Hepatocellular dysplastic nodules

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The multistep process of hepatic carcinogenesis is mirrored by the morphologic classification of lesions detectable in cirrhosis, that include large regenerative nodules (LRN), low grade dysplastic nodules (LGDN) and high grade dysplastic nodules (HGDN). The latter belong to the "bordeline malignancy" category requiring an accurate distinction from well-differentiated and early hepatocellular carcinoma. Nodules in cirrhosis are usually detected by non-invasive imaging techniques, being the latter unable to discriminate malignant from non-malignant forms, particularly in the 1-2 cm sized group. Liver biopsy is essential in providing practical diagnostic information to hepatologists in the management of cirrhotic patients with US detectable nodules. The histologic diagnosis on liver samples is based on the accurate search of a set of cyto-architectural features (cell atypia, cell crowding, trabecular thickness, microacini etc) and by a supplement of histochemical (Gomori staining) and immunocytochemical stainings. The latter rely upon the search of both well established and novel markers, targeted to evaluate stromal invasion (CK7/19), the vascular pattern (ASMA and CD34) or tumor markers (HSP70 and Glipican 3 among others). Still, the diagnostic sensitivity is limited by the type and size of sampling and by its representativity of the entire lesion. The best diagnostic approach thus requires the integration of clinical, morphological and immunocytochemical information with imaging data (US pattern, perfusional pattern, helical CT/MR pattern). Molecular data are still under evaluation as to their diagnostic efficacy in this controversial field. Discrepancies have emerged recently between Eastern and Western interpretation of these lesions, particularly in the category of "borderline" nodules, that are mostly labelled as early, well differentiated HCC by eastern pathologists and as HGDN by western pathologists. Novel and more objective phenotypical and molecular markers are needed to discriminate within the grey area of borderline lesions that, epidemiologically, are likely distinct between eastern and western geographic areas. These tools might allow a better understanding of the boundaries of the process going from high grade dysplasia to in situ HCC and from the latter to microinvasive HCC and advanced HCC, for a proper clinical management and optimal therapy.

KEY WORDS: Hepatocellular modules

Introduction

Space-occupying sizable nodules arising in cirrhosis are hyperplastic and neoplastic growths (benign, dysplastic and malignant) whose diagnostic criteria and nomenclature require a consensus between western and eastern pathologists. There is disagreement between pathologists as to the dividing line between dysplasia and well differentiated HCC and this disagreement occurs more frequently as the size of the lesion decreases. A great deal of morphological and molecular information on these lesions has been originally achieved through the systematic macro- and micro-scopical examination of native transplanted end-stage cirrhotic livers; however these livers have a background far advanced as compared that of cirrhotics, routinely followed up by US, for early HCC detection. Conversely there is a substantial lack of information on how to recognize lesions on liver biopsies as well as on the phenotypic and genotypic features useful to discriminate among early nodules. Available data on hepatocellular nodules heterogeneity

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and natural history in cirrhosis have ultimately rested upon imaging and the sampling of small <2cm lesions as well as on handful prospective studies carried out by eastern and western groups 8-16.

