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Measurements of Response to Chemotherapy Using Ultrasound in Metastatic Liver Involvement

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Abstract—*The liver is a frequent site of metastases and in several cases the only available target for assessing the activity of chemotherapeutic agents. A standard procedure for liver measurements by ultrasound was investigated. One hundred and twenty-three chemotherapy cycles were evaluated. This study shows that metastatic involvement of the liver can be measured by several ultrasound parameters which represent different features of the same process: the number and the surface of the nodules, the volume of the organ. Ultrasound parameters were correlated with liver function tests, CEA, hepatomegaly and measurements of other metastatic sites. The surface of metastases still appeared to be the most reliable criterion of response. Our results suggest that several liver ultrasound parameters may help to definitely assess the type of response to chemotherapy.*

INTRODUCTION

THE LIVER is a frequent site of metastases for a large number of tumors. In several cases, it is the only metastatic site and the only available organ for assessing the activity of chemotherapeutic agents. Before the development of modern imagery, the only accepted measurable parameters were hepatomegaly and, in some cases, liver scintigraphy. The accuracy of these methods was insufficient and patients with liver metastases were rarely eligible for phase II clinical trials [1].

Since the development of real time ultrasound and computerized tomography, visualization of liver lesions has considerably improved. Whether the morphologic changes occurring within the tumor after treatment are measurable or not is still unknown.

This led us to propose a standard procedure for liver measurements by ultrasound and to define liver parameters which are easy to reproduce and potentially accurate to measure the response to chemotherapy.

MATERIALS AND METHODS

All measurements were performed using a Toshiba real time ultrasound display, SSA 90 or SSA 100. A pilot study has demonstrated the possibility of identifying the following parameters:

- The number of lesions
- The measurement of one or two identifiable lesions
- The maximum thickness of the liver lobes
- If more than five lesions were observed, the metastatic status was defined as being a cluster. In a 'type I' cluster, metastases can still be recognized and measured, while in a 'type II' cluster, metastases are confluent and cannot be measured. In a type I cluster, the metastases measured were either the largest or the most clearly identifiable (e.g. close to a vessel, to the diaphragm, to the capsule, etc.)
- The maximum thickness of the liver lobes was measured, for the left lobe, on a sagittal section going through the aorta and, for the right lobe, on the mediorenal line in a parasagittal plane. A copy of the examination was kept for future comparison and the position of the probe was reported for each measured metastasis. Any member of the radiological staff was allowed to perform the procedure. Total duration of the procedure never exceeded 15 min.

PATIENTS

All patients with proven cancer metastatic to the liver receiving anticancer chemotherapy were eligible for the study. Liver measurements, as described above, were undertaken before treatment and at each evaluation time. Liver function tests

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(alkaline phosphatase, SGOT, SGPT) and CEA were determined at the same time; standard measurements of hepatomegaly by palpation and response of other metastatic sites were made if applicable. Due to its high cost and lesser availability, CT was performed less regularly.

EVALUATION OF THE ANTITUMOR RESPONSE

The parameters at the evaluation time were compared with those before treatment. Responses for the various parameters are defined as follows:

- Number of lesions: progression if at least one new lesion is identified, regression if at least one lesion has completely disappeared.
- Cluster type: type I can progress to type II. Progression of type II cannot be evaluated. Regression in type I occurs when the number of lesions falls below five and in type II when regressing to type I.
- Surface of metastases: a regression of the sum of the metastatic surfaces by 50% was, arbitrarily, considered as the main criterion of a partial response. It was established by measuring the sum of the products of the largest perpendicular diameter of two lesions. Progression was defined by a 25% increase in the metastatic surface. Lesions with a diameter >20 mm were suitable for evaluation. Regression of <50% or progression of <25% were considered 'no change'.
- Thickness of liver lobes: progression was defined by an increase of at least 5%, regression by a decrease of at least 5% in the sum of the thickness of both liver lobes.
- Liver function tests and CEA: compared to the value before treatment, progression occurs when there was an increase of at least 20% and regression occurs when there was a decrease of at least 20%.
- Complete response was defined as the disappearance of all the lesions.

Responses assessed on the basis of hepatomegaly and/or of any other site were established according to the WHO criteria [2].

