Computed Tomography or Contrast-Enhanced Ultrasonography for Follow-up of Liver Metastases After Cyberknife Therapy?

A Prospective Pilot Study

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Abbreviations

CECT, contrast-enhanced computed tomography; CEUS, contrast-enhanced ultrasonography; CT, computed tomography; SBRT, stereotaxic body radiotherapy; US, ultrasonography

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Objectives—Contrast-enhanced ultrasonography (CEUS) allows the study of vascularization of secondary liver lesions. The Cyberknife (Accuray, Inc, Sunnyvale, CA) is a therapeutic method that allows a tumor target to be subjected to a high radiant dose gradient. This prospective pilot study aimed to demonstrate the concordance of CEUS versus contrast-enhanced computed tomography (CECT) in determining the stability or disease progression of secondary liver lesions after treatment with the Cyberknife.

Methods—Twenty-four patients were consecutively enrolled, and 3 different operators evaluated the CEUS images and the intermodality concordance with CECT. All patients received CEUS at 1 and 2 months after the Cyberknife therapy. The intermodality agreement was evaluated by the Cohen κ coefficient and a multivariate analysis according to the method of Janson and Olsson (*Educ Psychol Meas* 2001; 61:277–289).

Results—Forty secondary liver lesions were detected and treated. Forty-one CECT and 51 CEUS examinations were performed without any adverse events in the 24 patients. The intermodality agreement rates, calculated for the operators as Cohen κ values, were κ = 1.00, 0.881, and 0.767, respectively. The multivariate analysis of intermodality agreement showed an almost perfect value (ι = 0.841).

Conclusions—This pilot study found excellent diagnostic correspondence between CEUS and CECT in the evaluation of local disease stability or progression after Cyberknife therapy in liver metastases. These findings suggest that CEUS could play an important role in the surveillance of these patients because of its high accuracy and reproducibility, thus reducing the need for CECT.

Key Words—contrast-enhanced computed tomography; contrast-enhanced ultrasonography; liver cancer; liver metastases; liver ultrasonography; stereotactic body radiation therapy

Abdominal ultrasonography (US) usually represents the first-step diagnostic procedure to investigate liver diseases. Contrast-enhanced ultrasonography (CEUS) using microbubble contrast agents has increased its performance, allowing for a dynamic evaluation of the vascular patterns of solid organs and

lesions. Contrast-enhanced US also provides the opportunity to carefully investigate and characterize small hepatic lesions previously evaluated only by computed tomography (CT) or magnetic resonance imaging.[1–4] For these reasons, this method is widely used for the screening and surveillance of primary or secondary hepatic lesions and could be potentially used in their follow-up after chemotherapy or radiotherapy.

Stereotaxic body radiotherapy (SBRT), called Cyberknife (Accuray, Inc, Sunnyvale, CA, USA), is a technique using robotic equipment with high spatial and topographic resolution for full-body radiosurgery. This technology uses image guidance, robotic technology, and dynamic target tracking with automatic correction of breathing movements to allow submillimetric accuracy together with a high radiation gradient. The result is the opportunity to irradiate the tumor target with a high dose of radiation while safeguarding surrounding organs.[5,6] In the setting of primary and secondary liver lesions, the Cyberknife allows delivery of double the radiation dose compared with conventional radiotherapy.[7,8] This ability provides an opportunity to treat liver lesions that are not amenable to surgery with greater accuracy and potency than conventional radiotherapy and a less-invasive approach compared with thermoablation or cryotherapy. Conventionally, 2 months after treatment, a follow-up evaluation is performed by CT with contrast media; however, although that method is widely used,[9] more recent studies have raised concern regarding the sensitivity of evaluations of arterial perfusion of hepatic lesions. In addition, CT is expensive, leads to considerable radiation exposure, and carries the risk of an iodine contrast allergic reaction.

Contrast-enhanced US[10] could be a valuable alternative to CT in the evaluation of liver lesions after SBRT with the Cyberknife, since, when directed to specific target lesions, it allows an accurate evaluation of the vascular pattern. In addition, CEUS has a low cost and is very safe, although it can be operator-dependent. The primary aim of this pilot study was to evaluate the concordance of CEUS compared with contrast-enhanced computed tomography (CECT) in the evaluation of secondary liver lesions at baseline and after SBRT with the Cyberknife.

