LIVER CANCER IN CHILDREN- A REVIEW

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ABSTRACT

It is unclear exactly what causes liver cancer, but researchers know that it develops due to mutations in liver cells. These cells grow without the usual regulation that tells liver cells when to replicate and when to stop replicating. When cells replicate without regulation, they can become a tumor. Some children are diagnosed with hepatoblastoma so young that scientists believe the cancer starts before the children are born. Hepatocellular Carcinoma is seen more frequently in areas of the world that have high rates of hepatitis. Infection with any one of several viruses that cause hepatitis is believed to be responsible. Only a few risk factors for hepatoblastoma are known for sure. Children with some genetic syndromes are more likely to develop hepatoblastoma than other children. Babies with low birth weights (less than 1,500 grams or about 3 1/2 pounds at birth) have a much higher risk of hepatoblastoma compared to normal weight babies. Smaller than average babies (3 pounds 5 ounces – 5 pounds 8 ounces) have a slightly increased risk of developing hepatoblastoma. The reasons for the high risk associated with lower birth weights are not clear. Most children who are born with low birth weight never develop hepatoblastoma. HCC is more common in males compared to females. Hepatitis B virus passed from mother at childbirth is a HCC risk factor. Other risk factors for HCC include inherited metabolic disorders such as hereditary tyrosinemia, alpha-1-antitrypsin deficiency, disorders that lead to bile accumulation in the liver (such as Alagille syndrome) and glycogen storage disease. Obesity, hereditary hemochromatosis (too much iron accumulation in the body) and Wilson's disease (too much copper accumulation) can also lead to liver damage and HCC.

keywords: Hepatacellular carcinoma, Hepatoblastoma, T-cell editor creating powerful immunotherapy weapon.

INTRODUCTION:

Hepatocellular carcinoma (HCC) is a major health problem worldwide. It is the fifth most common neoplasm in the world, with more than half million new cases yearly[1]. The incidence of HCC rose in the last decade. In the USA, the incidence of HCC is expected to increase over the next two decades, equalling that currently experienced in Japan [2]. HCC is now the leading cause of death among cirrhotic patients [3]. Liver Cancer: Liver cancers are a rare occurrence in children. There are two types of liver tumours, Hepatoblastomas and hepatic carcinomas.

Childhood liver cancer is a disease in which malignant (cancer) cells form in the tissues of the liver. The liver is one of the largest organs in the body. It has four lobes and fills the upper right side of the abdomen inside the rib cage. The liver has many important functions, including:

- Filtering harmful substances from the blood so they can be passed from the body in stools and urine.
- Making bile to help digest fats from food.
- Storing glycogen (sugar), which the body uses for energy.

Liver cancer is rare in children and adolescents (teenagers). There are two main types of childhood liver cancer:

- **Hepatoblastoma:** A type of liver cancer that usually does not spread outside the liver. This type usually affects children younger than 3 years old.
- **Hepatocellular carcinoma:** A type of liver cancer that often spreads to other places in the body. This type usually affects children older than 14 years old.

The treatment of two less common types of childhood liver cancer are:

- **Undifferentiated embryonal sarcoma of the liver (UESL):** The third most common liver cancer in children and adolescents. It usually occurs in children between the ages of 5 and 10 years.
- **Infantile choriocarcinoma of the liver:** A very rare tumor that appears to start in the placenta and spreads to the fetus. The tumor is usually found during the first few months of life.

MATERIALS AND METHODS:

Tumor Implantation.

The rabbit VX2 tumor (4,5,6,7) was selected for implantation in the liver because of the similarities of its blood supply to that of human hepatomas. Other attributes of this tumor include rapid tumor growth, development of a sizable tumor that can be readily identified by *X*-ray imaging (fluoroscopy; Ref. 4), and a biochemical phenotype (5) characteristic of advanced stage tumors, *i.e.*, high glycolysis and elevated levels of mitochondrial bound hexokinase (8,9). In addition, the rabbit is large enough that selective manipulation of catheters in the hepatic artery from the common femoral artery for delivery of agents is possible. Adult New Zealand White rabbits (32 total; Robinson Services, Inc.) weighing 3.5–4.2 kg were used. Studies with these animals were approved by the Johns Hopkins University Animal Care and Use Committee and carried out according to their guidelines. For successful implantation of the VX2 tumor into the liver, the tumor was first grown for 2 weeks on the hind leg of a carrier rabbit. Each carrier rabbit was used to supply tumor cells for implantation into the left lobe of the liver of two separate rabbits. All of the animals, carriers and recipients, were anesthetized with a mixture of acepromazine (2.5 mg/kg) and ketamine hydrochloride (44 mg/kg) administered i.m.; i.v. access was gained via a marginal ear vein, and sodium pentothal was given i.v. to maintain anesthesia. The VX2 tumor was then excised from the carrier rabbit and placed in Hanks' solution. Chunks of the tumor were minced in the same solution. Then, the abdomens of the recipient rabbits were shaved and prepped with betadine, after which a midline subxyphoid incision was made. The anterior surface of the liver was exposed and tumor cells (0.1–0.2 ml) from the minced donor tumor were directly implanted onto the left lobe of the liver using the outer cannula of a 21-gauge angiocatheter. This method allows the growth of a single solitary, well-demarcated tumor in the liver of each recipient rabbit. The abdomen was closed in two layers. Proper aseptic technique was rigorously observed during each implantation. After surgery, animals were returned to their cages, kept warm with blankets, and monitored in the animal laboratory under the direct supervision of a physician or a technician until they recovered from anesthesia. Buprenorphine (0.01 mg) was administered for analgesia when the animals were in pain or showed physical distress. The tumors were allowed to grow for another 14days,at which time they reached an ellipsoidal shape with dimensions of 1.5 × 1.8 × 2.5 cm.

