	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy	n
Cyto/ FISH	52.4%	100%	100%	81.5%	84.6%	65
FC	66.7%	100%	100%	89.3%	91.2%	34
DC	45.5%	90.0%	71.0%	75.0%	74.2%	31
FC/Cyto/FISH	77.8%	100%	100%	92.6%	94.1%	34
DC/Cyto/FISH	72.7%	90.0%	80.0%	85.7%	83.9%	31

Sa1465

ALPHA FETOPROTEIN AND A USEFUL TOOL FOR SURVEILLANCE OF INTERFERON-FREE TREATED CIRRHOTIC PATIENTS FOR HEPATOCELLULAR CARCINOMA AFTER SVR

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Background and aim: The risk of hepatocellular carcinoma (HCC) development decreases after obtaining sustained virological response (SVR) in patients treated with pegylated interferon and ribavirin. However, in DAA era, with very high SVR rates in patients with compensated and decompensated liver cirrhosis, the beneficial effect on occurrence of HCC is still controversial. The aim of our study was to evaluate the early occurrence and recurrence of HCC in cirrhotic patients treated with IFN-free regimens. Methods: We analyzed 356 consecutive patients with HCV liver cirrhosis genotype 1b treated with IFN-free regimens and followed for minimum 6 months. Twenty one patients had treated HCC and documented imaging without recurrence prior to initiation of antiviral therapy. The minimum time from treatment of HCC to initiation of IFN-free therapy was 3 months. Results: 3D and ribavirin regimen induced SVR in 99.2% of patients. During 6 months of follow-up, HCC was detected in 19 patients (5.3%): 4 patients out of 21 patients with previous HCC (19.04%) and 15 out of 336 patients (4.5%) without previous HCC. Fourteen patients with de novo or recurrent HCC had SVR, only one was nonresponder and developed de novo HCC. Also one patient with recurrent HCC was nonresponder. Patients with recurrent or de novo HCC had a median age of 62.5years, 55.6% were males, 88.9% were with HCC intraMilan, predominantly one nodule in 83.3%, with a median maximum size of the nodule of 2.8cm. The median time to de novo HCC was 5.7 months. According to BCLC classification 22.2% of patients were stage 0, 66.7% were stage A, 8.3% were stage B and 2.8% stage C. There was a significant difference regarding AFP value between patients with de novo HCC and those without HCC de novo at the end of antiviral therapy (78.3±40.7 vs 6.5±0.5 ng/ml, p=0.04). In the group without HCC de novo, AFP value decreased significantly between initiation and the end of the antiviral therapy (25.4 ± 7.9 vs 6.5±0.5 ng/ml, p=0.02). Conclusions: All cirrhotic patients with SVR following DAA therapy should be screened for de novo HCC as well as surveilled for recurrent HCC in patients with previous HCC prior to antiviral therapy every 3 months after the end of antiviral therapy. Association of AFP monitoring during antiviral therapy can increase the diagnostic accuracy in these patients with early stages of HCC. The rather high recurrence rate of HCC could reflect the presence of a more aggressive tumor biology and may be useful for guiding access to IFN-free therapy of these patients after a minimum observation period of 6 months before initiation of antivirals.

Sa1466

A NATIONAL STUDY OF CANCER DIAGNOSES IN IRISH LIVER TRANSPLANT RECIPIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

