Proton Beam Therapy for Hepatocellular Carcinoma

Li Jiamin, MD
Wanjie Proton Therapy Center
Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide.

- It is the eighth most common neoplasm.
- The fourth leading cause of cancer related death in the world.
- The incidence of Hepatocellular Carcinoma in China is **37.9** per 100,000 people.
• It is the major cause of death in patients with liver cirrhosis
• Risk factors for HCC are chronic infection of hepatitis B or C, alcoholic cirrhosis, aflatoxin, hemochromatosis, and Wilson’s disease
Mortality

- Mortality is about 250,000 yearly in the world
- It is about 110,000 yearly in China
The treatment of HCC is difficult because most patients are diagnosed when the tumor is in an advanced stage.

Good results can be achieved with surgical resection, but 80% are not eligible for surgery.

The management of technically unresectable and medically inoperable HCC remains challenging.
HCC is highly resistant to currently available chem drugs

Transarterial chemoembolization (TACE) showed improved survival but its antitumor effect was frequently incomplete
Tolerance of the liver to irradiation is poor:

- The tolerance is less than 35Gy to a limited volume
- The tolerance is 30Gy to the whole liver/3 weeks
- The poor tolerance has prevented delivery of tumoricidal dosage

WANJIE PROTON THERAPY CENTER
Radiation therapy has played a minor role in the treatment of HCC

Conventional radiation therapy for HCC has resulted in unsatisfactory outcomes for the past decades
- Conformal Radiation Therapy (3DCRT)
- Intensity Modulated Radiation Therapy
Local control and survival rate improved

While
- Massive normal liver tissue damage was found
- Radiation-induced liver disease (RILD) were also reported
Proton beam therapy can give excellent dose localization to the tumor.

Normal liver tissue can be well spared.

Compared to photons, protons deliver less than half of the dose to normal tissues: therefore,
- reduced acute and late morbidities
- increased target dose
Intrinsic characteristics of proton beam

- Bragg peak
- Lower lateral scattering
- Lower entrance dose with a sharp distal dose fall-off
- Less dose to normal tissue
Cases treated at WPTC

- 39 patients with HCC were treated at Wanjie Proton Therapy Center
- Male  37 cases  Female 2 cases
- Median age: 58yr
- Stage I, II:  17 cases
- Stage IIIA:  20 cases
- Stage IIIB:    2 cases
- Tumor size : 1.2 - 14.0cm ( median 7.0cm )
All of the patients were considered unsuitable for surgery for reasons such as:

A. Poor medical condition caused by intercurrent diseases (Coronary heart disease, poor lung function, diabetes mellitus)
B. Hepatic dysfunction caused by concomitant diseases (advanced cirrhosis with high level of serum bilirubin, ascites)

C. Multiple tumors

D. Advanced age

E. Patient refusal of surgery
● Solitary tumor was found in 23 patients
● Multiple tumors were found in 16 patients
● Child-Pugh Grade A in 25 patients
● Child-Pugh Grade B in 12 patients
● Child-Pugh Grade C in 2 patients
TPS was Varian- Eclipse Proton
- PTV=GTV+0.7~2.1cm
- 2~3 proton fields were used
- Double scattering mode
- Energy range was from 70-230MeV
90%~95% isodose line was used to cover the PTV
Relative biologic effectiveness 1.1 was used
Fractionation: 2.5-4.0CGE/13-28F, 5d/w
Total dose: from 52.0 to 72.0CGE
Case # 1
68Y, male
AFP>400ng/ml
Child grade A

Two foci 1.8 x 1.5cm, 1.2 x 0.8cm (T2)
Proton treatment planning

- PTV = GTV + 10~20mm (AP 10mm, CC 20mm)
- GTV 9.4cm³, PTV 142.7 cm³
- DT 66.0CGE/22F, 5d/w
- 95% isodose line to PTV
- Mean dose to liver 3.44CGE
isodose color wash

Beam1  AP
Beam2  RL

WANJIE PROTON THERAPY CENTER
Isodose lines

Isodoses (%)
105.0
95.0
90.0
70.0
50.0
30.0
10.0
95% dose distribution
Mean dose for liver: 3.44CGE
V30 = 5.53%
- Before PBT
  - 2005-6-15  AFP  500ng/ml

- Post PBT
  - 2005-7-19  AFP  400ng/ml
  - 2005-8-03  AFP  74.02ng/ml
  - 2005-8-23  AFP  19.89ng/ml
Follow up

