Phase I Dose Escalation Study of CyberKnife Stereotactic Radiosurgery for Liver Malignancies

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Purpose/Objective: Three-dimensional external beam radiation therapy has been used for patients with unresectable hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHCC) with encouraging results. Prospective studies have demonstrated that doses of 48-72.6 Gy (fraction size 1.5-1.65 Gy bid) can be given, achieving hepatic control rates of 50%. In addition, 3-dimensional treatment planning for liver metastases has allowed the safe irradiation of 2/3 of the normal liver to 48-52.4 Gy and 1/3 of the liver to 66-72.6 Gy (fraction size 1.5-1.65 Gy bid).

Based on these data, we developed a Phase I study to evaluate the safety and feasibility of single-fraction radiosurgery using CyberKnife for liver tumors. Through a dose escalation schema, we will attempt to determine the maximum tolerated dose (MTD) for such therapy. Radiographic response is a secondary endpoint to assess the efficacy of radiosurgical ablation of liver tumors.

Materials/Methods: Patients with HCC, IHCC, or three or fewer liver metastases who had a life expectancy of >6 months were eligible. Tumors did not exceed 5 cm in diameter and were unresectable. Laboratory tests confirmed adequate hepatic function.

Three to five gold fiducials for targeting purposes were placed percutaneously directly into the tumor under CT guidance. Within 7 days of fiducial placement, a Vac-LokTM was custom made for each patient, who then underwent a dual-phase contrast CT scan through the entire abdominal cavity, using 1.25 mm thick slices. The lesion representing the gross tumor volume (GTV) was outlined on sequential axial CT slices. The dose was prescribed to the maximum isodose volume which completely covered the GTV. Adjacent normal structures such as the surrounding liver, duodenum, kidneys, inferior vena cava, heart, pancreas, stomach, and small bowel within 5 cm of the GTV were contoured for the purpose of limiting radiation to these structures.

Treatments were delivered with motion tracking using X-ray detection of fiducial and surface light emitting diode (LED) positions and development of an algorithm that predicted tumor movement.

Follow-up abdominal CT, physician appointment, and laboratory tests were scheduled at 4-6 weeks, 3 months, 6 months, and annually until death. Toxicity beyond 3 months was scored according to the RTOG late Radiation Toxicity Scale.

Results: To date, 6 patients with 7 tumors have been treated (3 tumors with 18 Gy and 4 tumors with 22 Gy). One patient had IHCC and the remainder had metastatic disease. Mean planning target volume (PTV) was 18.45cc (range 11-42). Mean maximum dose to the PTV was 26.8 Gy (range 22.5-29.3). In the 18 Gy group, 4% of the liver volume received >20 Gy. In the 22 Gy group, 5-7% of the liver received >20 Gy.

Mean follow-up for the 4 living patients was 9.5 months (range 6-14). There was one incidence of Grade I GI toxicity, which consisted of nausea and vomiting for 1 week after treatment. Four patients had partial response on imaging: 1 progressed locally after 9.5 months, 1 progressed locally as well as distantly after 3.5 months, 1 progressed distantly after 3 months and died 4 months later, and the other continues to have stable response. One patient exhibited no change on imaging. One patient with two tumors treated died of metastatic disease before follow-up imaging could be obtained.

Conclusions: Results thus far indicate that single fractions of 18 and 22 Gy are safe to administer to liver tumors with the CyberKnife. We have not yet reached the MTD at 22 Gy. We plan to dose-escalate to 30 Gy.