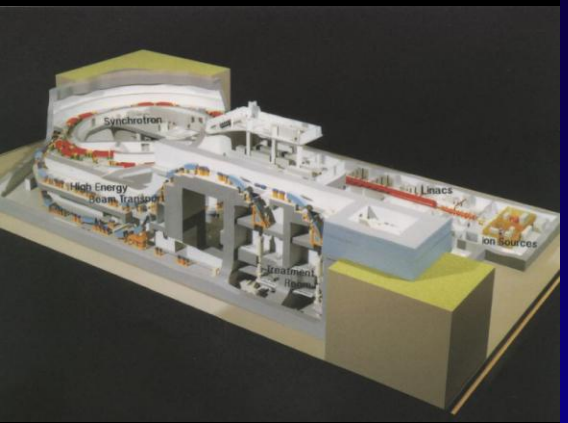



# *Carbon-ion therapy for patients with Locally Recurrent Rectal Cancer and Pancreas Cancer*

**Shigeru Yamada,Miho Shiomi, Tetsuro Isozaki,Makoto Shinoto, Kotaro Terashima,Shinichiro Mori, Shigeo Yasuda,Tadashi Kamada, and Hirohiko Tsujii**

**Research Center of Charged Particle Therapy Hospital, National Institute of Radiological Sciences Japan**

# Incidence and Mortality of Cancer

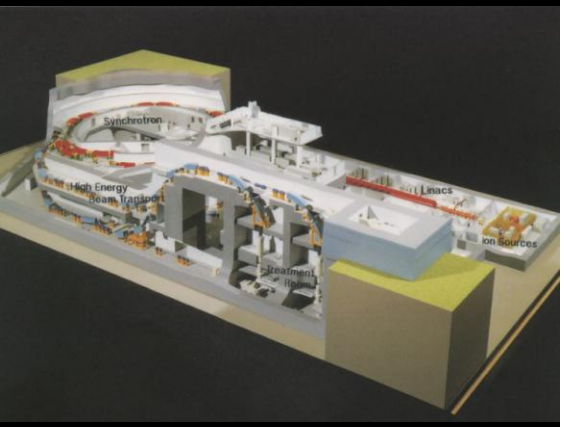
## (2012 USA)

| Cancer | Incidence (New patients) | | | Mortality | | |
|---|---|---|---|---|---|---|
| | M | F | Total | M | F | Total |
| Breast | 2,190 | 226,870 | 229,060 | 410 | 39,510 | 39,920 |
| Prostate | 241,740 | | 241,740 | 28,170 | | 28,170 |
| Colorectal | 73,420 | 70,040 | 143,460 | 26,470 | 25,220 | 51,690 |
| Pancreas | 22,090 | 21,830 | 43,920 | 18,850 | 18,540 | 37,390 |

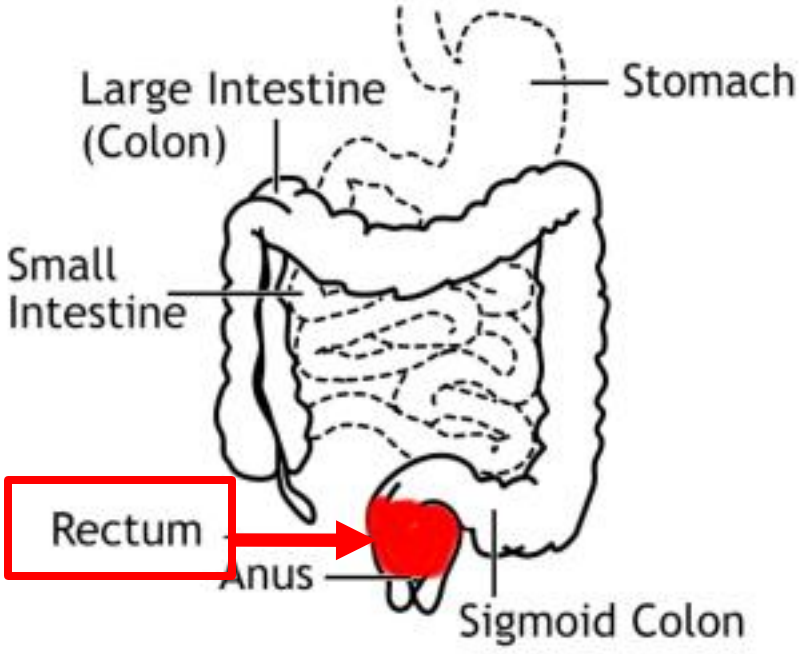
# Incidence and Mortality of Cancer

**Mortality number of colorectal cancer and pancreatic cancer are relatively high.**

| | M | F | Total | M | F | Total |
|---|---|---|---|---|---|---|
| Breast | | 50,695 | 50,695 | | 11,918 | 11,918 |
| Prostate | 42,997 | | 42,997 | 10,036 | | 10,036 |
| Colorectal | 59,900 | 44,834 | 104,734 | 22,965 | 19,835 | 42,800 |
| Pancreas | 13,108 | 11,691 | 24,799 | 14,094 | 12,697 | 26,791 |



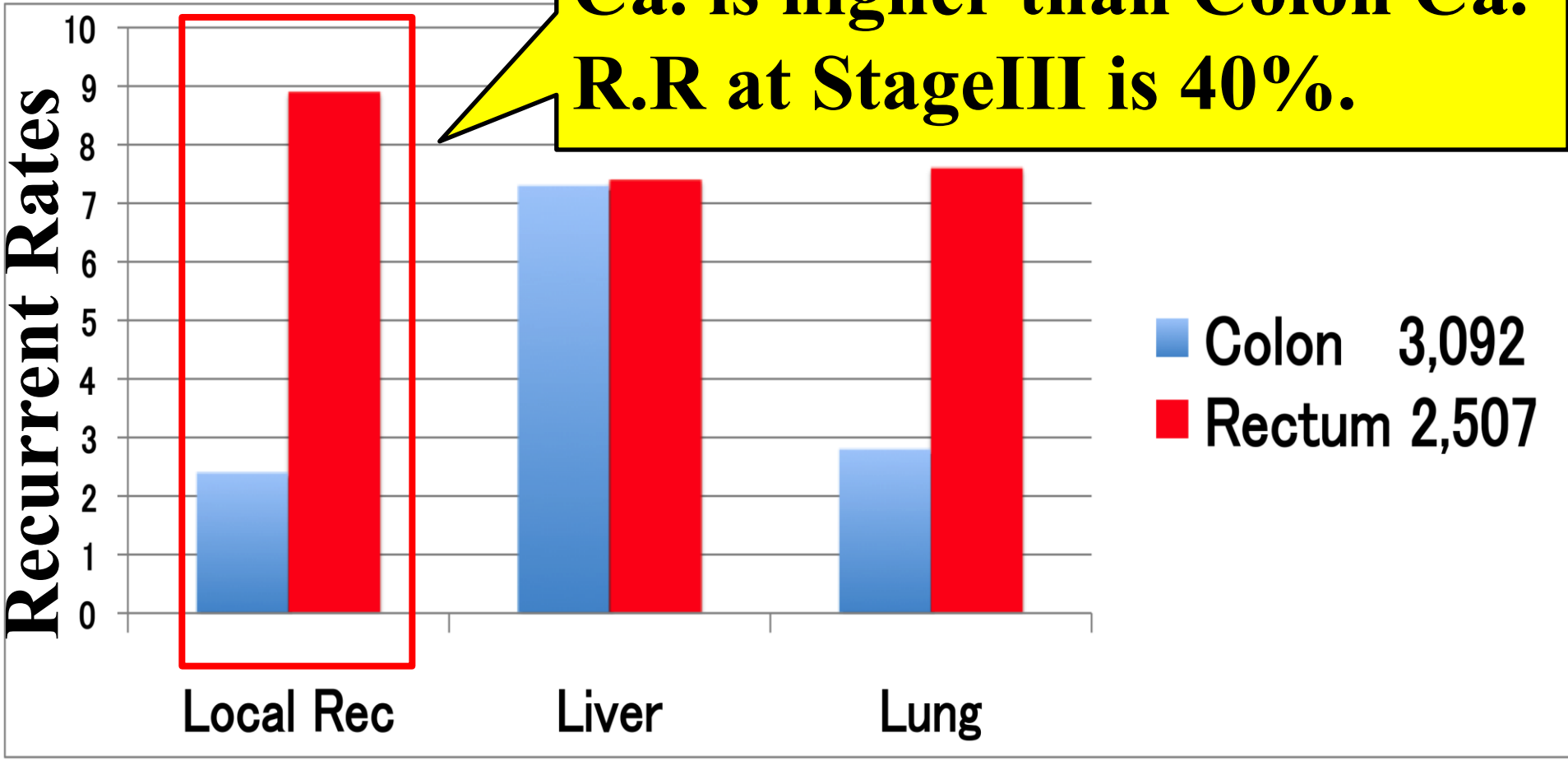

# CARBON-ION THERAPY FOR PATIENTS WITH LOCALLY RECURRENT RECTAL CANCER




Research Center of Charged Particle Therapy
National Institute of Radiological Sciences,

# Recur

**Recurrent Rates of Rectal Ca. is higher than Colon Ca. R.R at StageIII is 40%.**




Japanese Society of colon and rectum cancer 2004

# Res… …Rates …es

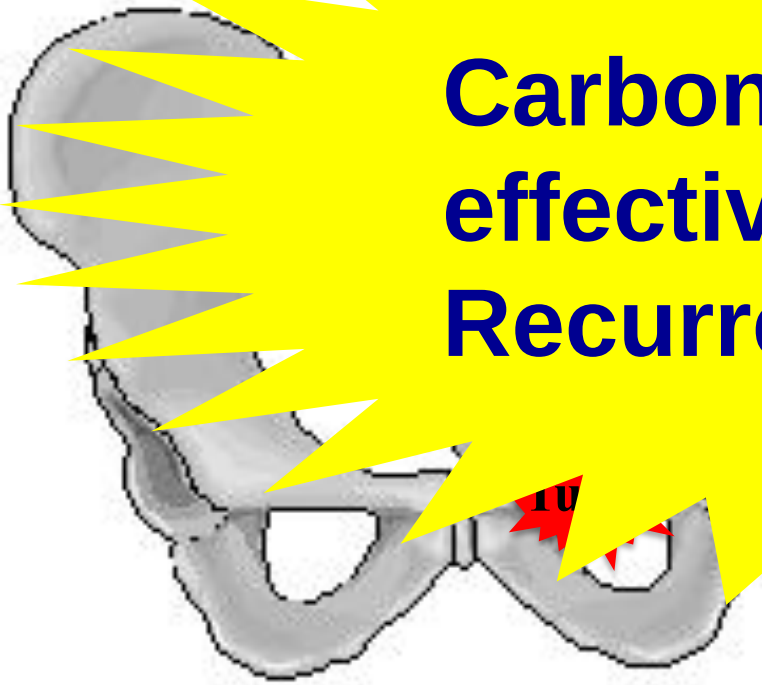
**Curative resection of LR brought good prognosis.**

| | | Surv |
|---|---|---|
| Local Rec | 10-30% | 30-45% |
| Liver M… | 40-50% | 35-45% |
| | …20-30% | 40-50% |