From these studies emerged that:
- most de novo or recurrent hepatocellular nodules >2 cm in cirrhosis are HCC or suspicious lesions proved to be HCC after short-term follow-up;
- imaging alone is not able to discriminate within a consistent fraction of <2cm lesions; 34% are hypovascular and 38% malignant nodules go unrecognized after imaging 8;
- the majority of <2cm hepatocellular nodules detected in cirrhotics are already malignant and their prevalence ranges from 60% (M Borzio, personal communication) to 70% 3 to 75% 3 to 85-90% 10;
- non-malignant, de novo or recurrent, <2 cm hepatocellular nodules are a consistent but heterogeneous group of lesions, ranging from 10%-40% in the different series; in in vivo series they include both regenerative (60%) and dysplastic nodules (40%) with various malignant potential and with a 1:1 ratio between low grade (LGDN) and high grade (HGDN) dysplastic nodules;
- high-grade dysplastic nodules carry the worse outcome as compared to the other non-malignant nodules, with a four-fold risk developing HCC as compared to non-dysplastic (Borzio et al, 2003); eastern authors tend to interpret these nodules as early, well-differentiated HCC (eWDHCC) 17,18;
- HCC more rarely develops from regenerative and low grade dysplastic nodules (10-25%) 9 while it is hard to estimate how many HCCs will develop from the inconspicuous cirrhotic background;
- all types of non-malignant nodules including HGDN can undergo internal remodeling with 20-73% nodule disappearance at US 9,14-16;
- the most controversial diagnostic issue is between HGDN and eWDHCC. The disagreement between pathologists on the most appropriate diagnostic criteria and related nomenclature 3 likely reflects a continuum spectrum of lesions (high grade dysplastic nodules, in situ HCC, micro-invasive HCC, overt HCC) whose boundaries are biologically (and consequently morphologically, phenotypically and genotypically) ill-defined 18. The incidence HGDN in a surveillance setting of cirrhosis and their further morphological sub-categorization is essential for the following reasons:
  - to make a correct diagnosis: a) candidating patients with malignant nodule(s) to surgical resection/waiting list for transplantation/ablative therapy; b) decreasing the likelihood of transplanting patients prematurely who don’t have HCC and, conversely, avoiding the exclusion of patients with multiple nodules, some of which could be non-malignant;
  - to perform the clinical staging of patients with malignant nodules in particular for those amenable to hepatic resection;
  - to make a correct prognosis: a) reassuring patients harboring regenerative/LGD nodules of their not aggressive nature and to plan a pertinent recall policy; b) in case of HGDN/eWDHCC discussing with patients the therapeutic options or planning a more aggressive recall policy (enhanced follow up);
  - to increase our understanding of the cirrhosis-dysplasia-HCC sequence by studying the natural history and the phenotypic and genotypic profile of the different lesions.
This will permit to find novel markers particularly useful to discriminate low from high malignant potential lesions (including in situ HCC) and the latter from well differentiated HCC with stromal and/or vascular invasion.

Liver biopsy is essential for the proper characterization and management of <2cm hepatocellular nodules. Despite a 10% false-negative rate 20, when the imaging profile is not characteristic for malignancy, liver biopsy still remains the diagnostic milestone; morphologic data should always be integrated with imaging that gives information about the whole lesion. For <2cm nodules a “wait and see” policy has been suggested particularly in patients waiting OLT, limiting an aggressive diagnostic and therapeutic strategy to >2cm nodules 21. Emerging data indicate that the smaller the lesion the less likely there is to be microscopic vascular invasion and more likely local ablation will be complete 3. It is therefore important to make the diagnosis of HCC as early as possible. However it is equally important not to apply invasive treatment to lesions that do not have any malignant potential and may still regress. Our opinion is that a distinction of <2cm malignant from non-malignant nodules in cirrhosis and their further morphological sub-categorization is essential for the following reasons:
  - HCC which could be non-malignant;
  - to perform the clinical staging of patients with malignant nodules in particular for those amenable to hepatic resection;
  - to make a correct diagnosis: a) candidating patients with malignant nodule(s) to surgical resection/waiting list for transplantation/ablative therapy; b) decreasing the likelihood of transplanting patients prematurely who don’t have HCC and, conversely, avoiding the exclusion of patients with multiple nodules, some of which could be non-malignant;
  - to perform the clinical staging of patients with malignant nodules in particular for those amenable to hepatic resection;
  - to make a correct prognosis: a) reassuring patients harboring regenerative/LGD nodules of their not aggressive nature and to plan a pertinent recall policy; b) in case of HGDN/eWDHCC discussing with patients the therapeutic options or planning a more aggressive recall policy (enhanced follow up);
  - to increase our understanding of the cirrhosis-dysplasia-HCC sequence by studying the natural history and the phenotypic and genotypic profile of the different lesions.
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We retain that an early distinction between malignant and non-malignant nodules, in particular between regenerative/LGD versus HGDN/ eWDHCC is an affordable task for liver-trained pathologists, provided the availability of pertinent clinical and imaging information, adequate sampling and accurate morphologic evaluation.
**Integrated clinico-pathological approach**

Approaching the biopsy of a focal liver lesion pathologists should be aware of:

- clinical setting: surveillance of patients with cirrhosis or in the liver transplant waiting list or with previous HCC;
- background liver: chronic hepatitis/cirrhosis;
- specific serologic markers: viral and oncofetal (AFP) number, location and size of nodule(s);
- US pattern (and variation during follow up); CT-, US-perfusional-, MRI- patterns when available;
- previous cyto/histopathologic liver sampling and diagnostic report(s);
- previous diagnosis of HCC and type of treatment.

