Accuracy of contrast-enhanced imaging in the pretransplantation staging of hepatocellular carcinoma (HCC) and pathologic predictive factors of HCC recurrence after liver transplantation (LT)

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Purpose

Liver Transplantation (LT) is the preferred treatment for selected patients with hepatocellular carcinoma (HCC), however a debate still exists over which patients should be considered for LT. The Milan criteria, first described in 1996 (1) and widely adopted, have been recently considered too restrictive and expanded selection criteria have been proposed (2).

Anyhow, with the prognostic relevance of tumor size and number of lesion, preoperative staging is crucial for patient selection based on the above-mentioned criteria and organ allocation. Both contrast-enhanced dynamic multidetector Computed Tomography (MDTC) and Magnetic Resonance Imaging (MRI) are widely used in the detection and pretransplantation staging of HCC. Unfortunately, concerns regarding the accuracy of pretransplantation imaging in both diagnosis and staging remain. The sensitivity of MDTC and dynamic MRI for HCC detection ranges from 50-89% and 61-91%, respectively, as reported by previois studies (3-5). Previous locoregional therapies, in particular transarterial chemoembolization (TACE), represent one of the major causes of false-negative and false-positive findings, as the difficulty in the differentiation of totally necrotic nodules from viable HCCs limits mainly the accuracy of CT but remains also on MRI (6).

Recent studies have demonstrated a recurrence in 8-15% of HCC patients after LT (7). Tumor size and vascular involvement are known to be the most important prognostic factors for tumor recurrence, while the role of tumor differentiation is still controversial (7-9).

The aim of this study was to assess the accuracy of imaging techniques (MDTC and MRI) in HCC pretransplantation staging, with histopathologic evaluation of the explanted liver as the reference standard. The secondary objective was to identify pathologic and imaging predictive factors for HCC recurrence after LT.

Methods and Materials

Patients.

Between October 2004 and November 2011, a total of 183 consecutive patients with HCC underwent LT at our hospital. Of them, 8 patients were excluded because of a short follow up period (#2 months), as a result of perioperative mortality. The remaining 175 patients (151 men, 24 women), who had a follow-up period longer than 2 months and had undergone dymanic-imaging evaluation at least 3 months before transplantation, were included. Previous treatment, including surgical resection and loco-regional therapies had been undertaken in 119 patients. Table 1 summarizes clinical characteristics of the included patients.

Pretransplantation Imaging.

The preoperative dynamic-imaging examination performed closest to the time of transplant and within 3 months prior to LT was contrast-enhanced multiphase MDCT in 138 patients and contrast-enhanced MRI in 37 patients. The mean interval between the last imaging examination and LT was 42 days with a range of 1-75 days.

MDCT examinations were performed using a 64-slice CT scanner (GE Medical Systems, Milwaukee, Wisconsin, USA) with contrast enhancement and bolus-tracking technique to obtain a multiphase (arterial, portal and hepatic venous phases) examination after an unenhanced scan. Dynamic MRI studies were conducted on a 1.5-T high field magnet (Achieva, Philips Medical System, Best, The Netherlands) with a Phased Array coil. The protocol included axial T1- and T2-weighted sequences with and without fat suppression and axial dynamic three-dimensional T1-weighted GRE sequences with fat suppression obtained before and after a bolus injection of gadopentetate dimeglumine (Gd-DOTA) in arterial, portal and hepatic venous phases.

Pretransplantation imaging examinations were retrospectively reviewed by consensus by two experienced radiologists blinded to the results of the pathologic reports, collecting data about the following features: presence of viable tumor, number of viable hepatic lesions, overall size of viable tumor, diameter of the largest viable lesion, lobar distribution of the tumor.

Histopathology of the explanted liver.

A pathologist experienced with liver pathologies reviewed all pathologic reports of the explanted livers. The same features examined on imaging studies were evaluated on pathologic reports. Moreover, other collected pathologic data were: presence of microsatellitosis, contact between tumor and hepatic capsule, macrovascular

and microvascular invasion, histological subtype (HCC or combined hepatocellular-cholangiocarcinoma) and differentiation degree, scored from grade 1 to 4 (10).

