Proton Beam Therapy for Small HCC: Is it Necessary?

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  – Clinical Genomics
Outline

• Protons for small HCC
  – Proton therapy: Why consider it?
  – Rationale and data for protons and small HCC

• Protons for advanced HCC
  – Selection of patients
  – Data for large HCC
  – Data for Central HCC
  – High Risk patients
HCC

- Multiple treatment options exist
- Complicated by a diseased liver
Treatment Options

- Surgical resection
- Liver transplant
- Ablation
  - Radiofrequency ablation
  - Microwave ablation
  - IRE
- Arterial embolization
- Radiotherapy
- Systemic therapy
### Risk of RILD


<table>
<thead>
<tr>
<th>Reference, Year</th>
<th>No. Patients</th>
<th>Total</th>
<th>NTCP Model</th>
<th>1/3 Liver</th>
<th>5% Risk of RILD</th>
<th>Whole Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>9, 1986</td>
<td>1</td>
<td>11</td>
<td>None</td>
<td>35 Gy†</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>2, 1991</td>
<td>27*</td>
<td>407*</td>
<td>None</td>
<td>50 Gy‡</td>
<td>35 Gy‡</td>
<td>30 Gy‡</td>
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<td>22, 1991</td>
<td>27*</td>
<td>407*</td>
<td>Lyman</td>
<td>43 Gy‡</td>
<td>34 Gy‡</td>
<td>30 Gy‡</td>
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<tr>
<td>9, 1992</td>
<td>9</td>
<td>79</td>
<td>Lyman</td>
<td>72 Gy§</td>
<td>45 Gy</td>
<td>35 Gy</td>
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<td>27, 1995</td>
<td>9</td>
<td>93</td>
<td>D-I</td>
<td>No limit</td>
<td>52 Gy</td>
<td>35 Gy</td>
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<td>28, 2001</td>
<td>19</td>
<td>183</td>
<td>Lyman</td>
<td>90 Gy§</td>
<td>47 Gy</td>
<td>31 Gy</td>
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<tr>
<td>28, 2001</td>
<td>19</td>
<td>183</td>
<td>D-I</td>
<td>99 Gy§</td>
<td>43 Gy</td>
<td>32 Gy</td>
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<tr>
<td>28, 2001</td>
<td>19</td>
<td>183</td>
<td>Mean dose</td>
<td>—</td>
<td>—</td>
<td>31 Gy</td>
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<td>Liver metastases</td>
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<tr>
<td>11, 2002</td>
<td>3</td>
<td>85</td>
<td>Lyman</td>
<td>107 Gy§</td>
<td>54 Gy</td>
<td>37 Gy</td>
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<tr>
<td>23, 2004</td>
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<td>85</td>
<td>Mean dose</td>
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<td>—</td>
<td>37 Gy</td>
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<td>Primary liver cancer</td>
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<tr>
<td>11, 2002</td>
<td>11</td>
<td>84</td>
<td>Lyman</td>
<td>93 Gy§</td>
<td>47 Gy</td>
<td>32 Gy</td>
</tr>
<tr>
<td>23, 2004</td>
<td>11</td>
<td>84</td>
<td>Mean dose</td>
<td>—</td>
<td>—</td>
<td>32 Gy</td>
</tr>
</tbody>
</table>
# SBRT for HCC

