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JOLLY HOTEL AMBASCIATORI
TORINO, 7-10 NOVEMBER 1990

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C. ROSSO - A. CELLERINO - G. L. TURCO
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COMMUNICATIONS

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KINETIC USE OF TUMOR MARKERS IN THE FOLLOW-UP OF PATIENTS OPERATED FOR PRIMARY BREAST CANCER

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INTRODUCTION

The clinical role of systemic therapies for metastatic breast cancer is currently under debate. Both death statistic studies (1-2) and clinical studies on patients with advanced breast cancer (3-7) suggested that the effect of therapies on patient survival is indeed very poor. On the basis of these findings the usefulness of the instrumental and laboratory follow-up programs for breast cancer has been questioned because the early detection of relapse does not affect significantly the prognosis of the disease (8-9).
Some authors report an improvement of survival due to the early detection of the recurrence if the disease was treated when still asymptomatic (10-12). However, the apparent gain in survival could have been ascribed to a longer lead time (8,13), that is, both patients and the medical staff were aware of the recurrence for longer time when asymptomatic disease had been identified.
The role of tumor markers is similar to that of other instrumental or laboratory tests. Actually, they are very effective, because they recognize the disease progression in a high percentage of cases. Moreover, in many instances tumor marker levels increase before any other clinical or instrumental sign of relapse. However, their use does not affect the overall survival. Tumor marker increases above the cutoff level are indeed very early, but at the present time, patients are treated only on the basis of clinical or instrumental evidence of relapse.
The aim of the present study is to verify if a kinetic evaluation of tumor markers during the follow-up may provide a long lead time with adequate accuracy performances, with the goal of the possible treatment of the relapse only on the basis of a biochemical identification.

MATERIALS AND METHODS

So far, 269 patients radically operated for primary breast cancer had been included in the study. Patients were divided into two groups, with high and low risk of relapse respectively, according to criteria shown in Table I.
The timing of the follow-up, as well as the instrumental tests currently requested, were not modified.
In high risk patients serum samples were collected three times within the month preceeding each clinical examination. In low risk patients a single serum sample was obtained before each clinical examination.
Serum samples were divided into several aliquots and stored at -70°C. CA15.3 and CEA were measured with commercially

available methods. When more samples were obtained from the same patient they were assayed in the same run. Assay precision was monitored by precision profiles.

Kinetic evaluation of tumor markers (three points within one month). Tumor marker variations were considered significant when the three serial points showed a progessive increase with the difference between the first and the third determination being higher than three times the coefficent of variation expected at a given dose. Patient follow-up was performed on the basis of tumor markers as shown in Table II.

Single sample (cutoff based) evaluation of tumor markers confirmed through kinetic study. In low risk patients tumor marker levels were evaluated according to the standard dichotomic criteria, based on a positive/ negative cutoff level. However, instead of a single cutoff point, two different levels were used: 1) normality threshold, calculated on the basis of tumor marker distibution in healthy subjects, that is the traditional cutoff value; and 2) alert threshold which was calculated on the basis of tumor marker levels found in patients with metastatic breast cancer. The threshold levels decision rule was used in the scheme shown in Table III in which the positivity detected using the cut-off criteria was confirmed through kinetic evaluation.

RESULTS

Low Risk Group. Among the 269 patients evaluated, 260 were free of disease, and 9 had clinical and/or instrumental sign of relapse.

Table IV summarizes tumor marker pattern in cases without evidence of disease. In the majority of cases CA15.3 and CEA showed values below the normality threshold.

In a second group CA15.3 in 9 cases and CEA in 10 showed values higher than the normality threshold; the kinetic evaluation on serial samples did not show any significant increase in tumor marker levels. The kinetic criteria is therefore in accordance with clinical conditions and suggests that cutoff based positivity should be considered as a false positivity.

In a third group of patients (3 for CA15.3 and 1 for CEA) tumor markers were higher than the normality threshold and showed a further increase during the following months. These patients should be considered as bearing occult disease and are currently evaluated each month.