**Sampling**

An intra- and extra-lesional sampling is highly recommended. Subtle architectural and cytologic abnormalities can be better appreciated through the accurate comparison with extra-lesional referenced liver. When both intra- and extra-lesional samples show overlapping, cirrhosis-like features, without a major nodule standing on the nodular background, the sample should not be considered adequate; as such a new sampling is recommended shortly after. We do not agree with the opinion that only a positive biopsy is helpful and that a negative one can never be taken as conclusive. There are criteria to distinguish inadequate from adequate but negative samples. Sample adequacy is not only linked to the size of biopsy but it is also dependent on the type of lesion, cell differentiation, liver background and on the consistency between morphologic and clinico-radiologic features. An important issue to be taken into account is when the patient harbors more than one small nodule. Given that the diagnostic uncertainty is greater in small lesions, we recommend to sample the smaller one, assuming that the larger is likely to be already malignant.

**Table I – H&E features to be looked for in order to preliminary distinguish the different categories of nodules in cirrhosis**

<table>
<thead>
<tr>
<th>LRN</th>
<th>LGDN</th>
<th>HGDN</th>
<th>eWDHCC</th>
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<tbody>
<tr>
<td>Clone-like foci</td>
<td>–</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Plate thickening</td>
<td>–</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Cell crowding</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Pseudoglands</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Stromal invasion</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Unpaired arteries</td>
<td>–</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Nuclear Atypia (*)</td>
<td>–</td>
<td>±</td>
<td>+</td>
</tr>
</tbody>
</table>

(*) hyperchromasia and nuclear irregularities

Legend: – absent; ±: may be present but not necessarily detectable in biopsy; +: usually present and detectable in biopsy.

**Imaging of dysplastic nodules**

At conventional US, these lesions are mainly hypoechoic with a well defined rim, but iso-hyperechoic patterns can also be found. Consequently US are unable to reliably distinguish benign from malignant or potentially malignant lesions. Recently, different imaging techniques (perfusional-US, helical-CT and MRI) have been introduced in the diagnostic workflow, relying on their ability to explore the vascular pattern. Unfortunately most dysplastic nodules and some well differentiated HCC do not achieve a mature arterial hypervascularisation, so eluding being detected by these techniques. In studies where the gold standard is the explanted liver, CT showed a lower sensitivity (40%) as compared to MRI (96%) in the detection and diagnostic accuracy of <2 cm nodules. Perfusional-US do not seem to add more information as compared to helical-CT, which is available in almost all general hospitals as opposed to perfusional-US and MRI, that are much less diffuse because expensive and experienced-operator dependent. In this setting only the CT showing arterial hypervascularization and venous wash-out is reputed enough for malignancy, not being usually followed by liver biopsy. Unfortunately CT, also in experienced hands, does not detect a consistent fraction (30-50%) of small hepatocellular nodules, because hypovascular or with undefined vascular pattern. In this “real word” scenario we think that the most quick and probably less expensive way to get a conclusive diagnosis is histology.

**Dysplastic nodules: general morphologic features on liver biopsy**

Dysplastic nodules are classified as LGDN or HGDN on the basis of cytologic and architectural atypia. More specifically, while LGDN only show cytologic atypia and minimal architectural disturbances, HGDN are characterized by both cytologic and architectural atypia but not so overt as to make a diagnosis of malignancy. At low magnification at least one or two unconnected portal tracts should be recognized within the nodules (Figure 1a). Key-morphological features of differential diagnosis are summarized in Table I.

**LOW GRADE DYSPLASTIC NODULES**

A lesion with low malignant potential. When looking a low grade dysplastic nodule under the microscope the
Table II – Differential diagnosis between HGDN and early WD HCC

<table>
<thead>
<tr>
<th>Feature</th>
<th>HGDN</th>
<th>early WD HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness of plates</td>
<td>2 or 3</td>
<td>&gt; 3 (*)</td>
</tr>
<tr>
<td>Pseudoglands</td>
<td>focal</td>
<td>plurifocal</td>
</tr>
<tr>
<td>Cell crowding</td>
<td>x 1,5/2 x&gt;2 (*)</td>
<td></td>
</tr>
<tr>
<td>Capillarized vessels (CD34+)</td>
<td>focal</td>
<td>plurifocal</td>
</tr>
</tbody>
</table>

(*) as compared to adjacent cirrhotic nodules.

b) Qualitative key-features diagnostic for malignancy (*)
- Decreased/absent reticulin framework (**)
- Stromal invasion (**)
- Vascular invasion (**)
- Nodule in nodule growth (expansive hypercellular nodule)
- Diffuse CD34+ capillarized vessels

(*) Each feature diagnostic for malignancy. (**) Each feature discriminating between in situ HCC and invasive HCC.