Preparation of 3-BrPA Solutions.

The solutions of 3-BrPA (Sigma Chemical Co., St. Louis, MO) were prepared in PBS. After adjusting the pH to 7.0 with NaOH the solutions were sterilized via Millipore's Millex GV 0.22 μm filter unit and used immediately. Freshly made solutions were used in all of the studies reported here.

Intraarterial Injection of 3-BrPA.

Administration of anesthesia, i.v. access, and sodium pentothal anesthesia were carried out as described above. Transcatheter hepatic artery injection of 3-BrPA was performed under fluoroscopy. The animals were brought to the angiography suite and intubated using a size 3.0-mm endotracheal tube (Mallinkrodt Medical, St. Louis, MO) but not ventilated. Surgical cut-down was performed to gain access into the right common femoral artery, after which a 3 French sheath (Cook Inc., Bloomington, IN) was placed. A specially manufactured 2 French catheter with a tip in the shape of a hockey-stick (JB1 catheter; Cook Inc., Bloomington, IN) was manipulated into the celiac axis, after which a celiac arteriogram was performed to delineate the blood supply to the liver and to confirm the location of the tumor. The tumor could readily be visualized as a region of hypervascular blush located on the left side of the liver near the gastric fundus. The left hepatic artery, which usually provides most of the blood flow to the tumor, was selectively catheterized via the common hepatic artery. When necessary, a steerable guidewire (0.010–0.014 inches Transend wire; Boston Scientific MediTech, Natick, MA) was used to help select the left hepatic artery. After having adequately positioned the catheter within the left hepatic artery, the 3-BrPA solution was infused directly into the artery. The animals were monitored after the procedure and given analgesics when they showed signs of physical distress.

Embolization.

This procedure was performed in a manner similar to the technique described above for 3-BrPA and as described earlier in detail (4). However, instead of using 3-BrPA, a mixture of Ethiodol and embolic material (polyvinyl alcohol; Target Incorporated, Fremont, CA) was injected into the left hepatic artery. The procedure was considered successful when forward flow was no longer demonstrated within the left hepatic artery. In addition, an intense tumor stain was identified in each case, which suggested a successful embolization procedure.

Histopathology.

Normal tissues and tumors were fixed in 10% formalin, sliced at 5-mm intervals for gross examination, and then embedded completely in paraffin, after which 4-μm sections were stained with H&E. Tumor viability was estimated by visual inspection and expressed as a percentage of viable tumor area for each slice. The overall percentage of viable tumor in each rabbit was calculated.

Statistical Analysis.

The mean fractions of tumor necrosis ± SD were compared using the unpaired Student *t* test for between-group comparisons. Differences were considered statistically significant for $P < 0.05$.

Direct Intraarterial Injection of 3-BrPA into Liver-Implanted VX2 Tumors Selectively Inhibits the Viability of Cells Therein without Altering the Viability of Surrounding Liver Tissue.

To test our hypothesis that direct intraarterial injection of a potent inhibitor of cell ATP production (3-BrPA) may selectively inhibit the viability of cells within the tumor, we employed the established VX2 tumor model for reasons described under “Materials and Methods.” Small chunks of a donor VX2 tumor were minced, surgically implanted in the livers of six rabbits/experiment, and allowed to grow for 14 days (Fig. 2*A*) . At this time, the single well-delineated tumor that developed in each liver exhibited a high degree of arterial vascularization because of the onset of angiogenesis. After fasting the animals for 24 h and administering anesthesia, a catheter was carefully inserted into the femoral artery and guided by fluoroscopy into the hepatic artery to a position near the tumor site (Fig. 2*B*) . Then, a single bolus injection of 3-BrPA was delivered in ~2 min directly into the artery. Animals treated identically, but not receiving 3-BrPA, served as controls. Optimal results were obtained by delivering 25 ml of 0.5 mm 3-BrPA, waiting 4 days, and then excising and subjecting each tumor and the surrounding liver tissue to histological analysis.

Experimental setup and effect of intraarterial injection of 3-BrPA on liver tumors. *A*, tumor implantation and growth. *B*, two representative hepatic arteriograms. Each shows the hepatic artery leading into a highly vascularized tumor (*circled*) located within the left lobe. *C*, histological section of a control “untreated” liver implanted tumor isolated 4 days after intraarterial injection of only a saline solution (see “Materials and Methods”). This section, obtained from a region of the tumor located outside of the necrotic tumor core, shows almost all viable cells. (×640). *D*, sections of a liver-implanted tumor isolated 4 days after intraarterial injection of 3-BrPA (see “Materials and Methods”). This section obtained from the same location of the tumor as the control, shows no viable

cells. (×640). *E*, sections from a 3-BrPA-treated tumor identical to *D* but showing a region near an artery (*arrow*) where a tiny cluster of cells remains viable. (×640) *F* and *G*, sections from the liver of a control untreated animal and from the liver tissue surrounding an implanted tumor into which 3-BrPA had been injected intraarterially. In both, all of the cells are viable. (×120). *H*, bar graph summarizing the killing efficacy of intraarterial 3-BrPA on liver tumors. Data are plotted as the mean ± SD. For the liver samples, there was no SD because all of the cells tested viable.

