

## SUMMARY OF THESIS\*

MELLO, Evandro Sobroza de - **Macronódulos em fígados cirróticos: estudo morfológico com ênfase nos aspectos macroscópicos, proliferação e apoptose.** São Paulo, 2001. (Tese de Doutorado - Faculdade de Medicina da Universidade de São Paulo).

### MACRONODULES IN CIRRHOTIC LIVER: MORPHOLOGICAL FINDINGS WITH EMPHASIS IN GROSS FEATURES, PROLIFERATION AND APOPTOSIS

**Aims:** To study macronodules in explanted cirrhotic livers, performing a detailed description of gross aspects and histological features according to each type. To study proliferation, apoptosis and regulatory proteins P53, Bcl-2, Bcl-x and Bax in these nodules. **Material and Methods:** Sixty one consecutive liver explanted specimens, handled by a single pathologist, following a pre-established protocol, were prospectively inspected for macronodules. From each identified nodule, a digital picture was examined to the following gross characteristics: a) hue; b) color; c) color variability; d) circumscription; e) capsule; and f) extra-capsular extension. International Working Party (1995) criteria were applied to classify nodules as large regenerative nodule (LRN) low grade dysplastic nodule (LGDN), high grade dysplastic nodule (HGDN), well differentiated hepatocellular carcinoma (WHCC) and moderately differentiated hepatocellular carcinoma (MHCC). Some histological variables not included as diagnostic criteria were also evaluated. All macronodules, 20 normal control livers and one additional section from regular cirrhosis from each liver were immunostained for PCNA, P53, Bcl-2 Bcl-x and Bax. Hematoxylin-eosin stained slides were used to count apoptosis. **Results:** Thirty two cases (52.45%) had 96 macronodules, including 13 (21.31%) with 21 hepatocellular carcinomas (HCC). Nine livers with HCC had other macronodules types, but four did not. Nodule size progressively increase, from LRN to MHCC. The distribution was similar in all kinds of lesions. Nine of 10 green color lesions were HCC or HGDN, whereas 19 of 22 brownish lesions were LRN or LGDN. Most lesions with high color variability were HCC. WHCC was frequently ill circumscribed and had no capsule. All MHCC had well circumscribed borders, and a thin capsule was the rule in LRN, MNR and HGDN. Apparent extracapsular extension was only seen in HCC and HGDN. Major fatty change was associated with HCC, specially

WHCC. Clear cells, Mallory bodies, interstitial fibrosis and siderosis resistance were also HCC features. There was a steady increase of proliferation from normal control liver to cancer. Apoptotic rate also roughly increased along the spectrum of macronodules, but with a flattened curve from cirrhosis to LGDN. P53 was immunodetected only in four MHCC, whereas Bcl-2 was positive only in seven cases of cirrhosis. Bcl-x was immunostained in a progressively reducing rate of cases from HGDN to MHCC. Normal livers and HGDN did not express Bax, but all other categories had a small percentage of positive cases. Forty percent of MHCC had immunohistochemically detectable Bax in cytoplasm. **Conclusions:** The steady increase in size, as well as in proliferation and apoptotic rates from cirrhosis to HCC, suggests a progression from each diagnostic class to the next. Although most HCC develop in macronodules harboring livers, some of them do not, suggesting an alternative pathway for hepatocarcinogenesis. The following gross aspects were found useful in selecting the most suspicious nodules: green color, marked color variation inside the nodule, and extracapsular extension were found as indicators of HCC. Steatosis, clear cells, Mallory bodies and intra - nodular fibrosis could be useful histological criteria to HCC. The deficit of apoptotic rate as compared to proliferation rate from cirrhosis to LGDN could reflect some dysregulation in the cell population control. Different patterns of expression of Bcl-2, Bcl-x and Bax could play a role in this process. P53 anomalous expression was present only in late stage of cancer development.

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