Biology

Hypofractionated Radiotherapy

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Hypofractionated Radiotherapy

Very high radiation doses can be given to patients with tumors of the parallel organs using hypofractionated radiotherapy with SBRT as well as charged particles without serious acute or long-term normal tissue morbidity.

Both lung and liver tumors have been successfully treated in this manner. Many other types of tumors like prostate cancer are also being challenged in C-ion RT using small number of fractions.
In the case of charged particles, indications for hypofractionated radiotherapy can be also extended to many types of tumors, particularly in C-ion RT.

There are ample knowledge and experiences we can learn from high-tech photon therapy such as 3D-CRT, SRT and IMRT.
Factors to be considered for Hypofractionated Radiotherapy

- Effect of proliferation
- Effect of reoxygenation
- Effect of volume
- Dose homogeneity and minimum dose
- Duration of single fraction delivery
- Tolerance dose of target organ: Parallel vs Serial organ
- High-LET effects
- Release of cytokines after high dose irradiation
Three-dimensional representation of a typical beam arrangement for stereotactic body Radiation therapy to a left-sided, early-stage lung cancer. **A:** The beams looking from a View directly in front of the patient. **B:** A view from the patient’s feet. Contoured normal Structures are shown as well as the tumor’s planning target volume (red).

Comparison of BED ($\alpha/\beta=10$) of representative dose regimens used in SBRT vs. conventional RT for early-stage NSCLC.

<table>
<thead>
<tr>
<th>Author</th>
<th>Dose</th>
<th>Biologic Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard radiotherapy</td>
<td>$2 \text{ Gy } \times 30-33 \text{ fx}$</td>
<td>72-79 Gy</td>
</tr>
<tr>
<td>Hara (58)</td>
<td>$30 \text{ Gy } \times 1 \text{ fx}$</td>
<td>120 Gy</td>
</tr>
<tr>
<td>Nagata (50)</td>
<td>$12 \text{ Gy } \times 4 \text{ fx}$</td>
<td>105 Gy</td>
</tr>
<tr>
<td>Timmerman (51)</td>
<td>$20 \text{ Gy } \times 3 \text{ fx}$</td>
<td>180 Gy</td>
</tr>
</tbody>
</table>
### Normal Tissue Dose Tolerance for SBRT delivered in 3 Fractions

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume</th>
<th>Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>Any point</td>
<td>18 Gy (6 Gy per fraction)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Any point</td>
<td>27 Gy (9 Gy per fraction)</td>
</tr>
<tr>
<td>Ipsilateral brachial plexus</td>
<td>Any point</td>
<td>24 Gy (8 Gy per fraction)</td>
</tr>
<tr>
<td>Heart</td>
<td>Any point</td>
<td>30 Gy (10 Gy per fraction)</td>
</tr>
<tr>
<td>Trachea and Ipsilateral bronchus</td>
<td>Any point</td>
<td>30 Gy (10 Gy per fraction)</td>
</tr>
<tr>
<td>Whole lung (right and left)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Tolerance dose depends on PTV*
The total duration of SBRT is shorter than the starting time ($T_k$) of accelerated repopulation in tumors, believed to be 3 to 5 weeks in tumors with the same rate of repopulation.

For analysis, a $T_k$ of 28 days was assumed with a repopulation doubling time ($T_p$) of 3 days.

It can be also assumed that no tumor cell repopulation occurs in the hypofractionated RT.

Recurrence-Free Survival in NSCLC

Only dismal results are obtained with conventional doses of 60-70 Gy (as 2-Gy fractions in 6 or 7 wks). Doses up to 100 Gy would be required to obtain success in the 90% region.

Dose was escalated to 103 Gy in 2-Gy fr given at 5 fr per wk.
Modeling Results from SBRT
- Effect of Proliferation -

It can be assumed that no tumor cell repopulation occurs in the hypofractionated RT.

\[ D_{50} = 70 \text{ Gy} \]

\[ D_{50} = 84.5 \text{ Gy} \]

RTOG Study (1993)
Cox JD et al: IJROBP 1993;27, 493-498

397 pats treated with 69Gy of multi-fractionated RT

3-yr Survival 17% without delay of treatment
1% with gaps exceeding 5 days (p=0.0001)
If radioresistant hypoxic cells were present in the tumors, or cells in a resistant phase of the cell cycles, the dose required would be 2.5 to 3 times greater than they were not.