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>N</th>
<th>CP</th>
<th>Tumor Size</th>
<th>Dose, Fx</th>
<th>OS, 1yr</th>
<th>LC, 1 yr</th>
<th>Gr≥3 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erasmus</td>
<td>2006</td>
<td>Phase I/II</td>
<td>8</td>
<td>A,B</td>
<td>0.5 – 7.2 cm</td>
<td>25-37.5 Gy, 3-5 fx</td>
<td>75%</td>
<td>75%</td>
<td>12.5%</td>
</tr>
<tr>
<td>KIRMS</td>
<td>2012</td>
<td>Phase II</td>
<td>47</td>
<td>A,B</td>
<td>1.3-8 cm</td>
<td>57 Gy, 3 fx</td>
<td>69% (2yrs)</td>
<td>95% (2yrs)</td>
<td>26%</td>
</tr>
<tr>
<td>Indiana</td>
<td>2010</td>
<td>Phase I</td>
<td>17</td>
<td>A,B</td>
<td>≤6 cm</td>
<td>36-48Gy, 3-4 fx</td>
<td>75%</td>
<td>100%</td>
<td>18%</td>
</tr>
<tr>
<td>PMH</td>
<td>2008</td>
<td>Phase I</td>
<td>31</td>
<td>A</td>
<td>9-1913 ml</td>
<td>26 Gy(24-54), 6 fx</td>
<td>48%</td>
<td>65%</td>
<td>26%</td>
</tr>
<tr>
<td>Ibarra, multiple</td>
<td>2012</td>
<td>Pooled</td>
<td>21</td>
<td>A,B</td>
<td>9.5-1494 ml</td>
<td>30 Gy (18-50), 1-10 fx</td>
<td>87%</td>
<td>64%</td>
<td>8% RILD</td>
</tr>
<tr>
<td>Tokai Univ.</td>
<td>2013</td>
<td>Retrospective</td>
<td>18 5</td>
<td>A,B</td>
<td>.8 – 5 cm</td>
<td>30-40Gy, 5 fx</td>
<td>95%</td>
<td>99%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Tanguturi S, et al. The Oncologist 2015
HCC- SBRT vs RFA

• U. Michigan
  – 161 treated w RFA to 249 tumors
  – 63 treated w SBRT to 83 tumors
  – FFLP -1
    • RFA- 84%
    • SBRT- 97%
  – FFLP-2
    • RFA- 80%
    • SBRT- 84%
  – OS-1
    • RFA- 70%
    • SBRT- 74%
  – Gr 3+ tox
    • RFA- 11%
    • SBRT- 5%

Wahl DR et al. JCO 2016
SBRT vs RFA- Importance of Size

< 2 cm

≥ 2 cm
Small HCC

• With RFA or SBRT
  – Local control and toxicity are already excellent
  – Is there a role for protons?
PROTONS

• Particles with charge and mass
  – Defined range in tissue
    • Proportional to energy
    • Unmodulated: deposit dose in sharp Bragg Peak
      – No dose delivered beyond that point
    • Bragg peak spread out toward surface to treat tumors
  – Contrast with photons (x-rays)
    • Continue to deposit dose beyond target in tissue
      – Unwanted dose to normal tissue
Pristine Bragg Peaks of Selected Energies at FHBPTC

Courtesy of H. Kooy, Ph.D.
Ideal Dose Distribution

15MV Photons vs SOBP Protons

Relative Depth Dose [%]

Depth [cm]

Tumor

Ideal Dose Distribution

Photons

Protons

Courtesy of H. Kooy, Ph.D.
AP/PA OPPOSED FIELDS

Courtesy of
Tom Delaney, MD
5 FIELD PLAN AP/RA/RP/LP/LA

Courtesy of Tom Delaney, MD
Hepatoma – 42 CGE in 15 fractions

Courtesy of
Tom Delaney, MD
Protons

Photons

Courtesy of Tom Delaney, MD
Should Randomized Clinical Trials Be Required for Proton Radiotherapy?

Michael Golfinos, Department of Radiation Oncology, Harvard Medical School, Boston, MA
James D. Cox, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Recently, several articles have been published in the Journal of Clinical Oncology and other journals reviewing and commenting on the record of proton beam therapy, as well as an analysis of some critical commentary by Brada et al.1 All of these studies make the unassailable point that there are almost no randomized clinical trials (RCTs) comparing proton beam therapy with conventional x-ray therapy. It is to address this issue of weight that, whether RCTs were appropriate or not, whether they are necessary before proton beam therapy is widely promulgated and reimbursed.

