ORIGINAL ARTICLE

Prospective Evaluation of Migration, Complications and Utility of Fiducial Placement for CyberKnife Treatment in HepatobiliaryTumors

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the most common primary tumor of the hepatobiliary system. The Cyberknife represents a new, frameless stereotactic radiosurgery system with image-guided radiation delivery using fiducials as markers to overcome the movement of intra-abdominal organs due to respiration. However fiducial placement and treatment have its issues such as migration and other complications.

Objectives: We evaluated the accuracy and feasibility of fiducial placement under image guidance and complications during and after placement such as migration including pain score.

Materials and Methods: A prospective observational study was carried out on 36 subjects with clinically and radiologically diagnosed hepatocellular carcinoma receiving Cyberknife based stereotactic based radiotherapy (SBRT). Fiducial markers for SBRT were introduced under percutaneous Ultrasound (US) or CT guidance. After placement, fiducial migration rate, pain score, fiducial placement related complications were noted during and after therapy. IBM SPSS statistical software version 21 was used for statistical analysis.

Results: 8.4% had gross fiducial displacement on the day of the procedure. 90.9% had minimal migration during treatment.There was no gross migration seen during treatment or post-treatment. Post fiducial placement, 2.8 % had a major complication in the form of liver decompensation resulting in death while minor complications were observed in 13.9%. The average pain score was minimal (0.86) post fiducial placement. There was no pain in any of the patients during or after the treatment.

Conclusion: Image-guided implantation of fiducial markers in the liver for stereotactic body radiation therapy had a high technical success rate and is a safe procedure with rare complications.There is minimal fiducial migration seen during the treatment. But being a descriptive study with a small sample size limits the generalizability of our study findings.

Keywords: Cyberknife, stereotactic based radiotherapy (SBRT), Hepatocellular carcinoma, Fiducial placement, Fiducial migration

INTRODUCTION

The hepatobiliary system refers to the liver, bile ducts and gallbladder. Tumors of the liver and biliary tree, mainly hepatocellular carcinoma and cholangiocarcinoma are the second leading cause of cancer-related death worldwide and the sixth leading cause of cancer-related death among men in developed countries.[1]The most common adult malignant liver tumors are Hepato Cellular Carcinoma (HCC), metastases to the liver, fibrolamellar HCC, Epithelioid Hemangio Endothelioma (EHE) and angiosarcoma. The yearly worldwide burden of hepatobiliary malignancy is estimated to be 782,500 new liver cancer cases and 745,500 liver cancer-related deaths, according to the Global Cancer Statistics of 2012.[2]The range of treatments for HCC may range from surgical resection, chemotherapy and radiotherapy alone or in combination.SBRT is a highly sophisticated, noninvasive, image-guided, radiation therapy that allows the delivery of a precise dose of radiation by using multiple, photon beams that intersect at a stereotactically determined target, and therefore emits higher doses of radiation delivery to the tumor while sparing surrounding normal tissue.[3]SBRT is an effective therapy for patients with HCC with an overall best response rate (CR + PR) of 73%.[3].The Cyberknife represents a new, frameless stereotactic radiosurgery system which efficiently incorporates advance robotics with computerised image reconstruction to allow highly conformal image-guided radia-

tion delivery.[4]There are some technical difficulties when SBRT is applied to the liver. The movement of intra-abdominal organs due to respiration has to be taken into consideration while using SBRT for effective dose delivery to the target. The liver is one of the organs moving continuously caused by respiration. Fiducial markers can be used for tumor tracking in Cyberknife based SBRT and are generally introduced under percutaneous Ultrasound (US) or CT guidance.[5] While previous studies[6-7] have reported the efficacy and safety of US or CT guided, fiducial marker implants in the liver, the number of these studies is limited due to the small number of patients. Moreover, they did not specifically mention the efficacy of guided, fiducial marker insertion in poorly conspicuous lesions. However, fiducial placement has it's own issues and need to be addressed. It leads to a delay in treatment. The procedure is associated with additional costs, and the fiducials can create significant imaging artefacts on CT.[8]The fiducial placement procedure is also associated with potential risks and complications like pain, vasovagal attack, pneumothorax, hemothorax, perforation of non-target organs, bile peritonitis, infection, hemobilia, neuralgia and tumor seeding.[9] The literature on fiducial related complications and migration-related parameters from India is very scarce, and also the compliance, acceptability and pain related issues might not be similar in the Indian population as seen in western population and studies. Therefore, we carried out our study to evaluate the accuracy and feasibility of fiducial placement under image guidance and to evaluate the fiducial migration rate, pain score and fiducial placement related complications.

