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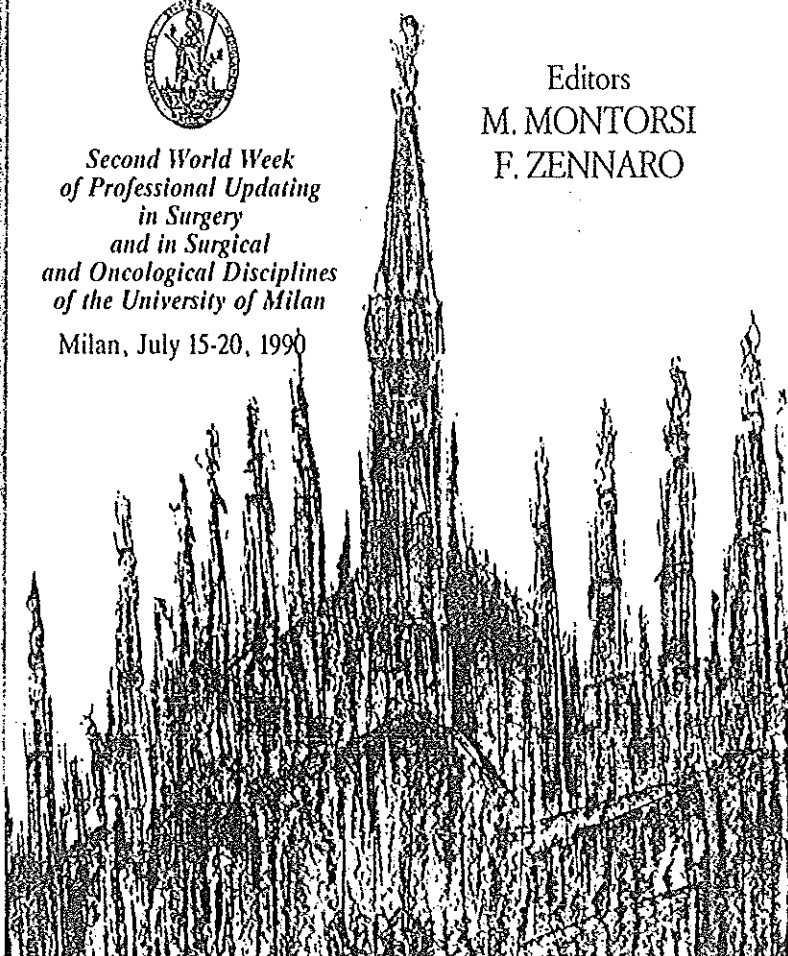
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MONDUZZI EDITORE

RECENT DIAGNOSTIC AND THERAPEUTICAL APPROACH ABOUT ON EARLY BREAST CANCER USING MONOCLONAL ANTIBODIES AND FLOW CYTOMETRIC ANALYSES

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Given the high incidence and persistent mortality of breast cancer, it is mandatory to establish reliable methods of diagnosis and fitted protocols of follow up so far the common effort to render a precise diagnosis of the disease in its early stages as undoubtedly produced positive results. A widely accepted approach, for instance, implies history, physical examination and mammography followed in cases considered suspicious by CT guided aspiration biopsy. In our opinion this is the best approach to breast cancer especially for patients at risk (because of their family, history, age, nulliparity, history of severe mammary dysplasia) so that it is recommended by the European Group For Breast Cancer Screening in order to carry out reliable protocols of screening, such a check up should be performed every 2-3 years. We are currently evaluating the accuracy of new diagnostic methodologies which do not require the use of radiations such as : ultrasound associated with fine needle aspiration biopsy and diaphanoscopy, however the results in terms of sensitivity and specificity are not comparable to the ones obtained by mammography. Despite the high specificity of the radiologic diagnosis, we noted as other authors reported previously that metastases from an occult breast carcinoma (meaning a carcinoma not detectable by X- rays) are infrequent, however present in the 0.5 - 7 % of the patients. More specifically the anatomic sites more often involved are respectively the lungs, above the diaphragma and the pancreas beneath the diaphragma. Metastases from occult breast carcinoma are present in the axillary lymph nodes in the 0.3 % of all cases and in the 0.5 % of cases N^o. We must also take into account, as stressed by Nyström and others (1977) that often the dissemination to the metastatic sites of occult carcinomas differs from that observed in cases of clinically manifested tumors. As a matter of fact bony metastases are present in 50- 80 % of patients with

clinically evident breast cancer, whereas they occur only in the 33 % of patients with occult disease.

