CIPHER

A Prospective, Multi-Center Phase III Randomized Trial of Carbon Ion versus Conventional Photon Radiation Therapy for Locally Advanced, Unresectable Pancreatic Cancer

David J. Sher, MD, MPH

Department of Radiation Oncology

UT Southwestern Medical Center

Unresectable Pancreatic Cancer

- Ideal model to use carbon therapy to improve local control

- LAP 07 (JAMA 2016)
  - Median survival 15.2 months
  - 2 year OS ~ 20%
  - Locoregional progression 32% (DM 60%)

- ECOG 4201 (JCO 2011)
  - Median survival 11.1 months
  - 2 year OS 12%

How Do We Improve Outcomes?

- Improve systemic therapy
- Improve local therapy
  - Improved sensitizers
  - Conventional dose escalation
  - Stereotactic dose escalation
  - Particle therapy
- Give up

Meta-Analysis

- **Durante, Tommasino, Yamada, Frontiers in Oncology 2015**

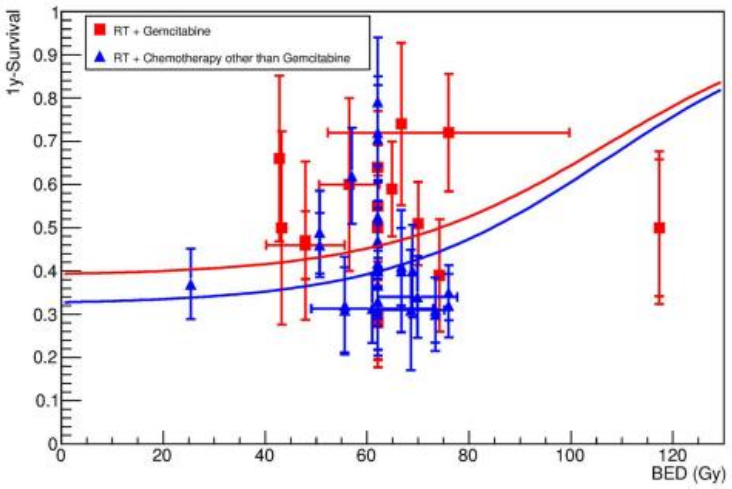


FIGURE 3 | One-year survival as a function of the BED for patients undergoing X-ray radiotherapy plus gemcitabine (red symbols), or other chemotherapy drugs (blue symbols). Data are reported in **Tables 2** and **4**. The lines show the result of the fit (Eq. 3), which was performed assuming that γ_{50} and D_{50} are obtained by fitting the data in treatments using radiotherapy only (**Figure 1**). The only free fitting parameter is the chemotherapy survival CS (see **Table 3**). The results suggest that the final outcome does not strongly depend on the specific chemotherapy treatment, although some advantage seems to be associated to the use of gemcitabine.

