the Uterine mass Magna Graecia risk score

Detecting malignancy in uterine lesions: an open challenge

Uterine fibroids are one of the conditions that most frequently we, as gynaecologists, have to deal with in our activity. More than a real disease, fibroids today should be considered as a 'paraphysiologic' condition, in a sense comparable to the what is aging of the human being. To date, the availability of medical management strategies reduce the need to surgery for uterine fibroid. Even more, as during 2014 the Food and Drug Administration banned the use of Morcellator during laparoscopic surgery because, if the uterine mass was not a fibroid but a sarcoma, it could add an unacceptable risk in cancer cells dissemination with a consequent upstaging of the disease. But despite such risk exists, recent data in the literature confirms that the risk is really minimal (1 possibility over 2.000 - 10.000 women operated). However, to exclude the risk of sarcoma in women with uterine masses has now become an ethical obligation for every gynaecologist before proposing to a patient to make medical treatment without removing thus the mass, or to undergo surgery in order to decide on the most appropriate approach.

Currenltly, no clinical data, no ultrasound and no biomarkers for preoperative risk assessment are known. Thanks to a retrospective analysis of data collected from 2004 until today at our hospital, the Pugliese Ciaccio - University Magna Graecia of Catanzaro, we have identified some markers which can be integrated into a score, allowing us to stratify patients into three risk categories, and to manage them accordingly. Because of the ease in its implementation, for its low cost and especially for its statistical validity, we strongly believe that our score will have an impressive and indisputable clinical impact. We are confident to launch, in a few months, a mobile phone App supporting a prospective multicenter validation process.

— Fulvio Zullo, M.D., Ph.D.

Fibroma or sarcoma?

by ANNALISA DI CELLO

Uterine fibroids are the most common uterus benign tumours, occurring in over two-third of all women. On the contrary, uterine sarcomas are rare and aggressive mesenchymal tumours that arise from smooth muscle of uterus, representing about the three per cent of all uterine neoplasms. Surgery is always a viable solution, but a significant public health concern in managing fibromas is represented by hysterectomy performed in women of reproductive age. Clearly, more conservative surgical approach as laparoscopy should be preferred; in particular, a very minimally invasive approach, called laparoscopic **morcellation** technique, has been proposed.

Obviously, the diagnosis of sarcomas is expressed by a pathologist only *after* the surgical treatment performed in women with a clinical suspicious of a uterine fibroid. The consequences of this fact are twofold: first, the best surgical treatment is not always offered at the upfront: morcellation or hysterectomy? Second: estimating about $3(\pm 2)$ occult malignancies cases over ten thousand surgeries, laparoscopy can not be consid-

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ered a free-risk techinque, posing a hazard of spreading unsuspected and miss-diagnosed cancerous tissue (i.e. uterine sarcomas) beyond the uterus. In fact, on April 2014 the U.S. Food and Drug Administration released a safety communication notice strongly discouraging the use of laparoscopic power morcellation for the removal of the uterus or uterine fibroids.