The behavior of tumor markers in the 11 patients which relapsed is shown in Table V. CA15.3 was below the cutoff in 4 cases in one of which the marker value increased significantly within one month. In 5 cases CA15.3 was above the normality threshold. In 3 of these cases the markers showed a further increase, in 2 others no significant variations were found. Similar patterns were found for CEA which showed however a high number of cases below the cutoff level in which the kinetic was positive.

No preliminary results are yet available for the 25 patients at high risk of relapse so far evaluable. Indeed, the study

protocol set up for the high risk group was started later with the aim of enhancing the diagnostic sensitivity of the markers.

DISCUSSION

In the present study we used kinetic criteria to verify the biological meaning of tumor marker positivity. When tumor markers were above the cutoff level, two different kinetic patterns were identified. In the first, tumor marker levels increased significantly within one month; in the second, tumor marker levels did not show significant variations. The two patterns were identifiable both in patients without evidence of relapse and in those with disease progression. In both groups the increase of tumor marker levels should indicate the presence of a tumor secreting the tumor marker. Therefore, in patients apparently free of disease this pattern should be an early indicator of the relapse. Cases with markers above the cutoff which do not show any increase should either represent false positive cases or indicate tumors with a slower production and/or secretion rate of the marker. The clinical evaluation of patient follow-up will indicate which of the above hypothesis is more probable. Moreover, the serial determination of tumors marker in patients with high risk of relapse will provide further insight into tumor marker kinetic behavior.

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TABLE I. Subdivision of patients included in the study in relation to the probability of relapse.

PROBABILITY OF RELAPSE	TIME FROM MASTECTOMY	AXILLARY STATUS	MENOPAUSAL STATUS	ER and/or PgR
LOW	>5 years	+ or -	PREM or POSTM	+ or -
	≤5 years	-	POSTM	+ or -
		-	PREM	+
HIGH	≤5 years	+	PREM or POSTM	+ or -
		-	PREM	-

TABLE II. Kinetic use of tumor markers in patients with high risk of relapse.

