25%, p=0.802), and colonic movement normalization rates were similar in the two groups. Considering both surgical procedures(colorectal , p=0.529 + liver resection, p=0.626), there was no significant difference between two group.

Conclusion: MLR can be feasibly and safely performed in selected patients at CRLM with similar perioperative outcomes and morbidities.

Keywords: Colorectal cancer liver metastases, Simultaeneous major liver resection

Oral Presentation 3

- Presentation Date: Saturday, April 25, 2015
- TIME: 15:30-16:30
- Chaired by: Kuk Hwan Kwon, Young Hoon Kim

OP-3-1

Influence of Preoperative Transcatheter Arterial Chemoembolization on Gene Expression in the HIF-1α Pathway in Patients with Hepatocellular Carcinoma

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Introduction: Hepatocellular carcinoma (HCC) is a major malignancy of the liver with high-incidence and mortality rates worldwide (Llovet et al., 2003). Due to the complexity and heterogeneity of hepatocarcinogenesis accompanying chronic liver disease, prognosis of HCC remains poor. More than 80 % of HCC patients are diagnosed at an inoperable stage (Okuda et al., 1985), and available treatment options are limited.

Transcatheter arterial chemoembolization (TACE) is a non-curative and the most common treatment modality for HCC. TACE has been shown to improve survival and effectively suppress tumor progression (Zhang et al., 2000). In contrast, other studies have reported that TACE increases the recurrence rate and aggravates prognosis in HCC patients (Harada et al., 1996; Lee et al., 2009). The principle of TACE is to block blood vessels branching to the liver from arteries with lipiodol and/or chemo agents such as adriamycin, leading to hypoxic tumor necrosis with the aim of maximizing anti-tumor effects. Due to the limitation of TACE to stimulate angiogenesis by inducing hypoxia (Li et al., 2004; Wang et al., 2008), combining TACE with anti-angiogenic therapeutics such as sorafenib has been considered a promising strategy to improve clinical outcomes of HCC and several clinical trials including the SPACE study have been conducted (Abou-Alfa, 2011). Thus, the precise effects of TACE on tumor biology of HCC and its prognostic relevance need to be clarified.

Hypoxia is an inevitable feature of solid tumors during tumor progression. Tumor cells experience hypoxia during natural growth (Semenza, 2003), or artificial manipulation to block blood vessels, such as TACE (Bismuth et al., 1992). Although deprivation of oxygen and nutrients could kill tumor cells, the surviving tumor cells or surrounding pre-neoplastic lesions under hypoxia gain an increased capability to survive and metastasize to other organs (Maxwell et al., 1997). HIF-1α plays critical roles in cells upon oxygen deprivation. In hypoxic conditions, HIF-1α is activated to regulate the transcription of downstream effectors driving tumor angiogenesis and epithelial–mesenchymal transition (EMT) integrating cell growth, invasion, motility, and loss of cell adhesion during metastatic cancer progression (Maxwell et al., 1997; Semenza, 2012; Yang et al., 2008). As a prerequisite step for successful dissemination of tumors from primary organs and subsequent colonization in distant organs (Bastid, 2012), EMT has been closely associated with poor prognosis of HCC. HIF-1α is responsible for hypoxia-induced EMT, which contributes to poor clinical outcomes of HCC (Kim et al., 2010; Mima et al., 2013; Ogunwobi and Liu, 2012). Additionally, elevated VEGF levels concomitant with increased angiogenesis in HCC patients undergoing TACE are attributable to activation of HIF-1α signaling (Huang et al., 2005; Wang et al., 2008). However, there is a lack of studies on relationship of expression of HIF-1α and its associated EMT molecules to prognosis of HCC patients subjected to TACE treatment.

In the current study, we investigated for the first time influence of TACE on expression of HIF-1α and its target genes involved in EMT and their prognostic relevance in HCC patients. Our findings provide molecular insights that should aid in improving treatment and prognosis of HCC.

Materials: A total of 50 patients were randomized 1:1 to preoperative TACE or not before curative resection for primary HCC in Ajou Medical Centers in South Korea. Among initial 25 HCC patients undergoing preoperative TACE, we analyzed 10 patients who met inclusion criteria of both the duration from TACE to resection within 50 days and one time of TACE. The interval between TACE and surgery was an average of 26.4 ± 14.5 days ranging from 6 to 49 days. TACE tissues were taken from the viable portion of necrotic HCC tissues. All tissues were obtained with informed consent from the patients, and the study protocol

was approved by the institutional review board. Table 1 summarizes the clinicopathological characteristics of the 35 HCC patients studied in the current study. We used BCLC stage and Edmondson and Steiner grade according to the traditional criteria (Patel et al., 2011; Villanueva and Llovet, 2011).