The results obtained from this novel approach proved to be quite dramatic. Compared with control "untreated" tumors, where representative sections (seven slides/tumor) obtained outside the central core region revealed nearly 100% viable cells (Fig. 2*C*) , similarly located sections obtained from tumors treated with 3-BrPA (Fig. 2*D*) contained almost all nonviable cells (nearly 100% necrosis). Viable tumor cells were detected only in small areas near arteries feeding the tumors (Fig. 2*E*) , and at the tumor periphery, where sinusoidal blood is available. This may reflect more active mitochondria in these oxygen-rich environments that are not completely debilitated at the concentrations of 3-BrPA used. Significantly, no damage occurred to liver tissue surrounding tumors that had been treated with 3-BrPA (Fig. 2 *F* and *G*) .

These results, reproduced in a number of experiments, were subjected to statistical evaluation. Tumors untreated with 3-BrPA (controls) contain 74 ± 5% viable cells in the entire population (Fig. 2*H* , *column 1*). The remaining cells, located within the hypoxic tumor core, have already become nonviable, a common feature of rapidly growing solid tumors. Treatment with a single intraarteria

l injection of 3-BrPA decreases the number of viable cells to 16 ± 5% (Fig. 2*H* , *column 2*), thus increasing the total number of nonviable cells in the population to 84 ± 5% ($P < 0.05$). The maximal number of nonviable cells observed in any one experiment was 90%. In sharp contrast, the surrounding liver tissue remained completely viable in all of the cases examined (Fig. 2*H* , *columns 3* and *4*).

In data not presented, the portal veins, sinusoids, and bile ducts remained completely intact, with the only apparent damage occurring occasionally in the peribiliary arteriolar complexes at much higher concentrations of 3-BrPA (5 mm). These and the above findings suggest that most of the 3-BrPA, injected directly into the tumor, remained therein, and if any leakage occurred, most was neutralized by natural reducing agents (*e.g.*, glutathione) present in the surrounding tissue (10,11).

In Contrast to Direct Intraarterial Injection of 3-BrPA, Conventional Therapy for

Advanced-Stage Liver Tumors Using Embolization Results in Significant Damage to Surrounding Liver Tissue.

We next inquired how this new strategy compares with the approach, called "embolization" or "chemoembolization," that is currently used to treat advanced stage liver cancer in humans (12 ,13,14,15,16) . Embolization involves blocking the hepatic artery feeding the tumor with a resin-like material mixed with an oil base (*e.g.*, polyvinyl alcohol in Ethiodol), thus depriving the tumor of its oxygen and nutrient sources. Chemoembolization refers to the same procedure but with the inclusion of one or more anticancer agents. Using the same rabbit model, we found that embolization alone of the hepatic artery (Fig. 3*A*) leading into the VX2 tumor causes such severe damage to the surrounding liver tissue that it is visually evident (Fig. 3*B*) . This is in sharp contrast to the normal-appearing liver tissue surrounding VX2 tumors that were not embolized but instead were subjected to direct intraarterial injection of 3-BrPA (Fig. 3*C*) . These findings were further substantiated by histological analyses that revealed extensive nonviable liver tissue surrounding tumors treated by embolization (Fig. 3*D*) , as opposed to only viable tissue surrounding the tumors treated by intraarterial injection of 3-BrPA (Fig. 2, *F* and *G*) .

Evidence for the benefits of intraarterial therapy for liver cancer using 3-BrPA over present therapy using embolization. *A*, view of the left hepatic artery observed microscopically after injection of embolization material (polyvinyl alcohol) and Ethiodol to block blood flow to the liver (12) . (×120). *B*, embolized livers harboring VX2-implanted tumors (*circles*). *Arrows*, damage 4 days after embolization. *C*, liver isolated 4 days after its implanted VX2 tumor (*circle*) received a single injection of 3-BrPA. There is no sign of liver damage. *D*, histological sections from those regions of livers shown in *B* that had been affected by embolization. Some tissue has suffered severe damage (nonviable region) and some has remained viable. (×120). *E*, sections of eight tissues from an animal harboring a liver-implanted VX2 tumor treated by intraarterial injection of 3-BrPA. All of the tissues exhibit a normal staining pattern. (×120). *F*, sections derived from the same animal showing metastatic lung tumors. (×120).

The Major Tissues of Animals Bearing 3-BrPA-Treated Liver Tumors Show No Apparent Damage, but the Lungs of these Animals and Identical Animals Not Receiving 3-BrPA Show Metastatic Tumors.