Recurrence analysis.

All available postoperative imaging examinations were retrospectively reviewed for evidence of recurrent HCC. Proof of recurrence was made on the basis of biopsy or growth of new lesions with appropriate radiologic features, combined with rising AFP levels or with negative work-up for another primary malignancy.

Statistical analysis.

The association between pretransplantation imaging features and explanted liver pathological features was evaluated by using the $\#^2$ test. Measure of association between imaging and pathology in the detection of viable tumor was also estimated separately for MDCT and MRI and for patients who had undergone pretransplantation treatment. Accuracy, sensitivity and specificity were calculated for imaging, MDCT and MRI and compared using the McNemar test and Fisher exact test to estimate their diagnostic performance in the detection of viable tumor. Incidence of recurrence was calculated and the Kaplan-Meier curve of disease-free survival rate was estimated. The above-mentioned imaging and pathological variables were evaluated as potential predictive factors for HCC recurrence after LT by means of univariate analysis ($\#^2$ test for categorical data and median test for continuous data). For all statistical analyses, a $p<0.05$ was considered to indicate a statistically significant difference.

Images for this section:

CLINICAL CHARACTERISTICS (n = 175)				
HIV + (%)				15 (8,6)
Etiology of the underlying hepatic disease	Viral (%)	144 (82,3)	HBV-related	31 (17,7)
			HCV-related	96 (54,9)
			Mixed	17 (9,7)
	Not viral (%)	31 (17,7)	Alcoholic	18 (10,3)
			Cryptogenetic	6 (3,4)
			Other	7 (4,0)
MELD score (± SD)				15,85 (7,38)
AFP (± SD)				289,24 (1893,4)
Previous treatment (%)				119 (68,0)
		Surgical resection (%)		23 (14,9)
		Transarterial Chemoembolization (%)		107 (61,1)
		Radiofrequency Ablation (%)		60 (34.3)

Table 1: Clinical characteristics of the studied population.

Results

Imaging and histopathological data.

Of the 175 patients who were included, 122 (69,7%) patients had evidence of viable tumor on imaging examination, 79 of them having undergone treatment before LT. The remaining 53 patients had no evidence of viable tumor and 40 of them had undergone treatment before LT. On histopathology, 125 patients (71,4%) had evidence of viable tumor, while there were no viable HCCs present on the explanted liver in 50 patients. The other collected imaging and histopathological features are summarized in table 2.

Correlation between imaging and histopathology.

A strong association was found between imaging and histopathology in the detection of the presence of viable tumor ($p<0,001$). This correlation was demonstrated to be highly significant also in patients who had undergone treatment before LT ($p<0,001$) and among them in those with previous TACE ($p<0,001$) and radiofrequency ablation, RITA ($p=0,006$) . It remained in patients who had CT as dynamic-imaging evaluation performed closest to LT ($p<0,001$) as well as in those who had MR ($p=0,007$). Strong associations between imaging and histopathology were also found in the assessment of the number of viable nodules ($p<0,001$), diameter of the largest nodule ($p<0,001$), overall viable tumor size ($p<0,001$) and lobar distribution of HCCs ($p=0,03$).

Accuracy of imaging techniques.

Of the 125 cases with pathologically proven viable tumor, 102 were found on both imaging and histopathology while 23 were missed at imaging. Twenty cases were overdiagnosed (positive on imaging and negative on pathology) while in 30 patients there was no viable tumor on both imaging and pathology. Therefore, in the detection of viable tumor, the sensitivity of imaging techniques was 81,6%, specificity was 60% and accuracy was 75%. The total population was then divided into patients who had MDCT as dynamic-imaging evaluation (n=138) and patients who had MR (n=37). Results about the performance of imaging, MDCT and MRI in the detection of viable tumor are summarized in table 3. The McNemar test showed no statistically significant difference between imaging and histopathology in the detection of viable tumor ($p=0,75$).

Representative cases of concordance and discordance of MDCT and MRI with histopathology are shown in figure 1 and 2.

Recurrence rate and predictive factors.