Table 1. Clinicopathological characteristics of HCC tissue.

Clinicopathologic parameters	TACE	Non-TACE	*P* value	Clinicopathologic parameters	TACE	Non-TACE	*P* value
Age			NS	BCLC stage			NS
<55 years	7	11		A	2	9	
≥55 years	3	14		B	4	11	
Gender			NS	C	4	5	
Male	10	19		AFP level			NS
Female	0	6		<100 ng/mL	7	13	
HBV			NS	≥100 ng/mL	3	12	
Absent	2	6		Vascular invasion			NS
Present	8	19		Absent	4	10	
HCV			NS	Present	6	15	
Absent	8	22		Tumor number			NS
Present	2	3		Single	8	16	
Liver cirrhosis	(−1)		NS	Multiple	2	9	
Absent	4	10		Tumor size			NS
Present	5	15		≤5 cm	2	12	
Tumor stage			NS	>5 cm	8	13	
I	4	11		Edmondson grade			NS
II	2	5		I	1	2	
III–IV	4	9		II	1	11	
Child pugh			NS	III	6	10	
A	10	24		IV	2	2	
B	0	1					
C	0	0					

NS not significant

Methods:

1. TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION

After the introduction of a selective catheter through the femoral artery using the Seldinger technique, an angiographic survey of the abdominal vessels was performed. The localization of the hepatic arteries was checked with celiac and mesenteric arteriography using selective catheterization. This was performed to define vascular anatomy. Next, indirect portography was performed to outline the portal circulation in the venous phase. A catheter was placed in the celiac trunk and advanced beyond the gastroduodenal artery. Depending on size, location, and arterial supply to the tumor, the tip of the catheter was advanced further into the segmental arteries. For superselective embolization, an infusion catheter was used. A 10 ml of iodized oil (Lipiodol Ultrafluide®, Laboratoire Andr Guerbet, Aulnay-Sous-Bois, France) and 1 mg/kg of doxorubicin hydrochloride (ADM®, Dong-A Pharm. Co. Ltd., Seoul, Korea) were mixed to be injected until stasis of the blood flow was observed. When an initial blockade of tumor feeding artery was insufficient because of the large tumor size or arterioportal shunting, an embolization was performed with gelatin sponge particles (Cutanplast®, Mascia Brunelli Spa, Viale Monza, Italy). After embolization, devascularization was confirmed with additional angiography of the hepatic artery.

2. QUANTITATIVE REAL-TIME PCR

Quantitative real-time RT-PCR was carried out as previously described (Kwon et al. 2010). Total RNA was isolated from frozen tissues using an RNeasy mini kit (Qiagen, USA). The RNA integrity was evaluated by a Bioanalyzer 2100 (Agilent Technologies, USA). Reverse transcription reaction was carried out with 4 μg of total RNA and 2 μL of 10 μmol/L oligo d(T)18 primer (Genotech, Korea) at 70°C for 7 min and then cooled on ice for 5 min. After adding the reverse transcriptase mixture to the primer-annealed total RNA, the reaction was incubated for 90 min at 42°C. Real-time PCR (ABI PRISM 7900HT, Applied Biosystems, USA) was performed in a total volume of 10 μL (2 μL cDNA, 2 μL of 5 pmol/μ primer, 1 μL of 1 pmol/μ probe, and 5 μL Taqman master mix) according to the following 3 steps: an initial denaturation step at 95°C for 10 min, 45 cycles of denaturation step at 95°C for 15 s, and elongation step at 60°C for 1 min. The primer and probe sequences were designed using Primer Express 3.0 software (Applied Biosystems, USA), and all the probes were labeled with FAM and TAMRA at the 5′ end and 3′ end, respectively. Primer and probe sequences for RT-PCR are listed in Supplementary data. The mRNA levels of genes (the threshold cycle, CT value) were measured in triplicate and then subjected to normalization with five reference genes (B2M, GAPDH, HMBS, HPRT1, and SDHA) by subtracting the average values of the mRNA levels of the reference genes as an internal control (Yang and Roberts, 2010).

3. IMMUNOHISTOCHEMICAL STAINING OF HIF-1α

Immunohistochemical staining was done on 4-μm-thick, formalin-fixed, paraffin-embedded tissue sections. Tissue sections were deparaffinized in xylene for 15 min and then rehydrated. Antigen retrieval was performed by boiling in Tris–EDTA buffer (pH 9.0) for 5 min. Slides were then incubated with anti-human HIF-1α mouse monoclonal antibody (Novus, USA) for 1 h at room temperature. The antigen–antibody reaction was detected using the DAKO REAL Detection System (LSAB+, USA) K5001 (DAKO, USA). All the immunohistochemically stained sections were evaluated in a semiquantitative fashion by two pathologists as previously described (Kwon et al., 2010). The HIF-1α expression was evaluated in 10 high-power fields (400×). Intensities were classified as 0 (negative staining), 1 (<5 % of samples stained), 2 (<25 % of samples stained), 3 (25–50 % of samples stained), and 4 (more than 50 % of samples stained).