Despite the promising results obtained in support of direct intraarterial injection of 3-

BrPA as a therapy for liver cancer, the possibility still existed that 3-BrPA may be damaging other organs. For this reason, nine major tissues were isolated from animals harboring liver-implanted VX2 tumors 4 days after receiving a single intraarterial injection of 3-BrPA. In no case was there evidence for damage to these tissues (Fig. 3, *E* and *F*) . However, the unexpected discovery was made that secondary tumors had developed in the lungs (Fig. 3*F*) , a finding observed also in animals bearing liver-implanted tumors that had not been treated with 3-BrPA. Because this was a consistent finding (*n* = six animals), and because there was no evidence of such tumors in the eight other major tissues examined, these distant lesions are most likely the result of metastatic spread of the VX2 tumor from the liver to the lung.

Systemic Delivery of 3-BrPA Has No Noticeable Effect on the Animals' Health or Behavior and No Effect on Liver-implanted VX2 Tumors, but Does Markedly Suppress the Growth of the Metastatic Lung Nodules.

Finally, it was important to examine the effect of 3-BrPA when delivered systemically (*i.e.*, via the general circulation) on both animal toxicity and its capacity to damage liver-implanted tumors. After delivery of 3-BrPA (25 ml, 0.5 mm) via a marginal ear vein, rabbits that had been harboring liver-implanted VX2 tumors for 14 days exhibited normal behavior and, on sacrifice, histological examination of nine major tissues revealed no obvious damage (Fig. 4*A*) . Moreover, there was no killing effect on liver-implanted VX2 tumors (Fig. 4 *B* and *C*) as we had observed earlier after direct intraarterial delivery of 3-BrPA (Fig. 2, *C* and *D*) , thus adding further support for this targeted approach as a preferred therapy for liver cancer. However, in sharp contrast to the failure of systemic delivery of 3-BrPA to be therapeutic for liver-implanted VX2 tumors (Fig. 4, *B* and *C*) , it was found to be therapeutic for secondary tumors that had developed in the lungs. Interestingly, animals bearing the liver-implanted VX2 tumors developed numerous "metastatic" nodules in their lungs, the largest of which were several mm in diameter (Fig. 4*D*) . Most striking in these animals after systemic treatment with 3-BrPA was the finding of only very small tumors (Fig. 4*E*) , and the almost complete disappearance of those with a diameter >1 mm (Fig. 4*F*) .

Effect of systemic delivery of 3-BrPA on animals harboring the liver-implanted VX2 tumor. *A*, histological sections of nine different tissues isolated 4 days after injecting 3-BrPA (25 ml, 0.5 mm) into a marginal ear vein. No damage to these tissues is evident. (×120). *B*, section from a liver-implanted VX2 tumor isolated from a control animal not

receiving 3-BrPA. *C*, comparable sample from an animal receiving 3-BrPA systemically. Cells in both appear completely viable. (×120). *D*, section of lung tissue isolated from an animal in which the liver harbored a VX2 tumor after 14 days of growth. *E*, comparable section isolated from the lung of an identical animal 4 days after receiving a systemic injection of 3-BrPA. (×64). The growth of metastatic tumors has been markedly suppressed. *F*, bar graph emphasizing that, of the total number of metastatic lung tumors counted (>27) in comparable histological sections, five were >1 mm in diameter in untreated (*no treat.*) animals harboring a liver-implanted VX2 tumor, and none were >1 mm in identical animals that received 3-BrPA systemically (*systemic treat.*) (Animals evaluated = 4).

In summary, we commenced this study with the objective of testing a novel strategy for the treatment of liver cancer, a strategy that envisioned direct intraarterial injection of 3-BrPA, a potent inhibitor of cell ATP production. We have shown that this strategy is highly effective, reducing in a single injection the total number of viable cells in liver-implanted rabbit tumors to as low as 10% without doing any apparent harm to the animals or their major tissues. As an unexpected extension of our original objective, we have shown also that systemic delivery of 3-BrPA to the same animals bearing the liver-implanted tumors, also does no apparent harm to the animals or their major tissues, but suppresses secondary metastatic tumors that appear in the lungs. Thus, it is possible with a single, carefully selected known chemical agent, and a combination of intraarterial and systemic delivery methods, to inflict extensive damage on both a primary tumor and a secondary metastatic tumor within the same host without doing noticeable harm to the host. Future studies will focus on how the animal’s natural defense mechanisms are able to cope with such a reactive alkylating agent as 3-BrPA whereas the liver and lung tumors studied are highly sensitive to this agent.

A retrospective chart review from 1975 to 2005 identified patients who were 18 years old or younger with a histologically confirmed diagnosis of primary liver cancer. Patients were staged according to the Children's Cancer Group and Pediatric Oncology Group (CCG/POG) system. Patients were followed up prospectively through clinic visits and mail correspondence. Standard statistical methods were used for comparison, risk, and survival analyses.

During five years (2002-2007), all the hepatic tumors of childhood (under 18 year-old) from the pathology file of Namazi Hospital of Shiraz University of Medical Sciences are recorded. This includes both resected specimens and biopsies. All the slides were

reviewed and the pathologic diagnosis was confirmed.