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Introduction: Primary sclerosing cholangitis (PSC) is associated with an increased risk of cholangiocarcinoma, colorectal cancer (CRC) and gallbladder cancer. Orthotopic liver transplantation (OLT) patients (pts) are at increased risk of developing de novo malignancies, however limited and conflicting data exists regarding cancer risk post OLT for PSC. **Aims:** To examine all recorded malignancies over 2 decades in OLT PSC pts and compare to our non-transplanted PSC cohort. To analyse factors associated with the development of malignancies post OLT. **Methods:** We retrospectively studied PSC pts attending the Irish National Liver Unit (INLU) and the Centre for Colorectal Disease (CCD) at St. Vincent's University Hospital from 1/1/94-30/9/16. We integrated this database with the National Cancer Registry in Ireland. This enabled accurate determination of the no. of malignancies recorded in the PSC cohort. Analyzed data included age of recipient at OLT, gender, primary OLT indication, immunosuppressive regime, de novo malignancy post OLT, time from OLT to diagnosis of malignancy or death. **Results:** 173 PSC pts (75.7% male) have attended the CCD or the INLU at SVUH since 1994. 107 (61.8%) pts have undergone 124 OLT. 27/107 pts were transplanted for cholangiocarcinoma. 12 post-transplant de novo cancers and 12 BCC/SCC carcinomas were found in 107 pts during 737.8 person years of follow-up. Median time to cancer diagnosis post OLT was 5 years (IQR 2.8-5.9). Post-transplant lymphoproliferative disease (PTLD) remains a major complication after OLT. Prior studies have reported rates of 1-3% in adult OLT pts. 5 pts were diagnosed with lymphoma post OLT representing 4.7% of cohort. Median time to diagnosis was 5.3 yrs [IQR 2.8-10.2]. Regarding CRC, 2 pts developed CRC post OLT. 4 pts developed colonic dysplasia; 3/4 underwent colectomy. All those who developed colonic dysplasia/ CRC post OLT had co-existing IBD. All 5 colectomy specimens for dysplasia/CRC showed significant co-existing inflammation. One pt post OLT underwent a completion proctectomy for rectal cancer. Statistical analysis was primarily descriptive (table 1). Cox Proportional Hazard Model was used to analyse factors associated with mortality in the PSC OLT cohort. As expected, cholangiocarcinoma as indication for OLT (p=0.005, RR 2.573, 95%CI 1.3-4.95) and an older age at transplant (p=0.05, RR 1.027, 95% CI 1-1.054) were associated with higher mortality. **Conclusion:**These findings represent national cancer figures in our PSC OLT cohort. The rates of PTLD are slightly higher than previously reported in unselected liver transplant groups. We could not find any association between the development of PTLD and aggressive immunosuppressive regimes for co-existing IBD post OLT. The study highlights that IBD/PSC patients remain at significant risk of colonic neoplasia after OLT and require intensive surveillance.

Cancer diagnoses in PSC cohort

	Non-OLT (%)		OLT(%)
All PSC patients (n=173)	66(38%)		107(62%)
	Non-OLT	Pre-OLT	Post-OLT
No. of patients with >=1 cancer diagnoses (excluding skin) n=54	16	27	11
Cholangiocarcinoma n=38	11	27	3 (recurrent)
Gallbladder cancer n=4	4	0	n/a
Gallbladder dysplasia n=2	2	0	n/a
Colorectal cancer n=6	3	1	2
Colonic dysplasia n=9 (Colectomy)	3 (2/3)	2 (1/2)	4 (3/4)
Lymphoma n=9	2	2	5
Other n=9	1	3	5

Sa1467

SERUM MONOMERIC LAMININ-Î"2 AS A NOVEL BIOMARKER FOR HEPATOCELLULAR CARCINOMA

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Background & aims: The diagnosis of hepatocellular carcinoma (HCC) in the early stages is important for successful clinical management. Laminins are a major extracelluar matrix protein, which are composed of 3 non-identical polypeptide chains, α, β, and γ. Laminin-332 (Ln-332), which consists of α3, β3, and γ2 chains is expressed in the basement membranes, and plays roles in cell adhesion, differentiation, proliferation, and migration. Interestingly, monomeric laminin (Ln)-γ2 expression has been reported in various types of malignant carcinoma including HCC, indicating that it may have potential for use as a novel serum biomarker. We have recently developed a quantitative fully automated chemiluminescent immunoassay (CLIA) to determine serum monomeric Ln-γ2 levels using the monoclonal antibody to human monomeric Ln-γ2 selectively. We used this assay to evaluate the diagnostic value of monomeric Ln-γ2 in sera from patients with chronic liver disease (CLD) and patients with HCC. Methods: Using our fully automated CLIA, we examined the monomeric Ln-γ2 concentration in 133 serum samples from 52 healthy volunteers, 24 patients with CLD, and 57 patients with HCC at the St. Marianna University School of Medicine Hospital between January 2007 and April 2015. Serum alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) were also examined in these subjects. Results: Median levels of monomeric Ln-γ2 were significantly higher in patients with HCC (173.2 pg/mL) compared with patients with CLD (76.7 pg/mL) and with healthy volunteers (41.1 pg/mL). When comparing healthy volunteers and patients with HCC, the discriminative ability of monomeric Ln-γ2 (ROC curve AUC = 0.952; 95% confidence interval [CI], 91-99%) significantly surpassed that of PIVKA-II (AUC = 0.821; 95% CI, 73-91%) and it was as effective as AFP (AUC = 0.929; 95% CI, 88-98%). The optimal cutoff value for Ln-γ2 that would distinguish HCC from non-malignant cases was 116.6 pg/mL. Elevated monomeric Ln-γ2 levels were observed in 0% of healthy volunteers, 17% of patients with CLD, and 63% of patients with HCC. The positivity rate in patients with HCC for the combination of monomeric Ln-γ2 and PIVKA-II was 89.5%, which was better than that for either of the two markers alone (63% and 68 %, respectively). Among patients with early-stage HCC (T1 or T2), the positivity rates for monomeric Ln-γ2, AFP, and PIVKA-II were 61%, 39%, and 57%, respectively. Conclusions: Monomeric serum Ln-γ2 may be a potential biomarker for HCC surveillance. The combination of monomeric Ln-γ2 and PIVKA-II may be more sensitive for laboratory diagnosis of HCC than the combination of AFP and PIVKA-II.