4. STATISTICAL ANALYSIS

All statistical analyses were performed with the open source statistical program R. The Cox proportional hazard regression model was used to assess prognostic significance of TACE for recurrence and disease-free survival (DFS). Kaplan–Meier survival curves were plotted using tumor

recurrence (defined as the first appearance of a tumor at any site following definitive treatment) or death as the end points. The significant differences in recurrence curve or DFS curves were examined by log-rank test. 2−ΔCt values of each gene were shown in box and whisker plot, and their significant differences between TACE and non-TACE tissues were evaluated by a Student's t test. Distribution of clinicopathologic values in TACE and non-TACE tissues was evaluated using $\chi 2$ and Fisher's exact test. A P value <0.05 was considered statistically significant in this study.

Results: Clinicopathological characteristics of 35 HCC patients at diagnosis were cataloged (Table 1). To exclude the effects of clinical parameters during studies on the influence of preoperative TACE on expression of genes involved in the HIF-1α pathway, chi-square and Fisher's exact tests were performed. There were no significant differences in clinicopathological features between patients in TACE and non-TACE groups.

The effects of preoperative TA CE on recurrence and survival were investigated using Kaplan–Meier survival curves. At a follow-up time of 2-years, 80 % (8/10) of the HCC patients in the TA CE group displayed recurrence, whereas recurrence rate of the non-TA CE group was 36 % (9/25) (P = 0.00402; Fig. 1a). For DFS, median survival times were 11.9 months (2.1–52.2 months) and 35.7 months (1.7–136.9 months) in TACE and non-TACE groups, respectively (P = 0.0182; Fig. 1b). In contrast, the differences in overall survival time between TACE and non-TACE groups were not significant (data not shown). To confirm the prognostic significance of TACE, the Cox regression analysis was performed. In a univariate Cox regression analysis, high Edmondson grade (P = 0.022), large tumor size (P = 0.017), and vascular invasion (P = 0.027) were associated with recurrence and TACE treatment before hepatectomy was a statistically significant risk factor for earlier recurrence in HCC patients (P = 0.007). For DFS, TACE was a poor prognostic factor along with vascular invasion (vascular invasion, P = 0.051; TACE, P = 0.024) (Table 2). A multivariate Cox model demonstrated that TACE was the strongest independent poor prognostic factor for recurrence (P = 0.007), as vascular invasion was shown to have borderline significance (P = 0.054). For DFS, both TACE (P = 0.010) and vascular invasion (P = 0.041) were found to be independent poor prognostic factors (Table 3).

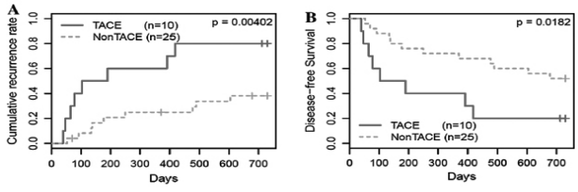

Fig. 1. Kaplan-Meier curves for cumulative recurrence rate and DFS of patients. Cumulative recurrence rate and Kaplan-Meier curves for DFS of patients who received preoperative TACE and did not (non-TACE). a Patients treated with TACE had a significantly higher recurrence rate compared to a non-TACE group (p=0.00402). b A significantly shorter time for DFS observed in patients with TACE than in non-TACE group (p=0.0182). Thin lines, patients received preoperative TACE (n=10); Broken lines, patients received only hepatectomy (n=25).

Table 2. Univariate Cox regression analysis for recurrence and DFS

Clinicopathologic parameters	TACE	Non-TACE	*P* value	Clinicopathologic parameters	TACE	Non-TACE	*P* value
Age			NS	BCLC stage			NS
<55 years	7	11		A	2	9	
≥55 years	3	14		B	4	11	
Gender			NS	C	4	5	
Male	10	19		AFP level			NS
Female	0	6		<100 ng/mL	7	13	
HBV			NS	≥100 ng/mL	3	12	
Absent	2	6		Vascular invasion			NS
Present	8	19		Absent	4	10	
HCV			NS	Present	6	15	
Absent	8	22		Tumor number			NS
Present	2	3		Single	8	16	
Liver cirrhosis	(−1)		NS	Multiple	2	9	
Absent	4	10		Tumor size			NS
Present	5	15		≤5 cm	2	12	
Tumor stage			NS	>5 cm	8	13	
I	4	11		Edmondson grade			NS
II	2	5		I	1	2	
III–IV	4	9		II	1	11	
Child pugh			NS	III	6	10	
A	10	24		IV	2	2	
B	0	1					
C	0	0					