If reoxygenation is incomplete so that only 1% of the tumor cells remain hypoxic, then many orders of magnitude (7 or 8) of resistant cells remain.

Therefore, total doses 2 to 3 times greater than 60 or 70 Gy would be required to obtain a finite chance of eliminating malignant cells from the target.
Why do we need high doses to sterilize tumors?

A large amount of reoxygenation can occur within 24 hrs.

**FIGURE 1.3.** Schematic diagram of cell survival curves for well-oxygenated cells (*full line with filled circles*), with a line of less slope representing 20% hypoxic cells remaining hypoxic throughout radiotherapy with 2-Gy fractions. The oxygen enhancement ratio is assumed to be 3. To reduce the proportion of surviving cells to $10^{-11}$ would require three fractions of more than 24 Gy.

Fowler JF, Tome WA, and *Welsh JS: SBRT, ed Kavanagh B, Timmerman R. Lippincott 2005
In IMRT, an apparently small-volume tail but of surprisingly low dose can appear on the DVH, unless a minimum tumor dose is specified. This problem can be avoided if the effective uniform dose (EUD) is calculated from the DVH of the target, and is not allowed to be less than the prescribed dose.
Volume Effect: Cold Spots in the Isodose Distribution

A fall of 10% in dose delivered to a 30% cold subvolume in the tumor will cause a modest fall of TCP to 35 to 40% TCP.

**FIGURE 1.4.** The decrease in TCP (tumor control probability), plotted against percent reduction in dose in each subvolume. Each curve is for a different tumor subvolume. It is assumed that a homogeneous treatment of $30 \times 2 \text{ Gy} = 60 \text{ Gy}$ would yield TCP = 50%.

Towe WA, Fowler JF, 2002
A fall of 25% in tumor dose delivered to a 20% subvolume of tumor lead to unacceptably low TCPs of 10%.

**FIGURE 1.5.** The same data as in Fig. 1.4 but plotted against percentage of tumor volume, each curve being for a different dose reduction. A 30% dose reduction in a 10% volume (lowest curve) gives a much lower tumor control probability (TCP) (8%) than a 10% dose reduction (second curve down) in 30% of the tu-
Estimated loss of biologic efficiency (BED) with prolonged fraction delivery

Radiation damage repair is not monophasic but consists of at least two components with different half time.

Duration of Rx delivery should be recorded.

**FIGURE 1.6.** Estimated losses of biologically effective dose (BED) (for late effects, $\alpha\beta = 3$Gy) as a function of prolonged delivery times for fraction sizes of 2 to 23 Gy. Two monoexponential repair rates are assumed (30), with two equally weighted half-times of 0.4 hour +4.0 hours (A) and 0.2 hours +4.0 hours (B). The effect of faction size is illustrated. The longer half-life has a small effect up to 1 hour’s duration. The loss of BED is ap-
Normal tissue considerations

An ablation with enormous increases in dose may be feasible if the organ is a good approximation to a “parallel organ” so that the loss of such small volume of functioning tissue is tolerated, and if it contains no particularly sensitive structures.

→ Lung, Liver, etc
Tolerance of target organ

Serial organ

- Spinal cord, GI tract, etc

Parallel organ

- Lung, Liver, Bone, etc

Mixed

Treatment of prostate
Volume effect and Hypoxia

<table>
<thead>
<tr>
<th>Diameter Of Sphere</th>
<th>Volume (cm³)</th>
<th>Dose that can be given</th>
</tr>
</thead>
<tbody>
<tr>
<td>5cm φ</td>
<td>66</td>
<td>1.0</td>
</tr>
<tr>
<td>4cm</td>
<td>34</td>
<td>2.0</td>
</tr>
<tr>
<td>3cm</td>
<td>9.5</td>
<td>5.0 - 7.0</td>
</tr>
</tbody>
</table>