Materials and Methods

Study Design

This work was a pilot single-center prospective study to compare the concordance of CEUS with CECT in the evaluation of characteristics and potential local progression/regression of secondary liver lesions after SBRT with the Cyberknife. The primary objective was to evaluate the concordance among CEUS and CECT (intermodality agreement) for detection of the stability or progression of hepatic lesions 2 months after therapy. Secondary objectives were the potential yield of a further CEUS evaluation 1 month after the treatment to detect earlier disease progression or treatment failure and the interobserver agreement of the CEUS findings among 3 different physicians to evaluate the reproducibility.

Disease progression was defined by the all of following parameters: size increase, increase in lesion numbers, and persistent arterial contrast enhancement (wash-in) and wash-out in the portal phase. Disease stability was defined as stable or reduction of lesion size, stable or reduction of lesion numbers and lack of wash-in and wash-out contrast enhancement compared with baseline. The parameters collected were interpreted according to the Modified Response Evaluation Criteria in Solid Tumors.

Patient Population

Consecutive patients with liver metastasis undergoing treatment with SBRT were enrolled from September 2015 at the Cyberknife Center of the Villa Ulivella and Villa Glicini Institute of Assistance and Care (Florence, Italy). Informed consent was obtained from all patients. Exclusion criteria for the study were those related to CECT (pregnancy, moderate-to-severe renal insufficiency, and allergy to iodine media) and CEUS (cardiac shunt, myocardial ischemia, and allergy to sulfur). All procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation and with the Declaration of Helsinki, sixth revision, 2008.

Methods

Before SBRT, all patients had baseline (T0) CEUS for evaluation of the characteristics and dimensions of the liver lesions at the Outpatient Clinic of the

Department of Gastroenterology of the Azienda Ospedaliera Universitaria Careggi Hospital. The US was performed with a ProSound α7 system (Hitachi-Aloka, Tokyo, Japan) equipped with a 3.75–7.5-MHz transducer (UST 91-30 multifrequency convex abdominal transducer). For each investigation, a baseline evaluation in B-mode was performed to visualize the lesion and detect the optimal scanning window for the CEUS. The contrast media used was 5 mL of sulfur hexafluoride (SonoVue; Bracco SpA, Milan, Italy) followed by 10 mL of saline injected into the cephalic or basilic vein at the level of the elbow cubital fold. A full digital recording of the complete examination was performed each time. The sizes of lesions were calculated during the B-mode examination and during the arterial phase of CEUS. As reported in the literature, we considered the arterial phase the time within 30 seconds from injection of contrast media, the portal phase up to 2 minutes after injection, and the late phase from 2 to 5 minutes after injection (Figure 1). The baseline CEUS was done blinded to the results of CECT.

For the purpose of fine targeting the SBRT treatment, gold fiducial markers (Gold Anchor 22G; Naslund Medical AB, Huddinge, Sweden) were positioned in the proximity of the lesion (Figure 2) to be detected by CT and used by the Cyberknife imaging-tracking system for precise localization of the lesions. Subsequently, 1 to 3 SBRT sessions were performed, following the standard procedure protocol. A follow-up evaluation of the treatment was performed after 2 months (T2) by CECT up to May 2016.

All patients also received CEUS at 1 (T1) and 2 (T2) months after the SBRT procedure (Figures 3 and 4). At T1, all patients with disease progression were scheduled for an earlier evaluation by CECT and subsequent oncologic management. In contrast, patients with stable findings compared with baseline were evaluated by CEUS and CECT at 2 months (T2). The CEUS and CECT were always performed within a time window of 5 days.

Figure 1. Liver metastasis evaluated by CEUS before Cyberknife. The US evaluation was performed up to 435 seconds after SonoVue injection. The liver lesion remained hypovascular with peripheral enhancement.

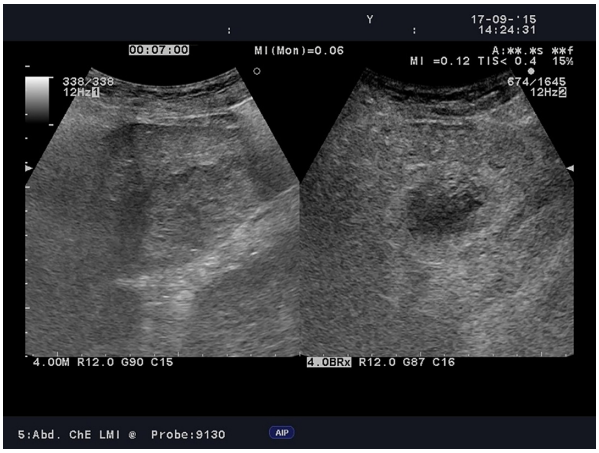


Figure 2. Hyperechoic gold fiducial marker positioned in the proximity of liver metastasis.

