no association was found between stent forces and the occurrence of pain, perforation, hemorrhage or fistula formation.
Conclusion: Both SAEs and recurrence of dysphagia following esophageal stent placement were not associated with RF, AF or degree of elongation. It can be speculated that their occurrence is a multifactorial process determined by a combination of stent-, tumor- and patient-related characteristics.
Disclosure of Interest: None declared

OP330 CLINICAL OUTCOMES FOLLOWING STENT PLACEMENT IN REFRACTORY BENIGN ESOPHAGEAL STRICTURE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: The management of benign esophageal strictures is challenging. Common causes are represented by peptic injury, caustic ingestion, radiation treatment and anastomotic ischemia after esophageal resection. The first management strategy includes endoscopic dilation using bougies or balloons. Although the immediate success rate is up to 90%, about 30% to 40% of patients experience recurrent dysphagia within the first year of follow-up. The management of such relapsing refractory cases consists of repeat dilations. To provide alternative and more definitive treatment option, self-expandable stents have been proposed. Three different types of stents have been used: metallic (SEMS), plastic (SEPS) and biodegradable stents (BD).
Aims & Methods: We performed a systematic review and meta-analysis to examine the efficacy of stent placement in the long-term resolution of dysphagia in patients with refractory benign esophageal stricture (RBES). PubMed, SCOPUS, Google Scholar were searched (up to January 2015). Studies recruiting adults with RBES treated with stent placement were eligible. The success, complication and migration rates were pooled by means of a random effect model to obtain an odds with a 95% confidence interval (CI).Statistical heterogeneity was tested using the Q^2 test (significance level: 0.05) and I^2 statistic. If high levels of heterogeneity among the trials occurred ($I^2 >= 50\%$ or $P < 0.05$), the sources of heterogeneity were explored by sensitivity analysis and meta-regression analysis.
Results: Eighteen studies (444 patients) were eligible for inclusion. The pooled clinical success rate was 40.5% (95%CI, 31.5%>49.5%), yielding an odds of 0.68 (95%CI 0.46-0.98) with high heterogeneity ($I^2 = 65.0\%$). The meta-regression analysis showed stricture etiology as the only influencing factor. Patients treated with plastic (SEPS) and metallic stents (SEMS) reported not significantly higher success rates than patients treated with biodegradable (BD) stent [SEPS > SEMS > BD: 46.2% (95%CI 27-66.3%) > 40.1% (95%CI 28.1-54.1%) > 32.9% (95%CI 23.1-44.1%)]. The migration rate was 28.6% (95%CI 21.9-37.1%) yielding an odds of 0.40 (95%CI 0.28-0.59), with SEPS and SEMS reporting not significantly higher migration rates than BD stent [SEPS > SEMS > BD: 33.3% (95%CI 19.4-51.5%) > 31.5% (95%CI 22.5-42.2%) > 15.3% (95%CI 8.3-25.4%)]. The complication rate was 20.6% (95%CI 15.3-28.1%) yielding an odds of 0.26 (95%CI 0.18-0.39) without significant difference between stents [SEMS = BD > SEPS: 21.9% (95%CI 11.5-37.5%) = 21.9% (95%CI 13.8-32.9%) > 19.4% (95%CI 12.3-30.1%)].
Conclusion: Stent placement for the treatment of RBES is effective in about 40% of cases. Since patients with RBES have only two possible treatment options, i.e. life-long dilations or surgery, the overall success rate reported by stent placement should not be considered negligible. Furthermore, the success rates might be even higher in subgroups of patients, according to the stricture etiology (i.e. post-surgery or post-radiotherapy strictures). Further studies should investigate whether the clinical success rate varies according to the stricture etiology.
Disclosure of Interest: None declared

OP331 PREDICTORS OF PARTIAL VS. COMPLETE SYMPTOMATIC RESPONSE IN PATIENTS WITH ESOPHAGEAL ACHALASIA TREATED BY PER ORAL ENDOSCOPIC MYOTOMY (POEM)