It is mandatory that the primary tumor be found in order to avoid possible complications and to promptly establish a therapeutic regimen able to improve the patients survival. Beside the above mentioned tests, the use of ultrasound and CT scan is important in order to rule out the involvement of classical sites of metastases from breast carcinoma, such as liver, lung, pancreas, bones and brain. Lately, the introduction of monoclonal antibodies capable of binding to specific glycoproteins present in the neoplastic tissue as allowed to better detect both primary tumors and metastases by visualizing neoplastic foci otherwise not evident. Particularly, a recent breakthrough is represented by the following monoclonal antibodies (Mabs) : anti- MCA, anti- CA 15-3 and Mab ER-D5. All of them are antigens associated with breast carcinoma, more specifically the D-5 is a protein linked to the estrogen receptor. As a consequence the Mab ER-D5 is specific only for (ER+) human tissues and is therefore a reliable marker for breast carcinoma. It is our belief that only by developing new diagnostic methodologies such as the one above mentioned, and combining TM and Flow Cytometry, we can accomplish a better staging of cancer: we could than not only render a diagnosis of cancer disease at a cellular level, but also choose an adequate therapy (immunotherapy, monoclonal antibodies) to fight a disease that in our opinion should be considered as sistenic from the beginning. In addition to the monoclonal antibodies, we think that it is necessary to develop other techniques such as:

- A) markers both morfological and circulating
- B) proliferative kinesis
- C) flow cytometry and ploidy

in order to define the relationship between the biologic aggressiveness and clinical behavior of neoplastic disease. The proliferative activity of the neoplastic cells determined on the basis of DNA synthesis, either by flow cytometry or by the incorporation 3-H thymidine, can than be studied in order to achieve a dynamic staging of the neoplasia and could therefore represent the elective approach to an early diagnosis of cancer in cases of severe mammary dysplasias. More specifically, the DNA analysis by flow cytometry, is of great relevance as to the clinical prognosis of the disease. As a matter of fact there is an unobst correlation between ploidy of malignant cells, size of the tumor and long term survival. The diploid cells, for instance, are associated with a smaller size of the primary tumor, as well as better grading and staging compared to what observed in carcinomas made up of aneuploid cells. There is also a correlation between ploidy and hormonal status of the patient: in particular because of the presence of estrogen receptors, assessed in the 64 % of cases, it is been possible to start a more fitted hormone therapy. Lastly, we noted both prolonged disease free interval and longer short term survival in patients with diploid breast carcinoma compared to those with aneuploid carcinoma. Once identify the patients at risk on the basis of their age, family history, hormonal status, parity, history of breast feeding....., in the presence of suspicious mammographic findings, we consider useful to employ specific monoclonal antibodies in order detect primary breast carcinomas which could not be diagnose otherwise. This methodology could be applie also to those patiens carrying a diagnosis of severe multifocal dysplasia on the basis of mammographic evidence of fibrocystic disease with microcalcifications which might hide multiple foci of cancer. In cases with suspicious mammographic findings it is necessary to perform, whenever possible, an aspiration fine needle biopsy, (FNAB) which can be either stereotassic or guided by ultrasound in order to obtain enough tissue for flow cytometry and eventually identify an incipient proliferation of neoplastic cells. It is also possible to apply modern techniques of

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immunohistochemistry to FNAB to better evaluate those patients presenting, at mammography, with suspicious nodules or with severe dysplasia, as to their prognosis. More specifically, the immunoperoxidase technique, by employing Mabs specific for the hormone receptors, allows us to detect their presence in the neoplastic cells in order to:

- 1) classify the incipient neoplastic disease
- 2) determine the hormonal status of the patient
- 3) choose an adequate therapeutic protocol.

In addition the test with Mabs, can be performed on patients with metastases from unknown primary to rule out an occult breast carcinoma as well as on patients with history of breast cancer surgically removed to eventually diagnose occult micrometastases. Lastly specific monoclonal antibodies, can be used at the time of surgery, to obtain a more precise staging as well as to carry out radioimmuno-guided operations. As a matter of fact a recently introduced monoclonal antibody (B 72.3), if used before surgery, allows to determine not only the size of the tumor, but also the presence of distant metastases and to select, subsequently, the most adequate treatment. More specifically, this new Mab (B 72.3), of murine origin, seems to be specific (85-92 %) for the surface antigen TAG-72 present on the breast cancer cells. After marking it with I-125 , this Mab works as a tracer and can therefore be injected 15- 20 days before surgery so that intraperitoneally, it is possible to detect through a neoprobe system 1000 the gamma rays emitted by those neoplastic cells which are bound to the complex Mabs - I-125.

In our opinion this new methodology, not only contributes to better define the extension of the primary tumor, but also allows to perform a new surgical procedure, the Radioimmunoguided Surgery which is more reliable as far as the size of the neoplasm as well as the occult micrometastases are concerned. Such a procedure either by itself or in association with other therapeutic modalities could become the elective treatment of mammary carcinoma as to removal of the primary tumor, recurrence and micrometastases with subsequent improve of the survival.

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