Bold values indicate P < 0.05

Table 3. Multivariate Cox regression analysis for recurrence and DFS

Variable	*n*	Recurrence			DFS		
		Coefficient	HR (95 % CI)	*P*	Coefficient	HR (95 % CI)	*P*
Edmondson grade (I–II vs. III–IV)	35	0.356	1.43 0.40–5.15	0.587	−0.147	0.86 0.28–2.67	0.799
Tumor size (≤5 cm vs. >5 cm)	35	0.699	2.01 0.52–7.83	0.313	0.104	1.11 0.37–3.35	0.853
Vascular invasion (absent vs. present)	35	1.458	4.30 0.98–18.87	**0.054**	1.439	4.22 1.06–16.75	**0.041**
TACE (non-TACE vs. TACE)	35	1.669	5.31 1.56–18.04	**0.007**	1.536	4.64 1.45–14.87	**0.010**

Bold values indicate P < 0.05

Since HIF-1α is activated through protein stabilization via reduced proteasomal degradation under hypoxic conditions, the protein was subjected to immunohistochemcal analysis in 35 HCC tissues. Immunostaining revealed that the average intensity of nuclear and cytosolic HIF-1α was higher in TA CE than non-TA CE tissues and their differences were statistically significant. (1.96 vs. 2.89, P = 0.0158; Fig. 2a). Fig. 2b represents moderate and weak intensities of HIF-1α expressed in non-TA CE tissues (a and b, respectively) and strong expression of HIF-1α in TA CE tissues (c). To investigate the influence of TACE on tumor biology, mRNA levels of HIF-1α target genes associated with EMT were measured using real-time RT-PCR (Fig. 3). The TACE group expressed lower levels of CDH1, a HIF-1α-regulated epithelial marker than the non-TA CE group (P = 0.0003; Fig. 3d). Conversely, mRNA expression HIF-1α-regulated mesenchymal markers, such as MMP9,

Twist1, and vimentin was slightly higher in TACE tissues compared to non-TACE tissues, but their differences were not statistically significant (P = 0.8140, P = 0.4586, and P = 0.3988; Fig. 3e–g). Additional mesenchymal genes TCF3 and ZEB1 were expressed at lower levels in the TACE compared to the non-TACE group (P = 0.6866 and P = 0.0468; Fig. 3h, i).

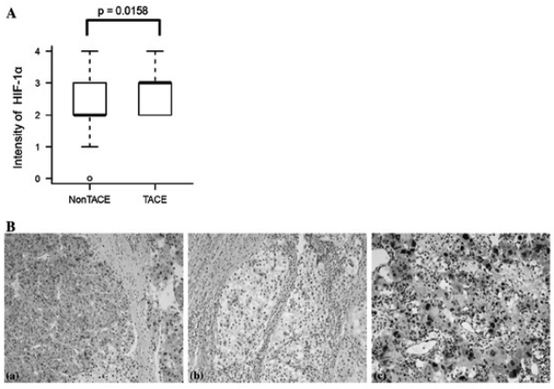

Fig. 2. Immunohistochemistry of HIF-1α in HCC tissues. A Box and whisker plot for HIF-1α expression levels in HCC tissues receiving preoperative TACE or not, determined by IHC. The box is marked by the first and third quartile with the median marked by a thick line. The whiskers extend to the most extreme data point which is no more than 1.5 times the interquartile range from the box. Statistically significant difference in HIF-1α protein expression between TACE and non-TACE tissues was found (p=0.0158). B Representative image of HIF-1α-positive samples at ×400magnification. Moderate (a) and weak (b) staining or HIF-1α in non-TACE tissues; strong (e) staining of HIF-1α in a TACE tissues.

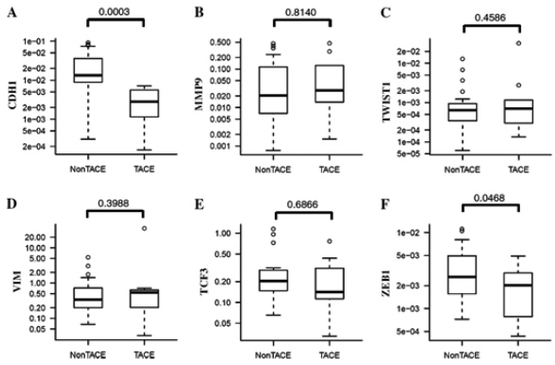

Fig. 3. Box and whisker plot for mRNA levels of HIF-1α-associated genes. Box and whisker plot for expression of CDH1 (a), MMP9 (b), TWIST1 (c), Vimentin (d), TCF3 (e), and ZEB1 (f) in non-TACE and TACE tissues determined by real-time RT-PCR. The box is marked by the first and third quartile with the median marked by a thick line. The whiskers extend to the most extreme data point which is no more than 1.5 times the interquartile range from the box.