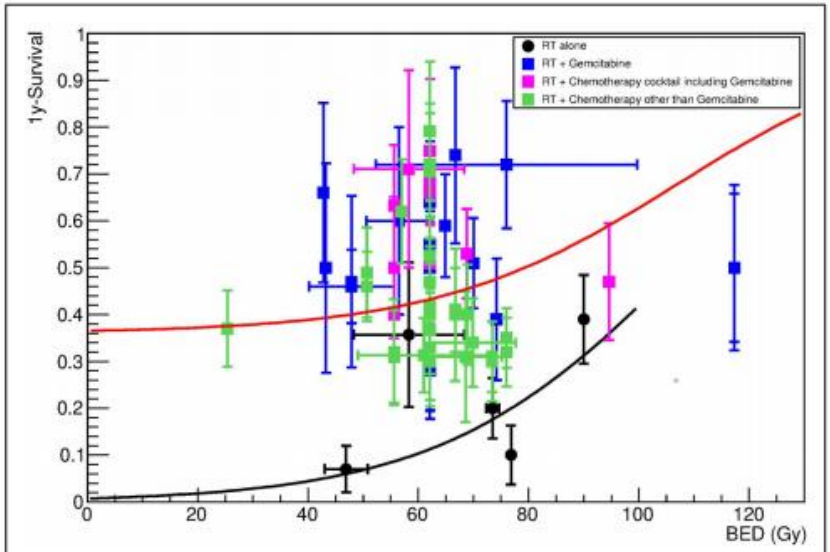


FIGURE 4 | One-year survival as a function of the BED for patients undergoing X-ray radiotherapy alone (black symbols), or in combination with any chemotherapy treatments. Details about chemotherapy regimen are reported in **Tables 4–6**. The lines show the result of the fit (black for radiotherapy-alone data, red for all chemotherapy data pooled together), which was performed assuming that γ_{50} and D_{50} are obtained by fitting RT-alone data. Fitting parameters with Eq. 3 are in **Table 3**.

Charged Particle and Dose

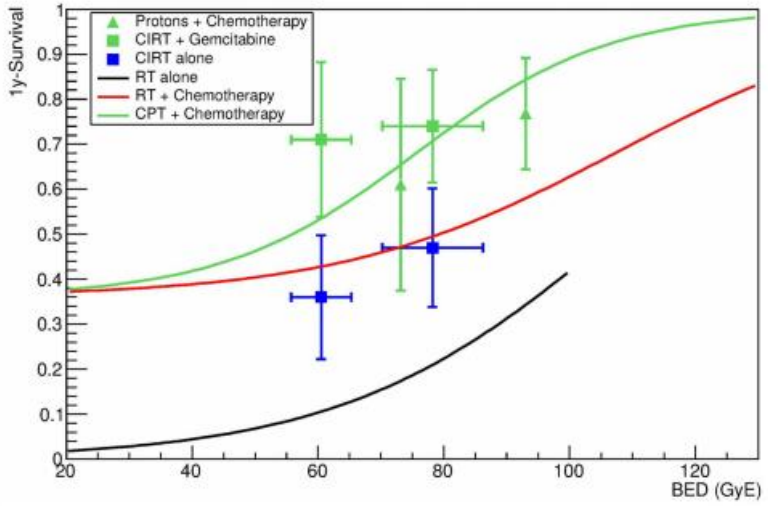
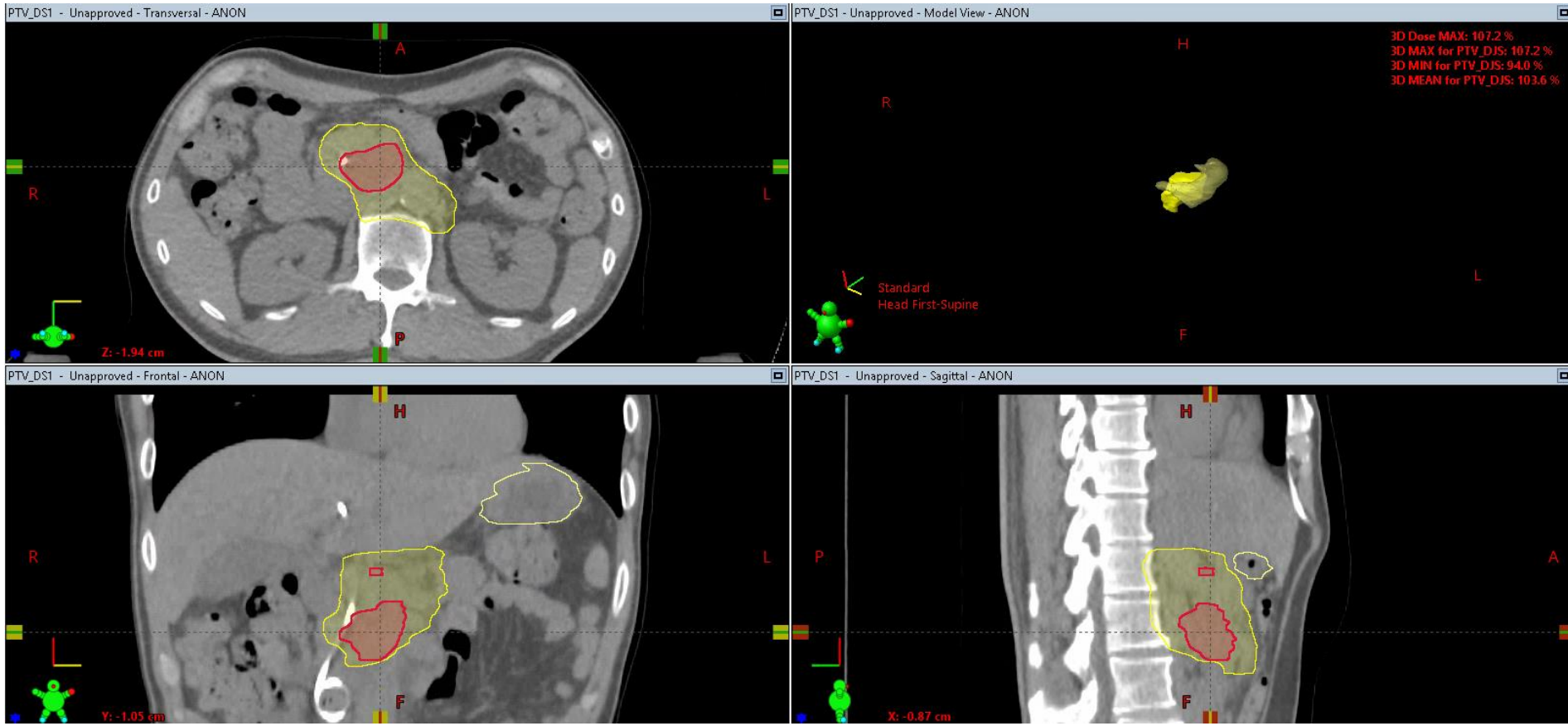