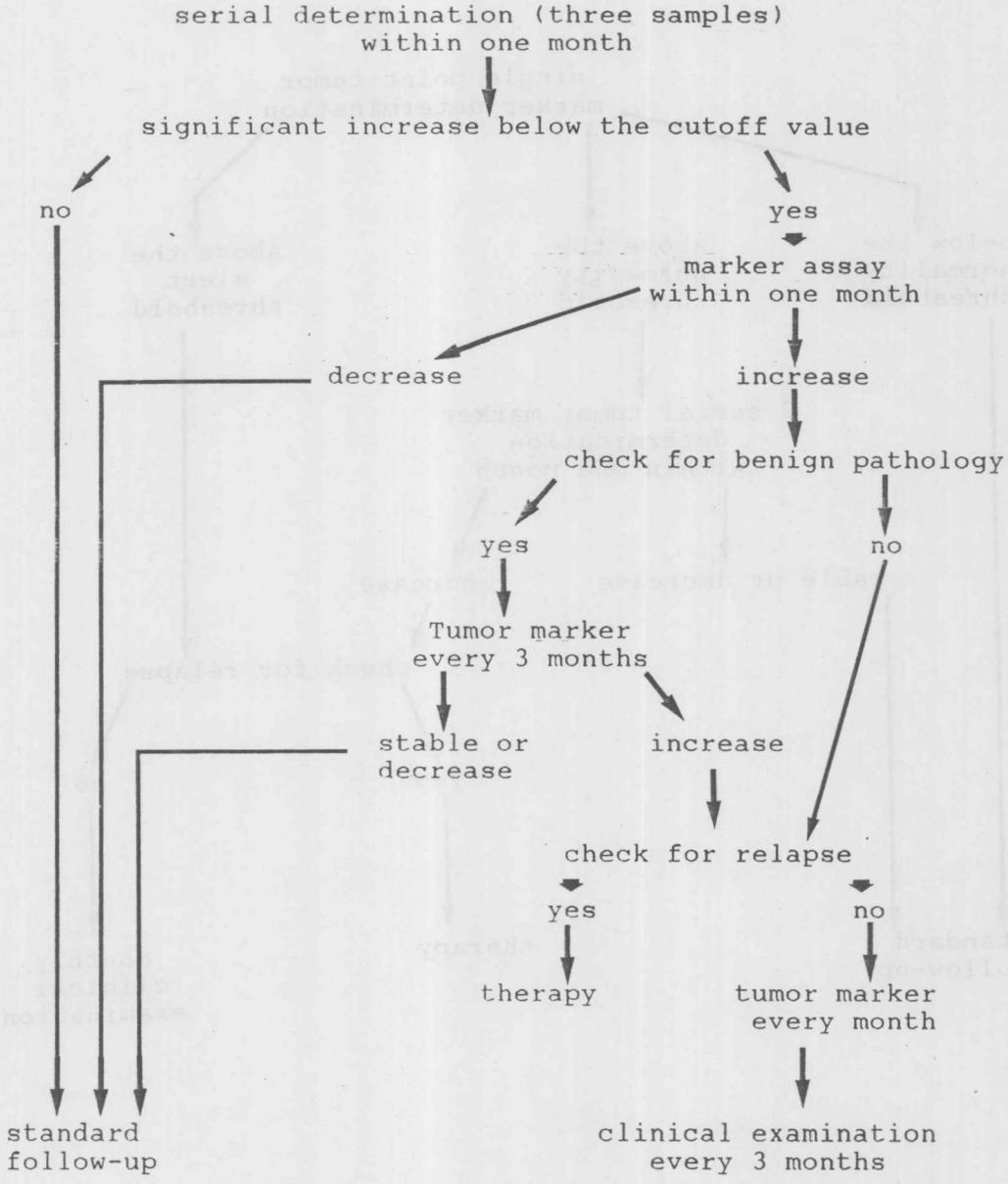

TABLE III. Dicothomic/Kinetic use of tumor markers in patients with low risk of relapse.