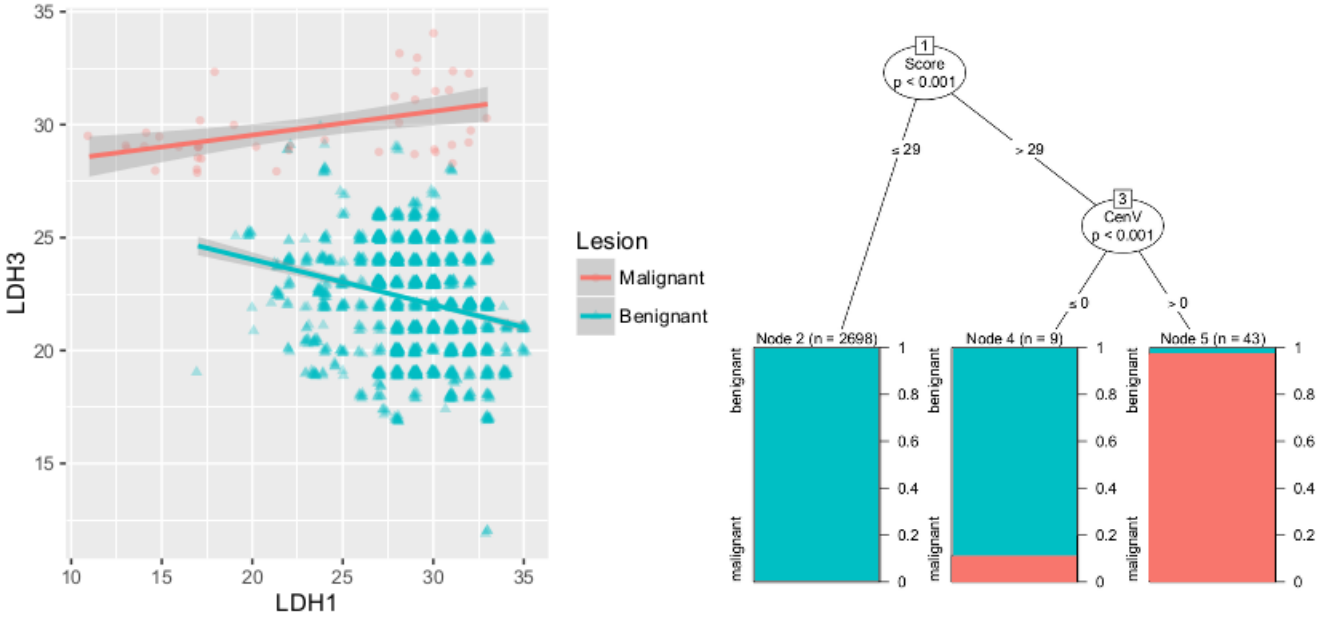
In conclusion, it is crucial to exclude preoperatively the risk of uterine sarcoma and this can be done creating a high-accuracy predictive tool to classify uterine masses, according to malignancy.

In the next section, Massimo explains how we were able to identify such a risk score, allowing to stratify patients with uterine mass with a maximal predictive value in excluding the risk of sarcoma. This tool could help clinicians in choosing, according to the identified class of risk, the most appropriate medical or surgical treatment for each patients.

Toward a reliable malignancy predictive algorithm

by MASSIMO BORELLI

Investigating over a total of 2750 complete cases (3107 patients enrolled) we were able to disclose the competing role of LDH-1 and LDH-3 lactate dehydrogenase iso-enzymes in predicting uterine lesions malignancy, as shown in the left panel of the picture below.



Joining enzymatic information with the ultrasonographic vascular observation can provide an extraordinary accurate decision criterion.

Optimizing such result, we were able to define *UmMG*, a **risk score** which encompasses the two biomarkers:

$$UmMG = LDH3 + \frac{24}{LDH1}$$

Increasing values of *UmMG* risk score are strongly associated to a malignant outcome; therefore, choosing a suitable cut-off (29 is the maximimum likelihood choice suggested by our data) and combining the *UmMG* risk score with the ultrasonographic information about central vascularization (no/yes) we were able to create a **decision algorithm**.

UmMG classifies patients into three not-overlapping categories, as you see on the right panel above: the low-risk class, in which the malignancy risk is not detectable; the high-risk class, with almost sure malignancy risk; the intermediate class, with a potentially high malignancy risk discouraging the laparoscopic approach. Within low-risk and high-risk classes the true positive and true negative ratioes are, accordingly, very close to certainity. The 'uncertain' intermediate class is very tiny in size, one or two magnitude order lower than others.

Lastly, exploiting Monte Carlo resampling methods, we were able also to lead a 'robustness' analysis in order to assure the internal validation of the decision algorithm. *UmMG* therefore appears to be very, very reliable.