The median follow-up period was 39,1 months. Of the 175 patients included, 24 (13,7%) had recurrence of HCC after the LT. Time to development of the recurrence ranged from 1,55 to 41,85 months after LT, with a median value of 12,36 months. The 1-, 3-, 5-years cumulative disease-free survival rates according to the Kaplan-Meier method were 92,96%, 83,9% and 82,84%, respectively. The mean duration of recurrence-free survival was 40,15 months.

Univariate analysis revealed various factors significantly associated with recurrence (Table 4).

Images for this section:

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Table 1: Clinical characteristics of the studied population.

IMAGING AND HISTOPATHOLOGICAL FINDINGS			
		Imaging (n=122)	**Histopathology (n=125)**
Number of viable nodules (%)	1	43,4%	42,4%
	2-3	43,4%	39,2%
	4-5	9,0%	12,0%
	>5	4,1%	6,4%
Diameter of the largest nodule (%)	<3 cm	75,4%	78,4%
	3-5 cm	20,5%	14,4%
	>5 cm	4,1%	7,2%
Overall viable tumor size (%)	<3 cm	56,5%	58,4%
	3-5 cm	32,0%	19,2%
	5,1-8,5 cm	4,9%	15,2%
	>8,5 cm	6,6%	7,2%
Distribution (%)	unilobar	76,2%	72,0%
	bilobar	23,8%	28,0%
Histopathological type (%)	HCC		96,8%
	mixed cholangiocarcinoma/HCC		3,2%
Histolopathological grade (%)	1		15,2%
	2		44,8%
	3		32,0%
	4		3,2%
	not assessable		4,8%
Presence of microsatellitosis (%)			13,6%
Presence of vascular invasion (%)	microvascular invasion		13,6%
	macrovascular invasion		4,8%
Contact with hepatic capsule (%)			44,8%

Table 2: Imaging and histopathological findings.

IMAGING TECHNIQUES DIAGNOSTIC PERFORMANCE				
		MDCT (n=138)	MRI (n=37)	Imaging (n=175)
Detection of viable tumor	Sensitivity	82.35 (84/102)	78.26 (18/23)	81.60 (102/125)
	Specificity	55.55 (20/36)	71.43 (10/14)	60.00 (30/50)
	VPP	84.00 (84/100)	81.81 (18/22)	83.61 (102/122)
	VPN	52.63 (20/38)	66.67 (10/15)	56.60 (30/53)
	Accuracy	75.4	75.7	75.4
	p-value			0,75

Table 3: Imaging techniques diagnostic performance in the detection of viable tumor.

PREDICTIVE FACTORS FOR RECURRENCE				
		Not recurred	**Recurred**	**p-value**
Presence of viable tumor	pathology	67,5%	95,8%	**0,003**
	imaging	65,6%	95,8%	**0,002**
Number of viable nodules > 3	pathology	12,7%	43,5%	**0,001**
	imaging	9,1%	30,4%	**0,006**
Diameter of the largest nodule > 3 cm	pathology	16,7%	43,5%	**0,004**
	imaging	19,2%	47,8%	**0,003**
Overall viable tumor > 5 cm	pathology	15,7%	52,2%	**<0,001**
	imaging	5,0%	39,1%	**<0,001**
Bilobar distribution	pathology	23,5%	47,8%	**0,018**
	imaging	24,2%	21,7%	0,834
Combined HCC-cholangiocarcinoma type (pathology)		0%	17,4%	**<0,001**
Histopathological grade > 1 (pathology)		80,2%	100%	**0,019**
Presence of contact with hepatic capsule (pathology)		35,3%	87%	**<0,001**
Presence of vascular invasion (pathology)		10,8%	52,2%	**<0,001**
Presence of microsatellitosis (pathology)		8,8%	34,8%	**<0,001**

Table 4: Imaging and pathological factors associated with recurrence.