Discussion: TACE is the most frequently applied locoregional therapy to HCC patients in Korea. In principle, TACE accompanied by tumor ischemia plays dual roles in the treatment of HCC. Firstly, TACE induces tumor necrosis by exclusively closing off blood vessels from the hepatic artery to HCC. In this case, TACE is effective for extension of patient survival. However, TACE can promote tumor recurrence and metastasis when incomplete tumor necrosis is triggered. Poor clinical outcomes resulting from TACE have raised questions about potential tumor biology alterations triggered by TACE. Increased tumor angiogenesis and invasiveness by TACE are found to be mediated by hypoxia signaling (Gupta et al., 2006; Sergio et al., 2008), which has been effectively suppressed by anti-angiogenic therapy (Jiang et al., 2007). In this respect, many types of clinical tests on combination therapy of TACE with anti-angiogenic agents have been performed (Abou-Alfa, 2011; Lencioni, 2012). Nevertheless, recent conflicting results from two clinical trials on combination of TACE plus sorafenib (Abou-Alfa, 2011; Kudo et al., 2011; Pawlik et al., 2011) strongly imply the need to study more detailed tumor biology in human specimens treated with TACE. Accordingly, we explored the influence of preoperative TACE treatment on prognosis and status of HIF-1α and its associated genes in human HCC specimens.
In current study, HCC patients subjected to preoperative TACE exhibited significantly higher recurrence rates and shorter DFS, relative to the non-TACE group (Fig. 1). Multivariate Cox model further indicated that TACE was an independent poor prognostic factor for HCC (Table 3). These results are supported by previous reports demonstrating poor prognosis in HCC patients treated with TACE before surgery (Choi et al., 2007; Kang et al., 2010; Kishi et al., 2012; Sasaki et al., 2006; Zhou et al., 2009). Additionally, a negative effect of TACE was reported in a mouse xenograft model of TACE (Liu et al., 2010). However, conflicting evidence has been reported with regard to the effects of preoperative TACE on HCC prognosis. For instance, Giorgio and other groups demonstrated that application of TACE before liver resection reduces HCC recurrence and improves DFS (Gerunda et al., 2000; Han et al., 1999; Majno et al., 1997; Zhang et al., 2000). The discrepancy in the prognostic effects of preoperative TACE may be attributed to differences in tumor size, liver function, borderline resectability, number of TACE treatments, or various TACE methodologies in each study. However, there is a general consensus supporting poor prognosis owing to incomplete tumor necrosis by TACE. To

elucidate mechanisms underlying poor clinical outcomes after preoperative TACE in our institution, specimens used in this study were selectively derived from viable portions of HCC after hepatic resection within 50 days following only one time of TACE. Our findings confirm that imperfect TACE treatment confers dismal prognosis in HCC patients after surgery. Protein expression of HIF-1α remains low in normoxic conditions through VHL-mediated ubiquitination and subsequent proteasomal degradation. When cells are subjected to hypoxic conditions, VHL dissociates from HIF-1α leading to reduced ubiquitination and subsequent stabilization of HIF-1α with concomitant heterodimerization with HIF-1β (Semenza, 2012). Since HIF-1α is stabilized in hypoxia setting, we initially examined the effect of TACE on HIF-1α protein expression using immunohistochemical staining. As expected, HIF-1α was more strongly expressed in TACE, compared to non-TACE tissues (Fig. 2). Consistently, stabilization of HIF-1α has been previously reported in animal tissues subjected to TACE treatment (Liu et al., 2010; Rhee et al., 2007). Therefore, our results clearly demonstrated the activation of HIF-1α in tissues of HCC patients undergoing TACE. HIF-1α activates transcription of genes involved in EMT. Hypoxic cells undergo EMT accompanied by loss of epithelial markers and gain of mesenchymal markers through HIF-1α activation. These gene expression changes confer increased tumor aggressiveness, invasiveness, and metastatic potentials to EMT cells (Semenza, 2012). Based on this background, clinical outcomes of TACE could be affected by expression of EMT genes concomitant with HIF-1α activation, but it has been rarely studied in patient tissues. In our results, CDH1 which is a repressive target of HIF-1α and one of epithelial markers (Krishnamachary et al., 2006) was dramatically down-regulated in tissues treated with TACE (Fig. 3d). MMP9, Twist1, and vimentin, mesenchymal markers and transcriptional target genes of HIF-1α known to increase upon hypoxia (Choi et al., 2011; Liu et al., 2010, 2012), were up-regulated in TACE tissues (Fig. 3e–g). However, mRNA expression of TCF3 and ZEB1 were down-regulated in a conflict with previous reports showing induction of TCF3 and ZEB1 by HIF-1α (Krishnamachary et al., 2006) (Fig. 3h, i). Considering that most of well-known target genes were expressed consistently with activation of HIF-1α in TACE tissues and that the tested samples were chosen with inclusion criteria within 50 days after TACE to exclude effects of HIF-1α signaling recovery from hypoxia upon TACE treatment, it may be ascribed to the small number of samples or regulation of TCF3 and ZEB1 by other unknown factors in complex physiological conditions of TACE.