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Introduction: POEM results in treatment success in more than 90% of operated patients. Treatment success is usually defined as an Eckardt score (ES) 0-2 (or 0-3). The aim of our study was to assess whether there are any predictive factors for only partial symptomatic improvement with residual symptoms (ES 1 or 2) vs. complete symptomatic response (ES = 0).
Aims & Methods: Since 2012, we performed 87 POEM procedures in 86 patients with achalasia. The overall treatment success at 12 months was 98%. We analyzed clinical outcomes of 59 patients who have had a treatment success (ES= 0, 1 or 2) and completed at least 6 months follow up (27 female, 32 male, mean age 48 years). We performed multivariate logistic regression with stepwise selection of predictors and tested equality of means for continuous variables for the two target levels and Fisher's exact test for independence of the target level and factor variables.
Results: Among 59 analyzed patients, 36 (61%) had a complete symptomatic response (post-POEM ES = 0) while 23 patients (39%) had partial symptomatic response (post-POEM ES 1 or 2). The mean age of patients with a complete response was lower(51 vs. 42 years) as well as the frequency of pre-POEM treatments (botulinum toxin injection or pneumatic dilatation; 11% vs. 35%). The patients with a complete symptomatic response had higher both the pre-POEM IRP (mean 30.1 vs. 23 mmHg) and the mean basal LES tonus (44 vs. 32 mmHg). The frequency of type II achalasia was higher in patients with a complete symptomatic response (83% vs. 61%). Both groups did not differ with regard to the procedure related data (length of the procedure, length of myotomy, etc.). The stage of the disease (duration of symptoms, esophageal width) and the frequency of partial recovery of esophageal peristalsis after POEM (33% vs. 30%) were similar in both groups. Post-POEM esophagitis was more frequent in patients with a complete symptomatic response (36% vs. 26%). In multivariate logistic regression analysis, only age (under 40, p = 0.03), pre-POEM basal LES-tonus (under 40 mmHg, p = 0.04) and any prior treatment for achalasia (p = 0.04) have been found as independent predictors of partial symptomatic response.
Conclusion: Among the patients with treatment success, approx. 40% do not have a complete symptomatic response. Younger age, lower pre-POEM basal LES tonus and previous treatment attempts with botulinum toxin or balloon dilatation are independently associated, despite the overall treatment success, with an incomplete symptomatic response.
Disclosure of Interest: None declared

OP332 PERORAL ENDOSCOPIC REMYOTOMY (RE-POEM): A SALVAGE OPTION FOR PERSISTENT/RECURRENT SYMPTOMS AFTER PREVIOUS POEM

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Introduction: Peroral endoscopic myotomy (POEM) has been described with high success rates for the treatment of achalasia. However, persistence/recurrence of symptoms can occasionally occur after POEM.
Aims & Methods: Our purpose was to evaluate the feasibility, safety and efficacy of salvage peroral endoscopic remyotomy (Re-POEM) for patients after failed POEM. Fifteen patients with persistence/recurrence of symptoms (Eckardt symptom score ≥4) after previous POEM were identified from a prospectively maintained database that included a total of 1454 consecutive achalasia patients. The primary outcome was symptom relief during follow-up, defined as an Eckardt score of ≤3. Secondary outcomes were procedure-related adverse events, lower esophageal sphincter (LES) pressure on manometry, and reflux symptoms before and after Re-POEM.
Results: All patients underwent successful Re-POEM after a mean of 13.5 months (range 4–37 months) from the time of the primary POEM. The mean operation time was 41.5 minutes (range 28–62 minutes). Submucosal tunnel infection occurred in one case and was successfully managed with conservative treatments. During a mean follow-up period of 11.3 months (range 3–18 months), treatment success was achieved in all patients. The mean symptom score pre-treatment was 5.6 (range 4–8) compared with a mean post-treatment score of 1.2 (range 0–3; $P < 0.001$). Mean LES pressure also decreased from a mean of 25.0 mmHg to 9.5 mmHg after Re-POEM ($P < 0.001$). The overall clinical reflux complication rate of Re-POEM was 33.3%.
Conclusion: Re-POEM seems to be a safe and effective salvage option for failed POEM, resulting in short-term symptom relief in all patients and without serious complications.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 15:45–17:15
BASIC ASPECTS OF HEPATOCARCINOGENESIS AND REGENERATION – ROOM E5