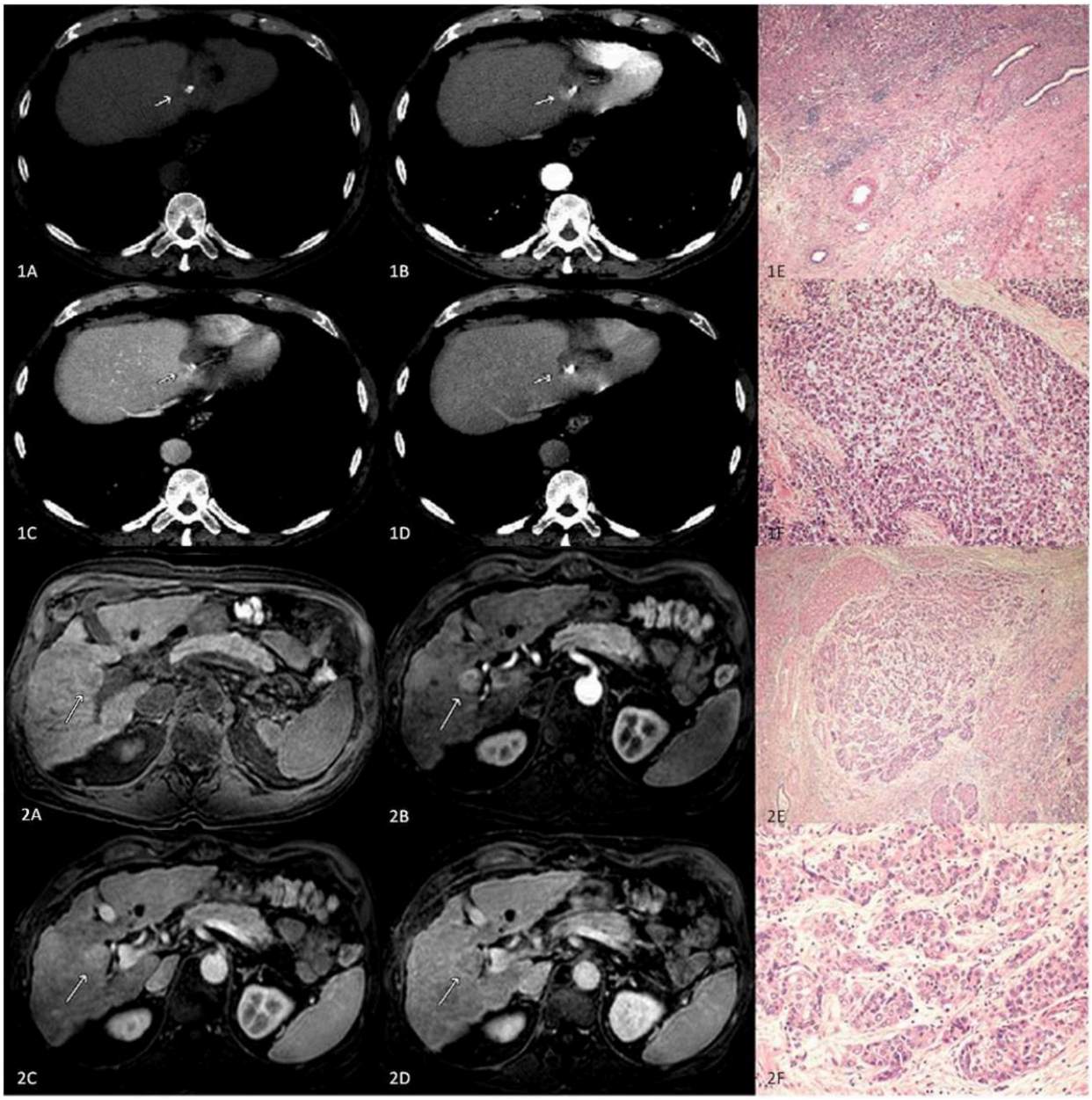

Fig. 1: Representative cases of concordance between imaging and histopathology. Panel 1: precontrast (A), arterial (B), portal (C) and hepatic venous (D) MDCT images showing presence of viable tumor marginally to a previously treated HCC nodule. Histopathological analysis (E,F) confirmed the presence of viable tumor. Panel 2: precontrast (A), arterial (B), portal (C) and hepatic venous (D) MRI images demonstrating a viable HCC nodule, as confirmed by histopathological analysis (E,F).