Sa1468

HEPATIC DELIVERY OF THERAPEUTIC AGENTS USING BIOLOGICAL NANOPARTICLES

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Background and aims: Extracellular vesicles (EVs) are biologically derived membrane-bound nanoparticles that can be isolated from body fluids such as milk. There is emerging interest in their potential use for therapeutic interventions as they can release their contents following their uptake by recipient cells. However, the safety and efficacy of their use as a therapeutic delivery approach for liver diseases are unknown. Thus, our AIMS were to evaluate the potential of bovine milk-derived EV for hepatic delivery of therapeutics, and to perform toxicological assessment of their safety. **Methods:** EV's were isolated by ultracentrifugation after casein depletion, and quantified by nanoparticle tracking analysis. Genotoxic effects were assessed by alkaline comet or micronucleus assays. Hematological and immunological effects were evaluated at two dose levels. Bio-distribution was assessed in male C57Bl/6 mice 6 hrs after administration of DiR lipophilic tracer labeled EV. Uptake and subcellular localization of PKH67 labeled EV in HepG2 cells was assessed by confocal microscopy or

immuno-EM. EV were loaded with doxorubicin (DOX), anti-sense oligonucleotide to miR-221 (anti-miR-221) or small interfering RNA to beta-catenin (si-B-CAT) using lipofectamine, and effects on cytotoxicity or cell proliferation and downstream protein and gene expression in HepG2 cells were assessed by viable cell assays, immunoblot or qRT-PCR respectively. **Results:** Genotoxic effects were not observed. However, dose-dependent effects of EV on hemolysis, collagen-induced platelet aggregation, leukocyte proliferation, and reduction of zymosan induced phagocytosis were observed. Bio-distribution studies revealed hepatic uptake after IV or IP administration of 2 $x10^{10}$ EV per body, but not after SC or oral administration. In vitro, EV was taken up within cytoplasm, in a perinuclear distribution separate from endosomes. An increase in cytotoxicity was observed with EV-DOX or EV-anti-miR-221 compared with EV alone. However, the cytotoxicity of EV-DOX was similar to that of DOX after 72 hours. EV-si-B-CAT decreased expression of wild-type and truncated mutant beta-catenin compared with EV alone, and decreased mRNA expression of beta-catenin and downstream target gene CyclinD1. **Summary and Conclusions:** EV can be taken up in the liver after systemic administration, are safe, and can be used for the delivery of therapeutic drugs, ASO or siRNA constructs with downstream effects on gene and protein effects or cytotoxicity following their uptake. The use of EV offers a novel approach for targeted delivery of therapeutic agents to the liver utilizing normal physiological processes.

Sa1469

PROGNOSTIC IMPACT OF HEPATITIS B OR C ON THE INTRAHEPATIC CHOLANGIOCARCINOMA

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Background/Aims: Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy arising from the peripheral intrahepatic bile duct epithelium. Hepatitis B virus (HBV) and hepatitis C virus (HCV) may be involved in the development of ICC. The aim of this study is to identify the prognostic value of hepatitis virus infections and the prognostic factors affecting survival in patients with ICC. **Methods:** A retrospective chart review was performed for patients diagnosed with ICC between August 2005 and April 2016 at a Konkuk university hospital. We identified a total of 133 patients with ICC. The overall survival rates between no hepatitis and hepatitis groups were analyzed. Univariate and multivariate analysis were used to estimate factors influencing survival outcome. **Results:** A total of 20.3% (27/133) patients were positive for hepatitis virus. The age of the hepatitis group tend to be younger than that of ICC patients without hepatitis virus infection (*P<0.05*). The median survival of hepatitis and no hepatitis groups were 319 days (±128.7) and 216 days (±15.6), respectively. The survival rates were not significantly different in the two groups (*P=0.405*). For significant prognostic variables in the multivariate analysis, a lower level of serum carbohydrate antigen 19-9 (CA19-9) (*P<0.001*), a lower level of T stage (*P=0.034*), the negative of lymph node metastasis (*P=0.009*) and in those patients who underwent operation followed by adjuvant chemotherapy (*P=0.029*) were independent predictors of good survival. **Conclusion:** Patients with hepatitis-associated ICC did not showed significantly different clinicopathological features and survival rates compared to patients with ICC without hepatitis virus infection. The prognostic factors influencing survival outcome of ICC were the level of CA 19-9, the level of T stage, the presence of lymph node metastasis and the patients who underwent the operation followed by adjuvant chemotherapy. **Key words: Intrahepatic cholangiocarcinoma, Hepatitis B virus, Hepatitis C virus, Survival rate**