FIGURE 5 | One-year survival as a function of the BED for patients undergoing CPT with or without additional chemotherapy. Blue symbols refer to patients receiving radiotherapy with C-ions without additional chemotherapy. Green symbols refer to data obtained with proton (triangles) and carbon ions (full squares) in combination with chemotherapy. Data are given in **Table 6**. The green line shows the result of the fit of data for chemotherapy combined with proton or carbon ions. The fit was performed using γ_{50} and CS from X-ray + chemotherapy data. The only free parameter is therefore D_{50}. The black and red lines show the results of the fit for X-rays alone and X-rays plus chemotherapy, and are reported for comparison. Fitting parameters are in **Table 3**.

NIRS Phase I Study

- **Shinoto, Yamada, Terashima et al, *IJROBP 2016***
- **Eligibility: unresectable pancreatic invasive ductal carcinoma, without direct invasion of a GI mucosal surface or metal stent**
- **Treatment involved 12 fractions of carbon ion radiotherapy plus weekly full-dose gemcitabine**
  - **Both CIRT dose and gemcitabine dose escalated**
- **Treatment volume included GTV plus relevant elective nodes**

Example Treatment Volume



Dose Escalation Levels

- **3+3 design, 72 patients total**

Table 2 Number of patients assigned to each dose level and dose-limiting toxicity

Dose level	C-ion RT (GyE)	GEM (mg/m^3)	No. of patients treated	No. (%) of DLT cases
1	43.2	400	6	0
2	43.2	700	6	0
3	43.2	1000	12	2 (3)
4	45.6	1000	7	0
5	48.0	1000	8	1 (1)
6	50.4	1000	11	0
7	52.8	1000	11	0
8	55.2	1000	11	0

Abbreviations: C-ion RT = carbon ion radiation therapy; GEM = gemcitabine.

Toxicity

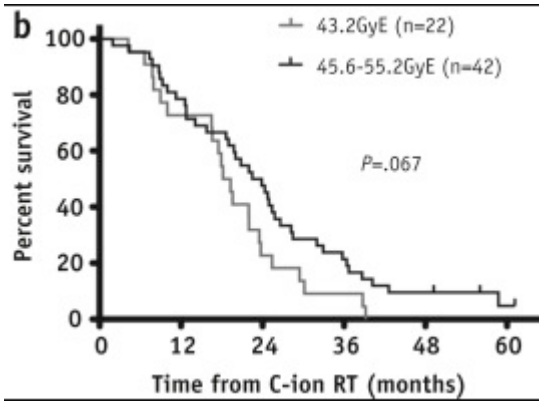
Table 3 Toxicities of grade 2 or greater

	Grade 2		Grade 3		Grade 4	
Toxicity	n	%	n	%	n	%
Leukopenia	29	40	35	49	1	1
Neutropenia	31	43	29	40	2	3
Thrombocytopenia	10	14	3	4	0	
Anorexia	12	17	6	8	0	
GI ulcer/bleeding	7	10	1	1	0	
Infection	0		1	1	0	

Abbreviation: GI = gastrointestinal.