Liver transplantation was performed in 17 children with unresectable hepatic tumors out of total number of 350 children transplanted. Hepatocarcinoma was present in 8 children, hepatoblastoma in 6 and benign giant hemangioma in 3. There was no other option for the treatment which would lead to the oncological cure of children with malignant tumors. All patients with giant hemangiomas were infants transplanted urgently due to circulatory and then multiorgan failure.

RESULTS AND DISCUSSIONS:

Survival within whole group is 75,5% (13 of 17 pts), 3 children died of malignant tumor recurrence, one of other causes. All 3 children with benign tumors are alive and well. Actual follow-up is from 3 months to 7 years.

Non -resectable hepatic tumours in children-Role of liver transplantation

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For this retrospective study with anonymized patients, approval from the institutional ethical committee was waived. Between October 2011 and July 2015, 71 patients (14 females, 57 males, median age 63.5 ± 10.8 years) with 103 liver tumors were treated via 83 interventions using IRE (NanoKnife® system; Latham, NY, United States) . These patients included 35 (49.3%) with primary liver tumors (hepatocellular and cholangiocellular carcinoma) and 36 (50.7%) with liver metastases. The median tumor diameter was 1.9 cm (range 0.4–4.5 cm).The median time period between resection of the primary tumor and the occurrence of liver metastasis was 22.3 ± 14.5 months. shows the baseline tumor characteristics.

Each patient was individually discussed within an interdisciplinary tumor board to ensure that all treating physicians agreed with the suggested therapeutic plan. All patients signed a written consent form in accordance with the institutional guidelines. All patients with a primary or secondary liver tumor had no clinical or radiological indications of extrahepatic tumor spread. Patients with cirrhosis of the liver and a related volume of ascites received ascites drainage prior to the start of intervention. illustrates the study inclusion/exclusion criteria.

Staging was performed pre-interventionally using computed tomography (CT) of the thorax, abdomen and pelvis . In addition, MRI of the liver was performed using a liver-specific contrast agent (GD-EOB-DTPA).

Pre-interventional computed tomography for intervention planning: arterial hypervascularized mass on the transition to liver segment I posterior to the main stem of the portal vein.

Same patient as in pre-interventional MRI with liver-specific contrast agent (Gd-EOB-DTPA): (**a**) Hyperintense visualization of the HCC (arrow) in native fat-saturated T2-weighted sequence posterior to the main stem of the portal vein at the transition to liver segment I. (**b**) Dynamic T1-weighted fat-saturated sequence after contrast in arterial phase shows sluggish arterial hypervascularization of the HCC (arrow).(**c**) Dynamic T1-weighted fat-saturated sequence after contrast in portal venous phase shows the directly adjacent main stem of the portal vein (tip of arrow). (**d**) T1-weighted fat-saturated sequence in hepatobiliary phase with wash-out (arrow).

All interventions were performed under general anesthesia and mechanical ventilation with complete muscle relaxation. The electrodes of the NanoKnife® system (Angiodynamics; Latham, NY, US) were percutaneously inserted into all patients using CT fluoroscopy (CareVision, Somatom 16, Siemens, Erlangen, Germany).

Control CT during irreversible electroporation of HCC mass posterior to the main stem of the portal vein. The intervention required the patient to be placed in prone position in order to insert the 3 electrodes (tips of arrows).

Depending on the size of the target volume, 2–6 monopolar 18 G ablation electrodes were inserted to completely destroy the tumor and healthy liver tissue within a 1 cm safety margin around the tumor. Accordingly, the length of the tip had to be adapted to the size of the ablation volume (0.5–2.0 cm in 0.5 cm increments). The optimum distance between 2 parallel electrodes enclosing the tumor is between 0.7 and 2.0 cm. Once the correct needle position was verified, a 270 volt test pulse was emitted to ensure adequate conductivity of the tissue prior to initiating the actual ablation algorithm. If conductivity was inadequate, the position of the electrodes must be correspondingly corrected, and the self-test was repeated. The parameters of IRE ablation were 1,650–3,000 V, the pulse length was 90 µs, and 70 pulses were applied per cycle under constant EKG monitoring to avoid life-threatening arrhythmias.

To rule out complications, CT and MRI of the liver were performed post-interventionally before the patients were discharged The post-interventional control CT the day after the

intervention shows hypodense demarcation of the ablation defect (arrow), and the adjacent portal vein (tips of arrows) is thoroughly contrasted. No post-interventional complications.

To evaluate the technical success of the intervention, an MRI of the liver was performed 6 weeks post ablation. The actual tumor response was first observed using MRI after 3 months and at 3-month intervals for 2 years after the intervention. Two years post-intervention, MRI scans of the liver were performed two times per year.

Same patient as in and Follow-up 2 years post-intervention: (**a**) Native, fat-saturated T2 sequence: cicatricial changes after IRE ablation with distinct shrinkage of the ablation defect. (**b**) Dynamic, fat-saturated T2 sequence after contrast: in arterial phase no indication of arterial hypervascularization (arrow), no indication of recurrence. (**c**) Dynamic fat-saturated T1 sequence after contrast: in portal venous phase continued full contrast of portal vein (tip of arrow). (**d**) Follow-up CT in the portal venous phase with full contrast of portal vein (tip of arrow) and distinct shrinkage of the hypodense ablation defect 2 years post-IRE (arrow).