Theoretically, the use of a single fraction is probably the worst radiobiologic alternative, because it gives no chance of reoxygenation or any shift out of a resistant phase of cell cycles or nutritional deprivation. It would be expected to require a considerably larger total dose to be effective on tumors than even a small number of dose fractions.
Characteristics of Ion Beams

1. Advanced dose distribution (Protons, C-ions)
2. Greater RBE and lower OER (C-ions)

Hydrogen

Proton (1+)

Carbon

Carbon ion (6+)

CO₂

CH₄
Hypofractionated Particle Beam Therapy

One of the most successful RT is the hypofractionated proton therapy for ocular melanoma.
Experiments with carbon ions and fast neutrons demonstrated that increasing their fraction dose tended to lower the RBE for both the tumor and normal tissues, but the RBE for the tumor did not decrease as rapidly as the RBE for the normal tissues.

These results substantiate that the therapeutic ratio increases rather than decreases even though the fraction dose is increased.

The experiments have also provided the biological evidence for the validity of a short-course hypo-fractionated regimen in carbon ion RT.

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**Biological Background for Hypo-fractionated radiotherapy with Carbon Ion beams**


RBE vs. Fraction Size in Carbon Beam Irradiation

**20 keV/μm**

- **Skin**
- **Tumor**

**42 keV/μm**

- **Skin**
- **Tumor**

**77 keV/μm**

- **Skin**

Dose Escalation Study in Carbon Ion Therapy at NIRS

Radiation Dose expressed by Biological Effective Dose (BED) ($\alpha/\beta=2.5\text{Gy}$)

- Head and Neck (H&N)
- Lung
- Liver
- Bone and Soft Tissue

Total Dose (GyE)

Number of Fractions
Hypofractionated Radiotherapy has been performed in Carbon Ion RT

The entire course of treatment has been given with carbon ions alone.

Average No. per pat: 13
Optimal dose-fractionations determined in dose escalation studies for carbon ion radiotherapy at NIRS

<table>
<thead>
<tr>
<th>Tumor Sites</th>
<th>Dose-Fractionation (GyE/fr/week)</th>
<th>Gy /fr</th>
<th>BED (α/β=10)</th>
<th>BED (α/β=2.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull Base</td>
<td>60.8 / 16 / 4</td>
<td>3.8</td>
<td>83.9</td>
<td>153.2</td>
</tr>
<tr>
<td>H &amp; N: ACC, MM etc</td>
<td>57.6 / 16 / 4</td>
<td>3.6</td>
<td>78.3</td>
<td>140.5</td>
</tr>
<tr>
<td>64.0 / 16 / 4</td>
<td>4.0</td>
<td>89.6</td>
<td>166.4</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>70.4 / 16 / 4</td>
<td>4.4</td>
<td>101.4</td>
<td>194.3</td>
</tr>
<tr>
<td>NSCLC: Hilar type</td>
<td>68.4 / 12 / 3</td>
<td>5.7</td>
<td>107.4</td>
<td>224.4</td>
</tr>
<tr>
<td>Peripheral type</td>
<td>90.0 / 18 / 5</td>
<td>5.0</td>
<td>135.0</td>
<td>270.0</td>
</tr>
<tr>
<td>(Stage I)</td>
<td>72.0 / 9 / 3</td>
<td>8.0</td>
<td>129.6</td>
<td>302.4</td>
</tr>
<tr>
<td>52.8 / 4 / 1 (T1)</td>
<td>13.2</td>
<td>122.5</td>
<td>331.6</td>
<td></td>
</tr>
<tr>
<td>60.0 / 4 / 1 (T2)</td>
<td>15.0</td>
<td>150.0</td>
<td>420.0</td>
<td></td>
</tr>
<tr>
<td>40.0 or 44.0 / 1 / 1 day</td>
<td>40.0 or 44.0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Liver: HCC</td>
<td>79.5 / 15 / 5</td>
<td>5.3</td>
<td>121.6</td>
<td>248.0</td>
</tr>
<tr>
<td>69.6 / 12 / 3</td>
<td>5.8</td>
<td>110.0</td>
<td>231.1</td>
<td></td>
</tr>
<tr>
<td>58.0 / 8 / 2</td>
<td>7.2</td>
<td>100.1</td>
<td>226.2</td>
<td></td>
</tr>
<tr>
<td>52.8 / 4 / 2</td>
<td>13.2</td>
<td>122.5</td>
<td>331.6</td>
<td></td>
</tr>
<tr>
<td>38.8 / 2 / 2 days</td>
<td>19.4</td>
<td>114.1</td>
<td>339.9</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>66.0 / 20 / 5</td>
<td>3.3</td>
<td>87.8</td>
<td>153.1</td>
</tr>
<tr>
<td>63.0 / 20 / 5</td>
<td>3.2</td>
<td>82.8</td>
<td>142.4</td>
<td></td>
</tr>
<tr>
<td>57.6 / 16 / 4</td>
<td>3.6</td>
<td>78.3</td>
<td>140.5</td>
<td></td>
</tr>
<tr>
<td>Bone / Soft tissue</td>
<td>70.4 / 16 / 4 (Pelvis)</td>
<td>4.4</td>
<td>101.4</td>
<td>194.3</td>
</tr>
<tr>
<td>64.0 / 16 / 4 (paraspinal)</td>
<td>4.0</td>
<td>89.6</td>
<td>166.4</td>
<td></td>
</tr>
<tr>
<td>Rectum (Post-ope recurrence)</td>
<td>73.6 / 16 / 4</td>
<td>4.6</td>
<td>107.5</td>
<td>209.0</td>
</tr>
<tr>
<td>Uterine Cervix (Adenocarcinoma)</td>
<td>74.4 / 20 / 5</td>
<td>3.7</td>
<td>102.1</td>
<td>185.1</td>
</tr>
</tbody>
</table>
**Local control and morbidity of carbon ion RT in hepatocellular carcinoma.**