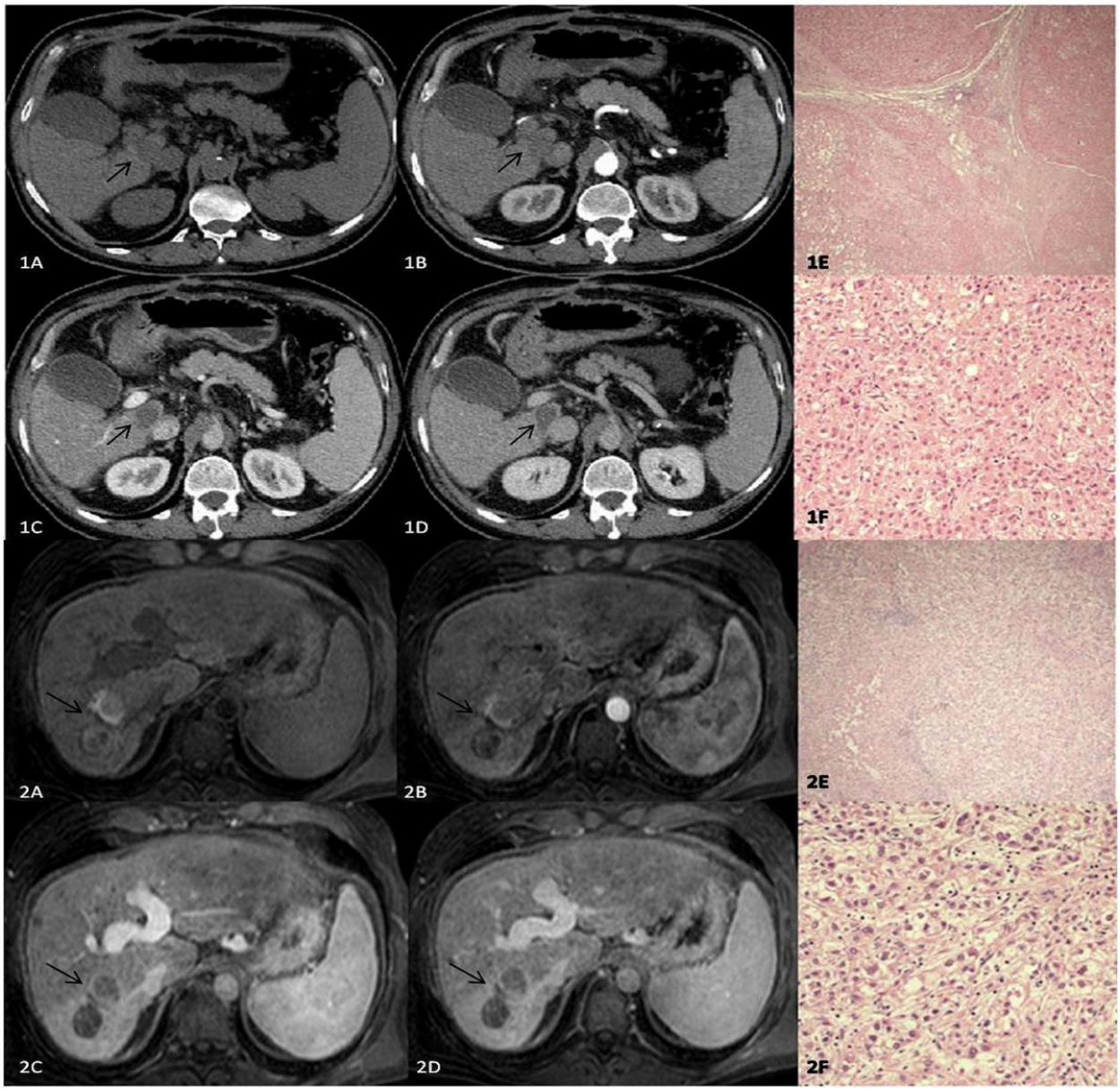

Fig. 2: Representative cases of discordance between imaging and histopathology. Panel 1: precontrast (A), arterial (B), portal (C) and hepatic venous (D) MDCT images showing a lesion previously treated with termoablation without signs of presence of viable tumor. Histopathological analysis (E,F) revealed the presence of viable tumor (10% of the total nodule). Panel 2: precontrast (A), arterial (B), portal (C) and hepatic venous (D) MRI images apparently showing the absence of viable tumor marginally to two lesions previously treated with chemoembolization, whereas histopathological analysis (E,F)demonstrated the presence of viable tumor.