**Resection of LR is difficult.**

Tepper, JE. J Clin Oncol; 21 3623-2628, 2003

# Summary of treatment for Locally Recurrent Rectal Cancer



**Carbon ion therapy is effective on locally Recurrent rectal cancer.**

**Surgery**

**difficult**

**ation**

**Radiation**

**esistant**

**Adenocarcinoma**

**Large hypoxic cell fraction**

**Close to radiosensitive structure**

**Intestine , colon , bladder**

# Carbon Ion Radiotherapy Techniques

## Treatment Planning

**CT acquisition; 2.5mm thick CT images throughout the pelvis**

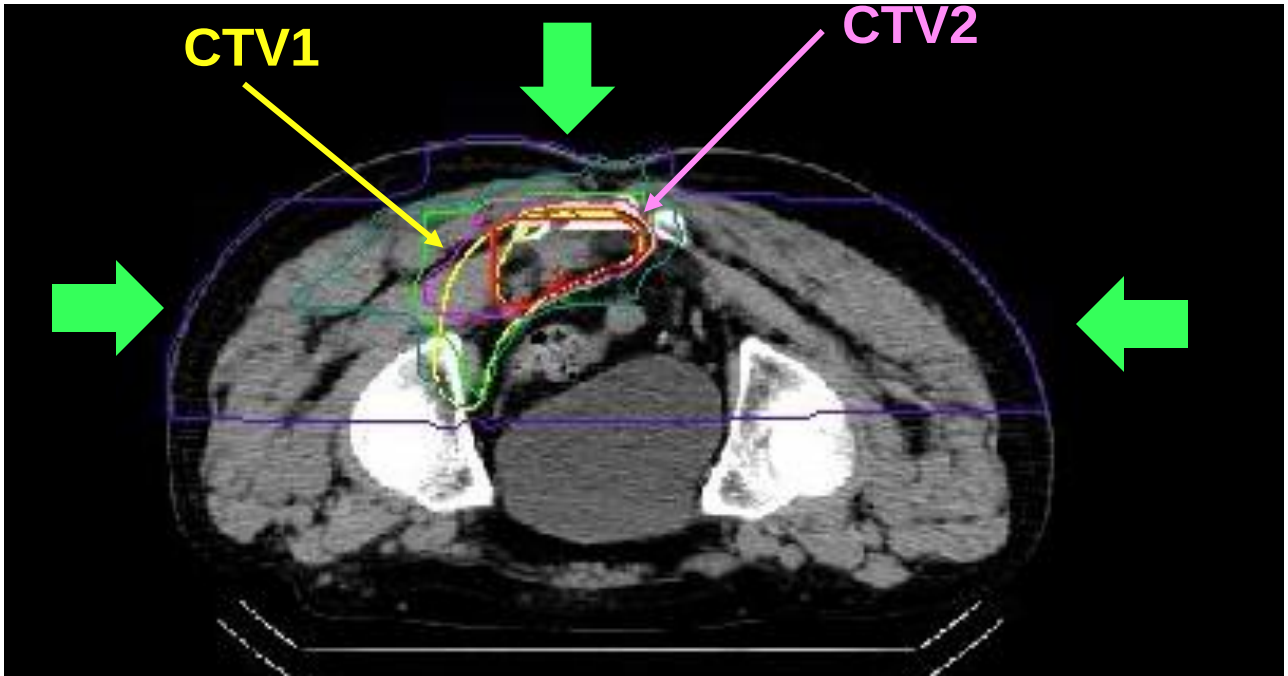
**Definitions of treatment volumes**

**GTV: Tumor demonstrated on CT scan**

**CTV:CTV1:GTV+possible subclinical spread of the tumor +regional lymph nodes**

**CTV2:GTV**

**PTV: CTV+5mm margin, except for the region close to the bowel**



# Carbon Ion Radiotherapy Techniques

## Treatment Planning

**Dose fractionation:**

**Dose to the CTV1 = 41.4Gy (E) / 9 fractions**

**Dose to the CTV2 = 73.6Gy (E) / 16 fractions**

**Organs at risk (OARs) & Dose constraints:**

- **i. Intestine** $D_{MAX} \leq$ 48 GyE/16Fr, 30Gy(E)/9Fr
- **ii. Rectum** $D_{MAX} \leq$ 60 Gy (E)/16Fr
- **iii. Bladder** $D_{MAX} \leq$ 60 Gy (E)/16Fr
- **iv. Skin** $D_{MAX} \leq$ 50 Gy (E)/16Fr

# *The course of Carbon ion therapy for patients with locally recurrent rectal cancer*

(year)

2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012

**Phase I/II**
16fr/4w

**Phase II**
73.6GyE/16fr/4w

| | |
|---|---|
| 67.2GyE | 10 |
| 70.4GyE | 15 |
| 73.6GyE | 13(+1) |
| Total | 38(+1) |

152(+8) Cases

189(+9) Cases

# *Acute and Late toxicities*
## *by NCI-CTC and RTOG/EORTC Scoring System*

(202 lesions in 189patients)

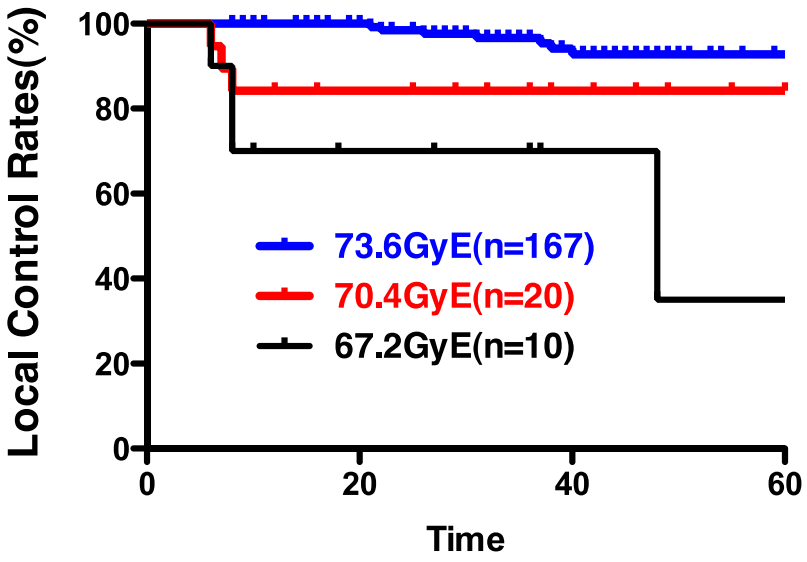
| | Acute(NCI-CTC) | | | | | | Late(RTOG/EORTC) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of lesions | Gr0 | Gr1 | Gr2 | Gr3 | Gr4 | No. of lesions | Gr0 | Gr1 | Gr2 | Gr3 | Gr4 |
| **Skin** | 202 | 35 | 159 | 8 | 0 | 0 | 202 | 115 | 84 | 1 | 2 | 0 |
| **GI tract** | 202 | 197 | 1 | 4 | 0 | 0 | 202 | 199 | 1 | 1 | 1 | 0 |
| **Urinary** | 202 | 201 | 1 | 0 | 0 | 0 | 202 | 199 | 1 | 2 | 0 | 0 |

**No grade 3 to 5 toxicity was observed.**

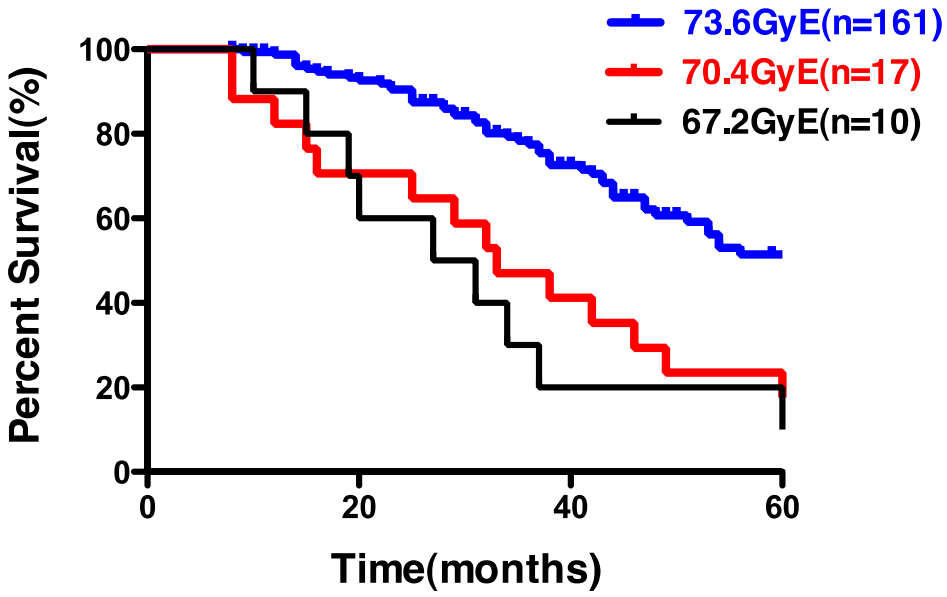
# Local Control Rates and Survival Rates

(locally recurrent rectal cancer)

## Local Control Rates




## Survival Rates




| Local Control | 3y | 5y |
|---|---|---|
| 67.2GyE | 70.0% | 35.0% |
| 70.4GyE | 84.2% | 84.2% |
| 73.6GyE | 96.6% | 92.8% |

| Survival Rates | 3y | 5y |
|---|---|---|
| 67.2GyE | 30.0% | 20.0% |
| 70.4GyE | 47.0% | 23.5% |
| 73.6GyE | 78.4% | 51.4% |

# Results on the Radiation Therapy of Locally Recurrent Rectal Cancer

| Study & Reference | Year | No | Rad Dose(Gy) | Survival Rate | | Local Control |
|---|---|---|---|---|---|---|
| | | | | 2 y | 5 y | |
| LybeertML M | 1992 | 76 | 6-66 | 61%(1y) | 3% | 28%(3y) |
| Knol HP | 1995 | 50 | 60 | 27% | 8% | - |
| Murata | 1997 | 18 | 12-60 | 44%(1y) | - | 46%(2y) |
| Hu JB | 2006 | 23 | 55-66 | 50%(2y) | 18%(3y) | |
| Kim MS | 2008 | 23 | 30-51/3f | 82% | 23% | 74%(5y) |
| Lee JH | 2011 | 22 | 54-66 | 66% | 40% | 56%(5y) |
| NIRS | 2013 | 161 | 73.6 | 90% | 51% | 93%(5y) |

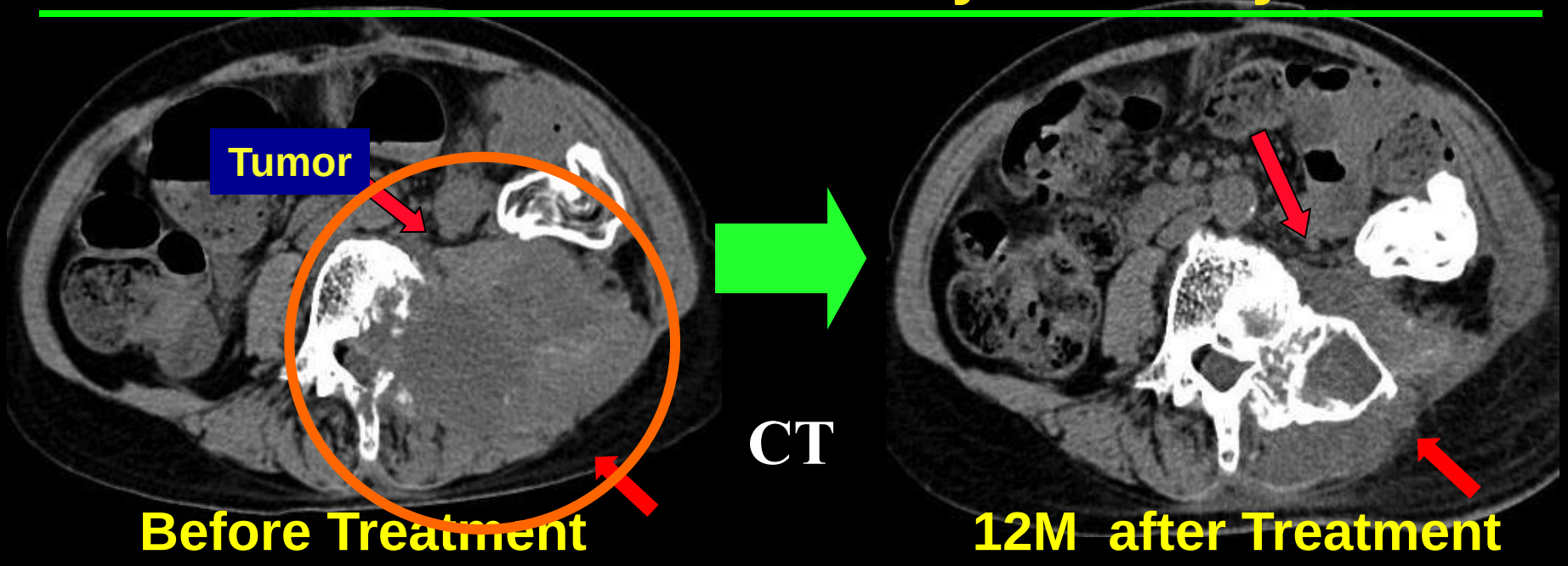
1)Acta Radiol Oncol 21:105, 1992, 2) Int. J. Radiat. Oncol, Biol. Phy, 8:1115,1995 3) Int. J. Radiat. Oncol, Biol. Phy, 21: 1291, 1997, 4) Int. J. Radiat. Oncol. Biol. Phys 23:241, 2006, 5) Strahlenther Onkol 173:43, 2008, 6) J. Jpn. Soc. Ther. Radio;. Oncol 9:63,2011, 7) 48th ASTRO meeting,2006