METHODS

We carried out a prospective observational study on 36 subjects after getting approval from the institutional ethics committee. Since no prospective study could be located in the existing literature to assess the accuracy of fiducial placement and the fiducial migration rate in hepatocellular carcinoma in the Indian population, we did a pilot study and included 30 consecutive patients who were clinically, radiologically or pathologically diagnosed with hepatocellular carcinoma and eligible for fiducial placement andCyberknife based radiation treatment in Amrita Institute of medical sciences, Kochi between May 2017 to August 2018. We excluded patients who were unfit for fiducial placement and with poor performance status.

All baseline blood investigations were performed including a complete hemogram, pre-operative serology, prothrombin time with the international normalised ratio, liver function tests and renal function tests. Fiducial placement was done under computed tomographic (Siemens Somatom Emotion 16 slice CT) or ultrasonographic (Philips IU 22 USG) guidance under sterile conditions by an interventional radiologist in the presence of radiation oncologist to guide the placement of the fiducials. Three gold fiducials were inserted percutaneously under image guidance using a cylindrical 20 cm long 18 gauze puncture needle, with a preloaded fiducial marker. Each fiducial was a cylinder made from 99 % pure gold with whorl on the surface. It weighed 17 grams and has a size of 1.2 mm x 5.0 mm. (Ref: GF1521 Gold fiducial marker, Mfg: IZI Medical products Owings Mills MD 21117 U.S.A).The accuracy of fiducial placement was scored by the interventional radiologist and the radiation oncologist independently based on a self-devised fiducial placement accuracy scoring system looking into parameters like inter-fiducial distance, inter-fiducial angle, distance from the centre of the tumor and any gross displacement or complications.

Points were given for each of the parameters accordingly and then summed up to get a total score and grade. Post-procedure pain scoring at 30 mins post procedure was done using Wong-Baker Visual analogue pain scale [10] and any complications during or after the procedure was recorded and graded using SIR [11] complication grading system. Any intervention for complications and the post-procedure recovery time was also documented and graded as per a self-devised grading system.A thin slice (1.25mm) CT scan along with anteroposterior and lateral X-Ray of the liver at the end of expiration using a stereotactic body frame (vacloc) for immobilisation in the supine position was performed in the in-house dedicated CT simulation machine (GE optima series 580 WRT 360 slice, 120 kV, 450 mA). The images were taken from manubrium sterni to L5 vertebrae to assess for any gross migration or complications. It was termed as the Day 0 scan.Planning CT was taken on day three post fiducial placement along with additional thin slice (1.25mm) CT and AP and lateral X-Ray of the liver at the end of expiration using a vacloc for immobilisation to assess the migration of fiducial from baseline.Pretreatment pain score, complications and intervention for complication on Day 3 post fiducial placement were also documented.The thin slice CT scans and the X-Ray images of Day 0 and Day 3 were fused on Medvision image viewing software. The X Y Z coordinates of the fiducial markers were analyzed, and the maximum and minimum migration from baseline were documented. The planning CT images were then transferred to the Cyberknife workstation [Accuray Multiplan Version 5.3.0 (53023)] where contouring of target volumes and organs-at-risk (OAR) were done according to the RTOG guidelines followed by planning.Treatment was started on Day 4 post fiducial placement, and it was delivered through AccurayCyberknife (Model: M6 F1+) over five days (Day

4 to Day 8). At the end of five days of treatment (Day 8 post fiducial placement), post-treatment pain score, complications and intervention for complication were documented.

Descriptive statistics was carried out by mean and standard deviation for quantitative variables, Chi square test was done for qualitative variables. A P value < 0.05 was considered statistically significant at 95% confidence Interval. IBM SPSS statistical software version 21 was used for statistical analysis.