<table>
<thead>
<tr>
<th>Fractionation</th>
<th>Local Control</th>
<th>Morbidity (3~12 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-yr</td>
<td></td>
</tr>
<tr>
<td>TD / Fx / Wk</td>
<td>No.</td>
<td>LC</td>
</tr>
<tr>
<td>49.5~79.5/15fx /5wk</td>
<td>24</td>
<td>81%</td>
</tr>
<tr>
<td>54.0~69.6/12fx /3wk</td>
<td>34</td>
<td>86%</td>
</tr>
<tr>
<td>48.0~58.0/ 8fx /2wk</td>
<td>24</td>
<td>86%</td>
</tr>
<tr>
<td>48.0~52.8/ 4fx /1wk</td>
<td>75</td>
<td>90%</td>
</tr>
<tr>
<td>32.0~38.8 / 2fx /2day</td>
<td>36</td>
<td>90%</td>
</tr>
<tr>
<td>Total</td>
<td>181</td>
<td>-</td>
</tr>
</tbody>
</table>

* All recovered to pre-treatment function.
S8/5, 7.7 × 7.0 cm

Pre-RT

38.8GyE/2fr

12 mo.

Tumor marker

AFP (ng/ml)

PIVKA-2 (mAU/ml)
DVH of the Liver for Early Change of GOT in C-ion RT of HCC

CTC Grade

D30%
Clinical Study on Carbon Beam Therapy for Stage I Non-Small Cell Lung Cancer

