Implantation of fiducial markers in the liver for stereotactic body radiation therapy: Feasibility and results

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Abstract
Purpose: Robotic stereotactic body radiation therapy (SBRT) for the treatment of hepatocellular carcinoma requires the perilesional implant of gold fiducial markers for detection by scopy. The purpose of this study is to determine whether the implant of gold fiducial markers is still possible and, if so, with which imaging technique and with what results.
Materials and methods: This is a prospective study based on the implant of fiducial markers in the liver in our department for a treatment by SBRT for a hepatocellular carcinoma in 38 patients (49 lesions to treat) over a period of one year. As the first choice, it consisted of sonographic guidance and, if not possible, CT-scan guidance was used.
Results: The mean number of fiducial markers implanted per procedure was 2.68(± 0.61) with almost exclusive sonographic guidance (36 out of 38 patients or 95% of the patients). The mean distance between the markers and the lesion was 32 mm (± 11 mm) and that between the markers was 17 mm (± 7 mm).
Conclusion: SBRT is being evaluated for the treatment of liver lesions. The radiologist has an important role to play since the implant of fiducial markers in the liver is indispensable. It is almost always possible with sonographic guidance, including for lesions not accessible to microbiopsies, a treatment by radiofrequency or for lesions poorly individualisable by sonography or CT-scan.

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Hepatocellular carcinoma (HCC) is the most common primary tumour of the liver, generally developed within a context of chronic liver disease, most often cirrhosis (90% of the cases including 70% of alcoholic origin in France). With 800,000 new cases per year in the world and 7000 in France (annual incidence of 11/100,000 in men and 2/100,000 in women), HCC is the 5th most common cancer in the world [1].

The reference treatment for localised HCC remains the liver transplant or excision. Radiofrequency and chemoembolisation are validated local treatments while waiting for a liver transplant or in inoperable patients.

Until now, conformational radiotherapy has had a limited place in the treatment of localised HCC due to the major exposure of healthy liver tissue [2–4]. The development of high conformity radiotherapy associated with live imaging may, in this type of lesion, allow for the delivery of a higher dose while limiting the exposure of the adjacent healthy tissue [5] and thereby propose an alternative “curative” solution for the inoperable patient [6,7]. Stereotactic body radiation therapy (SBRT) by Cyberknife is a new technology providing new therapeutic possibilities.

SBRT by Cyberknife® in the treatment of liver lesions delivers 100 to 200 photon beams of 6MV [5,8] (Fig. 1) with a permanent control of the position of the tumour. It requires the implant of gold fiducial markers in the periphery of the tumour for detection by scopy. These fiducial markers should ideally be situated 2 to 5 cm around the lesion to treat. In this way, the tumour moves in the same way as the fiducial markers so that the respiratory tracking model is adapted. The patients for which SBRT is proposed in a multi-disciplinary meeting (MDM) are mainly patients in which other therapeutic means are counter-indicated. In fact, the contra-indications may be due to the general state of the patient, in particular the possibilities of general anaesthetic as well as contra-indications due to the topography of the lesions and in particular lesions of the vault not accessible to a radiofrequency.

Materials and methods

This is a prospective study based on the implant of gold fiducial markers in the liver in our department for treatment by SBRT for hepatocellular carcinoma in 38 patients over one year. Fourty-nine lesions had to be treated. The indication for treatment by SBRT was always validated in MDM.

The study fell within the usual care and an authorisation by the local ethics committee was therefore not necessary. The gold fiducial markers were implanted by a single operator who was entrusted with the study of the feasibility and implant.

Gold fiducial markers 3 mm long were used. They were assembled on 12 cm syringes and a calibre of 18-gauges with

Figure 1. Planning of the treatment of two synchronous lesions.
use of a 17-gauge guide (Fig. 2). The guide either used Toshiba Aplio sonography or Philips Brilliance 40 CT-scan. The first choice was sonography and, if not possible, a CT-scan was used. The pre-procedure imaging file comprised a CT-scan and/or a liver MRI. An acquisition CT-scan was obtained seven days after the implant for the dosimetry after injection of iodine contrast agent with acquisitions at arterial and portal times. On this CT-scan, a single operator measured the distance between the fiducial markers and the lesion and the distance between the fiducial markers.

### Statistical analysis

The socio-demographic criteria were studied.

The number of procedures not carried out was calculated as well as the number of procedures per guidance technique. The number of fiducial markers implanted, the distance between the fiducial markers, the distance between the fiducial markers and the lesion were studied with mean calculations as well as the standard deviations and the bounds.

### Results

There were 30 men (79%) and 8 women (21%). The mean age was 69 years (standard deviation: 11.6 years) with extremes of 47 and 85 years.

The mean number of fiducial markers implanted per procedure was 2.68 with a standard deviation of 0.61 (between 1 and 3 fiducial markers implanted).