Conclusion: In conclusion, preoperative TACE treatment is a poor prognostic factor in HCC patients. Additionally, the biological effects of TACE are associated with HIF-1α activation and expression changes in downstream genes. Our data collectively suggest that preoperative TACE confers poor prognosis via alterations in gene expression patterns in the HIF-1α pathway. Additionally, our results confirm previous reports showing activation of hypoxia signaling upon TACE treatment and support current strategy targeting tumor biology by combining TACE and anti-angiogenic therapy for HCC treatment. The molecular evidence obtained in this study can be effectively applied to guide treatment options for HCC.

Keywords: Hepatocellular carcinoma, Transcatheter arterial chemoembolization, Prognosis, Hypoxia, Hypoxia-inducible factor-1α.

OP-3-2

Outcomes after Recurrence Following Resection of Intrahepatic Cholangiocarcinoma

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Background: Recurrence is common after surgery for intrahepatic cholangiocarcinoma (ICC). After recurrence, the prognosis is known to be dismal. Treatment for recurrence following resection of ICC has not been established.

Methods: Between April 2001 and April 2013, 131 patients underwent hepatic resection for intrahepatic cholangiocarcinoma. We analyzed the recurrence pattern and its outcomes after resection of intrahepatic cholangiocarcinoma, retrospectively.

Results: Recurrences developed in the 82 of 131 patients. (62%) There were 57 men and 25 women, with a median age of 63 years. The median time from resection to recurrence was 10 months (range, 0~54 month). According to the first recurrence sites, 36 patients had intra-hepatic recurrence only (IH) and 46, with extra-hepatic recurrence (EH). In the IH group, the median time to recurrence was12 months (range, 2~49 month). The median time from recurrence to death was 27 months (range, 0~108 months) and 1-, 3- and 5-year survival rates since recurrence were 68.9%, 34.4%, and 22.3%, respectively. In the EH group, the median time to recurrence was 9 months. (range, 0~54 month). The sites of recurrences included lymph nodes, peritoneum, lung, adrenal gland and bone. 15 of

46 patients had both intra- and extra-hepatic recurrences. In the EH group, the median time from recurrence to death was 11 months (range, 0~61 months) and 1-, 3- and 5-year survival rates since recurrence were 35.6%, 16%, and 0%, respectively. Whereas, Hepatitis B infection, perineural invasion on pathologic findings and lymph node metastasis were independent risk factors for recurrenc of ICC following partial hepatectomy , perineural invasion and lymph node metastasis for 3-year survival.
Conclusions: The IH group had better prognosis. Perineural invasion and LN metastasis were independent factors for both recurrence and poor survival rate of recurrent ICC. There were no definite treatment that improve the survival of recurrent ICC significantly.
Keywords: Intrahepatic cholangiocarcinoma, Recurrence, Survival rate, Treatment

OP-3-3

Pure Laparoscopic Liver Donor Right Hepatectomy for Adult LDLT

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Background: Minimally invasive liver surgery is a rapidly advancing field with demonstrated applicability to living donation. This report reviews our experience with a modified right hepatectomy (MRH) using laparoscopic techniques preserving the middle hepatic vein (MHV) branches in living donor liver transplantation.
Methods: Between November 2014 and February 2015, a total of 92 donors underwent a right liver procurement. 3 Pure Laparoscopic liver donor right hepatectomy for adult LDLT was performed in three young donors without vascular clamping.
Results: There were no open conversions, and the graft was transplanted without any problem in every case. The operative time for the donors was 545 min, 427 min and 447 min. None of the donors required transfusion or reoperation. Postoperative hospital stay of donors was 8 -11 days, respectively. They were discharged with normal liver function. A major complication no occurred.
Conclusions: A hepatectomy performed completely by laparoscopic techniques for a right graft with preservation of the MHV branches was technically feasible. But, Pure laparoscopy for right lobe donation needs to be more carefully evaluated in larger series with post-operative outcome data showing its safety and clear benefits before it can be recommended
Keywords: Minimally invasive liver surgery, Liver donor, Total laparoscopic heptetomy