Survival Results

- **Median overall survival: 19.6 months**
- **Two year overall survival: 35%**
- **In the higher dose group (≥ 45.6 GyE), the median and 2-year OS were 23.9 months and 48%**

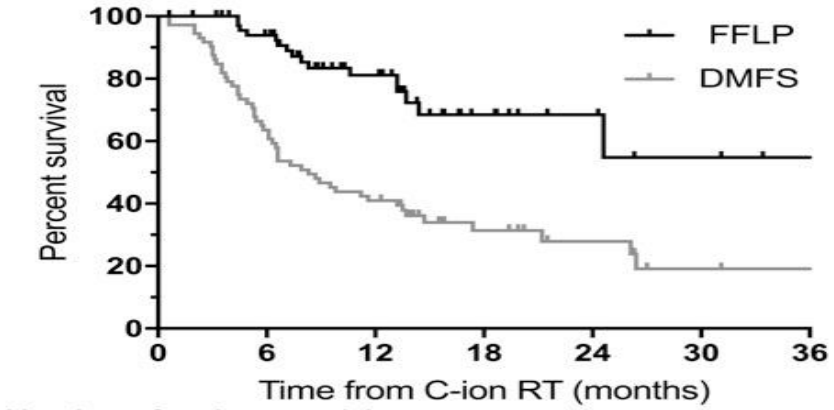


Retrospective Experience

- **Multi-institutional retrospective analysis of 72 patients with locally advanced, unresectable pancreatic cancer treated at one of 3 Japanese institutions with CIRT to either 52.8 GyE or 55.2 GyE in 12 fractions**
  - ***From Dr. Shigeru Yamada, with permission***
- **74% with chemotherapy preceding CIRT**
- **78% with concurrent chemotherapy (68% gem)**
- **A total of 19 patients (26%) developed grade 3 or 4 hematologic toxicities, 2 (3%) with grade 3 anorexia**
- **Late grade 3 toxicity only seen in 1 patient**

Recurrence

- Median follow-up for surviving patients 14.7 months
- 2 year freedom from local progression: 69%
- 2 year distant metastasis free survival: 28%

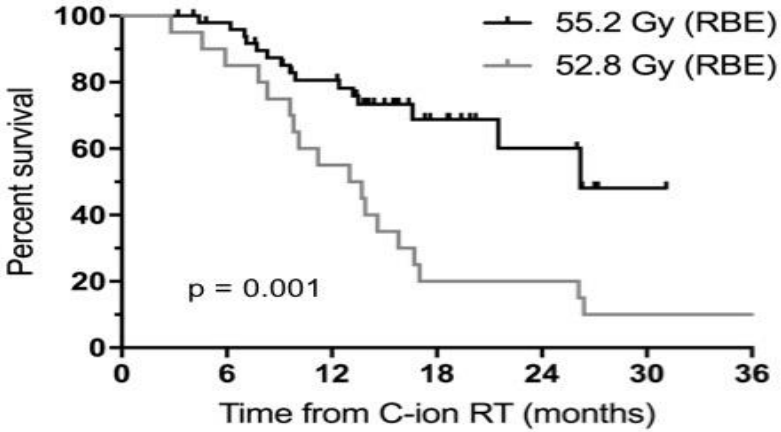


Number of patients at risk

FFLP	72	61	37	12	7	4	2
DMFS	72	46	30	13	8	4	3

Survival

- **Median and two year OS outcomes of 21.5 months and 46%, respectively**
- **Of those receiving 55.2 GyE, 2-year OS 60%**