The maximum number of targets detected and to treat were 2 in 11 patients or 29% of the patients.

The mean distance between the fiducial markers and the lesion was 32 mm (standard deviation: 11 mm, [21–43 mm]) and the mean distance between the fiducial markers was 17.3 mm (standard deviation: 7 mm, [10.3–24.3 mm]). In two cases, a single fiducial marker was implanted and in all other cases, at least two fiducial markers were implanted 20 mm apart.

In 36 of the 38 patients (95%), the procedures were carried out with sonographic guidance. In one case, the procedure used CT-scan guidance. One implant of fiducial markers in the liver was not possible due to persistent and abundant ascitis.

### Discussion

SBRT is a technique that is still being developed in France and few centres are equipped. Nevertheless, this treatment is promising and may be a resort when other techniques are not possible. It is interesting that it is possible to treat patients in which radiofrequency treatment has not been possible due to the topography of the lesion.

The involvement of the radiologist is important in this technique since they enable the detection of the lesion without which the treatment is not possible. In addition, the position and number of fiducial markers have an effect on the treatment. In fact, the farther the fiducial markers from the lesion and the fewer the number of fiducial markers, the more the radiotherapist will have to take considerable margins by exposing the healthy parenchyma [9]. This may aggravate the liver failure in cirrhotic patients with a high Child-Pugh score.

The dose delivered during the treatment was from 30 to 45 Gy in 3 or 4 sessions over 10 days (single dose prescription 80%). The treated target was the macroscopic volume of the imaging (Gross Tumour Volume [GTV]) assessed on the CT-scan and MRI with an infraclinal extension margin ranging from 3 mm to 1 cm (Clinical Target Volume [CTV]) and a safety margin of 2 to 3 mm related to the uncertainty (Planning Target Volume [PTV]).

In this study, the implant of fiducial markers was never rejected due to the topography of the lesion (by either using sonography guidance or CT-scan guidance). One implant of liver fiducial markers was not possible due to persistent and abundant ascitis. Nevertheless, the implant would have been possible if an approach was present without ascitis (Fig. 3).

One of the main difficulties in sonography is to be able to space the different fiducial markers. In fact, the constructor indicates that the minimum space between 2 fiducial markers should be 2 cm so that the software can provide translation and rotational movement. If there is less than 2 cm, only movement in translation is possible although,
often, the rotations are not important and an approximation of the movement with the translations alone may be sufficient. Once the guide is installed, it is fairly complicated to have this margin between the different fiducial markers without having to cross the liver capsule several times, increasing the risk of haemorrhage in patients presenting coagulation disorders.

One of the limits of sonography guidance is due to the fact that the lesions aren’t always visible by sonography, either due to a very heterogeneous parenchyma (hepatocellular carcinoma (HCC) on cirrhosis) or their high position, with only 33 out of 49 lesions clearly individualisable. Nevertheless, with the initial imaging, it is always possible to know the zone in which the fiducial markers have to be implanted so as to be within 5 cm of the lesion. In one case, sonography guidance was not possible. In fact, the liver was rearranged due to a past history of liver surgery with a high position and digestive interpositions. The implant was therefore carried out with sonography guidance.

In spite of the altered coagulation assessments in most patients, there were no secondary complications due to the procedure. The implant of liver fiducial markers is probably less of a risk than liver microbiopsies although this has to be assessed in larger series.

Only three fiducial markers or, in certain cases, two fiducial markers were implanted to reduce the risk of haemorrhage. In fact, the platelets were often around 70,000/mm³ with a prothrombin time at 60% and a patient/control ratio of 1.4. Thirty-five files had at least two fiducial markers 2 cm apart and, in two cases, a single fiducial marker was inserted due to the subcapsular lesions without the possibility of interposing a healthy parenchyma with ascitis and a perturbed coagulation assessment associated with thrombocytopenia not preventing the treatment by SBRT. For the same purpose, in case of double liver location, the fiducial markers were inserted to be able to serve two locations as soon as possible. In view of the possibility of implanting fiducial markers up to 5 cm around the lesion, this would enable the use of the same fiducial markers for lesions 8 to 9 cm apart.

There were several tumour locations to treat in 11 patients. In only one case, it was necessary to use two different approaches with fiducial markers only used for one of the two lesions. In fact, in this case, the distance between the two lesions was 150 mm.

**Conclusion**

SBRT treatment is still being assessed in the treatment of focal liver lesions. This technique is still not very much used in France. The radiologist has an important role to play in this treatment since the implant of gold fiducial markers in the liver is indispensable. This implant is almost always possible with sonography guidance, including in lesions not accessible by microbiopsy or treatment by radiofrequency or in lesions poorly individualised by sonography or CT-scan.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