**Dose-escalation**
- 59.4GyE
- 64.8
- 72.0
- 79.2
- 86.4
- 90.0
- 95.4

**Dose recommended**
- 90GyE
- 72 GyE

**Phase I/III**
- 18 fr / 6 wks
- 47 pats

**Phase I/II**
- 9 fr / 3 wks
- 34 pts

**Phase II**
- 9 fr / 3 wks
- 50 pats

**Phase I/II**
- 4 fr / 1 wk
- 79 pats

**Total**
- 129 pats

**Single-dose**
- 84 pats

- 72GyE for stage IA
- 52.8GyE for stage IB
- 28GyE

**Phase I/III (1994)**
- 9303

**Phase I/II (1997)**
- 9701

**Phase II (4/99 - 11/00)**
- 9802

**Phase I/II (12/00 - 11/03)**
- 0001

**Phase I/II (12/03 ~)**
- 0201
Local Control by Size and Histology

4 and 9 fractions

Stage IA: 98.6%
Stage IB: 89.7%

p = 0.063

Stage IA: 72
Stage IB: 59

ADENO 97.4%
SCC 91.1%

P = 0.208

SQ: 43
AD & others: 88
Survival in Stage I Lung Ca
4 and 9 fractions

Stage IA: 71
Stage IB: 58

Overall
IA 63.1%
IB 50.0%
P=0.063

Cause-specific
IA 90.3%
IB 63.2%
P=0.001
Local Control vs. Carbon Ion Dose for Different Fractionations in NSCLC

Patients’ data
- ■: 9 Fr.
- ●: 18 Fr.
- □: 4 Fr.

Patients’ data
- 30 GyE (TCP=0.95)
71y/o F (Sq Cell Ca, cT2N0M0)

Single fraction (40.0GyE)  After 18 mo,
### Local Control in Single Fraction (Baba, 2008)

N=152

<table>
<thead>
<tr>
<th>Total Dose GyE</th>
<th>T1 (&lt;3cm)</th>
<th>T2 (&gt;3cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 mo.</td>
<td>24 mo.</td>
</tr>
<tr>
<td>28.0 (n=6)</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>32.0 (n=27)</td>
<td>69.2</td>
<td>69.2</td>
</tr>
<tr>
<td>34.0 (n=34)</td>
<td>93.8</td>
<td>81.8</td>
</tr>
<tr>
<td>36.0 (n=18)</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>38.0 (n=14)</td>
<td>90.0</td>
<td>90.0</td>
</tr>
<tr>
<td>40.0 (n=15)</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>42.0 (n=15)</td>
<td>90.0</td>
<td>-</td>
</tr>
<tr>
<td>44.0 (n=23)</td>
<td>85.7</td>
<td>-</td>
</tr>
</tbody>
</table>
Tumor Control Probability in Stage I NSCLC

NSCLC Single Fraction

TCP

all: $\alpha=0.91$, $\sigma=0.46$
T1: $\alpha=1.69$, $\sigma=0.80$
T2: $\alpha=0.64$, $\sigma=0.33$

Clinical Dose [GyE]
Hypofractionated RT for Prostate Ca

- Recent reports of a low $\alpha/\beta$ ratio for prostate cancer lead to the background that prostate cancer can be safely and effectively treated with a very short course of external beam RT
  
  (Fowler; 2001, Brenner; 1999, Buchesne; 1999)

- A shortened course of radiotherapy is very attractive option for men who might not be candidates for brachytherapy or who find a 7-week to 8-week course of daily treatment prohibitive because of logistics or cost.
**Clinical Trials in Prostate Cancer at NIRS**

Total enrolled: 663 pts.  

562 treated with 20fr / 5wks,
97 treated with 16f / 4wks

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Period</th>
<th>Dose Fractionation</th>
<th>No. pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Escalation</td>
<td>95.6~00.2</td>
<td>54~72 GyE / 20fr / 5wks</td>
<td>96</td>
</tr>
<tr>
<td>Phase II</td>
<td>00.4~07.8</td>
<td>63 or 66 GyE / 20fr / 5wks</td>
<td>466</td>
</tr>
<tr>
<td>Current Fract.</td>
<td>03.12~07.8</td>
<td>57.6 GyE / 16fr / 4wks</td>
<td>97</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>95.6~07.8</strong></td>
<td></td>
<td><strong>659</strong></td>
</tr>
</tbody>
</table>
Carbon Ion Therapy of Prostate Ca

3 fields

5 fields

66Gy/16fr/5wks (3.3GyEx16)
T3bN0M0

CTV

GTV

PTV1

Cutting line for PTV2

Initial target

Second target
DVHs of the Rectum in Carbon Ion Therapy for Prostate ca

DVHs of the rectum (9402 All cases n=35)
DVHs of the Rectum in Carbon Ion Therapy for Prostate ca
Average DVHs of the Rectum
(according to Late Rectal Morbidity at 1st phase I/II study)