In brief, the arguments for the use of proton in radiation therapy are as follows: (1) Owing primarily to their depth dose characteristic (i.e., peak proton beam, normally no dose is administered beyond the target volume and substantially less dose is administered than x-rays to normal tissue), the dose distributions that can be achieved with protons are in almost all cases superior to those possible with x-rays both or without intensity modulation, which can be achieved with both modalities. There is, however, between two to three times less energy deposited by protons to the uninvolved normal tissue outside the target volume (specifically described as integral dose or the dose both); as compared with the energy that x-rays deposit. (2) There is virtually no difference in tumor response per unit dose between protons and x-rays, but only when differences are present, (3) Radiation delivered to normal tissues causes damage that, just as in dose to tumors, and the severity of that damage increases with increasing dose.

We have been mentioned extensively in treatment planning studies.1 There is a healthy body of in vivo and in vitro evidence underpinning this.1 This is corroborated by a number of clinical reports over many decades. These reports are not contested by any of the authors cited above, not our knowledge, by any criteria of proton beam therapy. They are not optional — they are demonstrated and true.

It is therefore hard to imagine how an objective person could avoid the conclusion that there is, at the very least, a high probability that protons can provide superior therapy in that possible with x-rays in most circumstances. It is practically for this reason that the practitioners of proton beam therapy have found it practically unacceptable to conduct RCTs comparing protons with x-rays. Such a comparison would not meet a general requirement for performing RCTs, namely that there be equipoise between the arms of the trial.1

Brada et al.1 base their opinion on what they understand to be the requirements of evidence-based medicine. In our opinion, the issue much more is the implications of evidence-based medicine than is the clinical effectiveness of protons. In short, dose evidence-based medicine means that, under all circumstances, positive RCTs are a precondition for the promulgation and reimbursement of new technologies. If it does, and those aspects of evidence-based medicine, as defined at the site for making medical decisions, then one would have no desire to agree with the position taken by Brada et al.1 and others. However, we feel that it is impossible to believe that medical clinical studies could be considered to be a prerequisite for the adoption of a medical therapy. It may, quite simply, there are circumstances under which even the most dedicated advocate of evidence-based medicine would agree that RCTs would be improper. In deciding whether the arms of a trial meet the equipoise standard, one can only rely on informed judgment. It is an argument that informed judgment leads to the conclusion that proton beam therapy is probably the most reasonable.

Advocates of RCTs argue that, although there may be good experimental evidence for the superiority of one arm, one does “know” that there is an advantage. In addition, to satisfy the conduct of trials that seem not to be to its advantage, they did trials in which the outcome was the reverse of what was expected. Taking this argument to its extreme, one would have to conclude that there is evidence that clinical medicine is not evidence-based. We know that things with varying levels of evidence. Even when RCTs are available, they may provide the information that is needed to be made more effectively for the patient. We must not overstate the level of evidence. It is given judgment (for example, virtually all informed persons judge that the ability of the proton-based system to establish an extremely high confidence), and we must base our actions on information about which we have good confidence.

Brada et al.1 make the point more than once that the apparent advantage of protons in several tumor sites may be due to patient selection bias. Indeed, selection bias is an issue in comparing randomized studies as are the slightly criteria in assessing the evidence of the conclusions of an RCT to the treatment of a
Limitations of Clinical Data: Proton Therapy at the MGH

• Clinical results still compelling, however
  – 95% local control cranial-base LGCS at 15 years
  – >95% LC uveal melanoma at 15 years
  – 80% LC paraspinal sarcomas at 5 years
  – 80% LC paranasal sinus scc without visual injury
  – Reduced early and late effects pediatric tumors

Courtesy of Jay Loeffler, MD
Protons and Parachutes

Joel E. Tepper, Department of Radiation Oncology, UNC Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, Chapel Hill, NC