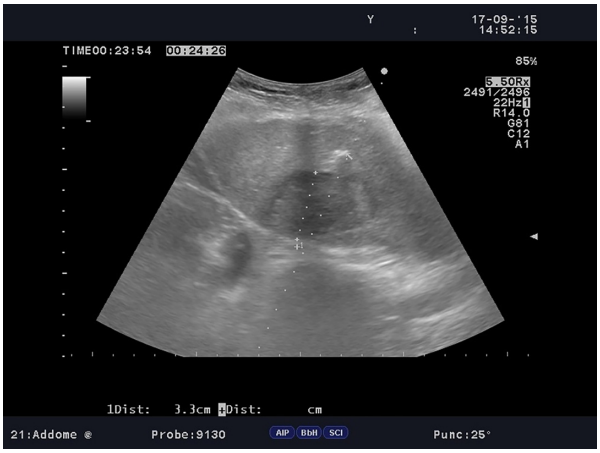


Figure 3. Liver metastasis evaluated 2 months after radiation therapy. The lesion was hypovascular with contrast enhancement of tumor septa.

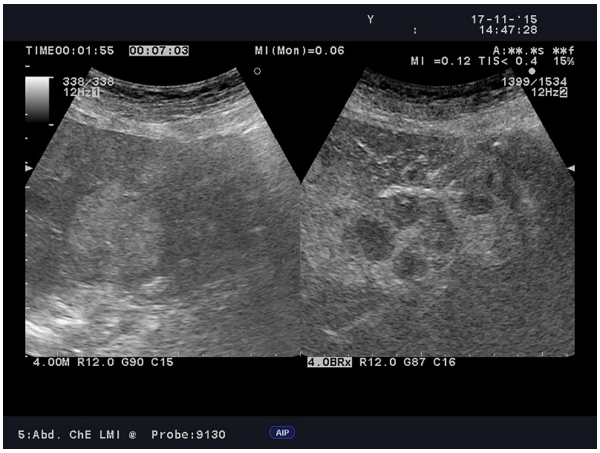
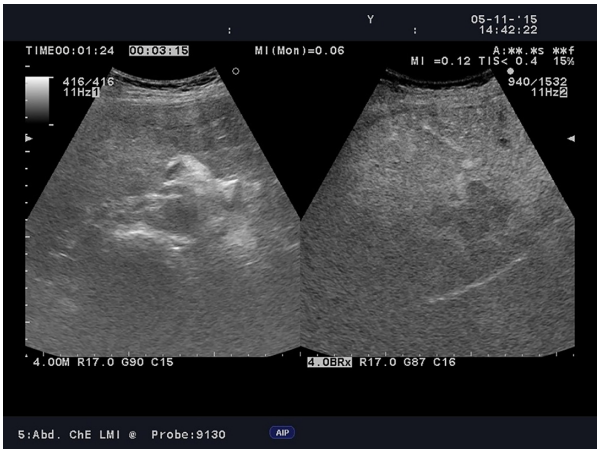


Figure 4. Liver metastasis evaluated 2 months after radiation therapy. The lesion remained hypovascular, and disease progression was shown by the increased diameter of the lesion.



The CEUS examinations were performed by a single physician (T.G.), holder of a master's degree in abdominal US from the Italian Scientific Society of Medical Ultrasonography at the Department of Gastroenterology of the Azienda Ospedaliera Universitaria Careggi Hospital. The interobserver evaluation of the digital recordings was performed by 2 other physicians (M.R.B. and M.M.) from the Azienda Ospedaliera Universitaria Careggi Hospital and the Azienda Ospedaliera Universitaria Maggiore Hospital (Bologna, Italy), respectively, holders of the same master's degree.

The CECT scans were performed with the CT equipment of each referral center by a standard 3-phase protocol using iodine contrast agents (Iomeron, 400 or 100 mL; Bracco Spa; or Ultravist, 370 or 100 mL; Bayer Healthcare, Berlin, Germany) and full digital recording. The CECT scans were evaluated by experienced independent radiologists in each referral center.

