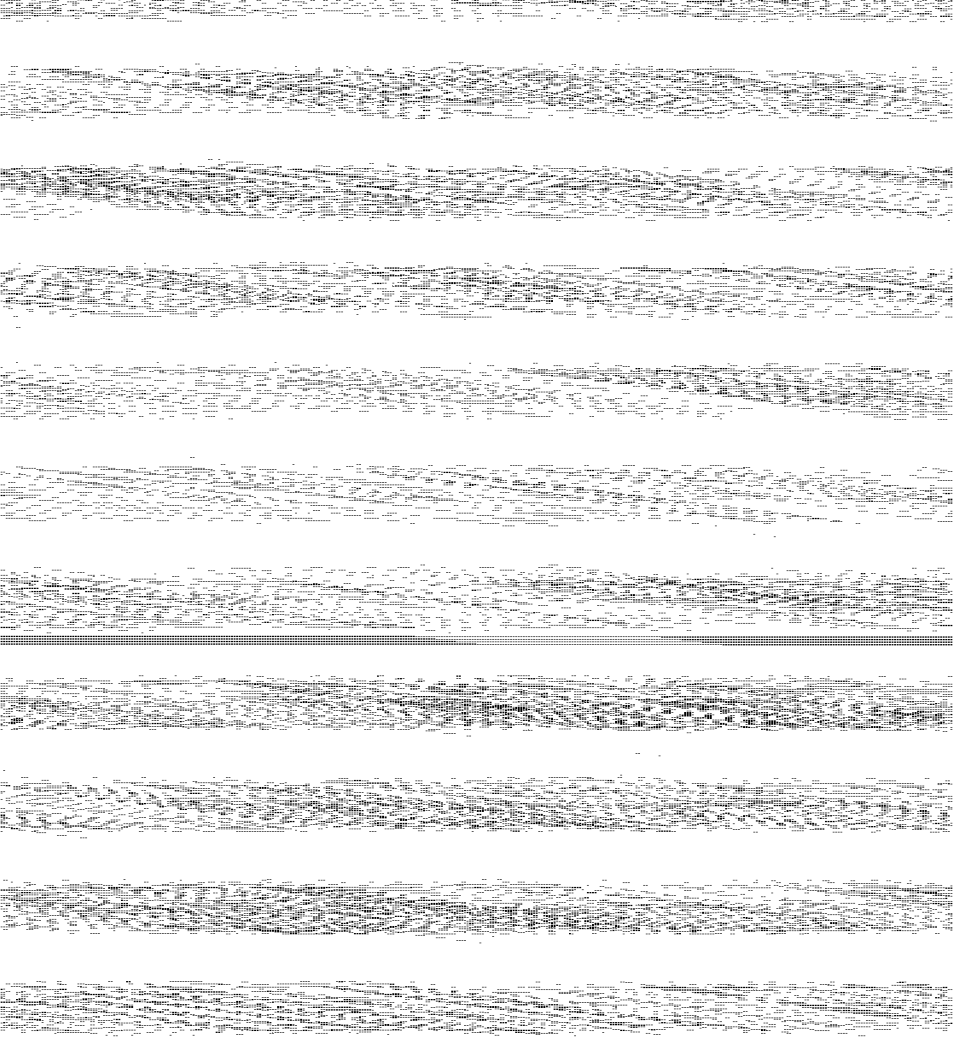
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表2 PCNA标记的图像分析结果

Tab 2 Results of PCNA labeling by image analysis

Pattern	n	Average area ($\times10^4\ \mu m^2$)	Numeral density ($\times10^{-2}/\mu m^2$)	Area density ($\times10^{-2}\ \mu m^2/\mu m^2$)	AIOD
HCC	19	9.18±1.07	0.24±0.12**	7.44±3.24△	4.64±0.21
Grade Ⅰ	8	9.86±1.15	0.18±0.06*	5.89±1.69	3.89±0.15
Grade Ⅱ	8	9.96±0.82	0.22±0.04*#	12.54±3.49	6.54±0.25
Grade Ⅳ	3	8.06±0.63	0.41±0.01#	9.97±1.15	4.09±0.14
TAL	15	8.75±0.35	0.05±0.01**	1.06±0.29△	3.18±0.19
NL	5	8.51±0.79	0.05±0.02	0.90±0.11	1.82±0.23
CH	5	9.12±0.55	0.06±0.03	1.37±0.11	3.36±0.30
LC	5	8.53±1.59	0.04±0.03	0.84±0.80	3.41±0.29

Abbreviation: AIOD average integral optical density, others as Tab 1

Compared with same marked value: *: $P>0.05$; **: $P<0.01$; △: $P<0.01$; #: $P<0.05$

表3 癌细胞PCNA相对含量的分析结果(%)

Tab 3 The relative content of PCNA in HCC cells compared with hepatocytes (%)