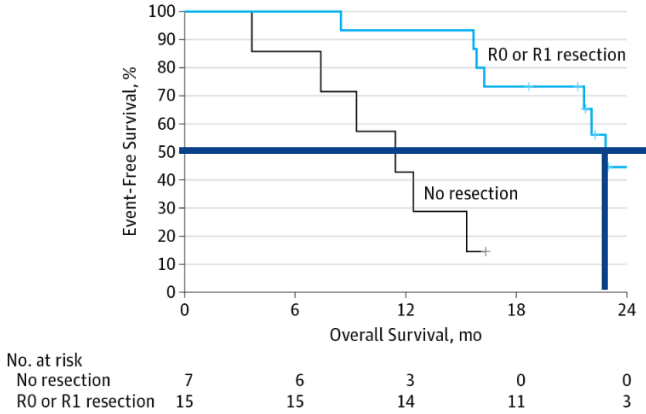


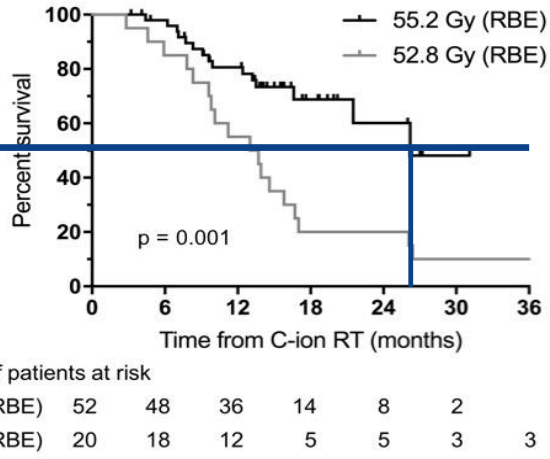
Number of patients at risk

55.2 Gy (RBE)	52	48	36	14	8	2	
52.8 Gy (RBE)	20	18	12	5	5	3	3

Back of the Envelope Comparison

- **Alliance 021101 (*Katz et al, JAMA Surgery 2016*)**
- **Induction FOLFIRINOX, CRT (50.4 Gy with capecitabine), then resection**
- **22 started chemotherapy, 21 patients initiated chemoradiotherapy, 15 went to surgery**