- Liver function was normal 3-mo post PBT
- CT: the two foci treated getting smaller (less than 60% in diameter)
Case # 2
45y, M, Child A
AFP 400ng/ml
4.1x2.7cm
2-mo later
1.9x2.0cm
Proton treatment planning

- PTV=GTV+10~15mm (AP 10mm, CC 15mm)
- GTV16.2cm³, PTV94.4cm³
- DT60CGE/20F, RBE=1.1, 5F/W, AP、RL
- 95% isodose line to cover PTV
- Mean dose to liver 14CGE
Isodose lines
Proton 3D-Photon Dose to liver

Photon

V10: 69%
V20: 57%
V30: 15%
Dmean: 19.7 Gy

Proton

V10: 27%
V20: 23%
V30: 8%
Dmean: 8.4 CGE

Prescribed dose: 60.0 CGE
Mean dose to liver: 17.7CGE

Mean dose to liver: 9.3CGE
Maximum dose to spinal cord: 26.4 CGE

Dose to spinal cord: 0 Gy
Isodose distribution for AP-PA field design
Case #3, Male, 42yr
locally advanced HCC,
AFP > 1000ng/ml
Child A
AP field
90% dose
distribution
AP and RL
95% dose distribution
Left lobe well spared
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C1/Plan1 Sum Liver-ctv</td>
<td>100.0 / 99.9</td>
<td>0.0</td>
<td>6246.1</td>
<td>1864.4</td>
<td>0.0</td>
<td>671.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2/Plan Sum3 Liver-ctv</td>
<td>93.6 / 100.5</td>
<td>175.9</td>
<td>4754.9</td>
<td>2015.0</td>
<td>839.3</td>
<td>1446.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Photon**
- Prescribed dose: 40.0 Gy
- Mean dose to liver: 20.2 Gy

**Proton**
- Prescribed dose: 56.0 CGE
- Mean dose to liver: 18.6 CGE
### Photon
- **Prescribed dose:** 36 Gy
- **Mean dose to liver:** 18.2 Gy

### Proton
- **Prescribed dose:** 56 CGE
- **Mean dose to liver:** 18.6 CGE

#### Significant reduction of normal liver dose with proton
It was reported (Park W et al) that radiation dose seems to be a significant prognostic factor in RT response for HCC.

More than 50 Gy had a significant response.
Pre-PBT  

During PBT, 40CGE/20F, 5F/w
The patient recovered from the ascites by injection a great deal of albumin and other medicines.
Case # 4, 34yr, M, GTV 2000cc
Pre-PBT Idolography showed iodized oil retention
Isodose distribution
DT 44.0
CGE/22F
2-mo Post proton

Pre-proton

WANJIE PROTON THERAPY CENTER
Pre-PBT Retained iodized oil

Post PBT

WANJIE PROTON THERAPY CENTER
Results

- Median duration of follow-up: 12-mo (2~23-mo)
- Stage I, II:
  - CR: 35.3% (6/17) (six-mo later)
  - 1-yr local control rate: 94.1% (16/17)
  - 1-yr survival rate: 88.2% (15/17)
- Stage IIIA, IIIB:
  - Response rate was 81.8%
● 2 patients with Child-Pugh Grade C died
  ● - One died from liver function failure
  ● - The other died from hemorrhage and distant metastasis
Side - effects

- Cutaneous reaction: grade I
- Upper gastrointestinal: grade 0~1
- No radiation induced pneumonitis was found
- Pain of thoracic wall was found in 1 patient 6-month post PBT and then released 9-month later
- Incomplete pyloric obstruction in 1 patient
  - eat only semi liquid diet
  - recovered after medication (dexamethasone and antibiotics)
Prognostic Factors Affecting Overall Survival

- Better prognosis
  - early stage
  - small GTV
  - Child–Pugh Grade A

- Poor prognosis
  - Child–Pugh Grade B and C
  - portal vein thrombosis
  - lymph node metastasis
Much attention should be given

A. The patient with
   - multiple tumors
   - diffused
     It is difficult to encompassed in a single irradiation field

B. Ascites around the liver

C. The tumor is located near the gastrointestinal tract

D. Distant metastases are found
● Proton beam therapy plays an important role in the radical treatment of early stage HCC.

● The radiation dose is a significant factor for increasing the objective tumor response and the survival rate when treating HCC.
• As for the locally advanced HCC, proton treatment significantly reduced dose to normal liver, stomach, kidney, and spinal cord.

• Proton therapy with dose escalation may translate to better local control and survival without increasing toxicities in HCC.
Thanks for your attention
Welcome to China