Thirty-three years ago the first patient was treated with fractionated proton radiation therapy at the Harvard University Cyclotron by a group from the Massachusetts General Hospital (Boston, MA). The argument for protons was at that time fairly compelling, given that the technical delivery of proton radiation therapy was crude by today's standards. However, since that time, the delivery of proton treatments has become much more sophisticated, and we are able to produce far improved dose distributions that theoretically should produce a clinical benefit. Over the course of the last 30 years since protons were first used, what clinical information do we have to suggest that protons add a clinical advantage over high-quality x-ray therapy for any of the common adult solid tumors? The argument has been made recently in the Journal of Clinical Oncology (Goitein et al) that randomized clinical trials are not necessary because of the clear advantage in dose distribution, which therefore "must" produce a better clinical result. The question of the need for randomized trials is one that arise in the use of new technology, and has been discussed in other sources related to protons. At times, a straw man argument has been constructed to suggest that randomized trials are not needed, and then nicely torn down—but what has been destroyed is only the straw man, not reality.

Radiation dose distributions are a model for clinical reality; they are not clinical reality. Models usually predict outcomes effectively when they are used to predict situations within the realm from which the models were derived (i.e., interpolated from the data). The use of those models to predict outcomes extrapolated beyond the range of the initial data, produces answers that are much more suspect. Some individuals have made fun of the possible use of randomized clinical trials for technology assessment. An article written a few years ago asked why we do not perform randomized trials of the value of parachutes compared with free falling from airplanes. It is clearly ludicrous to perform randomized trials of parachutes. I am not an expert on parachutes (to say the least), but I can make a pretty good guess as to what parachute makers do. I imagine that they do mathematical calculations based on their physics and engineering knowledge, develop a design that they test against the mathematical model, and then they send test parachutes. These they probably test in a model that is even closer to the real situation by using simulators, and then perhaps they throw a 70-kg dummy out of an airplane to determine how the parachute functions. They likely measure many parameters such as drag, and so on, against existing parachute designs. I am pretty confident that they do not just take their engineering models, build a parachute, and sell it to the public. They do not do randomized trials, but they come close.

With protons we are at the level of the initial parachute construction. There are virtually no clinical studies (only mathematical models) that even suggest an advantage to the use of protons for most adult solid tumors. When intensity-modulated radiation therapy, a somewhat controversial new technology, was initiated about 15 years ago, a substantial number of studies were done that strongly suggested a decrease in clinical toxicity in diseases such as prostate cancer, and head and neck cancer. Randomized clinical trials were generally not performed, but at least there was solid phase II data that gave a strong indication of decreased adverse effects. Those data simply do not exist for protons after more than 30 years of use. It is difficult to perform randomized phase II trials of an expensive new technology, given that the expensive equipment must be purchased up front; if the technology does not produce a benefit, then the purchaser is stuck with a huge financial burden. The health care system in the United States does not produce an easy way around that problem. In addition, it is not feasible or reasonable in a phase III study to evaluate formally every minor technical alteration of a therapeutic approach. However, that does not mean that phase III trials should not be done when possible, and in most situations at least some randomized trials can be performed. The idea that it is unethical to perform randomized trials is absurd. There are few situations where we have compelling enough data from phase II studies to state that we should not perform a randomized study, and the proton situation is certainly not one such situation. Clearly, there are unexpected effects with the use of protons that could result in a randomized trial with an outcome that not only is not positive, but that in fact could show a disadvantage to protons. If we cannot perform phase III studies, as an absolute minimum there needs to be compelling data arising from well-designed and extensive phase II studies; however, for protons, those compelling phase II data do not exist for common adult tumors. I am not a believer that everything can, or should, be tested in phase III trials. But I am a firm believer that strong and convincing clinical data are needed for the use of clinical interventions.