Differential diagnosis
LGDN VERSUS LARGE REGENERATIVE NODULE (LRN)
At high magnification LRN are microscopically indistinguishable from the surroundings. The intralesional parenchyma, when sampled in the middle and near periphery, may even simulate a normal liver, given the presence of portal tracts. Large cell changes, minimal nuclear abnormalities and clone-like changes can be detectable in low grade dysplastic but not large regenerative nodules.

LGDN VERSUS HGDN:
As shown in Table I this distinction is based on qualitative features such as the absence of architectural abnormalities in LGDN while the detection of clone-like changes, when present, should be restricted to minute foci. Overall, at first glance, LGDN do not alert pathologists.

HGDN VERSUS eWDHCC
The most useful morphologic features of differential diagnosis to be always looked for are summarized in Table II a,b. Overtly malignant, even if still well-differentiated HCC, likely corresponding to the so-called “distinctly nodular type” of eastern authors 17, does not enter in the differential diagnosis, being its malignancy easily recognizable at first microscopic glance. The diagnostic issue with eWDHCC can be preliminarily addressed by the accurate evaluation of a) hepatocyte plates; b) reticulin framework; c) neoangiogenesis; d) stromal invasion/pseudoinvasion.

Hepatocytes plates. A diagnosis of well differentiated...
hepatocellular malignancy should be considered when architectural for uncomplete, (mainly portal) neo-vascularization and it is reputed to grow without destruction of the adjacent liver parenchyma, by progressive replacing of cirrhotic nodules. As such it merges with normal hepatic plates, the sinusoids containing both arterial and venous portal flow. Japanese authors consider this eWDHCC to have peculiar macroscopic and microscopic features (average diameter 1,5 cm, unencapsulated, well differentiated histology, fatty changes) 17. They call it “indistinctly nodular type” as opposed to the “distinctly nodular type”, being the latter easily detectable for sharp boundaries at both imaging and on surgical resections. Small HCC of distinctly nodular type is reported to be more aggressive and angioinvasive than eWDHCC (a step further on the road of HCC progression) 17.

The eWDHCC may contain a few portal tracts (less than 1/3 as compared to hepatic surroundings) 17 (Figure 1i). A trabecular arrangement (which would facilitate the diagnosis) is not obviously detectable. It may contain clone-like populations with homogeneous cytoplasmic features (clear, fatty etc). Interestingly a still controversial feature between eastern and western studies is the relative lack of fatty change in western as opposed to eastern countries (30-40% of cases) 17,41. Indeed fatty changes in HGDN and early HCC are uncommonly reported in European explanted livers (L Libbrecht, personal communication 2004). Recently Rapaccini et al (2004) 12 showed, in a surveillance setting of prospective cirrhosis, that echogenicity of small HCC was unrelated to tumor differentiation, a notable feature given that fatty metamorphosis is the main cause of hypoechochogenicity in liver nodules. In our experience, both clear and fatty changes are the main clone-like features detectable in small, eWDHCC (Figure 1l) as well as in HGDN. Further studies are needed comparing the rate of fatty metamorphosis and clear cell changes in western and eastern series in both HGDN and eWDHCC.

**Reticulin framework.** HGDN always display a well preserved reticulin framework (Figure 2a), while obviously invasive HCC do not. Pathologists agree that if the reticulin framework is decreased or lost the tumor is malignant. However, eWDHCC by growing in a replacing pattern, may be associated with a still intact (Figure 2b) or slightly decreased (Figure 2c) reticulin framework. In conclusion a decreased reticulin is very helpful and indicates malignancy but a preserved one does not necessarily exclude malignancy.