HCC grading	Relative content of PCNA (multiple)				Ratio of AIOD
	1	1.5~2	2.5	Beyond 2.5	
Grade Ⅰ	66.8	15.5	4.9	12.8	1.27
Grade Ⅱ	47.9	16.8	5.9	29.4	2.16
Grade Ⅳ	41.6	18.6	6.2	33.6	2.76

3 讨论

3.1 肝癌细胞与癌旁肝细胞PCNA标记的意义

采用PCNA标记方法研究肝细胞癌的增生活性国外仅见少数报道[3,4],国内尚无文献报道。本研究对30例人肝细胞癌PCNA的检测结果表明,大多数属Ⅰ~Ⅲ级分化肝癌平均标记率为40.59%±11.51%,而3例Ⅳ级肝癌平均标记率高达86.90%±5.15%。这种PCNA标记率随肝癌分级的升高而增高($P<0.01$)及在中度分化(Ⅰ~Ⅲ级)肝癌间无明显差别的结果与Taniai M等[3]的同类研究报道基本一致。PCNA是与细胞增生直接相关的核内因子[5],低分化肝细胞癌的PCNA标记率较高,反映其增殖能力强及肿瘤进展快。已有研究表明,肝癌PCNA标记率除可预示其预后外,尚与肿瘤的转移密切相关[4]。

本研究首次对人原发性肝细胞癌癌结节邻近肝细胞的增殖活性进行了初步探讨,结果在近癌肝检测到PCNA阳性肝细胞,且各癌旁病变肝PCNA阳性标记率及阳性强度差别不大,提示背景肝病变对其影响不是主要因素,而与邻近于癌结节的位置密切相关;对距癌结节稍远肝细胞的初步观察,表明不同癌旁病变肝其PCNA的阳性标记率不甚一致。Harrison RF等[6]提出肝转移性癌癌旁PCNA肝细胞阳性也呈临近癌结节的区带(zonality)分布特点。结合作者以往对癌旁近癌肝细胞AFP及ras p21表达研究的结果[2],本研究进一步支持部分近癌肝细胞已具肿瘤性增殖活性的观点。至于癌旁肝细胞表达PCNA是否与肝癌细胞的旁分泌作用(如IGF-Ⅰ等)有关,尚需研究。

3.2 肝癌细胞中PCNA相对含量测定的意义

有研究指出,PCNA含量在细胞周期中变化较小,多数肿瘤(包括肝细胞癌)PCNA标记研究也不计PCNA表达强度,但肿瘤细胞PCNA表达强度的异质性确实存在。为探讨这种差异性与肝癌病理特征的关系,本研究利用相对含量概念及图像分析技术对肝癌细胞PCNA表达强度进行了测量,显示癌细胞PCNA平均含量均高于癌旁肝细胞,且随肝癌分级升高,PCNA高含量癌细胞的比例呈上升趋势。结合病理形态分析,显示癌细胞PCNA相对含量的增高与癌细胞低分化核增大关系较密切,为从PCNA定量角度辅助诊断及判定肝细胞癌的预后提供了实验依据及新的途径。然而,PCNA含量的不同也可能反映癌细胞处于细胞周期的不同阶段。因此,在评价肿瘤PCNA阳性标记率及相对含量的确切意义时应慎重。

3.3 图像分析技术是判定实体肿瘤PCNA标记率的良好方法

免疫组化法标记实体肿瘤中PCNA阳性细胞,在标记阳性率及阳性强度上均存在明显的异质性,这一特征在Siitonen SM等[7]对乳腺癌的研究及本研究中均得到证实。鉴于这种异质性的存在,作者采用图像分析技术,在较大范围内(低倍镜100×)对每例具代表

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性的较完整癌结节内 PCNA 阳性细胞进行了定量测量，并证实其测量结果与常规计数方法有较好的一致性，在条件允许时是一种快捷而更为客观的研究方法。

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Quantitative study of proliferative activity of human hepatocellular cancerous cells and cancer-adjacent hepatocytes

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Abstract The proliferative activity of hepatocellular cancerous cells (HCCs) and cancer-adjacent hepatocytes were quantitatively studied with immunohistochemical assay of the proliferating cell nuclear antigen (PCNA) and computerized image analysis. The findings were as follows: (1) The average rate of PCNA labelling was 45.22%±17.90% and 12.74%±4.89% in HHCs and cancer-adjacent hepatocytes respectively ($P<0.01$) and the rate of PCNA labelling tended to increase with the increase of the pathological grading of hepatocellular carcinoma. (2) The relative contnet of PCNA in 40% of HCCs was similar to the average content of PCNA of cancer-adjacent hepatocytes. In combination to the histopathological findings, it is concluded that the increase of PCNA content in HCCs was closely related to the increase of their nuclear size. (3) A coincidence was obtained between the numeral density of PCNA-positive cells with image analysis and the labelling rate with routine counting and the former was considered as a more objective index.

Key words hepatocellular carcinoma; proliferating cell nuclear antigen; immunohistochemistry; image analysis

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