Can we believe the mathematical models? It is what we do not know that is likely to get us into trouble, but even from what we do know, would we predict that protons would be superior for some common diseases? What about prostate cancer? Sophisticated x-ray therapy at present produces few acute adverse effects, and the adverse effects that do occur generally are related to the immediate proximity of the rectal wall (which cannot be avoided with protons), and the presence of the urethra in the radiation field. Given that the urethra goes directly through the prostate, the urethra also will not be avoided with protons. What about head and neck cancer? Low-energy x-rays
Current and Future Treatment Sites for Proton Delivery

Existing Site

In Development

Loma Linda Univ Med Ctr

MPRI

U. Pennsylvania

MGH- Boston

MDACC

U. Florida

2006
(Philadelphia, PA) – The University of Pennsylvania Health System (UPHS) has announced today that they will begin construction on a new proton therapy treatment facility to provide patients in the greater-Philadelphia region and beyond with the most advanced and sophisticated form of cancer treatment available. To be equipped by the Ion Beam Application, S.A. (IBA) company based in Louvain-la-Neuve, Belgium, the proton therapy center will be located adjacent to The Raymond and Ruth Perelman Center for Advanced Medicine, a $302 million structure that is now being built to house Penn’s outpatient cancer, cardiovascular, diagnostic, and surgical services. Receiving final University Board approval on June 15th, the UPHS Proton Therapy Treatment Center will cost approximately $140 million and take about three years to complete. The first patient is expected to be treated in 2009. The UPHS Center – the first such facility between Boston and Florida – will greatly enhance the mission of the Abramson Cancer Center of the University of Pennsylvania to continually expand and integrate optimum patient services and clinical care.
## HCC Proton Prospective Data

<table>
<thead>
<tr>
<th>Site</th>
<th>Yr</th>
<th>N</th>
<th>CP</th>
<th>Tumor size</th>
<th>Dose, fraction</th>
<th>OS</th>
<th>LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsukuba Prospective</td>
<td>2009</td>
<td>51</td>
<td>80% A 20% B</td>
<td>45pts&lt; 5cm</td>
<td>66GyE, 10 fx</td>
<td>38.7% at 5 yrs</td>
<td>87.8% at 5 yrs</td>
</tr>
<tr>
<td>Loma Linda</td>
<td>2011</td>
<td>76</td>
<td>24% C</td>
<td>Mean size 5.5cm</td>
<td>63 GyE, 15 fx</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>MGH/MDA CC/UPenn</td>
<td>2016</td>
<td>44</td>
<td>73% A 21% B</td>
<td>Mean size 5 cm</td>
<td>67.5 GyE, 15 fx</td>
<td>60% at 2 yrs</td>
<td>95% at 2 yrs</td>
</tr>
</tbody>
</table>
Small Tumors

• Most prospective studies have evaluated larger tumors
• Data for smaller tumors is sparse
Tsukuba: Protons/HCC- Impact of size

- 2002-2009
- Observational study
- 129 pts with HCC
- Assessed according to BCLC stage for:
  - Local Control
  - OS

Therapy

• Proton therapy
  – If within 2 cm of GI tract- 77 GyE in 35 fx
  – Central- 72.6 GyE in 22 fx
  – Peripheral- 66 GyE in 10 fx
Patient characteristics by BCLC

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 129)</th>
<th>BCLC 0/A (n = 30)</th>
<th>BCLC B (n = 34)</th>
<th>BCLC C (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor no., n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>96 (74.4)</td>
<td>22 (73.3)</td>
<td>23 (67.6)</td>
<td>51 (78.5)</td>
</tr>
<tr>
<td>2</td>
<td>23 (17.8)</td>
<td>8 (26.7)</td>
<td>6 (17.6)</td>
<td>9 (13.8)</td>
</tr>
<tr>
<td>≥3</td>
<td>10 (7.8)</td>
<td>0 (0)</td>
<td>5 (14.7)</td>
<td>5 (7.7)</td>
</tr>
<tr>
<td><strong>Maximum tumor size, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>39 (10–135)</td>
<td>22 (10–30)</td>
<td>42 (32–86)</td>
<td>40 (15–135)</td>
</tr>
<tr>
<td>≤3 cm</td>
<td>50 (38.8)</td>
<td>30 (100)</td>
<td>0 (0)</td>
<td>20 (30.8)</td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>79 (61.2)</td>
<td>0 (0)</td>
<td>34 (100)</td>
<td>45 (69.2)</td>
</tr>
</tbody>
</table>
Local Control