RESULTS

A total of 36 participants were included in the final analysis.As shown in Table 1, among the study population,13 (36.1%) participants were aged up to 60 years, and 23 (63.9%) were more than 60 years. Of the total study population, 33 (91.7%) participants were male, and 3 (8.3%) participants were female. Among the study population, 19 (52.8%) participants had ECOG performance score 0, 14 (38.9%) participants had ECOG performance score 1 and 2 (8.3%) participants had ECOG performance score 2. Among the study population, 32 (88.9%) participants had Child-Pugh score A, 3 (8.3%) participants had Child-Pugh score B and 1 (2.8%) participant had Child-Pugh score C. Among the study population, 23 (63.9%) participants had associated portal vein thrombosis (PVT). The mean total dose delivered was 37.51±8.034 Gy. (Table 1)

Among the total study population, in 25 (69.4%) participants, CT was used as the imaging modality for fiducial placement, USG was used in 7 (19.4%) participants and in 4 (11.1%) participants both CT and USG guidance were used. For all 36 (100%) participants, three fiducials were placed. The mean duration of the procedure was 23.83 ± 13.34 minutes, ranged between 9 to 56 mins. The mean of maximum inter fiducial distance was 4.77 ± 1.12 cm, mean minimum inter fiducial distance was 2.54 ± 0.81 cm.The mean for maximum inter fiducial angle was 82.7 ± 26.58 degrees and mean of minimum inter fiducial angle was 28.47 ± 11.86 degrees. The mean maximum distance from the tumor centre was 5.09 ± 1.24 cm and mean minimum distance from the tumor centre was 2.09 ± 0.65 cm. Among the study population, 3 (8.4%) participants had gross fiducial displacement on the day of the procedure. (Table 2)

As shown in Table 3, the mean post fiducial placement pain score (day 0) was 0.86 ± 1.46. Among the study population, 30 (83.3%) participants had no complication on the day of fiducial placement post procedure, 5 (13.9%) participants had a minor complication, and 1 (2.8%) participant had a major complication. (Table 3)

Table 1:Baseline demographic and clinical parameters among the study population (n=36)

Demographic parameter	Cases (%)
Age group	
Up to 60 years	13 (36.1 %)
More than 60 years	23 (63.9 %)
Gender	
Male	33 (91.7 %)
Female	3 (8.3 %)
ECOG performance score	
0	19 (52.8 %)
1	14 (38.9 %)
2	3 (8.3 %)
Child-Pugh score	
A	32 (88.9 %)
B	3 (8.3 %)
C	1 (2.8 %)
Presence of PVT	
Yes	23 (63.9 %)
No	13 (36.1 %)
Total dose(Mean ± SD)	37.51 ± 8.034Gy

Table 2: Summary of parameters assessed during fiducial placement (n=36)

Parameter	Cases (%)
Imaging modalityN (%)	
CT	25 (69.4)
USG	7 (19.4)
CT + USG	4 (11.1)
Duration of procedure (Mean±SD)	23.83±13.34mins
Inter fiducial distance (Mean ± SD)	
Maximum	4.77 ± 1.12 cm
Minimum	2.54 ± 0.81 cm
Inter fiducial angle (Mean ± SD)	
Maximum (degree)	82.7 ± 26.58
Minimum (degree)	28.47 ± 11.86
Distance from tumor centre (Mean ± SD)	
Maximum	5.09 ± 1.24 cm
Minimum	2.09 ± 0.65 cm
Gross fiducial displacement (%)	
Yes	3 (8.4)
No	33 (91.6)

Table 3: Summary of post fiducial placement pain and complications (n=36)

	Summary
Post fiducial placement Pain score (Mean ±SD)	0.86 ± 1.46
Post fiducial placement Complication grade(%)	
No complication	30 (83.3%)
Minor complication	5 (13.9%)
Major complication	1 (2.8%)

The mean of average maximum inter fractional migration was 0.29 ± 0.03 mm. The mean of average minimum inter fractional migration was 0.1 ± 0.02 mm. The mean of total migration at the end of treatment on day eight post fiducial placement was 2.37 ± 0.27 mm. Among the study population, 1