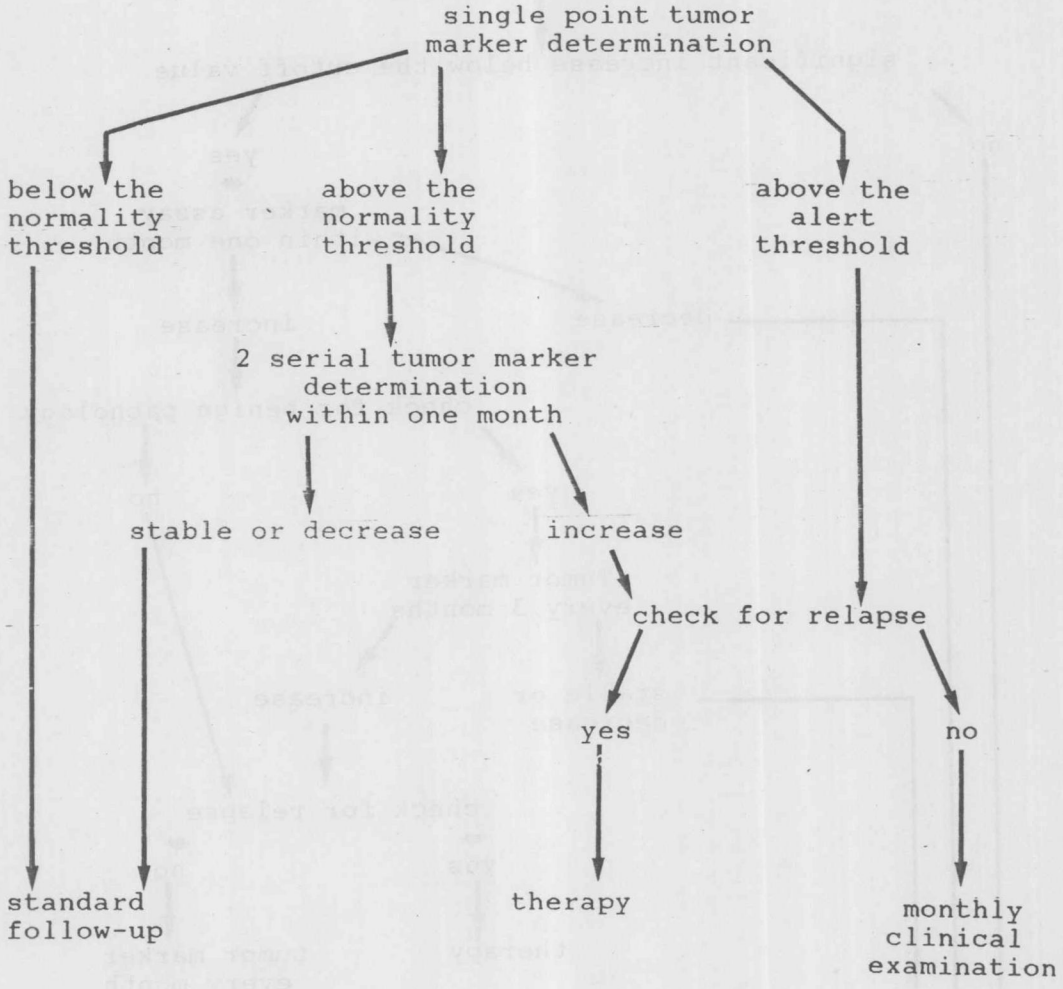

TABLE IV. Tumor marker patterns in patients without evidence of relapse

	CUTOFF-	CUTOFF+ KINETIC-	CUTOFF+ KINETIC+
CA15.3	248	9	3
CEA	249	10	1

- CUTOFF+: values above the normality threshold (31 U/ml for CA15.3, 5 ng/ml for CEA).
- KINETIC+: cases in which tumor markers increased within one month more than three times the coefficent of variation expected.

TABLE V. Tumor marker patterns in patients in which relapse was identified simultaneously or after tumor marker increase

	CUTOFF- KINETIC-	CUTOFF+ KINETIC-	CUTOFF- KINETIC+	CUTOFF+ KINETIC+
CA15.3	3	2	1	3
CEA	1	1	4	3

- CUTOFF+: values above the normality threshold (31 U/ml for CA15.3, 5 ng/ml for CEA).
- KINETIC+: cases in which tumor markers increased within one month more than three times the coefficent of variation expected.

PERIOPERATORY KINETIC EVALUATION OF TUMOR MARKERS IN BREAST AND COLORECTAL CARCINOMA

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INTRODUCTION

A great number of studies are continually published in which tumor markers are evaluated as qualitative parameters categorized using a conventional cutoff value. Different tumor markers are compared on the basis of their performance characteristics, that is sensitivity, specificity, positive and negative predictive values, which are calculated using the cutoff point. However, the use of a dichotomic criteria in the clinical utilization of tumor markers suffers two main drawbacks:

1) differences in the subjects selected as control group may account for differences in the performance characteristics of a given tumor marker;

2) quantitative variations below the cutoff point are usually unrecognized.

In the present investigation perioperatory variations of tumor marker serum levels were evaluated in patients radically operated for breast and colorectal cancer. The aim of the study is to verify the possibility of identifying any significant decrease of tumor markers due to the tumor resection, independently from the preoperatory positivity or negativity of the marker.

PATIENTS AND METHODS

Forty one patients mastectomized for primary breast cancer and 60 patients radically resected for colorectal carcinoma have been so far evaluated. Serum samples for tumor marker assays were collected before, 10 and 30 days after tumor resection and stored at -70 C°. We measured serum levels of CEA and CA15.3 in breast cancer, CEA and CA19.9 in colorectal cancer. Both intra-assay and inter-assay variability of the evaluated tumor marker were below 10% when measured at three different dose levels. Assay precision was also monitorized by precision profiles. The variation of tumor marker levels after the surgery was considered significant when it was higher than three times the coefficent of variation expected at a given dose level.

RESULTS

The distribution of positive and negative cases according to both cutoff point and kinetic criteria showed four different patterns, which are summarized in Table I for breast cancer and in Table II for colorectal cancer.