Kaplan-Meier curves were plotted using SPSS (SPSS for Mac, Version 22, Chicago, IL, USA). The Cox proportional hazards model was used for multivariate analysis to evaluate prognostic factors. Factors determining local overall survival were compared using log rank analysis ($p < 0.05$ was considered significant). The investigated variables were the number of treated lesions, tumor diameter, underlying tumor disease, BCLC and Child-Pugh classification.

Results

At the end of the study, 36 patients were still alive. Complete ablation, as documented during the 6-week follow-up, was achieved in 95 of 103 lesions (92.2%); 8 lesions required re-treatment due to incomplete ablation (7.8%). The median total survival time was 26.3 months. Local tumor response was not the object of the study. However, after a median follow-up of 35.7 months, 33 of 103 treated lesions (31.7%) demonstrated local recurrence. Therapy-associated side effects were also not the primary aim of this study. However, during 83 interventions, we observed 5 major complications (liver abscess, $n = 4$; myocardial infarction, $n = 1$) and 7 minor complications (pneumothorax, $n = 2$; cardiac arrhythmia, $n = 2$; hematoma, $n = 3$). No minor complications required any further treatment.

The median survival of patients with secondary liver tumors was 19.9 months, which was shorter than that of patients with primary liver carcinoma (26.8 months). However, the

survival rate did not significantly differ between these two groups (p(LogRank) = 0.41; p(Wilcoxon) = 0.73).

Patients whose tumor was greater than 3 cm (p(Log-Rank and Wilcoxon) < 0.001) exhibited a considerably shorter lifespan. The average survival time of patients with a tumor diameter ≤3 cm was 24.5 months (median survival time was not achieved). The survival time of patients with a tumor diameter >3 cm was 12.9 months (median survival time 9.5 months).

Furthermore, patients with 3 or more lesions demonstrated significantly shorter survival rates (p(Log-Rank) < 0.005; p(Wilcoxon) < 0.005). The median lifespan of patients with no more than 2 lesions was 32.8 months. Those with 3 or more lesions survived for 12.4 months.

Kaplan-Meier curves: (**A**) The solid line shows the survival time for patients with primary liver tumors (hepatocellular and cholangiocellular carcinoma); the dashed line illustrates the survival time of patients with liver metastases. The survival time of both groups did not exhibit a significant difference. (**B**) The Kaplan-Meier survival curves show significantly better survival for patients with fewer than 3 tumors (solid line) when compared with patients with 3 or more tumors (dotted line). (**C**) Compared to patients with a tumor diameter greater than 3 cm (dashed line), the Kaplan-Meier survival curves show significantly better survival for patients with a short axis diameter less than 3 cm (solid line).

In a sub-group analysis of patients with HCC , the survival times of patients with Child-Pugh B or C cirrhosis of the liver were significantly shorter that those in the Child-Pugh A cirrhosis group (p(Log-Rank) < 0.05). Average survival for Child-Pugh A cirrhosis was 19.3 months (median survival time was not reached). In Child-Pugh class B, mean survival was 14.5 months (median: 9.7 months), and in Child-Pugh class C, survival was 12.7 months (median: 10.4 months).

The Kaplan-Meier survival curves for patients with hepatocellular carcinoma: (**A**) significantly better survival of patients with Child-Pugh class A cirrhosis of the liver (solid line) compared to those with Child-Pugh class B (dashed line) and C (dotted line). (**B**) Significantly longer survival of patients with very early stage HCC (dashed line) according to the BCLC classification compared to patients with early stage HCC (solid line).

Also, patients with early stage HCC (stage 1) according to the Barcelona Clinic Liver

Cancer Classification[17] (single or max. 3 nodules smaller 3 cm, Child Pugh A, performance status 0) showed significant shorter survival rates in comparison to patients with very early stage (stage 0) HCC (single tumor with a diameter smaller then 2 cm, Child Pugh A, performance status 0): median survival was 22.3 vs. 13.7 months ($p < 0.05$).

Discussion

During the past two decades, image-guided percutaneous ablation techniques, such as radio frequency ablation or microwave ablation, have achieved a high level of acceptance, particularly – but not exclusively – with respect to inoperable liver tumors. Various studies have proven that radiofrequency ablation (RFA) is a safe therapeutic option with both low mortality and morbidity[18,19]. RFA has shown satisfactory results, with a local post-RFA tumor response rate of over 80% complete tumor ablation in most studies[20]. Likewise, when compared to percutaneous ethanol injection or chemotherapy alone, RFA has demonstrated a significantly higher probability of survival[17]. However, thermal ablation techniques are limited by the so-called heat sink effect. Tumors adjoining larger blood vessels cannot be ablated due to the temperature reduction caused by perfusion. Another limitation of thermal ablation is the risk of thermal damage to the tissue of adjacent structures[21] or the blood vessels themselves. Typical examples of thermal damage after RFA on the liver are damage to the gallbladder, bile ducts and intestine[22]. Numerous strategies to protect adjoining structures against accidental thermal damage have been described[23,24,25.] Nevertheless, complete ablation of larger tumors (greater than 3 cm) or ablation of lesions in high-risk locations (such as adjacent to other organs or direct subcapsular position) remains problematic[26]. Several studies of thermal ablation have demonstrated that tumor size and/or an unfavorable (high-risk) site are considered negative prognosis factors for tumor recurrence[27]. The high local recurrence rate in these sites has a negative influence on the long-term outcome and is one of the main reasons thermal ablation is inferior to surgical resection with respect to outcome[28]. For example, Lam *et al*. prospectively treated 298 HCC patients using RFA and demonstrated a significantly shorter survival time for 25 patients whose tumors had been incompletely ablated[29].