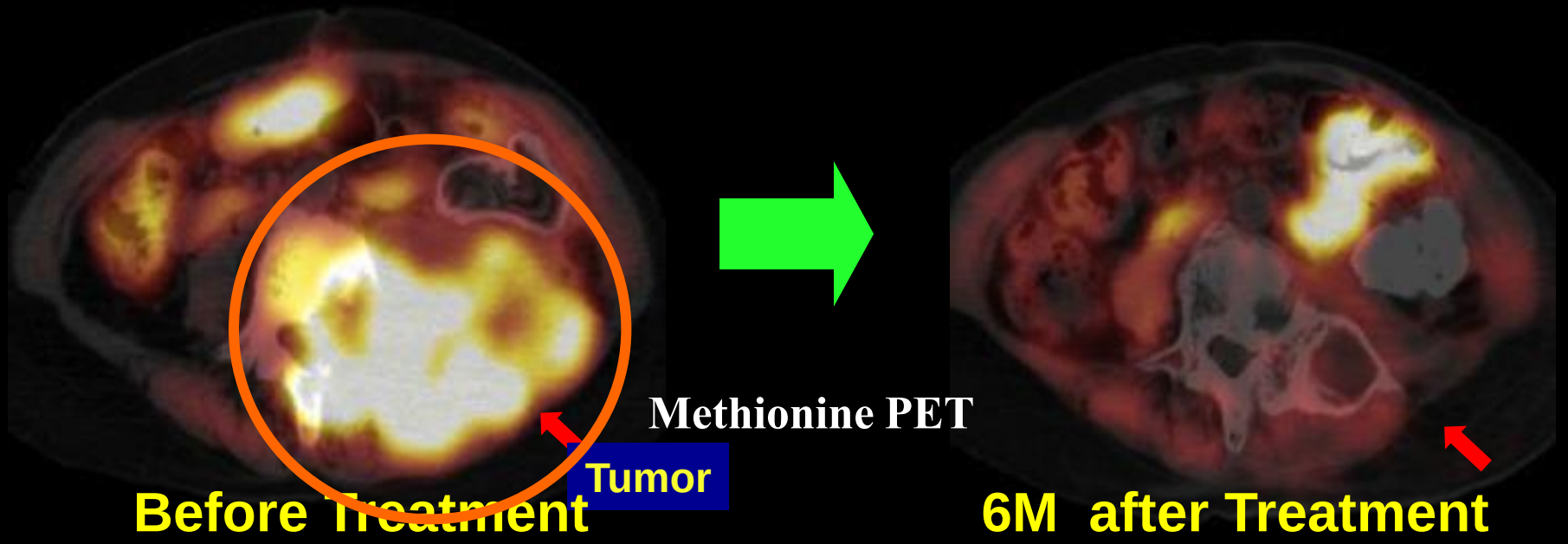
# Results on the Surgical Treatment of Locally Recurrent Rectal Cancer

| Study and Reference | | Number of patients | Survival rate 1 y | Survival rate 2 y | Survival rate 5y |
|---|---|---|---|---|---|
| Garcia-Aguilar J [1] | 1999 | 42 | 88% | 62% | 35% |
| Wanebo [2] | 1999 | 53 | 91% | 62% | 31% |
| Salo JC [3] | 1999 | 71 | 88% | 75% | 31% |
| Saito N [4] | 2003 | 43 | 91% | 78% | 39% |
| Moriya [5] | 2004 | 48 | 95% | 76% | 36% |
| Melton [6] | 2007 | 29 | 92% | 65% | 20% |
| NIRS [7] | 2013 | 161 | 99% | 90% | 51% |

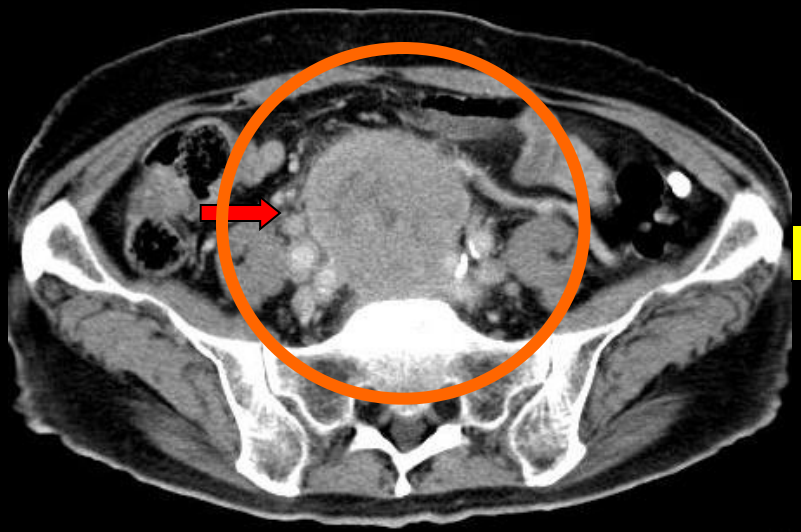
1) Dis Colon Rectum 42:1438, 1999, 2) Dis Colon Rectum 42:1438, 1999, 3)Ann Surg Oncol 6:171, 1999, 4) Dig Surg 20:192, 2003, 5) Dis Colon Rectum 47:2047,2004, 6) Dis Colon Rectum 49:1099, 2007 7) 48th ASTRO meeting,2006