OP-3-4

Analysis of the Liver Volumes of Korean Adults Using Dr. Liver

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The accurate standard liver volume (SLV) estimation is vital at the preoperative stage to assess the adequacies of graft size in LDLT and remnant liver in major hepatectomy. SLV estimation formulas have been developed using height, weight, and liver volume measured by computed tomography (CT) or postmortem examination from cohorts varied in race, ethnicity, age, and gender ratio. The present study is to develop SLV estimation formulas for Korean adults using liver volume data measured by CT volumetry and compare their performances with those of existing formulas. Biometric data were collected at Chonbuk National University Hospital including body height (BH) and body weight (BW) measured by a stadiometer, skeletal muscle mass (SMM), body fat mass (BFM), body fat percentage (BFP), and waist hip ratio (WHR) measured by a body composition analyzer, and total liver volume (TLV) analyzed by Dr. Liver™ for abdominal CT data. Excluded cases with hepatic lesions and liver cirrhosis, a gender-balanced, age-matched dataset of 220 cases in 30s to 70s of age was formed for statistical analysis. Two regression models were roposed by considering biological significance as well as statistical significance in estimating SLV: TLV = 117 + 15.8 × BW (adjusted R2 = 0.527) and 237 + 15.7 × BW - 4.15 × BFP (adjusted R2 = 0.541). An error analysis of TLV estimation showed that the average error ratios (%) of the two proposed formulas ranged 11.5 to 11.7 (SD = 9.4 to 9.6), similar estimation performance could be observed in existing formulas from Asian cohorts based on CT volumetry, and quite different performance for those from Western cohorts based on postmortem examination. Further research is needed to develop better validated formulas for Korean adults by including data from other medical centers, forming a larger dataset balanced by age as well gender, and using prospective cases.
Keywords: Standard Liver Volume, Korean, Dr. Liver

OP-3-5

mTOR Inhibitor & NAC Exerts Synergistic Inhibition on Stellate Cell Activation

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Background: Activation of hepatic stellate cell (HSCs) is the dominant event in hepatic fibrosis. A previous study has shown that mTOR inhibition by either sirolimus or everolimus was more effective in reducing the progression of fibrosis in vivo than treatment with the FK506 and cyclosporine A, suggesting that mTOR could be a crucial target for inhibition of the fibrosis. Also, other have previously demonstrated that n-acetylcysteine (NAC) effectively suppresses stellate cell activation-dependent expression of smooth muscle α-actin in HSCs, indicating that NAC could be a candidate for the clinical treatment of hepatic fibrosis. In this study, we investigated the effect of immunosuppressive drugs including mTOR inhibition drugs and NAC on primary hepatic stellate cells in vitro, and find out the effective drugs, concentration and combination therapy.

Methods: Effects of immunosuppressive drugs (Cyclosporine, FK506, Sirolimus, Everolimus, Mycophenolate mofetil (MMF)) and NAC were investigated in primary hepatic stellate cell activation in vitro for 2 weeks. Cultured rat hepatic stellate cells were evaluated for morphology phenotype, and type | collagen, alpha-SMA desmin genes.

Results: We observed that mTOR inhibitor inhibited the extracellular matrix deposition and alpha-smooth muscle actin in the cultured hepatic stellate cell until day 14. At clinical relevant concentration of 10ng/ml rapamycin and everolimus significantly reduced collagen production. However, cyclosporine, FK506, MMF at clinically relevant concentration of 200ng/ml, 20ng/ml, 1mM did not reduce collagen production than mTOR inhibitor. In addition, treatment with everolimus and NAC reduced type | collagen and alpha-SMA expression more effectively than other treatment group.

Conclusions: These result demonstrated that mTOR inhibitor combined with NAC had a synergistic action in reducing hepatic stellate cell activation in vitro, suggesting therapeutic potential for enhanced antifibrogenic effect in clinical use.

Keywords: Hepatic stellate cell, Activation, Immunosuppressive drug, Combination treatment, Fibrosis

OP-3-6

Cognitive Ability in 43 Korean Pediatric Solid Organ Transplantation Recipients: A Cross Sectional Cohort Study in Single High Volume Living Donor Transplantation Center

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Background: Cognitive development after transplantation is important for pediatric recipients as well as allograft function during long-term follow-up. However, the course of cognitive development after transplantation is poorly understood especially in living donor dominant Korean pediatric recipients.