BCLC A-LC-5 94%
Local Control

(a) Local tumor control rate (%) over time for different stages.

(b) FLP Probability over time for SBRT and RFA treatments, with fewer than 2 cm lesions.

No. at risk:
- SBRT: 35 15 4 4 1 1 0
- RFA: 133 84 50 32 11 4 2
Overall Survival

BCLC A
OS-5 65%
## Predictors of Survival

### Table 2. Multivariate analysis using the cox regression model for LTC and OS

<table>
<thead>
<tr>
<th>Predictor</th>
<th>LTC HR (95% CI)</th>
<th>LTC P</th>
<th>OS HR (95% CI)</th>
<th>OS P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 vs. ≥75</td>
<td>0.57 (0.13–2.62)</td>
<td>0.472</td>
<td>1.62 (0.84–3.13)</td>
<td>0.148</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female vs. Male</td>
<td>1.43 (0.32–6.46)</td>
<td>0.643</td>
<td>1.22 (0.63–2.34)</td>
<td>0.559</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HCV vs. HCV</td>
<td>0.49 (0.07–3.26)</td>
<td>0.460</td>
<td>1.23 (0.54–2.80)</td>
<td>0.619</td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 vs. 1, 2</td>
<td>3.57 (0.75–17.0)</td>
<td>0.111</td>
<td>2.16 (1.08–4.32)</td>
<td>0.030</td>
</tr>
<tr>
<td>Platelet (× 10^9/mm^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 vs. &lt;10</td>
<td>0.57 (0.09–3.57)</td>
<td>0.544</td>
<td>1.57 (0.83–2.98)</td>
<td>0.168</td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 vs. ≥20</td>
<td>2.36 (0.55–10.0)</td>
<td>0.246</td>
<td>1.36 (0.74–2.51)</td>
<td>0.325</td>
</tr>
<tr>
<td>DCP (mAU/mL)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 vs. ≥100</td>
<td>0.15 (0.02–1.09)</td>
<td>0.061</td>
<td>1.47 (0.77–2.80)</td>
<td>0.238</td>
</tr>
<tr>
<td>Child–Pugh class A vs. B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single vs. Multiple</td>
<td>1.31 (0.29–6.05)</td>
<td>0.727</td>
<td>1.07 (0.55–2.09)</td>
<td>0.838</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 vs. &gt;3</td>
<td>2.33 (0.42–12.8)</td>
<td>0.330</td>
<td>1.32 (0.70–2.49)</td>
<td>0.397</td>
</tr>
<tr>
<td>Tumor thrombi</td>
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<tr>
<td>Vp0/1 vs. Vp2/3/4, IVC</td>
<td>0.85 (0.08–9.25)</td>
<td>0.894</td>
<td>0.85 (0.38–1.89)</td>
<td>0.682</td>
</tr>
<tr>
<td>Protocol</td>
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<tr>
<td>Standard or Hilar vs. GI</td>
<td>2.89 (0.61–13.7)</td>
<td>0.180</td>
<td>0.96 (0.48–1.90)</td>
<td>0.904</td>
</tr>
</tbody>
</table>
Protons and Small HCC

- Results are very good
- But difficult to argue different from SBRT or RFA
- Given the COST of protons, difficult to rationalize routine use for small HCC
What is the role for protons in HCC?

- To be discussed this afternoon:
- Protons for Advanced HCC