# Recurrent Rectal Cancer : 69y F 73.6GyE/16Fr

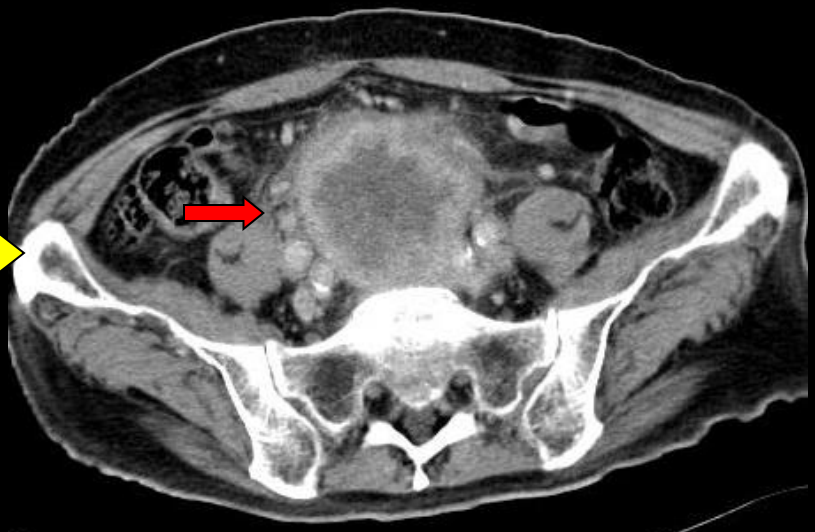


# Recurrent Rectal Cancer : 66y M 67.2GyE/16Fr

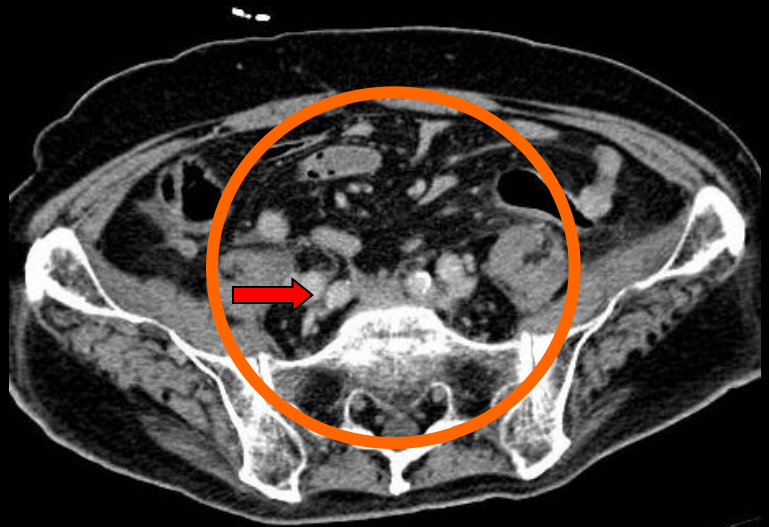


Before Treatment



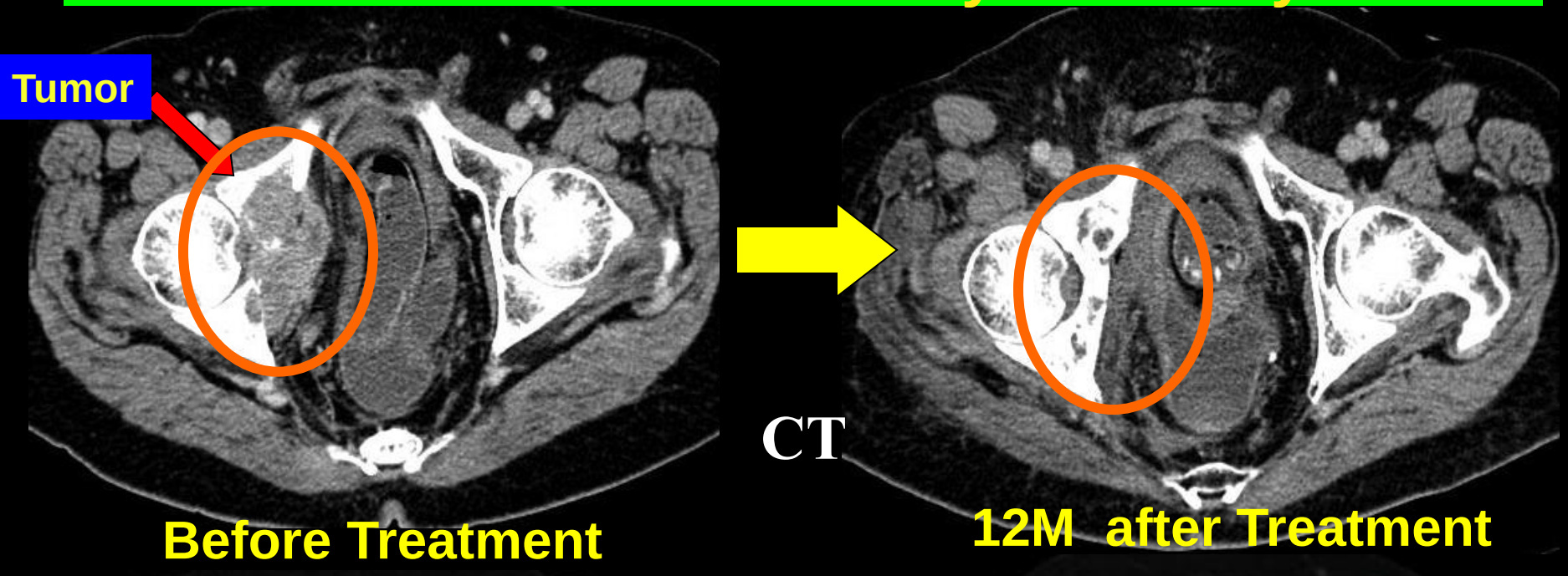
2M after Treatment

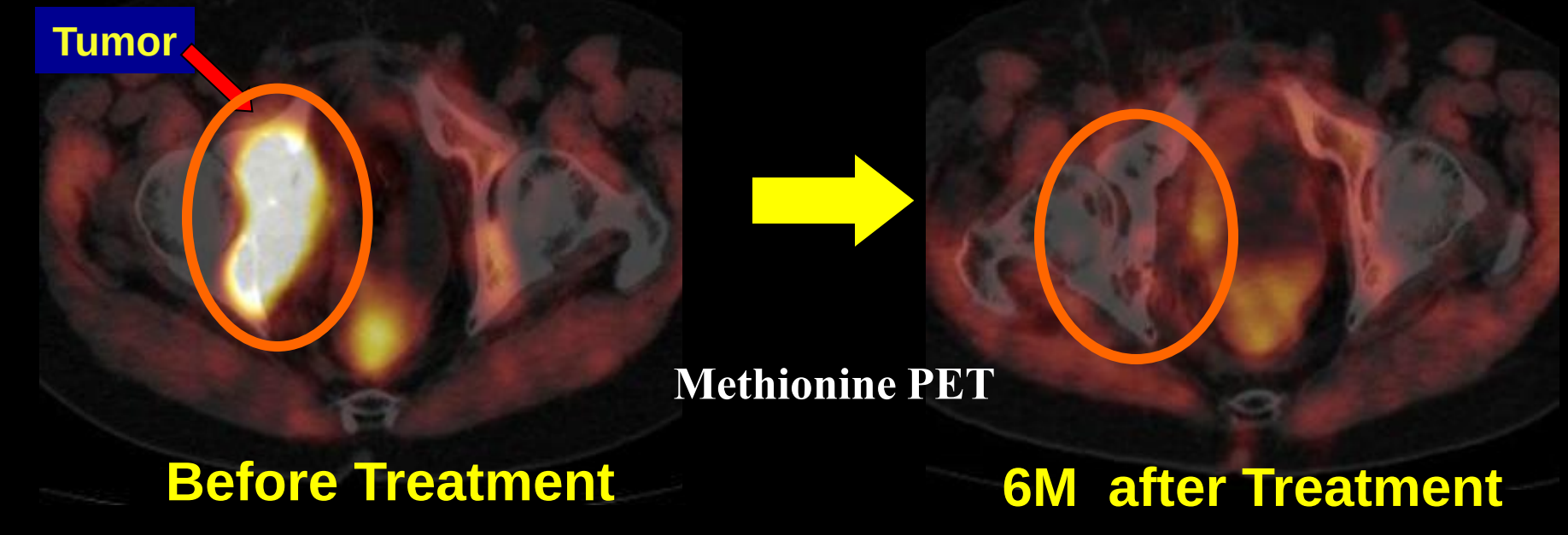
4M after Treatment



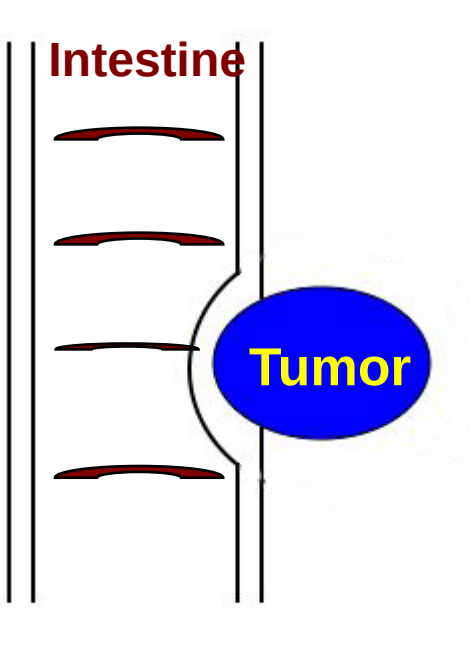
24M after Treatment

# Recurrent Rectal Cancer : 65y M 73.6GyE/16Fr



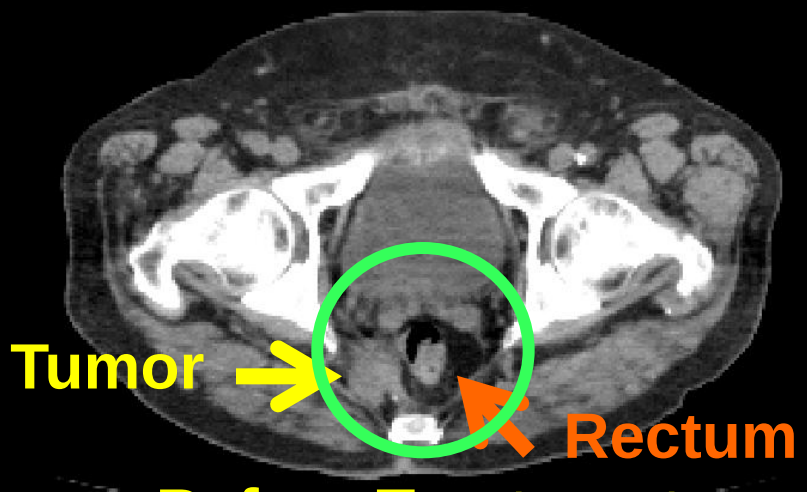
# Widen the criteria for recipients of Carbon ion radiotherapy.



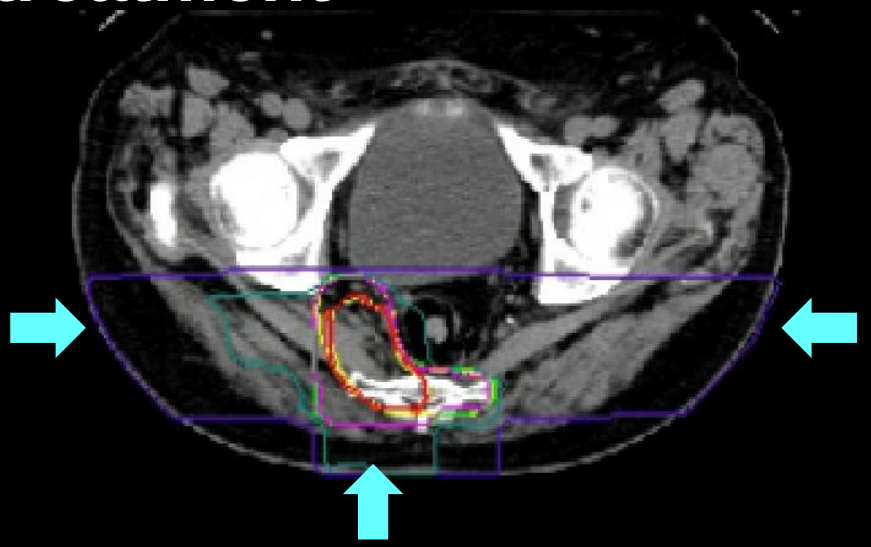

**Intestines: Critical Organ**

# Recurrent Rectal Cancer : 68y M 73.6GyE/16Fr

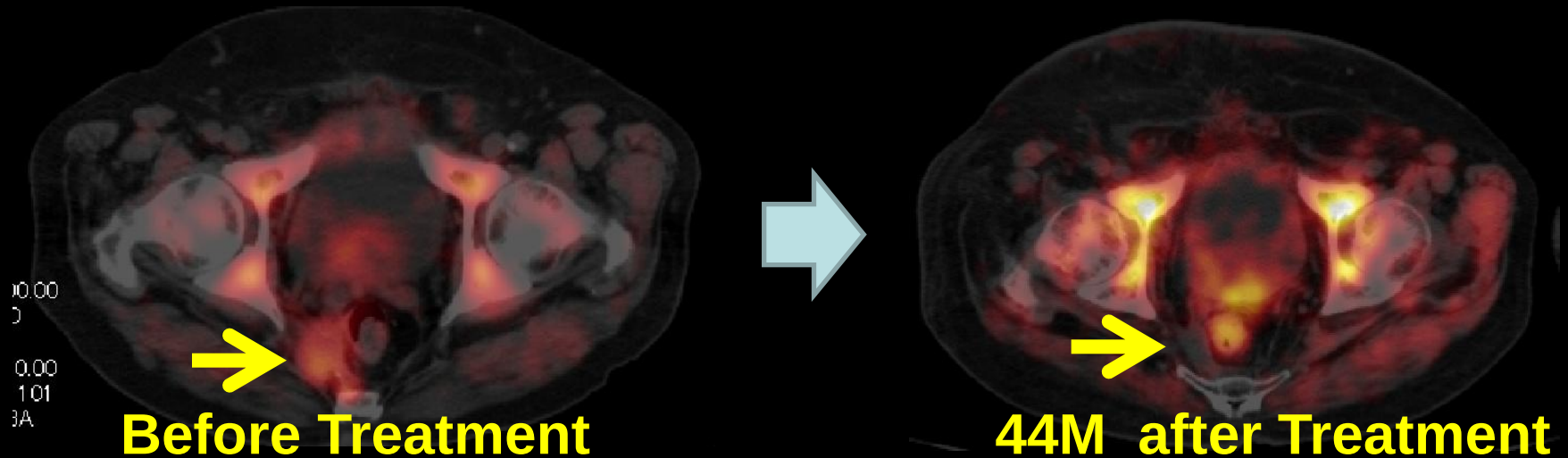
**This case can be treated by carbon ion radiotherapy without pretreatment**




Before Treatment



73.6GyE/16fr

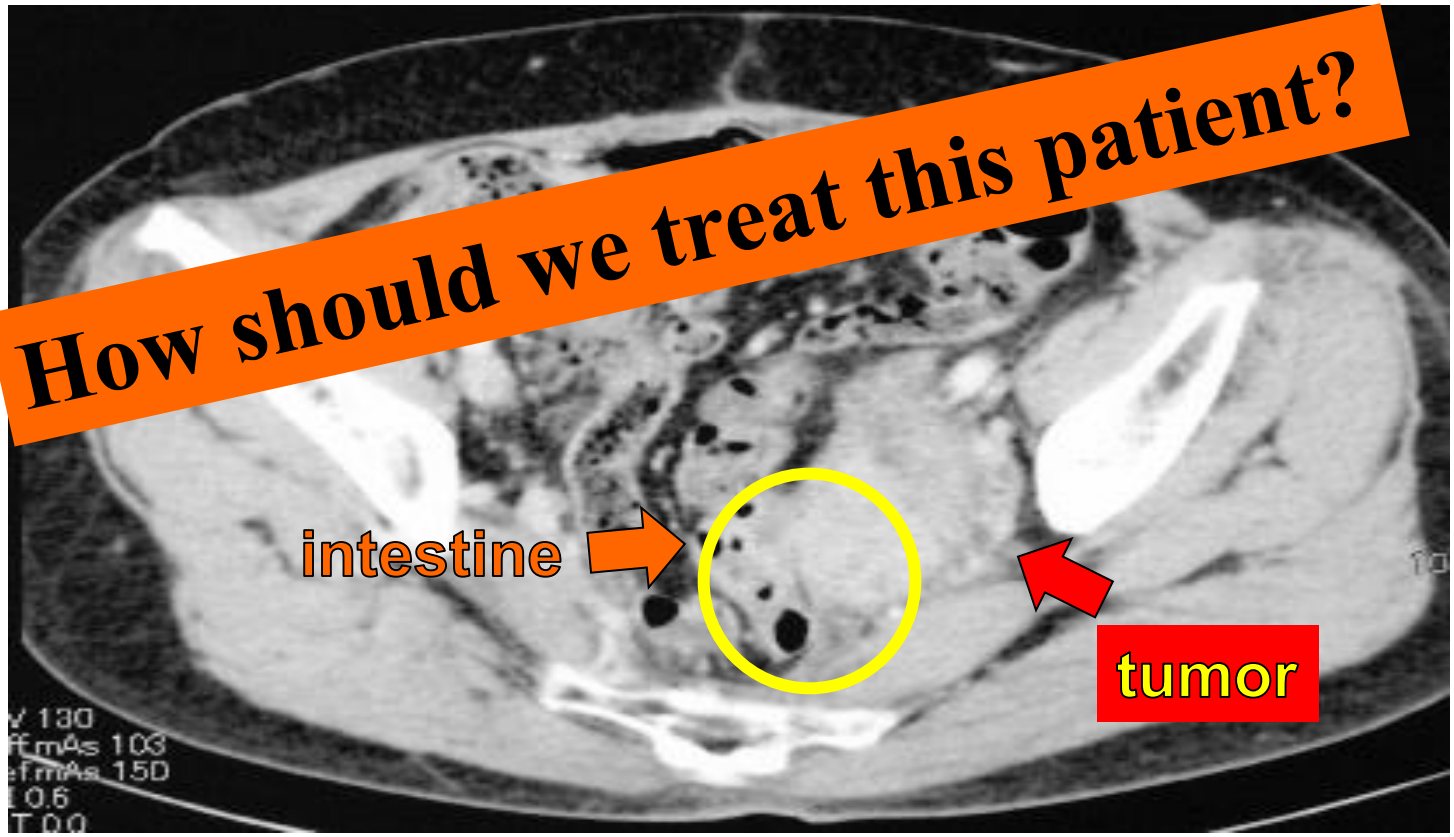


Before Treatment

44M after Treatment

# Recurrent Rectal Cancer : 58y F

**Previously this patient could not receive carbon ion radiotherapy**



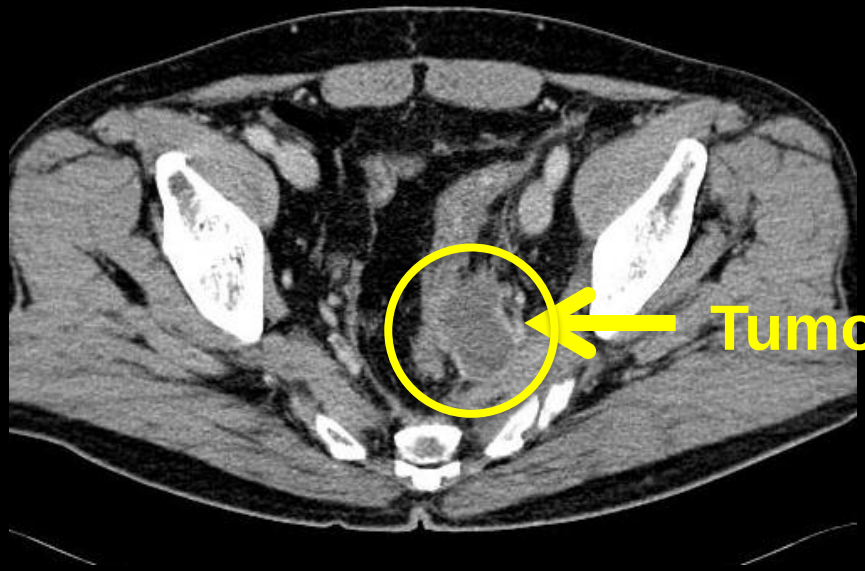

**CT scan reveals a tumor mass  in contact with intestine.**

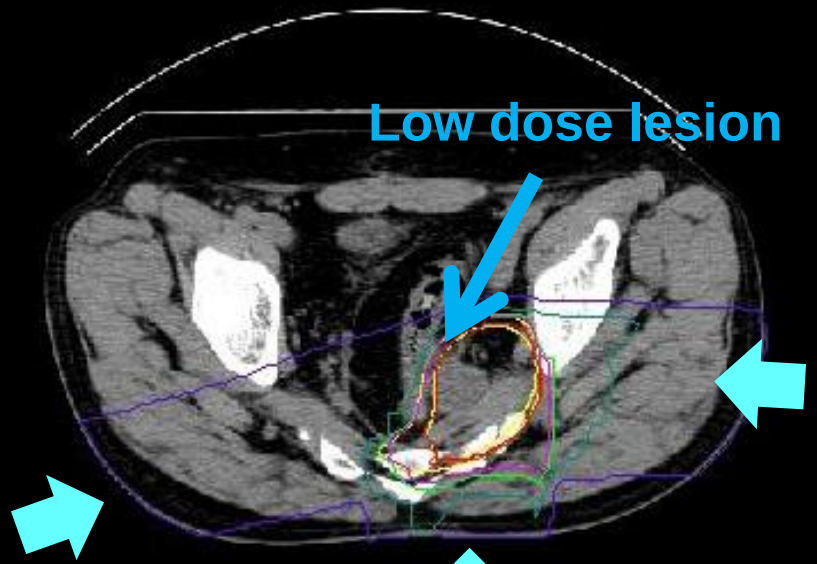
# The way of avoiding radiosensitive organs from radiation field