OP333 CONTRIBUTION OF NATIVE AND ACTIVATED HEPATIC STELLATE CELLS IN LIVER REGENERATION AFTER PARTIAL HEPATECTOMY AND 2-ACETYLAMINOFLUOREN INJECTION

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Introduction: Actual problem of modern hepatology is to find new and athogenetic treatment of liver diseases. One of these methods could be cell therapy with using hepatic stellate cells (HSC), that are thought to be regional stem cell of the liver. Experiments on freshly isolated rat HSC transplantation confirmed their participation in liver regeneration after partial hepatectomy (PH). However, the role of freshly isolated and activated in vivo HSC transplantation to rats undergoing PH and the injection of 2-acetylaminofluoren (AAF) is still unknown.
Aims & Methods: To study the influence of transplanted HSC on activity of liver regeneration after PH and AAF injection.
Before transplantation HSC were labeled by the gene of Enhanced Green Fluorescent Protein (GFP). We selected the classical model of acute liver damage – partial hepatectomy. In one case, we transplanted native HSC, in the other – in vivo activated HSC. Activation was carried out by lead nitrate injection into the tail vein of rats donor, HSC were isolated 2 days thereafter.

To inhibit hepatocyte proliferation in the recipient rats, animals were administered intraperitoneally AAF 5 days before and after surgery. The animals were sacrificed after 1, 2, 3, 5, 7 and 14 days after the transplantation of HSC. Paraffin slices were stained by immunohistochemistry with antibodies to desmin – marker of HSC and è-SMA - myofibroblast marker.
Results: GFP + hepatocytes were detected (found, stained) in liver parenchyma even at the first days after transplantation. All groups showed an increase in the number of desmin - positive cells in the parenchyma. After transplantation of freshly isolated and activated HSC to rats after PH and AAF administration, the maximum number of such cells was found 2 days after surgery, then their number gradually decreased. Desmin-positive HSC in animals after PH without AAF injection retained in the liver longer: in case of freshly isolated HSC transplantation – till the 5th day, after in vivo activated HSC transplantation - till the 7th day. In all the groups è-SMA positive myofibroblasts were not detected.
Conclusion: Transplantation of native and activated HSC stimulates liver regeneration and contributes to hepatocytes repopulation without the risk of liver fibrosis.
Disclosure of Interest: None declared