(3.0%) participant had moderate migration (3-6), 30 (90.9%) participants had minimal migration (2-3) and 2 (6.1%) participant had no migration (<2) from baseline when measured on day eight post fiducial placement at the end of treatment. There were no gross migrations during treatment or post-treatment. The only gross displacement seen was just after fiducial placement procedure on day 0. (Table 4)

Table 4: Summary of fiducial migration assessment (n=36)

Parameter	Summary
Migration(Mean ± SD)	
Average Maximum migration	0.29 ± 0.03 mm
Average minimum migration	0.10 ± 0.02 mm
Total migration	2.33 ± 0.27 mm
Migration score on day 8[N (%)]	
Moderate migration (3.1-6 mm)	1 (3.0 %)
Minimal migration (2-3 mm)	30 (90.9 %)
No migration (<2 mm)	2 (6.1 %)

DISCUSSION

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver, generally developed within a context of chronic liver disease, most often cirrhosis.[12] SBRT is a technique that allows the delivery of a precise dose of radiation to a tumor while sparing adjacent normal tissues. However, the movement of intra-abdominal organs due to respiration has hampered the use of SBRT. The CyberKnife is a unique noninvasive radio surgical system, capable of treating any part of the body from any of approximately 1600 different targeting angles, creating a highly conformal three-dimensional radio surgical treatment volume, guided by orthogonal X ray-based targeting feedback, and delivering radiation by a highly collimated, robotically controlled linear accelerator. There is no well-known prospective study looking into the actual rate of fiducial migration, the accuracy of fiducial placement and its utility in treatment planning, pain score and procedure related parameters in the Indian population. Hence, we undertook this study.Our study objectives were similar to that of Park SH et al, Ohta K et al, Choi J-H et al.Park SH et al evaluated the efficacy and safety of ultrasound (US) -guided marker implantation for SBRT. Ohta K et al evaluated the technical and clinical success rates of the procedure of fiducial markers placement for SBRT and the frequencies of complications.[5, 13-14] Choi J-H et al determined the safety and technical feasibility of endoscopic ultrasonography (EUS)-guided fiducial placement for SBRT.[14]In our study, the proportion of people with successful fiducial placement in the liver was 91.6%. 8.4% (n=3/36) had gross fiducial displacement on the day of the procedure.Two fiducials (2.7%) migrated into the lung while one fiducial (5.5%) migrated into the abdomen. There was no gross migration seen during treatment or post-treatment.

The only gross displacement outside the liver was seen just after the fiducial placement procedure on Day 0.Technical success was achieved in 291 (97.3%) fiducial marker implantations by Park SH et al which was slightly higher than seen in our study.[5]Park SH et al in their study observed eight markers (2.7%) developed migration.[5]. Of those eight, migrated markers, seven were not seen on the planning CT.Post fiducial placement, no complications were observed in 83.3% of the patients in our study. In the study byPark SH et al.[5], no one had major complications while 12% had minor complications. In our study, 2.8 % had a major complication in the form of liver decompensation resulting in the death of the subject within 24 hours of the procedure. Further, two more patients had decompensation prior to the start of treatment and hence could not continue. 13.9% of patients had minor complications in the form of either pain, mild pneumothorax or fatigue post procedure which required symptomatic treatment only.The amount of pain reported after post fiducial placement was very minimal in our study, with the average pain score being 0.86. Pain scoring was not evaluated by Park SH et al and Choi J-H et alfor comparison with their studies.[5,14] Choi J-H et al in their study observed that one patient (3.1%) developed mild pancreatitis post-treatment.[14], but in our study, no one had any pain or complication during or post-treatment. Park SH et al in their study also observed no complications during this interval.[5] No major complications such as coil migration or bleeding were observed by Ohta K et al.[13].In our study, 90.9% had minimal migration from baseline in the range of 2 to 3 mm when evaluated at the end of treatment with the mean for total migration being 2.33 ± 0.27 mm.