Conclusion

According to our results, contrast-enhanced imaging can be considered accurate in pretransplantation staging of HCC as a high radiologic-pathologic correlation was found in the detection of viable tumor and in the assessment of parameters such as number of nodules or diameter of the larger nodule, which are crucial for HCC staging.

The association between imaging and histopathology in the detection of viable tumor remained also when pretransplantation treatment and in particular TACE ($p<0,001$) and RITA ($p=0,006$) had been undertaken before LT. This result is remarkable as the presence of marginal recurred HCCs around previously treated nodules, especially lipiodolized nodules, is known to be one of the most common imaging pitfalls (6).

Accuracy of imaging techniques was 75,4%, with no substantial difference between MDCT (75,4%) and MRI (75,7%). Comparatively with previous studies which evaluated MDCT and dynamic MRI with extracellular contrast agents, imaging sensitivity was 81,6%, with a slight difference between MDCT (82,35%) and MRI (78,26%)(3-5).

In our population the tumor recurrence rate was 13,7%, which is similar to the rates observed in other studies with comparable follow-up period and in which Milan selection criteria were adopted (7).

Potential imaging and pathological predictive factors for HCC recurrence after LT have been previously investigated. The most important significant predictive factors included tumor size and vascular invasion, while the role of microsatellitosis, poor histological differentiation and number of nodules is still controversial (7-9). In our study, imaging and pathological features which were associated in univariate analysis with recurrence after LT were the presence of viable tumor, > 3 viable nodules , > 3 cm diameter of largest nodule, >5 cm overall viable tumor size, whereas other pathological predictive factors for recurrence were bilobar distribution, combined HCC-cholangiocarcinoma type, differentiation grade > 1, contact between tumor and hepatic capsule, micro- or macro-vascular invasion and microsatellitosis.

References

1. Mazzaferro V, Regalia E, Doci R et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996 Mar 14;334(11):693-9.
2. Yao FY, Ferrell L, Bass NM et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology. 2001 Jun;33(6):1394-403.
3. Noguchi Y, Murakami T, Kim T et al. Detection of hepatocellular carcinoma: comparison of dynamic MR imaging with dynamic double arterial phase helical CT. AJR Am J Roentgenol. 2003 Feb;180(2):455-60.
4. Addley HC, Griffin N, Shaw AS et al. Accuracy of hepatocellular carcinoma detection on multidetector CT in a transplant liver population with explant liver correlation. Clin Radiol. 2011 Apr;66(4):349-56.
5. Lencioni R. Surveillance and early diagnosis of hepatocellular carcinoma. Dig Liver Dis. 2010 Jul;42 Suppl 3:S223-7.
6. Lee DH, Kim SH, Lee JM et al. Diagnostic performance of multidetector row computed tomography, superparamagnetic iron oxide-enhanced magnetic resonance imaging, and dual-contrast magnetic resonance imaging in predicting the appropriateness of a transplant recipient based on milan criteria: correlation with histopathological findings. Invest Radiol. 2009 Jun;44(6):311-21.
7. Kim YS, Lim HK, Rhim H et al. Recurrence of hepatocellular carcinoma after liver transplantation: patterns and prognostic factors based on clinical and radiologic features. AJR Am J Roentgenol. 2007 Aug;189(2):352-8.
8. Parfitt JR, Marotta P, Alghamdi M et al. Recurrent hepatocellular carcinoma after transplantation: use of a pathological score on explanted livers to predict recurrence. Liver Transpl. 2007 Apr;13(4):543-51
9. Ciccarelli O, Lai Q, Goffette P et al. Liver transplantation for hepatocellular cancer: UCL experience in 137 adult cirrhotic patients. Alpha-foetoprotein level and locoregional treatment as refined selection criteria. Transpl Int. 2012 Aug;25(8):867-75.
10. Ishak KG. Histological typing of tumors of the liver. Geneva: World Health Organization, 1994.