The reference line for rectal dose constraint is used for a bew treatment planning.
## Comparison of Late Toxicities

<table>
<thead>
<tr>
<th>Institutes</th>
<th>RTx</th>
<th>Dose/fr.</th>
<th>No. of pts.</th>
<th>Morbidity ≥ G2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rectum</td>
</tr>
<tr>
<td><strong>Maximum Reaction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAnderson CC. 1)</td>
<td>3DCRT</td>
<td>78Gy/39f</td>
<td>151</td>
<td>26.0%</td>
</tr>
<tr>
<td>Cleveland CF. 2)</td>
<td>IMRT</td>
<td>70Gy/28f</td>
<td>770</td>
<td>4.4%</td>
</tr>
<tr>
<td>Loma Linda U. 3)</td>
<td>Proton</td>
<td>75CGE/40f</td>
<td>901</td>
<td>3.5%</td>
</tr>
<tr>
<td>NIRS 5)</td>
<td>Carbon</td>
<td>63-66GyE/20f</td>
<td>288</td>
<td>1.8%</td>
</tr>
<tr>
<td><strong>At Last Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fox Chase CC. 4)</td>
<td>3DCRT</td>
<td>≥76Gy/38f</td>
<td>232</td>
<td>11.0%</td>
</tr>
<tr>
<td>NIRS 5)</td>
<td>Carbon</td>
<td>63-66GyE/20f</td>
<td>288</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

1) DA Kuban et al. IJROBP 70; 2008
2) PA Kupelian et al. IJROBP 68; 2007
3) RW Schulte et al. Strahlenther Oncol 176; 2000
4) GE Hanks et al. IJROBP 46; 2000
5) H.Tsuji, et al. IJROBP 63; 2005
Survivals

N=457

Probabilities:
- Overall: 97.8% at 120 months
- Cause-specific: 94.8% at 120 months
- Overall: 93.9% at 120 months
- Overall: 76.7% at 120 months

References:
# Comparison with other RTx

(5-year bNED, iPSA>20)

<table>
<thead>
<tr>
<th>Institutes</th>
<th>RTx</th>
<th>Dose</th>
<th>pts.</th>
<th>NED (iPSA&gt;20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson CC. 1)</td>
<td>3DCRT</td>
<td>78Gy/39f</td>
<td>53</td>
<td>39% (8y-rate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(PSA&gt;10)</td>
</tr>
<tr>
<td>Fox Chase CC. 2)</td>
<td>3DCRT</td>
<td>≥76Gy/38f</td>
<td>232</td>
<td>26-63%</td>
</tr>
<tr>
<td>Cleveland CF. 3)</td>
<td>IMRT</td>
<td>70Gy/28f</td>
<td>770</td>
<td>72%</td>
</tr>
<tr>
<td>Loma Linda U. 4)</td>
<td>Proton</td>
<td>75CGE/45f</td>
<td>901</td>
<td>45%</td>
</tr>
<tr>
<td>NIRS 5)</td>
<td>Carbon</td>
<td>66.0GyE/20f</td>
<td>186</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>72% (8y)</td>
</tr>
</tbody>
</table>

1) DA Kuban et al. IJROBP 70; 2008
2) GE Hanks et al. IJROBP 46; 2000
3) PA Kupelian et al. IJROBP 63; 2005
4) JD Slater et al. IJROBP 59; 2004
5) H. Tsuji, et al. IJROBP 63; 2005
### Comparison ofSurvivals

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (Gy/f)</th>
<th>OS* in each Risk Group**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Group 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No.pts</td>
</tr>
<tr>
<td><strong>RTOG Meta analysis#</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT alone (65-70GyE/35f)</td>
<td>443</td>
<td>82%</td>
</tr>
<tr>
<td>RT+ Hormone</td>
<td>114</td>
<td>76%</td>
</tr>
<tr>
<td><strong>Carbon</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT+ Hormone</td>
<td>118</td>
<td>95%</td>
</tr>
<tr>
<td>(66.0GyE/20f)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Overall Survival Rate  **Risk Group:  Group 2; GS2-6, T3 or GS7, T1-2  
Group 3; GS7, T3 or GS8-10, T1-2  
Group 4; GS8-10, T3