CIPHER

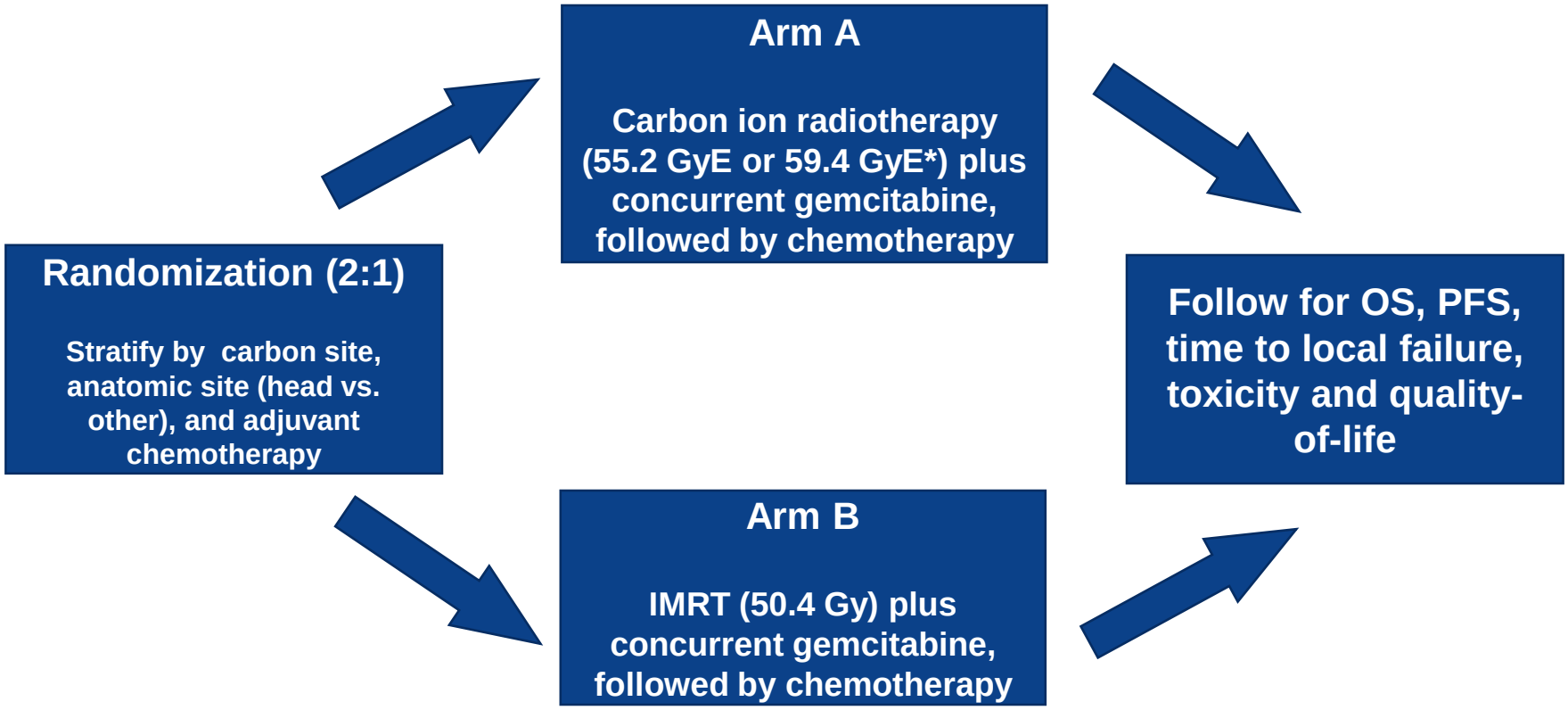
- Phase III randomized trial comparing carbon ion RT (55.2 GyE) with IMRT (50.4 Gy), both with concurrent gemcitabine, followed by gemcitabine/nab-paclitaxel

- Eligibility
  - Locally advanced, unresectable pancreatic cancer
    - Encasement of SMA or PHA, abutment of celiac trunk, major thrombosis of PV or SMV
  - Distance between tumor and viscera $\geq$ 3 mm
  - $\leq$ 100 kg
  - No metal stents
  - Ability to travel to foreign country within 2 weeks

Participating Patients and Centers

- Patients will receive CIRT at either NIRS, Gunma, or CNAO (Italy)
- Patient recruitment will occur in these centers, plus UTSW, Peking Union Medical College (Beijing), Yonsei University (Seoul)
  - Patients randomized to CIRT will be flown to Japan for treatment, with adjuvant treatment and follow-up at home
  - Patients randomized to IMRT will receive entire treatment at home
- Sponsored by Toshiba

Schema



- Adjuvant chemotherapy: 4 cycles of gemcitabine/nab-paclitaxel

Endpoints

- **Overall survival**
  - **With a total of 93 patients (62 CIRT, 31 IMRT), there will be 80% power to detect a difference in 2 year OS between 22% to 48% at a 0.05 significance level**
- **PFS**
- **Cumulative incidences of LRR and DM**
- **Quality-of-life (FACT-Hep, EQ-5D)**
- **Rate of grade 3-4 non-hematologic toxicity**

Quality Assurance

- All contours will be reviewed by NIRS physicians prior to planning (CIRT or IMRT), with NIRS contours reviewed by CNAO physicians
- All CIRT plans will be reviewed by NIRS physicians prior to treatment, with NIRS plans reviewed by CNAO physicians
- All IMRT plans will be reviewed by UTSW physicians prior to treatment

Why CIPHER Is Important

- **Medical**
  - **Does CIRT improve overall survival by improving local control in LAPC**
  - **Groundbreaking question**
- **Trial design**
  - **Particle therapy study powered for overall survival**
- **Collaboration paradigm**
  - **Three continents!**

Ready, Set, Go!

- First enrollment targeted in the first quarter of 2018
- Anticipate taking 3 years to enroll all patients