Electroporation is a dynamic phenomenon in which an external electrical field is used to exceed the capacity of the cell membrane, allowing nano-sized pores to be generated in the cell membrane. Depending on the amplitude and duration of the pulse application, electroporation is either reversible or irreversible. IRE results in the loss of cell homeostasis; however, the exact mechanism resulting in cell death remains unexplained.

The hypothesis posed by Davalos *et al*. that IRE could be an independent method to ablate soft tissue has been confirmed by subsequent studies of liver cells and in animal models[30,31,32]. Moreover, the animal model demonstrated that blood vessels and bile ducts within or directly adjacent to the ablation zone remain undamaged[33]. Because thermal ablation techniques are frequently unsuitable for patients with inoperable tumors, chemotherapy frequently remains the sole palliative treatment, thus giving rise to significant interest in a new curative treatment option[34]. For most patients, IRE is currently considered the “last resort” from a therapeutic viewpoint. Likewise, the tumors investigated in this study were inoperable and not treatable using conventional thermal ablation. Nevertheless, an average survival time of 24.3 months was demonstrated for CRLM. This result is promising because chemotherapy would otherwise remain as the only palliative therapeutic alternative for these tumors. After chemotherapy, similar survival times of approximately 18 months have been reported for CLRM in palliative care (fluorouracil with oxaliplatin)[35,36] and 21.7 months for capecitabine, irinotecan and oxaliplatin[37], but without the burden of therapy associated systemic side effects.

Preclinical studies have demonstrated that IRE creates a well-defined boundary between ablated and non-ablated tissue; thus, the cells are either destroyed or remain intact. Compared with thermal ablation, perivascular tumor ablation with IRE appears to result in less frequent recurrence, indicating that the effectiveness of IRE is not influenced by the heat sink effect[38]. The current state of information does not permit a final statement on IRE. Larger prospective randomized studies will have to confirm these observations. The initial results with smaller hepatic tumors abutting vascular structures and the portal vein are very promising. The success rate is up to 90% but decreases rapidly in relation to tumor size[39]. Our previous study analyzing the risk factors for an early local recurrence demonstrated that similar to conventional (thermal) ablation techniques, a larger tumor diameter represents an independent risk factor for local recurrence[40]. Based on a study of 44 patients, Cannon *et al*. postulated that the best indication for IRE is in the case of tumors with a diameter ≤3 cm that are not accessible using a thermal ablation technique[41]. The results of our study point in the same direction because patients with a tumor diameter >3 cm die significantly earlier than those with smaller tumors ($p < 0.001$). However, this difference arises primarily because larger tumors are generally associated with greater biological activity and aggressiveness. Thus, larger tumors (diameter greater than 3 cm) may remain the domain of transarterial rather than percutaneous therapy.

In a prospective study, Thomson *et al*. investigated 63 tumors that had been treated using IRE. They found that HCC had distinctly better therapeutic results compared with liver

metastases[42]. Likewise, an earlier study by our working group investigated early recurrence after percutaneous therapy using IRE and found that HCC tumors exhibited fewer earlier recurrences compared with other diagnoses[43]. In our current study, patients with HCC demonstrated a longer survival time (26.8 months) compared with those with liver metastases, yet this difference was not comparatively significant. One possible explanation for this phenomenon is that there is different tumor biology between primary and secondary liver cancer leading to different IRE effectiveness.

Overall, it is difficult to draw broad conclusions regarding the impact that percutaneous therapeutic procedures, specifically IRE in our case, have on the total survival time or which additional factors affect treatment using IRE. In addition to this general problem, our analysis has several further limitations, the most important of which is the retrospective nature of the study. Moreover, the patients investigated in the study represent a selected population with distinctly heterogeneous tumor characteristics. In addition, the number of included patients is small, and the follow-up was limited to only 3 years.

Nonetheless, we consider these initial results to be highly promising for the treatment of malignant liver tumors compared with other therapeutic concepts, at least with respect to comparable survival times. Prospective randomized controlled studies with a larger number of patients and longer-term follow-up are required to demonstrate whether IRE, compared with other therapeutic regimes, is superior with respect to survival, local therapeutic outcome and side effects.

As part of a $6 million effort to establish new therapies for high-risk pediatric liver cancer, **Navin Varadarajan**, associate professor of chemical and biomolecular engineering at the **Cullen College of Engineering**, will modify T cells to recognize and kill glypican-3, a molecule found in liver cancer cells.