**6.3.3 Neoangiogenesis.** There is a progressive increase in the number of unpaired arteries (barely visible by H&E and better visualized by smooth muscle actin immunostaining) and capillarized sinusoids (documented by CD34 immunostaining) from LGDN to HGDN to eWDHCC to overt HCC 41,42. However a threshold of vessels/mm² separating pre-malignant from early malignant lesions has not been determined possibly because these lesions form a continuum spectrum. As for reticulin framework, an uncomplete sinusoidal capillarization (that is more easily detectable on liver biopsies than unpaired arteries) would still be in keeping with a pre-malignant nodule (HGDN) (Figure 2d) or eWDHCC (Figure 2e), while diffuse CD34 immunoreactivity is, in our experience, a feature of overt malignancy (Figure 2f). However there is a lack of studies on the variation of both reticulin

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**Fig. 1:** a) LGDN: arrow points to an unconnected portal tract; b) HGDN: nuclear crowding merging within bland-looking hepatocytes; c) HGDN: focal increased hepatocytes plate thickening; d) HGDN: isolated pseudoglands (arrows); e) HGDN: a focus of clear cell clone-like changes (bulging-type); f) eWDHCC growing within a HGDN; g) G1/G2 HCC growing within an eWDHCC with fatty changes; h) eWDHCC: evenly distributed architectural abnormalities; i) eWDHCC with fatty changes containing a portal tract (arrow); l) eWDHCC with fatty changes at higher magnification.
framework and vascular capillarization in the sequence HGDN-eWDHCC.

Stromal invasion/pseudoinvasion. Given that HGDN have features partly overlapping those of eWDHCC, the only difference being the less extensive and uneven pattern of growth of the former, there is the suggestion that the most critical feature separating HGDN from eWDHCC is stromal invasion. Stromal invasion may occur in eWDHCC and therefore the infiltration of portal tract/fibrous septa by single hepatocytes is expected to be a cardinal feature of malignancy that should be carefully looked for in intralesional biopsy samples (Figure 2g). It has been preliminary suggested that CK7/19 immunostaining, by highlighting the ductular reaction that takes place only around non-malignant hepatocellular nodules, might also prove useful to distinguish true invasion (lack of staining) (Figure 2h) from pseudoinvasion (positive staining) (Figure 2i) (NY Park, personal communication, 2004).

In conclusion HGDN should be suspected when features of eWDHCC are focally and unevenly distributed, merging with normal-looking hepatocytes, in a setting of preserved reticulin framework, incomplete sinusoidal capillarization and lack of stromal invasion. Conversely when stromal invasion is the only feature missing in a morphologic scenario of diffuse architectural changes, retained/slightly decreased reticulin framework and discrete sinusoidal capillarization the most likely diagnosis should be eWDHCC (possibly in situ HCC). The differential diagnosis between in situ HCC and HGDN is obviously very difficult because these two lesions are biologically very close. We can concur with eastern authors that a demarcation line cannot be drawn between HGDN and in situ HCC. However, a number of novel phenotypic, genotypic and expression markers are expected to provide information on the putative heterogeneity of this spectrum of lesions.

Novel immunocytochemical markers

Several immunocytochemical markers have been proposed as helpful for a diagnosis of malignancy. Particularly interesting are novel markers of cycling cells such as those of the MCM (minichromosome maintaining proteins) family, (A Quaglia et al, personal communication 2005), or true markers of hepatocellular malignancy such as as glypican-345-47, HSP 7048,49 and glutamyne synthetase 50. However the specificity, sensitivity and heterogeneity of the above markers is largely unknown; a comprehensive study evaluating their expression along the morphologic sequence cirrhosis-dysplasia-HCC is still lacking.

Molecular markers

It has been shown that dysplastic nodules are monoclonal proliferation of hepatocytes51; progressive chromosomal instability under the form of allelic imbalance characterizes the sequence LGDN-HGDHCC (Maggioni et al, 200052; reviewed by Libbrecht et al, 200553 and an increased number of chromosomal gains
and loss (reviewed by Moinzadeh et al, 2005) is a feature of the multistep progression towards malignancy. Recently Oh et al. reported telomere shortening involving up regulation of telomere-binding proteins. We have preliminary results confirming that genetic abnormalities affecting key-cancer genes such as p53 and ?-catenin mutations occur in a fraction of overt HCC but not in their precursors; interestingly we are also detecting an increased number of epigenetic changes, such as RASSF1A and p16 genes methylation in dysplastic nodules, likely related to early hepatocarcinogenesis.