#RTOG: Radiation Therapy Oncology Group  
Hypofractionated schedule in C-ion RT for prostate cancer

57.6/16f \approx 63.0/20f
\approx 76\sim 84\text{GyE} \text{ for Tumor}
\approx 70\sim 76\text{GyE} \text{ for Normal tissue}

66.0/20f \approx 83\sim 90\text{GyE} \text{ for Tumor}
\approx 78\sim 83\text{GyE} \text{ for Normal tissue}
Stereotactic hypofractionated radiotherapy of the prostate, 33.5Gy in five fractions for localized disease: first clinical trial results (Madsen et al: IJROBP 67; 1099-1105, 2007)

- Phase I/II trial: 40 pats (2000-2004)
  - Low-risk disease; GS<6, PSA<10ng/mL, <T2aNxMx
  - Prostate volume; median 56.4cc (13.7 - 134.5 cc)
  - Total dose; 33.5 Gy (6.7 Gy x 5 fr)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Acute GU</th>
<th>Acute GI</th>
<th>Late GU</th>
<th>Late GI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>49%</td>
<td>61%</td>
<td>55%</td>
<td>63%</td>
</tr>
<tr>
<td>1</td>
<td>28%</td>
<td>26%</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>21%</td>
<td>13%</td>
<td>20%</td>
<td>8%</td>
</tr>
<tr>
<td>≥3</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
# Toxicity
(Scoring with RTOG-LENT)

<table>
<thead>
<tr>
<th>Dose GyE/f.</th>
<th>No. pts</th>
<th>Rectum G0</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>Bladder/urethra G0</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66.0/20f</td>
<td>288</td>
<td>81.3</td>
<td>17.0</td>
<td>1.7</td>
<td>0</td>
<td>35.1</td>
<td>58.3</td>
<td>6.6</td>
<td>0</td>
</tr>
<tr>
<td>63.0/20f</td>
<td>169</td>
<td>91.1</td>
<td>7.1</td>
<td>1.8</td>
<td>0</td>
<td>76.3</td>
<td>23.1</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>57.6/16f</td>
<td>87</td>
<td>89.7</td>
<td>10.3</td>
<td>0</td>
<td>0</td>
<td>74.7</td>
<td>25.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Last F/U</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66.0/20f</td>
<td>288</td>
<td>93.1</td>
<td>6.6</td>
<td>0.3</td>
<td>0</td>
<td>80.9</td>
<td>16.0</td>
<td>3.1</td>
<td>0</td>
</tr>
<tr>
<td>63.0/20f</td>
<td>169</td>
<td>94.7</td>
<td>4.7</td>
<td>0.6</td>
<td>0</td>
<td>94.7</td>
<td>5.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>57.6/16f</td>
<td>87</td>
<td>94.3</td>
<td>5.7</td>
<td>0</td>
<td>0</td>
<td>95.4</td>
<td>4.6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median follow-up period:
66.0/20f;49.2m, 63.0/20f;15.1m, 57.6/16f;21.4m
A Shorter Fractionation: $57.6\text{GyE} / 16f$

87 patients (out of 97 pts)
Average age: 69.5 y.o. (51~80)
Follow-up: Median 21.4 months (6~49 m)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No.pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>17(20.7%)</td>
</tr>
<tr>
<td>Interm.</td>
<td>19(21.8%)</td>
</tr>
<tr>
<td>High</td>
<td>49(57.5%)</td>
</tr>
</tbody>
</table>

Probability

98.7%  Overall Survival
98.4%

Biochemical Relapse Free Rate

N=87

Time after C-ion RT (months)

63~66GyE/20f/5w
Summary

• There is a significant advantage in shortening the overall time and fractions of radiotherapy at least to 3 - 4 weeks or even shorter, which has been done effectively in radiotherapy with C-ion RT.

• This means that the facility can be operated more efficiently, offering treatment for a larger number of patients than is possible with other modalities over the same period of time.