Colostomy

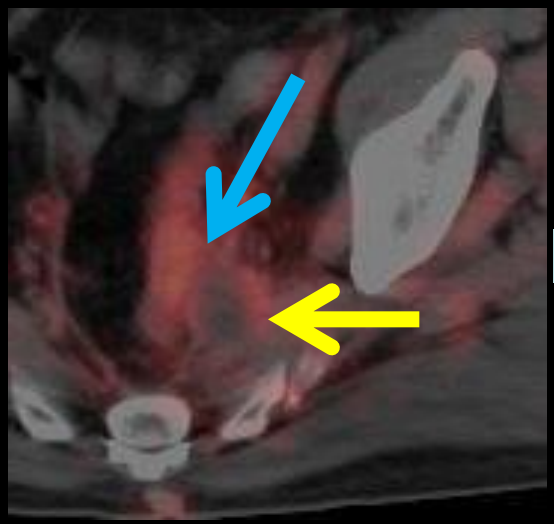
- Shrinking Field
- Multi Field

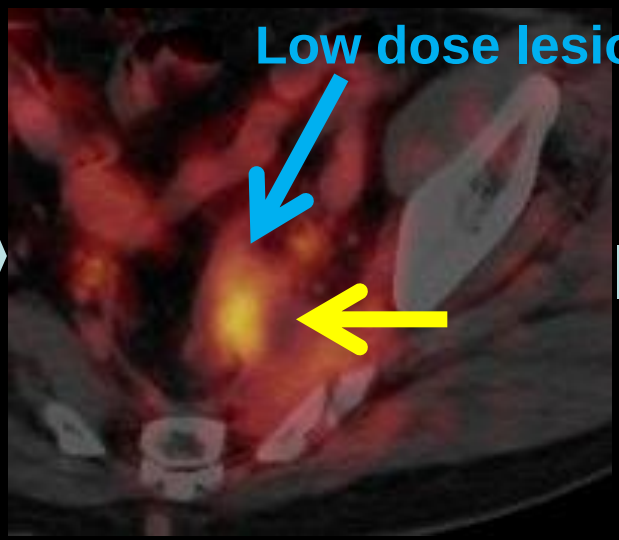
# Recurrent Rectal Cancer :58y M  73.6GyE/16Fr

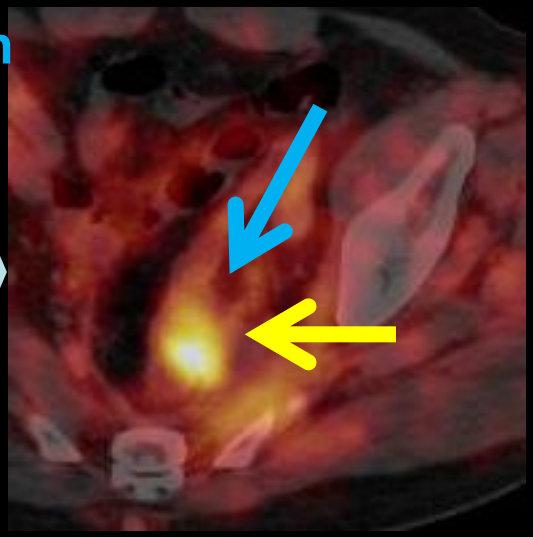



Before Treatment





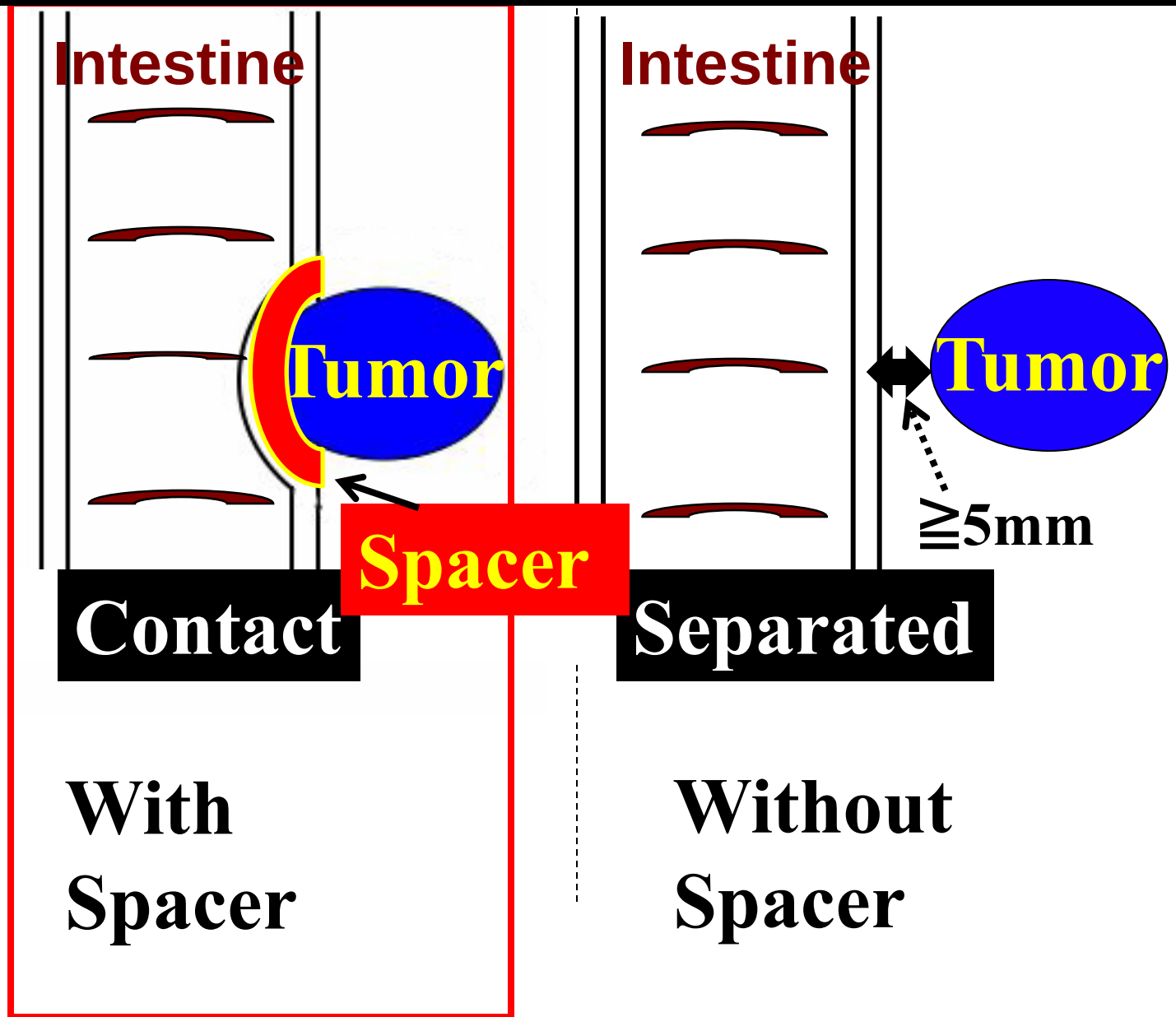



One M after treatment

14M after Treatment

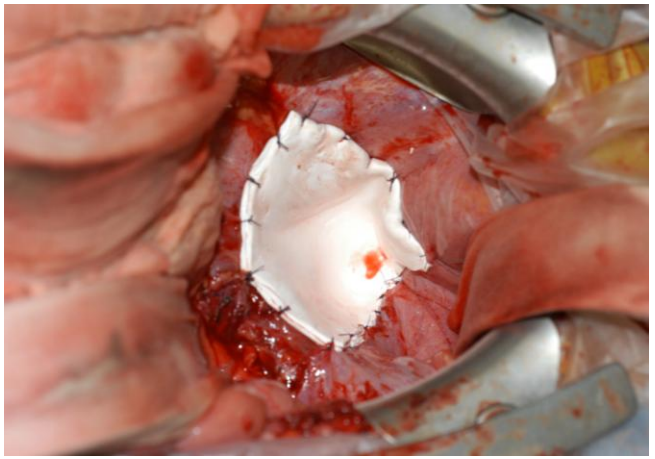
17M after Treatment

# *Classification of tumor location*
# *By distance between tumor and intestines*

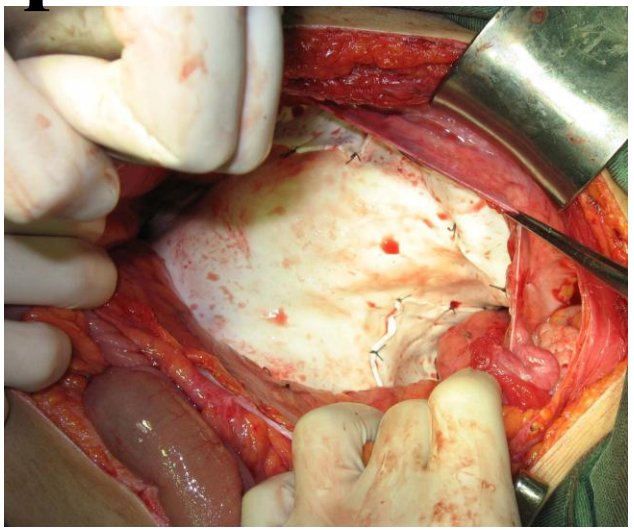


# Gore-Tex Soft Tissue Patch

**Gore-Tex Sheet is made of expanded polytetrafluoroethlene(PTFE) and is inert, preventing significant inflammatory responses**



**Operative Finding**

# Patients Characteristics used with the spacer

（2003.4～2012.8：87Cases）

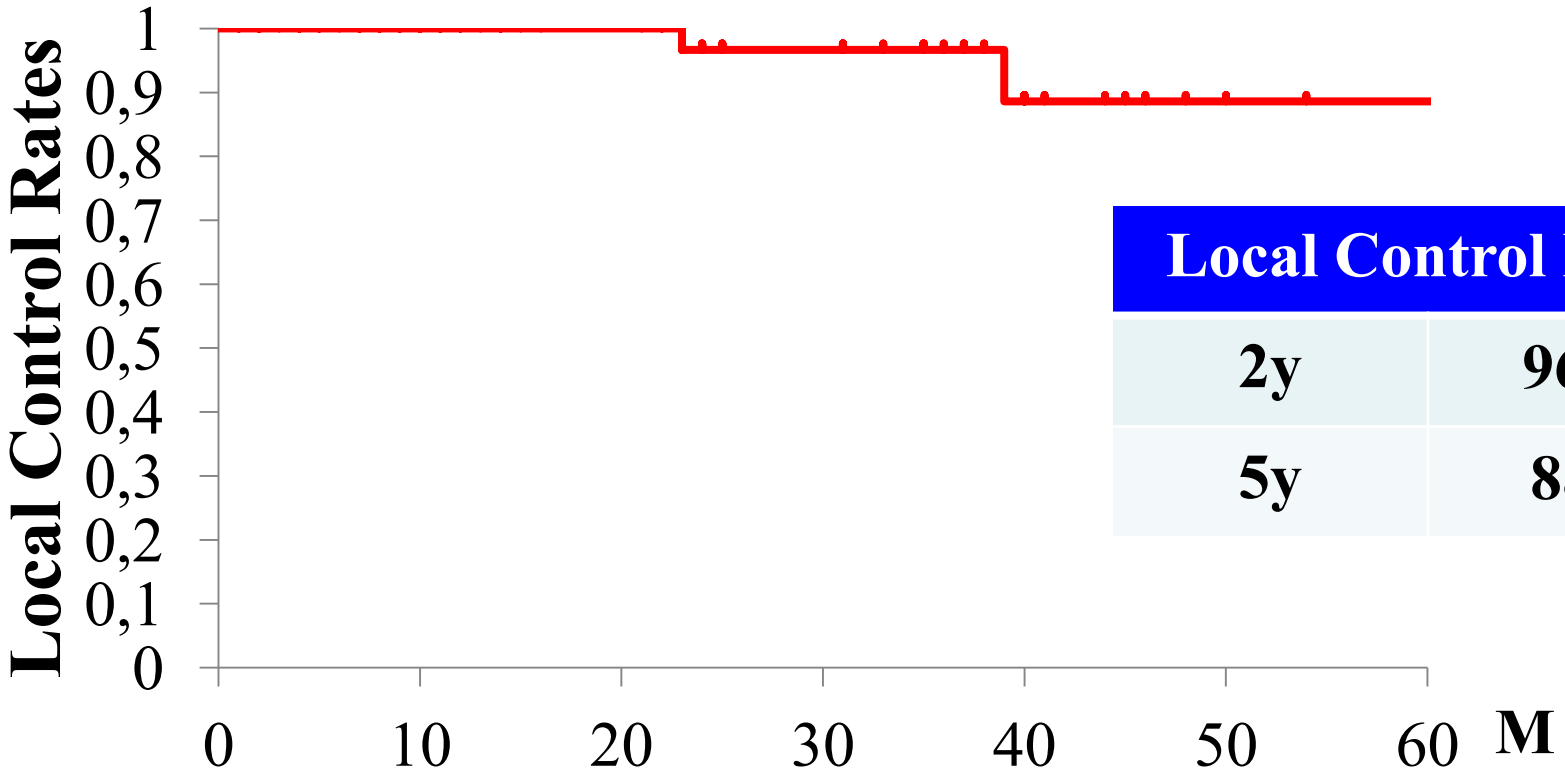
| | | |
|---|---|---|
| Age | 60y（30～75y） | |
| Male／Female | Male／Female＝57：30 | |
| Tumor Sites | Side wall | 39 |
| | Presacrum | 40 |
| | Anastomosis | 2 |
| | other | 6 |