With regards to socio demographic factors affecting our study results, the majority of our participants (63.9%) were aged more than 60 years, and 91.7% were males. Similarly, Park SH et al also observed the majority were males (73%).[5]In their study, 82% had a Child-Pugh score of category "A", and similarly, in our study, 88.9% of participants had a Child-Pugh score classification of"A". In our study Liver segments VIII (44.4%), VI (38.9%), IV (27.8%), V (27.8%) and VII (27.8%) were commonly involved.In our study, 63.9% had associated portal vein thrombosis, but only 5% had portal vein thrombosis in the study by Park SH et al.Park SH et al also observed a higher tumor incidence in segment IV.[5]SBRT typically consists of one to five treatment sessions delivered over the course of one to two weeks.Among our study population, the mean dose per fraction was 8.342± 2.06 Gy while the mean total dose given was 37.51±8.034 Gy. Park SH et al in their study did not mention the dose of

radiation used.[5].Similar to our study, Choi J-H et al in their study delivered fractional doses of 6 to 8 Gy, delivered to target volume for consecutive four days.[14]

In CyberKnife based SBRT using the x-ray based real-time image-guidance system, a fiducial marker is usually placed in or near the tumor for tumor tracking during treatment. Depending on the location of the tumor, a radiation oncologist may work with a pulmonologist, gastroenterologist or interventional radiologist to have one to four fiducial markers placed near the tumor. Placement of the fiducial marker is almost always an outpatient procedure. Optimal positioning of fiducials in relation to a lesion might vary according to the equipment used for SBRT. When performing fiducial implantations for SBRT using CyberKnife, it is advised to maintain a minimum spacing of 15 mm and a minimum 15 degree angle between the fiducials.[7]At least a 1-cm distance between the fiducial marker and the tumor was recommended in order to avoid tumour-margin blurring. Fiducial markers can develop artefacts and obscure margins of the tumor, especially in small lesions. This is important as an indistinct tumor margin offers only limited evaluation of a tumor on planning and follow-up CT studies.Kothari et al reported that if the tumor diameter is less than 2 cm, a marker inserted into the tumor may obscure the tumor margin.[5,7].In our study, 69.4% had CT as the imaging modality forfiducial placement while 19.4% had USG. Park SH et al in their study performed all procedures under USG guidance[5]The mean duration of fiducial placement was 23.8 minutes in our study. Other authors (Park SH et aldid not assess or mention the duration of fiducial placement as a significant factor in their studies[5]In our study, the mean maximum distance from the tumor centre was 5.09 cm while the minimum was 2.09 cm. The mean distance between the tumor margin and the markers was 3.1 cm in their study.[5]Oldrini G et al in their study also observed the mean distance between the markers and the lesion was 3.2 cm.[15] Park SH et al in their study found 72% had fiducial markers located in an ideal location.[5]. In our study, the maximum mean inter fiducial distance was 4.77 cm while the minimum means inter fiducial distance was 2.54 cm but Oldrini G et al in their study observed the mean distance between the markers was only 1.7 cm.[15]. This variation could have been caused due to the tumor size and other morphological differences. The mean inter fiducial angle in our study was 82.7 degrees with a range of 12 to 117.5 degrees. Other authors did not focus on these angles, and hence data from the literature regarding these angles were limited.

Strength and limitations: Our study was the first of its kind in our region to prospectively evaluate the fiducial placement related parameters, complications and fiducial migration. The key limitation of the current study was the descriptive nature of the study and a very small sample size without a proper sampling frame. Due to the descriptive nature of the study, no analysis could be done on the factors associated with post fiducial complications among the study population. The role of potential confounding factors also could not be evaluated due to limited sample size and the descriptive nature of the study. Considering the single centre nature of the study, the generalizability of study findings is limited.Use of Activated breath coordinator system during simulation and treatment would have resulted in stricter immobilisation and hence a more accurate assessment of fiducial migration compared to other studies.

CONCLUSIONS

In conclusion, our study results showed that imaging-guided implantation of fiducial markers in the liver for stereotactic body radiation therapy had a high technical success rate and is a safe procedure with rare complications. There is a minimal migration of fiducials seen post fiducial placement and during the treatment and it does not lead to any break in treatment or complications. Hence, there is also a potential for shortening the waiting time before starting treatment post fiducial placement.

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