OP334 O-GLCNAC TRANSFERASE PROMOTES FATTY LIVER-ASSOCIATED LIVER CANCER THROUGH ACTIVATING JNK AND NF-KB PATHWAYS

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Introduction: O-GlcNAc transferase (OGT), a unique glycosyltransferase, is involved in metabolic reprogramming. Using transcriptome sequencing, OGT was identified to be highly expressed in non-alcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (NASH-HCC) compared to their adjacent non-tumor tissues of 18 patients. However, the role of OGT in NASH-HCC is still unclear.
Aims & Methods: We aim to investigate the functional role of OGT in NASH-HCC and its potential clinical implication. The biological function of OGT was determined by proliferation, clonogenicity, migration and invasion experiments through gain- or loss- of OGT functional assays *in vitro* and in nude mice. OGT target factors and pathways were identified by promoter luciferase assay, DNA binding activity assay and Western blot. The effects of OGT on oxidative stress, reactive oxygen species (ROS), lipid peroxide and endoplasmic reticulum (ER) stress and ER stress-related cascades were also investigated. The clinical impact of OGT was evaluated in 209 serum samples of 137 NAFLD patients and 72 control subjects by ELISA.
Results: OGT was upregulated in 12 out of 18 (66.7%) NASH-HCC tumor tissues compared with their adjacent non-tumor tissues by transcriptome sequencing. Enhanced OGT expression was further confirmed in an independent set of 9 pairs of human NASH-HCC tissues (66.7%) by Western blot and in six HCC cell lines and two NASH-HCC cell lines, but silenced in normal livers and weak in immortalized normal hepatocyte cell lines MIHA and LO2. OGT production was significantly induced in MIHA cells treated with insulin ($P<0.01$) or cholesterol ($P<0.01$). Ectopic expression of OGT in MIHA and LO2 cells promoted cell growth, clonogenicity, migration and invasion ability; whereas stable knockdown of endogenous OGT in two NASH-HCC cell lines had opposite effects. Moreover, subcutaneous tumor xenografts of LO2 cells with stable OGT expression in nude mice exhibited an increased tumor growth compared with the control cells ($P<0.01$). Mechanistically, OGT induced ROS production, increased lipid peroxide levels and enhanced the protein expression of ER stress markers GRP78 and IRE1α in LO2 and MIHA cells. In this connection, OGT significantly activated JNK cascade as evidenced by increased protein expression of p-JNK, p-c-Jun and activation of AP-1; induced NF-κB pathway through enhancing the protein levels of p-IKKα/ p-IKKβ, p-p65, p-p50 and the NF-κB DNA binding activity in OGT-transfected LO2 cells compared to the control cells. Moreover, the serum levels of OGT were significantly higher in patients with steatosis (3.30 ng/ml vs 1.83 ng/ml, $P<0.0001$) or NASH (3.49 ng/ml vs 1.83 ng/ml, $P<0.001$) compared with control subjects. The AUROC of diagnosing NAFLD was 0.741 (95% CI: 0.671-0.812) and diagnosing NASH was 0.749 (95% CI: 0.681-0.816). Multivariate analysis showed that OGT was an independent risk factor for NASH patients.
Conclusion: OGT plays an oncogenic role in NASH-associated HCC through inducing ER stress and ROS production and consequently activating oncogenic JNK and NF-κB pathways. Serum detection of OGT may serve as a potential diagnostic marker for NASH patient.
Disclosure of Interest: None declared

OP335 ANTI-ANGIOGENIC TREATMENT WITH OCTREOTIDE ATTENUATES PORTAL HYPERTENSION OF THE CIRRHOTIC RATS THROUGH SOMATOSTATIN RECEPTOR 2

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Introduction: Angiogenesis is pivotal for the devolvement of portal hypertension in cirrhosis. Somatostatin (SST) and its analogue octreotide are widely used for the management of gastroesophageal varices bleeding. However, the molecular and cellular mechanism of SST and octreotide on portal hypertension remains unclear.
Aims & Methods
Aims: To investigate the mechanism of octreotide on regulation of portal hypertension.
Methods: Peritoneal injection of thiacetamide (TAA) was employed to induce liver cirrhosis (200 mg/kg every 3 days for 16 weeks). 36 male Sprague-Dawley rats were randomized into control, TAA and TAA + octreotide with 12 animals in each group. TAA + octreotide group received TAA plus octreotide (50 mg/kg/day) from the initiation of TAA administration. TAA group received TAA plus placebo and control group received injections of normal saline. Scanning electron microscope of vascular casting, hematoxylin-eosin staining (HE), Masson trichrome staining (MT) were applied to evaluation of cirrhosis and angiogenesis. Portal pressure was also measured. Immunohistochemistry (IHC), quantitative real-time PCR (qRT-PCR) and Western blot for alpha-smooth muscle actin (a-SMA), collagen III, CD31, vascular endothelial growth factor (VEGF), phosphorylated extracellular signal-regulated kinase (p-ERK) and somatostatin receptors (SSTRs) were determined. *In vitro*, human umbilical vein endothelial cell line (HUVEC) was treatment with vehicle, octreotide, octreotide plus SSTR-2 antagonist (CYN154806) or octreotide plus SSTR-5 antagonist (BIM23056) for 24 hours. Afterwards, wound-healing assay for cell migration, tube formation assay for angiogenesis, immunocytofluorescence and Western blot for VEGF and p-ERK were carried out.
Results: *In vivo*, compared with TAA group, liver fibrosis and portal pressure in TAA + octreotide group were remarkably decreased by 40.4% and 17.1%, respectively. And the mRNA levels of a-SMA and collagen III in TAA + octreotide group were also reduced. Histological sections, vascular casts of hepatic portal vein, IHC and qRT-PCR for CD31 showed that angiogenesis in TAA + octreotide group were dramatically reduced when compared with TAA group. The up-regulation of VEGF, p-ERK and SSTR-2, SSTR-5 induced by TAA administration were significantly inhibited after treatment with octreotide. *In vitro*, compared with vehicle treated cells, the migration rate, tube length, VEGF and p-ERK protein were obviously substantially decreased in octreotide treated cells. However, these inhibitory effects afford by octreotide were remarkably restored by SSTR-2 antagonist but not SSTR-5 antagonist.
Conclusion: Octreotide could ameliorate portal hypertension in cirrhotic rat through inhibition of intrahepatic angiogenesis. The anti-angiogenesis effect afford by octreotide may attribute to regulation of integrated signal pathways involving SSTR-2 - p-ERK – VEGF.
Disclosure of Interest: None declared