# Acute and Late toxicities
## by NCI-CTC and RTOG/EORTC Scoring System

| | Acute(NCI-CTCAE) | | | | | | | Late(NCI-CTCAE) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | G0 | G1 | G2 | G3 | G4 | | Total | G0 | G1 | G2 | G3 | G4 |
| Ileus | 87 | 77 | 0 | 8 | 2 | 0 | | 87 | 86 | 0 | 1 | 0 | 0 |
| Infection | 87 | 79 | 0 | 3 | 5 | 0 | | 87 | 78 | 0 | 4 | 5 | 0 |
| Ischemic | 87 | 86 | 0 | 0 | 1 | 0 | | 87 | 87 | 0 | 0 | 0 | 0 |
| Enterocolitis | 87 | 87 | 0 | 0 | 0 | 0 | | 87 | 87 | 0 | 0 | 0 | 0 |

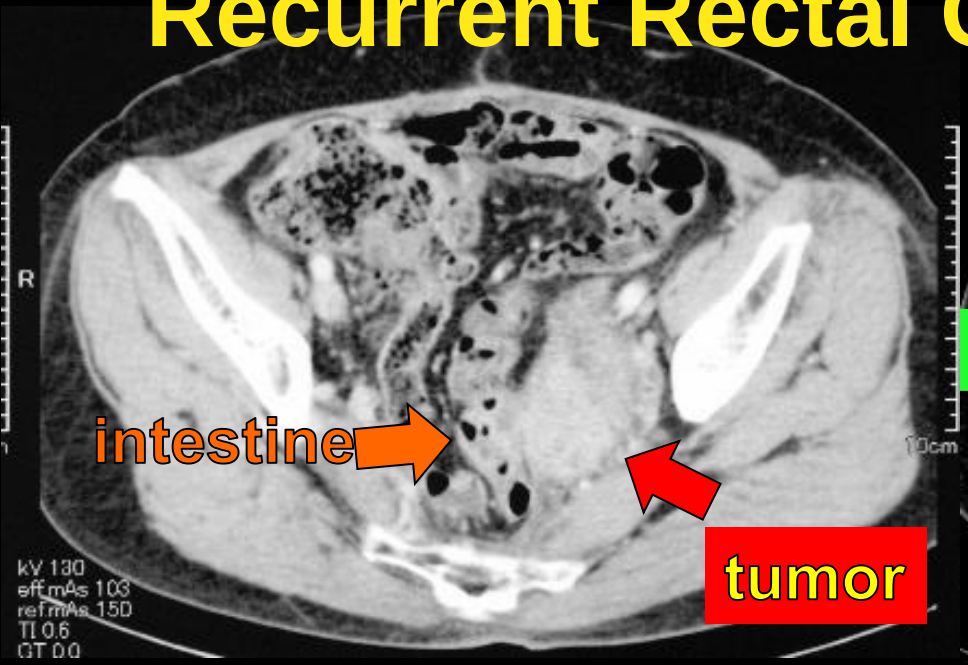
# *Local Control Rates of patients used with the spacer with locally recurrent rectal cancer*