A few studies attempted to address the issue of the molecular profile of dysplastic nodules in the cirrhosis-HCC sequence, by gene expression analysis. Anders et al. reported that novel genes including caveolin1, semaphorin E and FMS-like TK3 ligand are abnormally regulated in dysplastic nodules. More recently Nam et al. were able to identify 240 out of 3084 genes that could accurately classify tumors according to histological grade, especially when attempting to discriminate LGDN, HGDN and grade 1 HCC. Interestingly enough these authors reported that G1 HCC are molecularly heterogeneous, sitting on the border between the transition from pre-malignant lesions to overt malignant carcinoma and that this heterogeneity is distinguishable at the molecular level. It is expected that genomic and proteomic studies, targeted to address gene expression profile in the sequence cirrhosis-dysplasia-HCC, should provide specific markers to distinguish among early lesions and, hopefully, to more accurately predict the risk of malignant transformation of non-malignant nodules.

**Natural history of dysplastic nodules**

While large regenerative nodules are thought to carry a malignant potential not greater than that of the adjacent cirrhosis, dysplastic nodules are considered precancerous. LGDN have a natural history showing malignant transformation in a few cases; as such these lesions can be considered to have a low malignant potential. Conversely, HGDN have been reported to be statistically associated with malignant transformation. These lesions can thus be considered at high malignant potential. Both low and high grade dysplastic nodules can undergo internal remodeling with nodule disappearance. In the clinical practice the suggested management of LGDN is surveillance with repeat biopsy when the imaging features of the lesion changes, while HGDN have to be at least strictly monitored or ablated by percutaneous ethanol injection or termal therapy.

**Riassunto**

La sequenza di eventi molecolari coinvolti nel processo di epatocarcinogenesi si rispecchia nelle lesioni che sono essere individuate nel fegato cirrotico: noduli rigen-erativi (NR), noduli con displasia a basso grado (NDBG), noduli con displasia ad alto grado (NDAG); l’ultima entità si colloca nel contesto delle lesioni a “mali-gnità borderline” e deve essere distinta con attenzione dall’epatocarcinoma in fase iniziale (c.d. early-EC) e dalle forme ben differenziate. La presenza di noduli nel contesto di un fegato cirrotico è in genere appannaggio di metodiche non invasive, tuttavia queste ultime non sono in grado di discriminare tra forme maligne e forme non maligne, specie se la lesione è di dimensioni < 2 cm. In questo contesto diviene essenziale, ai fini di una diagnosi ed un corretto approccio terapeutico, valutare una biop-sia della lesione (meglio se unitamente ad una biopsia perilesionale). La diagnosi istologica verte su di una accurata valutazione di caratteri cito-architettruali (attipia cito-logica, affollamento delle cellule, ispessimento delle trabecole, formazione di microacini, ecc), supportate da indagini istochimiche (colorazione per il retilco sec. Gomori) ed immunoistochimiche. Queste ultime costano nell’utilizzo di marcatori elettivi, in parte nuovi e in parte di comprovata validità, in grado di evidenziare l’infiltrazione stromale (CK7/19), il pattern vascolare (actina muscolo liscio e CD34) o la trasformazione neo-plastica degli epatociti (HSP70 e Glypican-3, fra gli altri). Nonostante ciò la sensitività nella diagnosi è drastica-mente limitata dal tipo di prelievo, minimamente rappresentativo della intera lesione. L’approccio migliore, dunque, è rappresentato da una integrazione dei dati cli-nici, morfologici ed immunoistochimici con le informa-zioni di imaging (ecografia, pattern di perfusione, RMN/TC). Il ruolo della biologia molecolare è ancora dibattuto. Infatti i dati prodotti hanno dato adito a discrepanze di interpretazione, specie all’interno della categoria delle lesioni a “malignità borderline”, fra patologi occidentali ed orientali: i primi a favore della diagnosi di NDAG, i secondi a favore del d.c. early-EC. Si auspica che nuovi, e più obiettivi, marcatori molecolari e fenotipici possano aiutare a discriminare la zona grigia rappresentata da queste lezioni a “malignità bor-derline”, seppur queste, almeno da un punto di vista epidemiologico, risultano ben separate fra paesi occidentali ed orientali. Questi putativi marcatori dovrebbero anche permettere di meglio comprendere i confini di questo processo che inizia dai NDAG, evolve nell’EC in situ, si modifica ulteriormente assumendo i caratteri dell’EC microinvasivo sino a divenire un EC avanzato, ai fini di ottenere una migliore gestione di questo paziente e un trattamento terapeutico ottimale.

**References**