Sa1470

NATURAL HISTORY OF SMALL SPORADIC NONFUNCTIONING PANCREATIC NEUROENDOCRINE TUMORS (NF-PNETS)

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Background / Aims : Asymptomatic sporadic nonfunctioning pancreatic neuroendocrine tumors (NF-PNETs) are rare disease but are diagnosed more frequently than before. The aim of this study was to evaluate the natural course of small NF-PNETs. **Methods :** We performed retrospective study of patients with suspected NF-PNETs from 1999 to 2015. Patients older than 18 years with NF-PNETs who were recommended surveillance without surgical resection were included. Patients with clinical symptoms of hormonal hypersecretion, more than 20 mm in size, local invasion, nodal or distant metastasis, and follow-up period of less than 6 months were excluded. **Results :** Sporadic small NF-PNETs in patients initially recommended surveillance (n=69 ; mean age, 58.9 ± 11.1 years) were mainly located in the pancreatic head (n=32, 46.4%) with mean mass size of 10.9 ±3.1 mm. The average follow-up period was 52.2 ± 38.7 months. Tumor size changes during the follow-up period were as follows: increased (n=19, 27.5%), sustained (n=48, 69.6%), decreased (n=2, 2.9%). The mean growth rate of tumors was 0.9 ± 2.9 mm/yr and predicting factors for tumor growth were not found. Thirteen patients (18.8%) underwent surgery later during the follow-up at mean 32.9 ± 46.2 months. On histologic examination of operative or biopsy specimens, WHO grade 1 was found in 18 patients, grade 2 in 1 patients, and grade 3 in 0 patient. The pathologic AJCC stage of surgically resected tumor was Ia in 14 patients, IIa in 2 patients, IIb in 2 patients. There was no distant metastasis except in 2 patients (2.9%) in whom tumor recurred at 34.0 and 50.1 months after surgery. Total 3 patients died during the study but none were identified as disease-related deaths. **Conclusions :** Almost of small NF-PNETs showed benign disease courses during the surveillance period; no significant size change, rare distant metastases, and no disease-related deaths. Wait-and-see strategy can be applied for NF-PNETs less than 2 cm in size.

Sa1471

THE DEVELOPMENT OF NON-INVASIVE METHOD FOR THE MOLECULAR DIAGNOSIS OF GALLBLADDER CANCER

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Background: Gallbladder cancer (GBCa) has often diagnosed at advanced stage resulting poor prognosis, because the patients with early GBCa has not showed any symptoms and the tissue cannot be obtained easily with anatomical reason. To overcome the weakness of the current methods for the diagnosis of GBCa, we focus on the possibility of "liquid biopsy" with bile juice on the concept of non- invasive diagnostic method as circulating tumor DNA in blood. To achieve good treatment effect in future, so called "precision medicine" approach based on the character of the each tumor is mandatory. Methods: Twenty three patients with GBCa were enrolled in this study. Bile juice obtained from 18 of 23 patients was analyzed for mutations of 50 oncogenes (Cancer panel; Haloplex, Agilent Technology) by next generation sequencing (NGS; Illumina, San Diego, CA, USA). Tumor tissues from 16 of 23 patients were analyzed as well as bile juice. Each sample was obtained prior to the treatment. As negative controls, 18 non-GBCa bile juice and 20 non-GBCa tissue samples were analyzed for mutations of 50 oncogenes in the same way. Results: The median (range) age was 77 (44-90) years and the male/female ratio was 0.43 (7/16). Four, three, five, and eleven patients were diagnosed as stage I, II, III, and stage IV, respectively. We set cut-off value at 5% for rare mutation rate based on the results of healthy samples to avoid false positive. Eight of 16 (50%) tumor tissue samples were positive for mutation. TP53, MET, SMAD4, CTNNB1 and AR were detected in 4/16 (25.0%), 1/16 (6.3%), 1/16 (6.3%), 1/16 (6.3%) and 1/16 (6.3%), respectively. In this study, 11 of 23 (47.8%) patients had both tumor tissue samples and bile juice samples. Six of 11 (54.5%) tumor tissue samples were positive for mutation. In these six patients, 4 (66.7%) bile juice samples had the same mutation (TP53, ERBB2/3 were detected in 3/6 (50%), 1/6 (16.7%), respectively). On the other hand, bile juice samples of other 5 patients without tumor tissue mutation (100%) had no mutation. With regard to only bile juice, 9 of 18 (50%) bile juice samples with GBCa were positive for mutations. TP53 mutation, ERBB2/3, KRAS were detected in 7/18 (38.8 %), 1/18 (5.6%), 1/18 (5.6%), respectively. Bile juice analysis for mutations indicated that sensitivity, specificity, positive predictive value (PPV) and negative predict value (NPV) were 50%, 100%, 100% and 67%, respectively. None of negative control samples had any mutations. Conclusion: Mutations in tumor could be detected in bile juice using NGS. Liquid biopsy with bile juice may help us to diagnose GBCa because of high PPV (100%). It may allow us to make new genetic diagnosis of GBCa.