（2003.4～2012.8　87cases）




| Local Control Rate | |
|---|---|
| 2y | 96% |
| 5y | 88% |

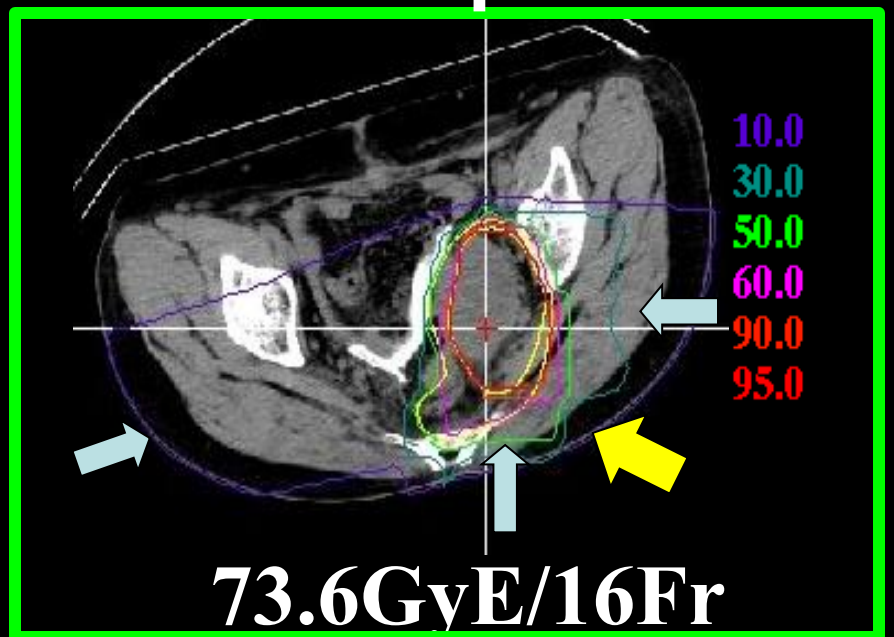
# Recurrent Rectal Cancer : 59y F



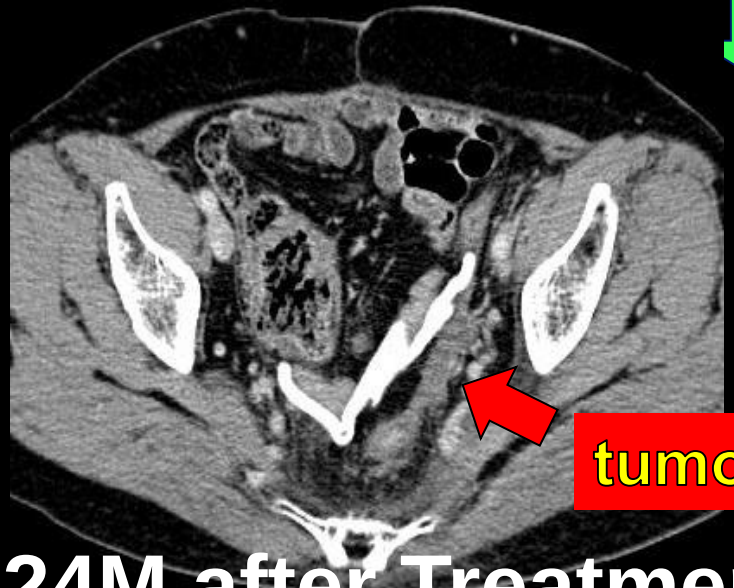

Before Operation




After Operation



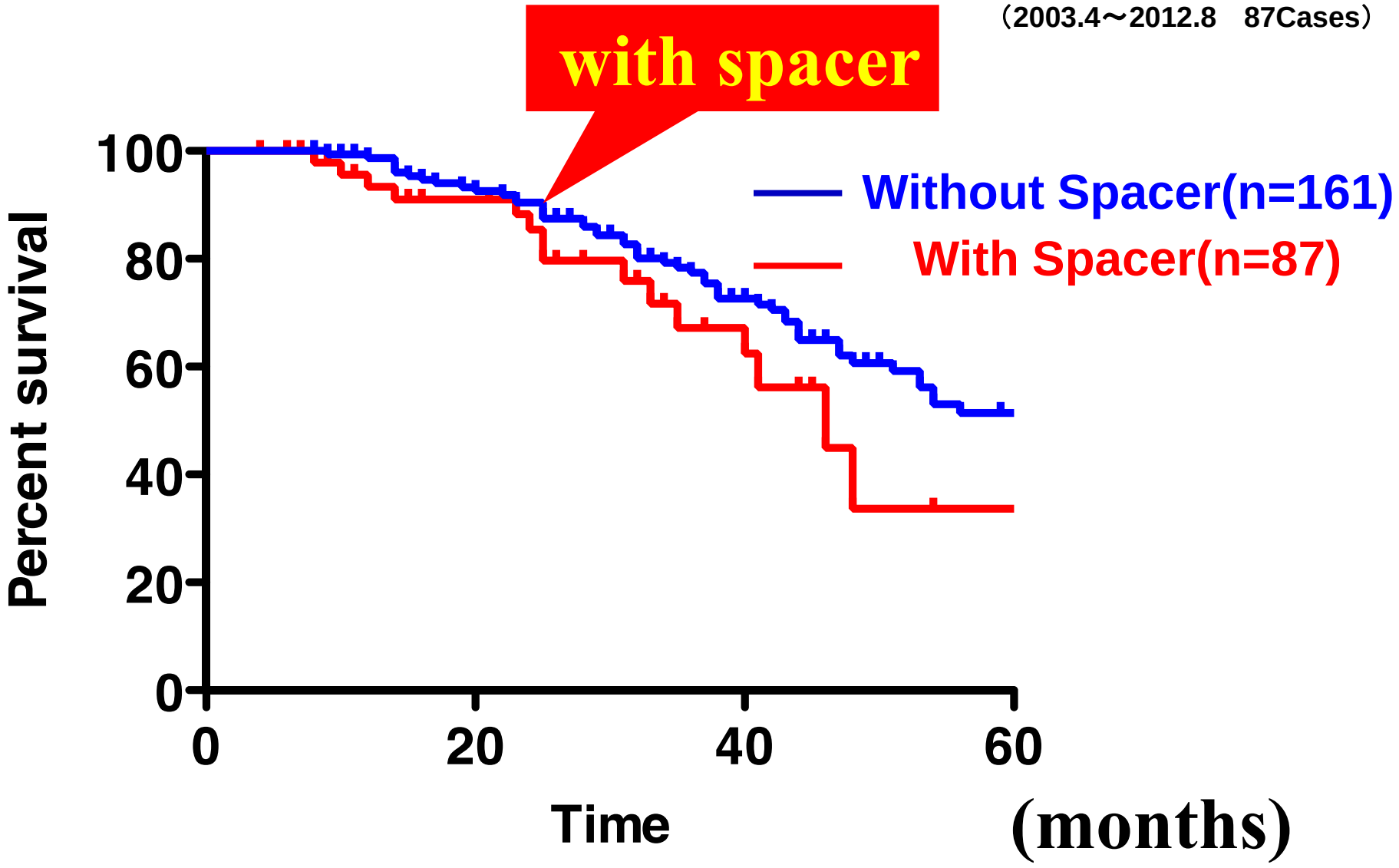

73.6GyE/16Fr




24M after Treatment

# *Survival rates of patients used with the spacer with locally recurrent rectal cancer*

（2003.4～2012.8　87Cases）



# Widen the criteria for recipients of Carbon ion radiotherapy.

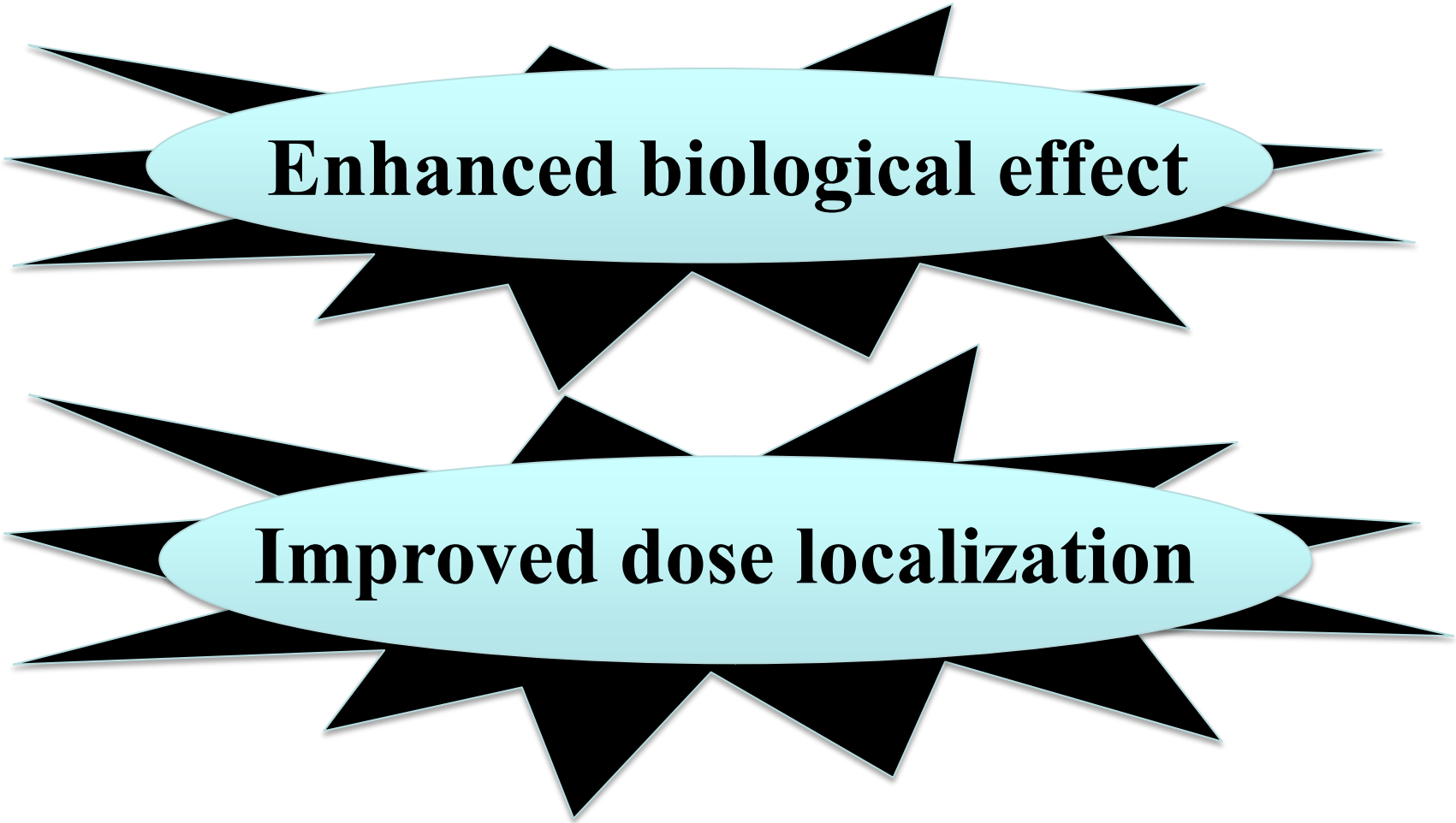
## Reirradiation

X-ray → Recurrence → Carbon Ion

70.4GyE/16f

**The median dose of prior X-ray was 47.6Gy (range, 20-70Gy)**

# Backgrounds of Reirradiation



# Patients and Treatment Characteristics

| Characteristic | Median (Range) or Number of Patients(%) |
|---|---|
| Total | 23cases(23locations) |
| Age at Retreatment | 56(40～74) |
| Male／Female | 19／4 |
| Tumor Sites | |
| presacral | 9cases |
| Indication for prior treatment | |
| Neoadjuvant or adjuvant | 8cases |
| For recurrent tumor | 15 |
| Prior Radiation Dose | 47.6Gy(20-70) |
| Retreatment Interval | 25months(4-66) |
| Size of recurrent tumor | 38.4mm(14-104mm） |
| Spacer before retreatment | 5cases |

**The dose of Carbon Ion is 70.4GyE/16fr**

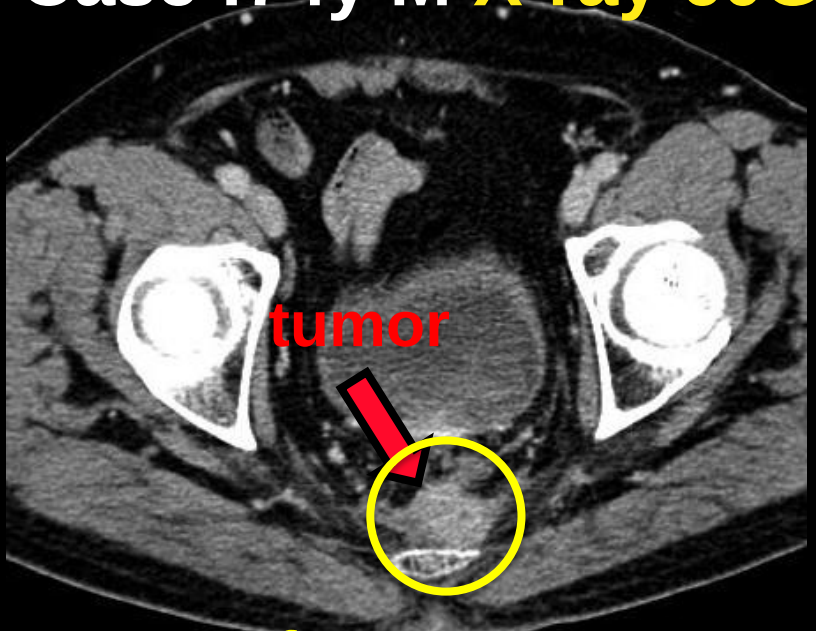
# Comparison between Maximum Normal Tissue Damage by primary CIRT and CIRT as reirradiation

- Primary CIRT :70.4GyE/16回・・17cases
- Reirradiation by CIRT:70.4GyE/16回・・23cases

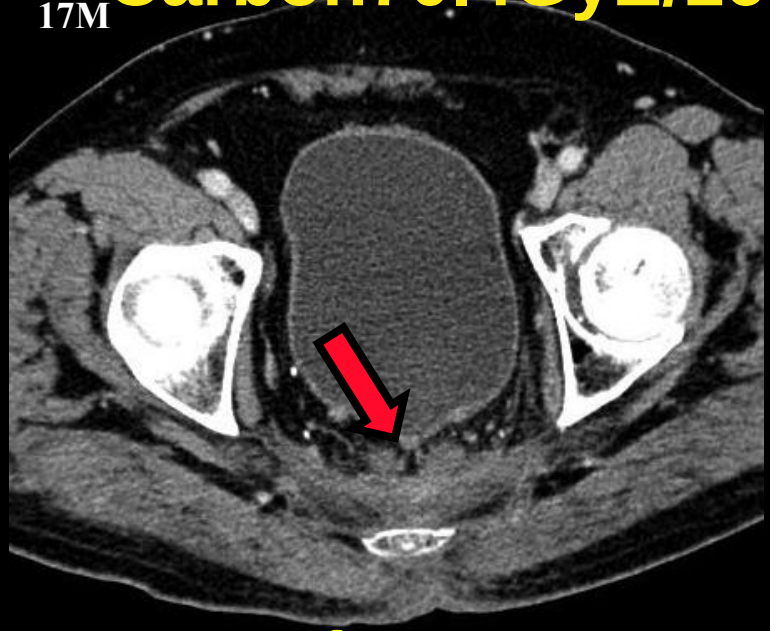
| | Neuropathy | | | | | Gastrointestinal | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Toxicity | No | G0 | G1 | G2 | G3 | No | G0 | G1 | G2 | G3 |
| Primary CIRT | 17 | 6 | 6 | 4 | 1 | 17 | 10 | 4 | 3 | 0 |
| Reirradiation | 23 | 8 | 7 | 6 | 2 | 23 | 17 | 1 | 2 | 3* |

*All of three grade 3 were attributed to operations for spacer before treatment

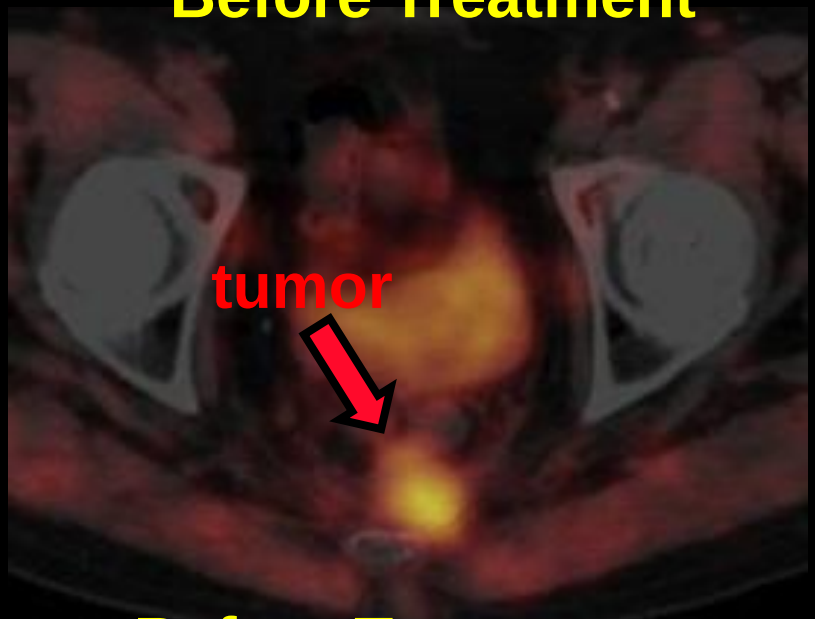
# Case :74y M X-ray 60Gy/30fr. → Carbon70.4GyE/16fr.