RESULTS

One hundred and twenty-three chemotherapy cycles were evaluated in 42 different patients with breast (27), colorectal (8), lung (3), anal (2), esophageal (1) and bladder cancer (1). The various echographic parameters were correlated with each other and with the clinical and biological indicators or tumor involvement. Table 1 gives the evaluation of these parameters for the patients with a ≥50% regression of the surface of the metastases. Ultrasound parameters, when available, did not change in one third of the cases and showed a regression in all the others. CT showed regression in 6/6 cases. Hepatomegaly regressed in 2/4, other sites regressed in 3 and progressed in 7/12, liver function tests improved in 3 and worsened in 5/14, CEA decreased in 5 and increased in 3/13.

Table 2 gives the evaluation of the various parameters for the patients with a >25% progression of the surface of the metastases. Ultrasound parameters, when available, did not change in 56% of the cases and showed a progression in almost all the others. In one patient, the thickness of the liver lobes did not correlate with progression observed by measuring the surface of the metastases. CT showed progression in 6/8 cases, hepatomegaly worsened in 8 and improved in 1/16; the other sites progressed in 17 cases and regressed in 1/24, liver function tests worsened in 17 and improved in 5/40, CEA increased in 23/33. Changing the criteria of tumor responses that were previously defined did not significantly influence the correlation mentioned above. The ability to evaluate response to treatment did not seem to be influenced by the type of the primary tumor.

DISCUSSION

This study indicates that metastatic involvement of the liver can be measured by several parameters which represent different features of the same process: the number and the surface of the nodules, the volume of the organ. It also suggests that the method of measurement can be standardized and that the results are reproducible in the same patient even if the procedure is performed by different radiologists.

The surface of metastases as measured by this method still remains the most reliable criterion of response. The level of <50% and >25% which defines regression and progression, respectively, in other tumor sites [1] also seems suitable for ultrasound measurements.

The other ultrasound parameters that were measured do not necessarily reach their response criteria at the same time. Indeed, the surface of metastatic nodules may significantly change without influencing their number, the cluster status or the thickness of the lobes. Nevertheless, when the parameters are responding in the same way, they seem to definitely assess the type of response (Tables 1, 2).

There is no golden standard to which ultrasound can be compared: liver function tests may be normal when the tumor involvement is minimal [3], steatosis which can be produced with anticancer agents [4] may induce hepatomegaly and abnormal liver function tests, masking a tumor regression: the increase of CEA with liver tumor regression could be explained by the fact that the majority of our cases were breast cancers who had multiple sites of involvement which did not respond to the treatment

Table 1. *Clinical laboratory and ultrasonic parameters for patients with a* ≥50% *decrease of liver metastases surface*

	Total evaluable	Response by target No change	Regression	Progression
Echographic parameters (other than metastases surface)				
Number of lesions	16	6	10	0
Cluster	7	3	4	0
Thickness right + left lobes	9	3	6	0
CT scan	6	0	6	0
Hepatomegaly	4	2	2	0
Other sites	12	2	3	7
Liver function tests	14	6	3	5
CEA	13	5	5	3

Table 2. *Clinical, laboratory and ultrasonic parameters in patients with a* >25% *increase in hepatic metastases surface*

	Total evaluable	Response by target No change	Regression	Progression
Echographic parameters (other than metastases surface)				
Number of lesions	45	28	0	17
Cluster	19	12	0	7
Thickness right + left lobes	24	10	1	13
CT scan	9	3	0	6
Hepatomegaly	16	7	1	8
Other sites	24	6	1	17
Liver function tests	40	18	5	17
CEA	33	10	0	23

and also by the hepatic toxicity of the chemotherapeutic drugs which may by itself increase CEA [5]. As expected, other sites of tumor involvement may respond differently to chemotherapy and are of no help in corroborating tumor regression at the hepatic site.

CT scan was not mandatorily required in this study. When available, CT corroborated echographic findings suggesting that doubtful cases should also have CT measurement of their metastatic lesion.

A meaningful comparison of clinical trials requires the establishment of uniform criteria for assessing and reporting the response of tumors to chemotherapy. This standard method for ultrasound measurements of liver involvement is now being investigated by the EORTC Gastrointestinal Tract Cooperative Group for further evaluation.

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