Statistical Analysis

The intermodality agreement of the imaging modalities for each operator was evaluated by the Cohen κ coefficient,[11] whereas the concordance for CEUS among 3 physicians was evaluated by the Fleiss κ coefficient.[12] The concordance between CEUS and CECT among all of the operators was evaluated by a multivariate analysis according to the method of Janson and Olsson[13] and expressed as the ι coefficient. The ι and kappa values obtained were evaluated as follows: no concordance, $\kappa = 0$; low concordance, $\kappa = 0.1$ to 0.20; insufficient concordance, $\kappa = 0.21$ to 0.40; sufficient concordance, $\kappa = 0.41$ to 0.60; good concordance $\kappa = 0.61$ to 0.80; and excellent concordance, κ greater than 0.80, as suggested by Landis and Koch.[14] The statistical significance was set at $P < .05$. The statistical analysis was performed with SPSS software for Windows (IBM Corporation, Armonk, NY) and R Statistics (Bell Laboratories, Inc, Madison, WI) by T.G. and reviewed by the senior investigator (V.A.).

Results

Twenty-four consecutive patients were enrolled in the study (10 female and 14 male; mean age ± SD, 64 ± 12.5 years). All patients had liver metastasis from colorectal (10), breast (2), prostate (2), gastrointestinal stromal (2), stomach (2), melanoma (1), pancreatic (1), thyroid (1), adrenal gland (1), gallbladder (1), and ovarian (1) cancers. All patients had failure or disease recurrence despite previous therapies, including chemotherapy, radiotherapy, surgery, or a combination of these according to the cancer characteristics. Nine patients had a single lesion, whereas the remaining patients had 2 or more lesions, ranging in size from 0.8 to 7 cm. In total, 40 liver lesions were detected and treated: 3 in the left lobe and 37 in the right lobe. The mean tumor size was 30.75 ± 15.8 mm. A further patient had complete structural derangement of the liver and was excluded from the study because of rapid disease deterioration and death.

Of the 24 enrolled patients, 17 completed the follow-up, and 3 were excluded because of rapid disease progression from the tracking CT scan to the start of SBRT; 3 other patients died before the end of follow-up. Another patient was excluded because of failure of gold marker positioning for technical reasons.

When evaluated by CEUS at 1 month (T1), 7 of 17 patients (41%) showed disease progression and were referred to the oncologist for different therapeutic management; 3 of 17 patients showed disease progression when evaluated by CEUS at 2 months (T2). In 7 of 17 patients (41%), there was no disease

progression after treatment at the T2 evaluation. No adverse events related to the use of contrast media were reported in a total of 41 CECT and 51 CEUS examinations.

Interobserver Agreement

The interobserver concordance for CECT computed as the Fleiss κ was excellent (κ = 0.84). The concordance for the CEUS findings was evaluated at T0, T1, and T2 among the physician performing the US studies (operator 1) and the other 2 who evaluated the digital recordings. The concordance at T0, T1, and T2 was excellent (κ = 1.00 and 0.84) and good (κ = 0.75), respectively.

Intermodality Agreement

The agreement between CECT and CEUS was evaluated at baseline and 2 months after the SBRT; when the evaluation at 2 months was missing because of disease progression, the evaluation of concordance was performed at the 1-month follow-up. More specifically, the findings of 10 patients were compared at 2 months, whereas the remaining 7 patients were evaluated at 1 month because of disease progression. At 2 months of follow-up in 7 patients, the lesions were stable, whereas in the remaining 3 patients, disease progression was found.

The concordance at baseline (T0) of the CECT with the physician who performed the CEUS (operator 1) was excellent (κ = 1.00). In the 17 patients evaluated after the treatment, the concordance among the physician who performed the CEUS (operator 1) with the CECT findings was excellent (κ = 1.00).

The intermodality agreement among CECT and CEUS was also calculated for the other 2 physicians who evaluated the digital recordings of the US. The concordance was κ = 1.00 and 0.881 (excellent) for operator 2 and κ = 1.00 and 0.767 (good) for operator 3 at T0 and the T1 and T2 follow-ups, respectively. The multivariate analysis considering all 3 operators evaluating CEUS compared with CECT resulted in an ι value of 0.841.

