (B) Representative H&E images of biopsies from LP and RP patients used for transcriptome profiling. Scale bar: 2mm (left), 200µm (right). (C) Kaplan-Meier survival analysis of RP and LS patients. (D) Expression heatmap of 504 genes in the RP-LS signature in advanced iCCA patients. The LS group is significantly enriched in predicted responders to gemcitabine (GemPred), the RP group is significantly enriched in predicted responders to checkpoint inhibitors (TIDE). *: P<0.05, Fisher's exact test.

The RP-LS chemoresistance signature is prognostic independent of tumor stage and mutation status in resected iCCA

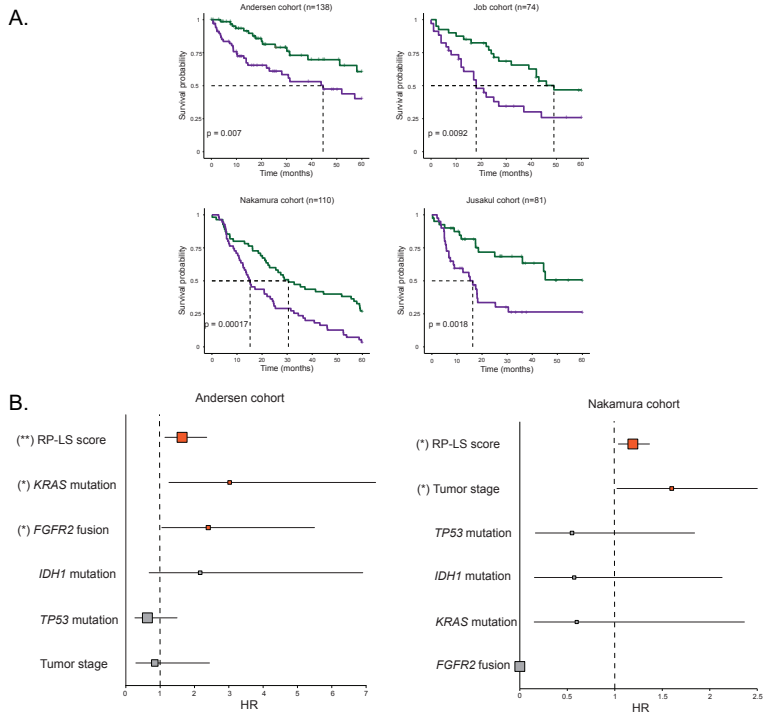

Figure 2: (A) Kaplan-Meier survival analysis of resected iCCA patients stratified into low (below median) and high (above median) RP-LS signature expression. (B) Multivariate Cox proportional hazards analysis of RP-LS signature expression, tumor stage and recurrent genomic alterations for survival of resected iCCA patients. HR: hazards ratio. *:P<0.05. **:P<0.01.

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