Methods: This cross-sectional single center study examined the prevalence of cognitive impairment in a cohort of 43 pediatric patients who received solid organ transplantation between 1999 and 2011. Cognitive impairment defined as mental retardation (MR, IQ <70), lower intelligence (LI, IQ <85), and attention-deficit-hyperactivity disorder (ADHD) via Composite scores for the WPPSI-III and Continuous Performance Test. Clinical factors associated with cognitive impairment were evaluated.

Results: Male patients were 20 (46.5%) and the median age was 2.9 (0.5~15.3) years at the time of transplantation. The median interval time from disease onset to the transplantation was 1.6 (0~13.5) years. Living donor transplantations was in 73.9%. The prevalence of MR, LI and ADHD in the patients was 12%, 33%, and 30%, respectively. IQ showed a negative correlation to pre-transplant duration of illness and age at the time of transplantation.

Conclusions: Korean pediatric organ recipients had higher prevalence of low intelligence and ADHD although three quarters were living donor transplantations of this cohort. Early transplantation intervention would be better for cognitive development after transplantation.
Keywords: Pediatric transplantation, Cognitive development, Intelligence quotient, Living donor

Oral Presentation 4

- Presentation Date: Saturday, April 25, 2015
- TIME: 16:50-17:50
- Chaired by: In-Sang Song, Donglak Choi

OP-4-1

Modulation of Specificity Protein 1 (SP1) is a Novel Therapeutic Strategy for Pancreas Cancer

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Background: Pancreas cancer is a relatively rare disease but, it was the fourth leading cause of cancer related mortality in Korea. The 5-year survival rate reported to be lower than 5%, the disease is associated with an extremely poor prognosis. Curative surgical resection is the only potentially curative treatment modality with gemcitabine based postoperative adjuvant chemotherapy. However, the clinical impact of gemcitabine varies significantly in individual tumors because of chemoresistance. Specificity Protein 1 (SP1) is a zinc-finger transcription factor that regulates multiple cellular functions and promotes tumor progression by controlling expression of genes involved in cell cycle, apoptosis and DNA damage. Previous studies suggested that inhibition of SP1 decreases the growth of various cancers. However, the role of SP1 in pancreas cancer is unclear. Thus, we investigated SP1 expression in pacers cancer and its association with clinical outcome and the role of SP1 on various pancreas cell lines.
Methods: Between 2002 and 2012, 84 pancreas cancer patients were reviewed. The expression of SP1 in pancreas cancer was evaluated by Immunohistochemcal staining. All 84 patients had clinical follow-up information and were evaluated for survival. MiaPaca-2, AsPC-1 and BxPC-3 human pancreas cancer cell line ware used. We examined the inhibition of SP1 were measured by WST solution dependent method, RT-PCR and western blot analysis in various pancreas cell lines.
Results: We demonstrates high expression level of Sp1 in pancreas cancer cell lines and human cancer tissues. Sp1 over expression was associated with higher perineual invasion and lymphovasclar invasion ($p < 0.043$, and $p<0.068$, respectively). In disease free survival, patients with over-expression of SP1 had a much shorter DFS than patients with low expression of SP1 ($p=0.0043$). In various pancreas cancer cell lines, inhibition of Sp1 decreased cell growth and induced apoptosis using WST method. The results of the present study indicates that inhibition of SP1 had anti-proliferative effect on the growth of pancreas cancer cell lines in a dose- and time -dependent manner. The treatment of MiaPaca-2, AsPC-1 and BxPC-3 with inhibition of SP1 led to a significant reduction in growth and induced apoptosis, followed by the regulation of SP1.
Conclusions: SP1 expression increses during cancer transformation and plays an important role in the maintenance and development of tumors. Downregulation of Sp1 is useful for treating tumor cells and clinical studies are necessary to describe the clinical application and potential unexpected toxicities.
Keywords: Specificity Protein 1, Pancreas cancer, Biomarker, Apoptosis, Prognosis

OP-4-2

The Atrophy of Remnant Pancreas after Pancreatoduodenectomy: Its Risk Factors and Effects on Auality of Life, Nutritional Status and Pancreatic Exocrine/Endocrine Function

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Background: Remnant pancreas atrophy after pancreatoduodenectomy has been reported in previous studies. However, the factors aggravating atrophy and the effects of the atrophy were not studied well. The aim of this study was to evaluate the clinical factors to affect remnant pancreas atrophy and to assess effects of atrophy on quality of life, nutritional status and pancreatic exocrine/endocrine functions.
Methods:
Prospectively collected data of 122 patients who completed 12 months follow-up with CT and quality of life questionnaire after pancreaticoduodenectomy were analyzed. Preoperative, remnant and 12 months follow-