OP336 GENOMIC MUTATIONS AND PATHWAYS IDENTIFIED BY WHOLE-EXOME SEQUENCING IN NAFLD-ASSOCIATED HEPATOCELLULAR CARCINOMA

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Introduction: Epidemiological studies have shown that obesity and its related non-alcoholic fatty liver disease (NAFLD) promotes the development of hepatocellular carcinoma (HCC). However, the underlying genetic mechanism of obese-related HCC is still largely unknown.
Aims & Methods: We aimed to uncover the genetic alterations of obesity-associated HCC using cross-species oncogenomics and whole-exome sequencing. HCC development in genetic obese (*db*/*db*) mice and dietary obese mice kept on high-fat diet was monitored in comparison with wild-type lean mice kept on normal diet treated with diethylnitrosamine (DEN). Paired HCC tumor and adjacent normal samples from obese mice and lean mice were subjected to whole-exome sequencing and cross-species oncogenomics to reveal genetic alteration landscapes. Candidate mutation genes were further validated in HCC tumor and adjacent normal samples from 16 genetic and 13 dietary obese mice and 16 control lean mice by PCR Sanger sequencing. The bio-functional significance and molecular pathways of the candidate mutation genes was evaluated.
Results: Significantly higher tumor incidence, multiplicity and larger tumor size of NAFLD-HCCs were found in both genetic and dietary obese mice compared with those of lean HCCs in wild-type mice. Totally 277 and 268 genes were found to be mutated in liver tumors from obese mice and control lean mice, respectively, with only 8 genes overlapped by whole-exome sequencing. Eight important metabolic or cancer-related pathways were significantly enriched in mutated genes found in obese HCC, whereas only two pathways were enriched in mutated genes found in lean HCC. Mutation frequency of *Cel* was significantly higher in obese HCC than in lean HCC (34.5% *vs.* 6.3%, $P < 0.05$). Mutations in *hRas* were detected in 10.3% of obese HCCs, all located at codon 61, but not in lean HCCs. *CEL* inactivating mutation and *hras* activating mutation promote liver cell growth. Inactivating mutation in CEL (D454E and D555N) led to the accumulation of cholesteryl ester, which activated ER stress and consequent IRE1α/JNK/c-Jun/AP-1 signalling cascade; whist activating mutations in hRas (Q61R and Q61K) activated MAPK and PI3K/PDK1/Akt signaling cascades to promote cell growth.
Conclusion: The genetic alterations of NAFLD-associated HCC are distinguished from that of lean HCC. Mutations in *CEL* and *hRas* play important roles in NAFLD-associated hepatocellular carcinogenesis.
Disclosure of Interest: None declared