Sa1472

PROPOSAL OF HIGH RISK GROUP FOR HEPATOCELLULAR CARCINOMA IN JAPANESE PATIENTS WITH DIABETES MELLITUS: NEED FOR EXTENSIVE SURVEILLANCE WITH ULTRASONOGRAPHY

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Background/Aim: Diabetes mellitus (DM) has been increasing worldwide. Although DM has been thought to play a great role for onset of hepatocellular carcinoma (HCC), the effective surveillance for HCC in DM has not been established. The aim of this study is to elucidate the risk factor for HCC in DM patients. **Methods**: From 2000 to 2014, 80 naïve HCC only with DM were enrolled as DM-HCC group. Moreover, from 2005 October to 2014 after introducing abdominal ultrasonography (US) report data base, 2083 DM patients were enrolled as DM-US group. The patients of these groups had no viral hepatitis, no known autoimmune hepatic diseases and/or no alcohol abuse (≤60g/day). The reports of first screening US were evaluated. Elderly was defined over 65 years. In addition, we enrolled 1499 Japanese subjects with DM [male:female=971: 528, median 54 years old (range: 23 to 85)] who underwent a medical checkup at our hospital as a normal control group. They had no chronic liver diseases, habitual alcohol use and past history of HCC. We evaluated the clinical feature of DM-HCC group and compared it with the clinical features of HCC in DM-US group. **Results**: Elderly were 86.8% in DM-HCC group (74.1±8.5 years, male:female=54:26, Child-Pugh A:B:C:unknown=63:13:2:2, HbA1c 7.3±1.3%, tumor diameter: 5.7±3.5cm, single:multiple=56:24). FIB-4 index was 4.50±3.42. In DM-US group (elderly: 45.4%), HCC was detected in 0.14% of them (3 cases) and 0.3% of elderly DM-US. Average age and Fib-4 index of the 3 cases were 75.6 years (67-92 years) and 4.84 (2.87-6.98). Especially in elderly DM patients with high FIB-4 index (≥4), HCC was detected in 5.0%. Meanwhile there were only three of control group showed high FIB-4 index (0.2% in all control group, 1.7% in elderly control group). **Conclusions**: Elderly and high Fib-4 index were the characteristics of DM-HCC. HCCs in DM-US group showed similar tendency. Surveillance for HCC in DM patients with US should be recommended especially in elderly and showed high Fib-4 index.

Sa1473

ASSOCIATION BETWEEN BODY MASS INDEX AND PROGNOSIS IN ADVANCED BILIARY TRACT CANCER PATIENTS WHO UNDERWENT PALLIATIVE CHEMOTHERAPY

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Background/Aims: Recently many studies have been conducted to investigate the association between obesity and survival in cancer patients. Cancer have a significant influence on the nutrient status of patients and obesity can affect on the pharmacokinetics of anti-cancer drugs. The impact of obesity on survival is known to vary in different cancers. Biliary tract cancer was less frequently analyzed and most of the studies were on the relationship between obesity and cancer incidence. We performed this study to investigate the association between BMI and overall survival in advanced biliary tract cancer patients with chemotherapy. Methods: Between January 2005 and December 2013, Three hundred and sixteen patients who underwent chemotherapy for biliary tract cancer were retrospectively reviewed. The relationship between BMI (kg/m^2) and overall survival (OS) was assessed. Based on World