Inherently that’s what the immune systems' white T cells do –they fight invaders or infections. It is also what Varadarajan does. With two previous awards from the **Cancer Prevention & Research Institute of Texas (CPRIT)**, Varadarajan is working to improve effectiveness of T-cell immunotherapy. On this CPRIT multi-investigator research award, he joins **Andras Heczey,** a physician researcher at Baylor College of Medicine, in examining one of the most common forms of liver cancer in adolescents, hepatocellular (HCC) carcinoma. HCC patient survival rates are under 30 percent.

No effective cure is available for most metastatic hepatocellular tumors. Current

treatment includes surgical resection or liver transplantation in combination with dose-intensive chemotherapy regimens -associated with significant morbidity in HCC – or which may cause low blood cell counts, hearing impairment, speech and cognitive delay and long-term damage to the heart. “It is thus critical to develop new, effective and safer therapies,” said Varadarajan.

T cell-based immunotherapy has worked in other types of cancers, like leukemia and lymphoma. The team at Baylor will isolate the T cells, modify them with synthetic receptors and then Varadarajan will get to work.

“We have a platform for documenting how well T cells work and we will use it to determine which T cell properties are essential in fighting the cancer cells,” said Varadarajan, whose team built the microscopy-based methods for monitoring cellular function.

Once determined, certain functions can be added or subtracted through genetic editing to make the T cell the best cancer fighter possible. The modified cells will deliver targeted and tailored therapy in clinical trials at Baylor.

“The hope is to get consistent and durable patient responses in pediatric HCC by using the power of immunotherapy,” said Varadarajan, who credits CPRIT with the steps forward in immunotherapy.

“Texas taxpayers are amazing for funding CPRIT. Much of this research would not be possible without it,” said Varadarajan. CPRIT’s goal is to expedite innovation in cancer research and product development, and to enhance access to evidence-based prevention programs throughout the state of Texas.

RESULTS:

Fifty-two patients were confirmed to have primary liver cancers, where 24 (46%) patients had HB, 22 (42%) had HCC, 3 (6%) had sarcomas, and 3 (6%) had other histologies. Mean ages at presentation for HB and HCC were 3.2 and 13.1 years old, respectively. The most common presentations were abdominal mass (67%) and pain (40%). Most patients underwent major liver resection (n = 45, 87%), including: lobectomy (n = 25, 48%), and trisegmentectomy (n = 11, 21%). Three patients underwent liver transplantation (n = 3, 6%) for advanced local disease. Forty-five (87%) received primary or neoadjuvant and/or adjuvant chemotherapy. Patients had the following CCG/POG stages: I (n = 31, 60%), II (n = 6, 11.5%), III (n = 9, 17%), and IV (n = 6, 11.5%). Complete gross resection (stage I and II) was achieved in 37 (71%) patients. The perioperative mortality and morbidity rates were 0% and 29%, respectively. Patients with

complete resection had significantly better 5-year DSS and median survival compared with incomplete gross resection: 62% vs 9% and 216 vs 18 months, P < .001. Patients treated during the period 1995-2005 had better 5-year DSS and median survival compared with those treated during 1975-1994: 68% vs 32% and 117 vs 27 months, P = . 032. All 3 patients who underwent transplantation for conventionally unresectable disease are alive without disease recurrence (follow-up period, 1-15 years).

RESULTS:

We detected 53 liver tumor cases in children (below 18 years of age). Among these tumors, 36 (67.9%) were malignant. Male to female ratio was 1.5 to 1. Hepatoblastoma was the most common liver tumor in this age group accounting for 22 patients (41.5%). The second most common primary tumor was hepatocellular carcinoma (HCC), with five patients. Another malignant tumor was embryonal sarcoma. Benign tumors included adenoma, mesenchymal hamartoma, vascular tumors, focal nodular hyperplasia, and inflammatory pseudo tumor. There were also seven metastatic tumors during these five years.

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***Establishing Immunotherapy For Pediatric Liver Cancer**

Posted on November 5, 2018

By: Laurie Fickman

T-Cell Editor Creating Powerful Immunotherapy Weapon

***Outcomes of primary liver cancer in children: an appraisal of experience.**

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***Pathology of pediatric liver tumors, a single center experience from south of Iran.**

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CONCLUSION:

Liver transplantation should be considered as option in the treatment of all children with unresectable hepatic tumors. With the careful and individual patient selection significant chances for survival can be achieved in this group of patients which would otherwise not survive with the conventional treatment.The spectrum of hepatic tumors in children is different from that found in the older age group (adults) and also different in different

populations.Hepatoblastoma is the most common primary liver tumor in children. The primary treatment is surgical resection, and the use of preresection chemotherapy can increase the number of tumors that are resectable. The prognosis for patients with resectable tumors is fairly good in combination with chemotherapy. However, the outcome for those with nonresectable or recurrent disease remains poor and new therapies are needed.Complete resection of the pediatric primary liver tumors remains the cornerstone of treatment to achieve cure. Major liver resection can be performed with minimal perioperative mortality and morbidity. Patients with HB appeared to have better survival compared with patients with HCC, and there was significant improvement in the DSS of children treated in the recent decade. Liver transplantation in conjunction with chemotherapy may have an increasing role in the management of locally advanced primary liver cancers.

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Posted on November 5, 2018

By: Laurie Fickman

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41.Outcomes of primary liver cancer in children: an appraisal of experience.

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