Discussion

Stereotaxic body radiotherapy is an emerging treatment modality frequently adopted to treat primary and secondary tumors that are not amenable to surgical treatment and after failure or relapse following chemotherapy.[15] The evaluation of the efficacy or disease progression is usually performed with CECT, which is considered the reference standard. In this pilot prospective study, we compared the concordance of CEUS with CECT as an alternative imaging modality in patients with liver metastasis, and we found an excellent agreement (Cohen κ = 1.00).

Contrast-enhanced CT is surely the most-used imaging procedure for staging and follow-up of oncologic patients, thus ensuring a progressive increase in radiation exposure in the last decades. From 1998 to 2007, the proportion of adverse events correlated with radiation exposure for diagnostic and therapeutic procedure increased in the United States by 150% (from 6% to 15%).[16] In western and developed countries, the total radiation exposure for patients due to medical procedures is comparable with the yearly absorption of total radiation from the atmosphere, the cosmos, and radionuclides.[17] More specifically, CT scanning is responsible for two-thirds of the entire radiation exposure from medical procedures and represents a considerable cost for health services.[18] The progressive rise in health costs strongly suggests an exploration and validation of new methods in terms of safety and cost without jeopardizing their diagnostic accuracy. Contrast-enhanced US is a method that has been extensively validated for the evaluation of benign and malignant hepatic lesions and, more specifically, hepatocarcinoma and liver metastasis.[19] It is considered the first-choice method for evaluation of liver lesions when there is no need for panoramic imaging of the parenchyma, with the additional advantages of low cost and absence of radiation exposure. Moreover, contrary to the iodine contrast agents used for CECT, the media used for CEUS have no renal excretion or risk of allergic reactions.

To the best of our knowledge, this work was the first study aimed at investigating the concordance of CEUS with CECT in the context of patients after SBRT, and it showed excellent concordance. Some studies already have been published comparing CEUS with CECT (as the reference standard) in the follow-up of patients after radiofrequency treatment of primary renal or liver cancers, also showing a high degree of concordance, similar to our experience.[20–23]

In a recent study by Kong et al[24] regarding the concordance among CEUS and CECT in patients after radiofrequency treatment of renal lesions, the concordance was also 100%.

Potential limitations of CEUS and US in general are the experience of the operator, the opportunity to accurately identify lesions, and the concordance among different investigators.[25] In this study, in all patients, CEUS successfully recognized and adequately visualized the lesions. In addition, in all 4 patients in whom no uptake of the US contrast agent was shown, the CECT scans confirmed the absence of contrast enhancement, and with either imaging modality, the response to treatment was managed only on the basis of the size and number of nodules. More importantly, the agreement of CEUS findings among 3 different physicians was evaluated: 1 was directly performing the procedures, whereas the other 2 evaluated the digital recordings. The overall agreement with CECT was 0.84, whereas for CEUS at different time points, it was 0.91 (ı values from the multivariate analysis).

Another important achievement of the study was that at the T1 evaluation with CEUS after 1 month of follow-up, 7 of 17 patients (41%) already had disease progression; therefore, an earlier change in the oncologic plan was made. If these data can be confirmed, then the follow-up after the procedure could be managed differently with more frequent and repeated CEUS evaluations, given the low cost and lack of radiation.[26] Finally, it is remarkable to note that no adverse events were reported, as expected, from the CEUS contrast media.

This pilot study had some limitations. The sample size was small because of the short time window for patient enrollment (9 months, as required by the department's Study Committee), the slow enrollment of patients for Cyberknife, which is still a procedure under validation, and the deterioration and disease progression with incomplete follow-up durations in some patients. In addition, a test of concordance among radiologist could not be performed because of the different equipment in the respective hospitals. However, the important strength of the study was the high concordance among 3 different physicians in evaluating CEUS and comparing CEUS with CECT.

This pilot study also clearly showed high diagnostic concordance among CEUS and CECT at baseline and after SBRT with the Cyberknife in patients with liver metastasis, with accurate evaluation of the efficacy of the therapy (obtained in 59% of cases) or disease progression. In addition, because of the high interobserver concordance of the CEUS findings, the low cost and lack of radiation exposure, this method could replace CECT in the follow-up of Cyberknife therapy efficacy. Also, CEUS could be performed more frequently during follow-up to detect a lack of efficacy and disease deterioration earlier. We can speculate that after reference imaging with CECT at the beginning of treatment, we could follow the therapeutic evolution only with CEUS; thus, CECT would be performed only intermittently. Further controlled studies with larger sample sizes are awaited to confirmation our preliminary findings.

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