5 GROWTH SUPPRESSION BY ALTERATION IN KEAP1/NRF2-NOTCH-STAT3 SIGNALING IN CHOLANGIOCARCINOMA
S. Kunnimalaiyaan, T. C. Gamblin and M. Kunnimalaiyaan
*Corresponding author. Muthusamy Kunnimalaiyaan, Medical College of Wisconsin, USA

Background: Recently, we have reported that xanthohumol, a prenylated chalcone showed anti-proliferative effect in CCA cell lines both in vitro and in vivo. However, the exact mechanism of action remains unclear. Our objective is to test the hypothesis that xanthohumol will effectively inhibit CCA proliferation by altering keap1/Nrf2-Notch-STAT3 axis.

Methods: Human CCA cell lines were used for the treatment with increasing concentrations of xanthohumol for three days. Western analysis was carried out for the levels of keap1/Nrf2-Notch-STAT3 axis proteins as well as apoptotic markers. Notch1, Keap1, and Nrf2 loss-of gene function by shRNAs and their effects were analyzed.

Results: Dose dependent reduction of Keap1 with corresponding level of Notch1 reduction with XN treatment was observed. Importantly, this is associated with a reduction in phosphorylated STAT3 without affecting the levels of total STAT3 proteins. Notch1 depletion significantly reduced the levels of STAT3 phosphorylation. Growth suppression due to apoptosis was evidenced by an increase in the pro-apoptotic marker, cleaved PARP and caspase-3.

Conclusion: Xanthohumol treatment reduced keap1, Notch1 and phosphorylated STAT3 proteins. Notch1 specific depletion showed reduction in STAT3 phosphorylation suggested that Notch1 affects STAT3 pathway. This provides evidence to the role of keap1/Nrf2-Notch-STAT3 signaling pathway in CCA. Importantly, this study provides insight into dual targeted therapies such as Notch and STAT3 inhibitors in combination. This is the first study to show the regulation of keap1/Nrf2-Notch-STAT3 by xanthohumol in cholangiocarcinoma.

6 LONG-TERM OUTCOMES OF PATIENTS WITH INTRADUCTAL GROWTH SUB-TYPE OF INTRAHEPATIC CHOLANGIOCARCINOMA
Ozgür Akgül, Fabio Bagante, Matthew Weiss, Katiuscha Merath, Sorin Alexandrescu, Hugo P. Marques, Luca Aldrighetti, Shishir K. Maithel, Carlo Pulitano, Todd W. Bauer, Feng Shen, George Poultsides, Olivier Soubrane, Guillaume Martel, Bas G. Koerkamp, Guglielmi Endo, Alfredo Itaru and Timothy M. Pawlik
*Corresponding author. Fabio Bagante, The Ohio State University, USA

Background: Intrahepatic cholangiocarcinoma (ICC) is morphologically classified as mass forming (MF), periductal infiltrating (PI) or intraductal growth (IG) type. IG tumors typically present as papillary lesions and may be associated with a different prognosis. We sought to define the characteristics of patients with IG ICC and characterize long-term outcomes of IG patients relative to patients with MF and PI tumors.

Methods: 1,083 patients who underwent curative-intent liver resection for ICC between 1990 and 2015 were identified using an international database. Data on clinicopathological characteristics, operative details, and morphological status, were recorded and analyzed.

Results: ICC morphology consisted of MF (n = 911, 84%), PI (n = 142, 13%), or IG (n = 30, 3%) subtypes. Among patients with IG ICC, 63% has a T1a/T1b tumor and the majority of patients (67%) were node negative. In contrast, most patients with MF (52%) or PI (78%) tumors had more advanced T2/T3/T4 disease; the incidence of lymph node metastasis among MF (34%) or PI (59%) was comparable (both p > 0.05). On final pathology, the incidence of R0 margins was also similar among IG (93%) and MF tumors (89%)(p = 0.46), yet lower among patients with PI ICC (77%)(p = 0.04). Lympho-vascular invasion (IG, 13% vs. MF, 29% vs. PI, 46%) was lower among patients with IG ICC (p < 0.001). In addition, the incidence of perineural invasion was also lower among IG patients (IG, 17% vs. MF, 18% vs. PI, 38%; p = 0.03). While 5-year overall survival was comparable among patients with IG ICC (41%) and MF ICC (42%), long-term outcome was lower among patients with PI ICC (25%)(p = 0.04).

Conclusion: Patients with IG ICC tended to present with earlier T-stage disease, yet had the same overall incidence of nodal metastasis. Long-term outcomes were comparable to the most common MF morphological ICC subtype, yet was better than PI ICC.

7 DOES ADDITIONAL RE-RESECTION OF A POSITIVE PROXIMAL MARGIN IN HILAR CHOLANGIOCARCINOMA AFFECT SURVIVAL? MAYO EXPERIENCE
L. Yohanathan, K. P. Croome, C. A. Puig, M. Traynor and D. M. Nagorney
*Corresponding author. Lavanya Yohanathan, Mayo Clinic, USA

Background: The impact of additional resection for positive proximal bile duct margins during hepatic resection of
hilar cholangiocarcinoma (HCCA) on survival and disease progression remains unclear. We sought to determine whether additional resection of positive proximal bile duct margins during resection of HCCA affected outcomes.

Methods: Single institution, retrospective review of all patients undergoing HCCA resection between 1993 and 2017 was undertaken. Both frozen section and final margin status for all patients was reviewed. Patients were categorized based on margin status on frozen section and final pathology as: Group A (margin – to margin –), Group B (margin + to margin –) and Group C (margin + to margin +). Overall survival and disease progression were primary outcomes.

Complication rates and need for adjuvant therapy were secondary outcomes.

Results: 154 patients underwent hepatic and bile duct resection with regional lymphadenectomy and Roux Y hepaticojejunostomy for HCCA. Median survival (months) for Group A, Group B, and Group C was 45, 33, and 30. There was no significant difference in overall survival.

Conclusion: Current evidence fails to support survival advantage for re-resection for initially margin positive HCCA.

9 LAPAROSCOPIC PARENCHYMA-SPARING LIVER RESECTION FOR COLORECTAL METASTASES

Davit L. Aghayan, Egidijus Pelanis, Ásmund A. Fretland, Airazat M. Kazaryan, Mushegh A. Sahakyan, Bárd I. Røsok, Leonid Barkhatov, Bjørn A. Bjomme, Ole J. Elle and Bjørn Edwin

*Corresponding author. Davit Aghayan, Oslo University Hospital, Norway

Background: Laparoscopic liver resection (LLR) of colorectal liver metastases (CLM) is increasingly performed in specialized centers. While there is a trend toward a parenchyma-sparing strategy in multimodal treatment for CLM, its role is yet unclear. In this study we present short- and long-term outcomes of laparoscopic parenchyma-sparing liver resection (LPSLR) at a single center.

Methods: LLR were performed in 951 procedures between August 1998 and March 2017 at Oslo University Hospital, Oslo, Norway. Patients who primarily underwent LPSLR for CLM between August 1998 and March 2016 were included in the study. LPSLR was defined as non-anatomic LLRs, i.e. the patients, who underwent hemihepatectomy and sectionectomy were excluded. Perioperative and oncologic outcomes were analyzed. The Accordion