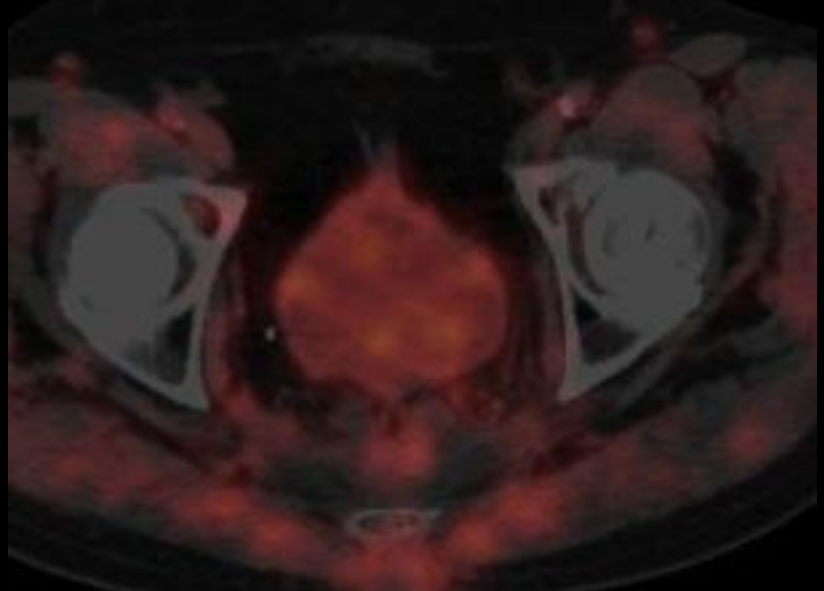

Before Treatment



17M after Treatment

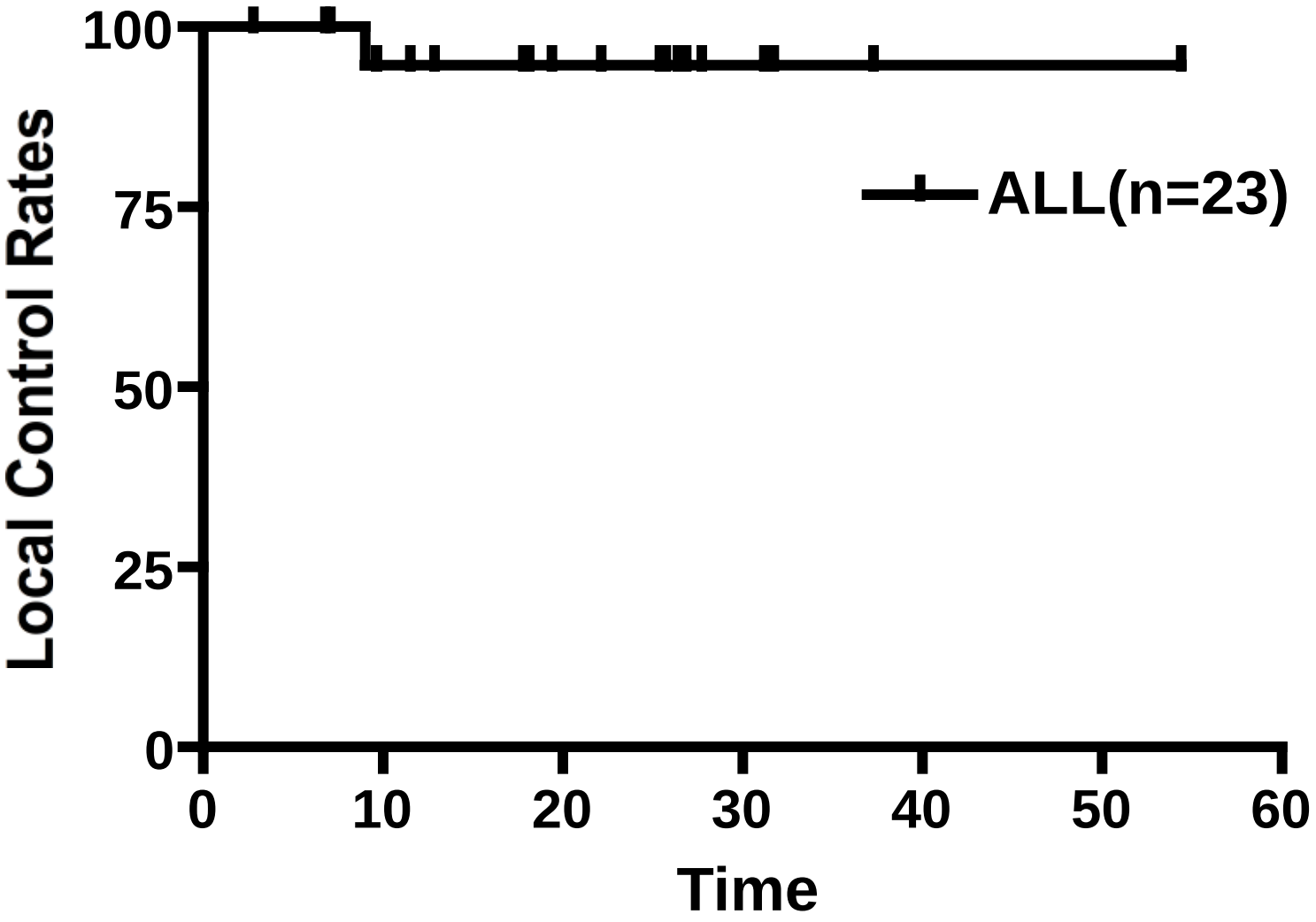



Before Treatment



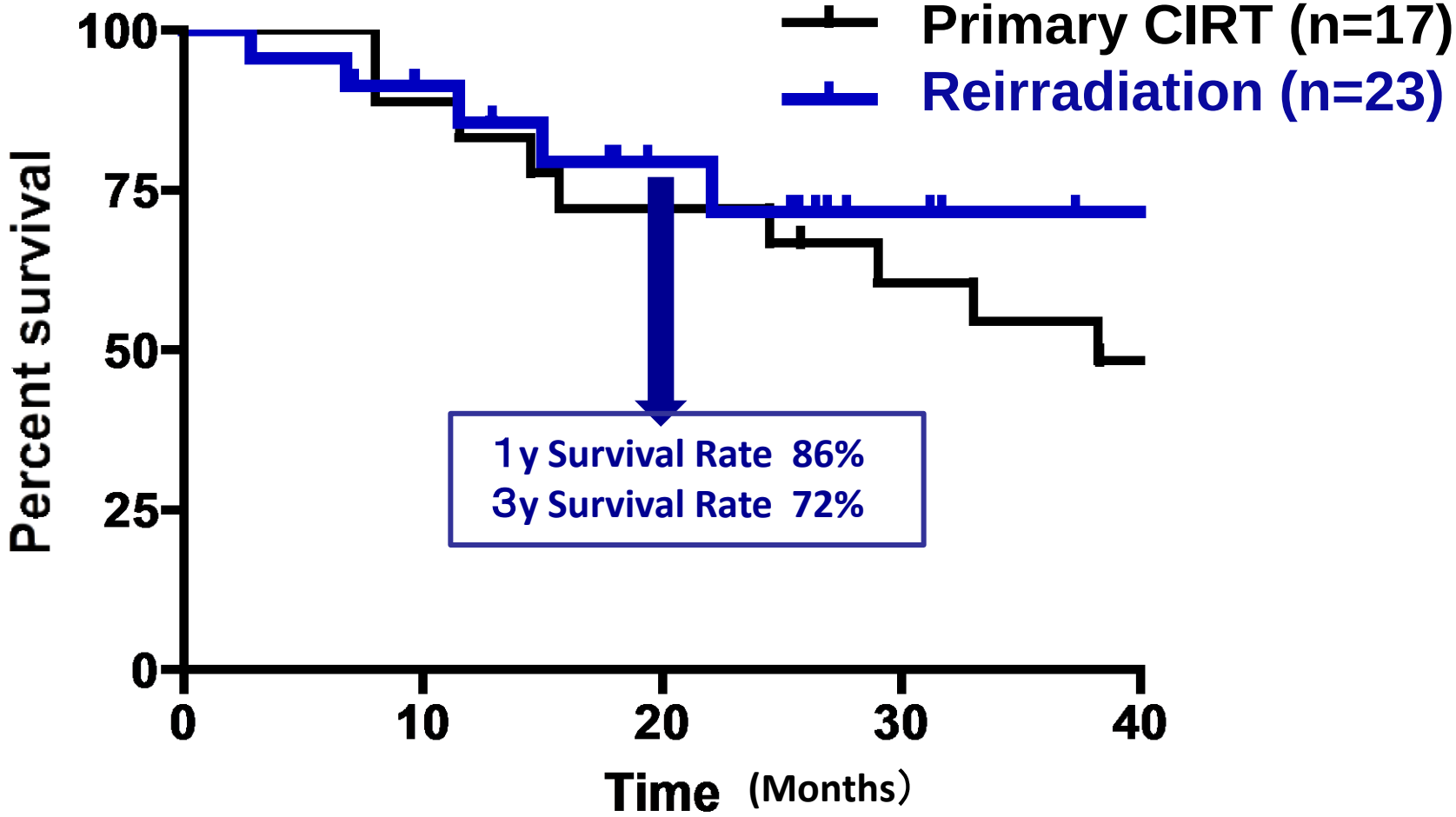
30M after Treatment

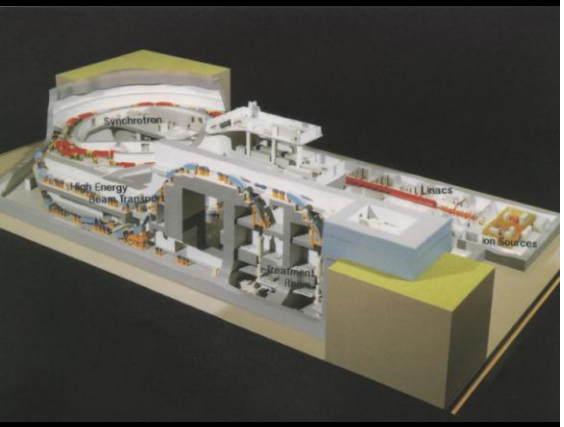
# Local Control Rate of locally recurrent rectal cancer by CIRT as reirradiation



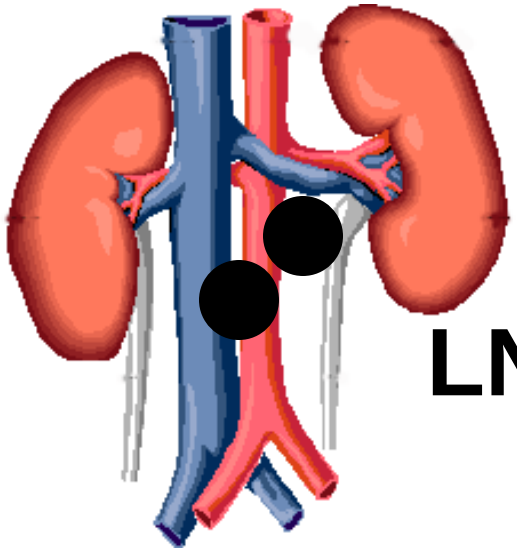
# Overall Survival Curves of locally recurrent rectal cancer by primary CIRT and CIRT as reirradiation

- Primary CIRT :70.4GyE/16f・・17cases
- Reirradiation by CIRT:70.4GyE/16f・・23cases






# Carbon-ion RT for Para-Aortic Lymph node Metastasis from Colorectal Cancer

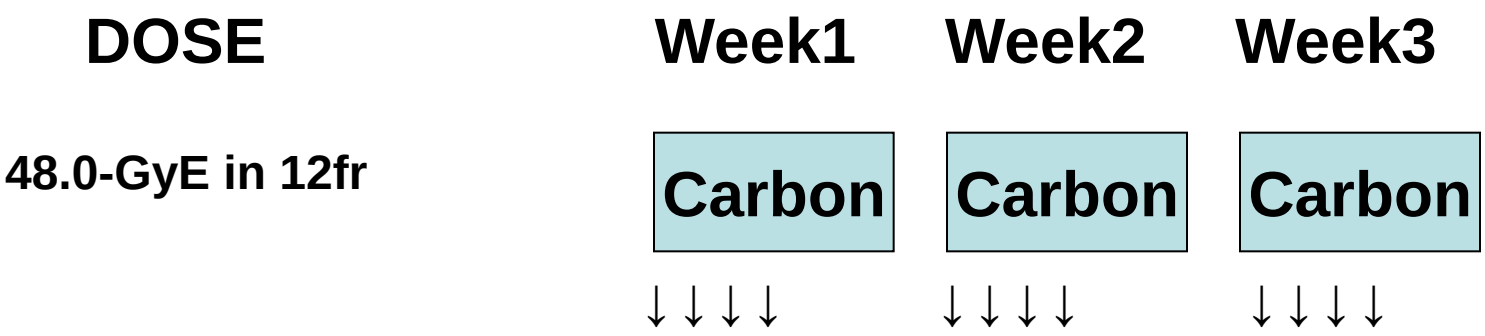


LN meta

Division of Radiation Medicine,
Research Center of Charged Particle Therapy
National Institute of Radiological Sciences,

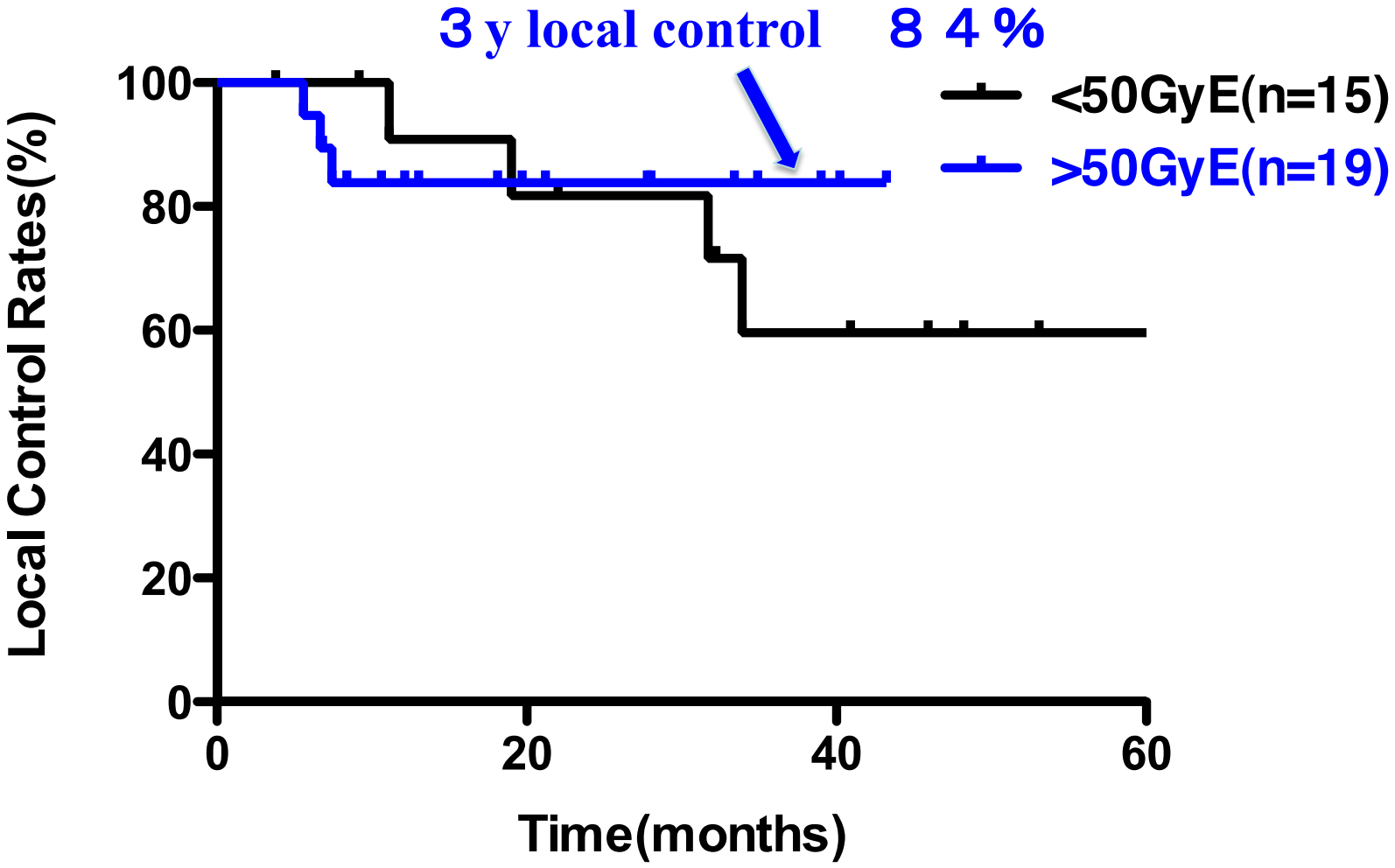
# *Carbon-ion therapy for patients with para-aortic lymph node metastasis from colorectal cancer*

| Total Dose | Number |
|---|---|
| 48GyE/12fr | 12(+3) |
| 50.4GyE/12fr | 7 |
| 52.8GyE/12fr | 12 |

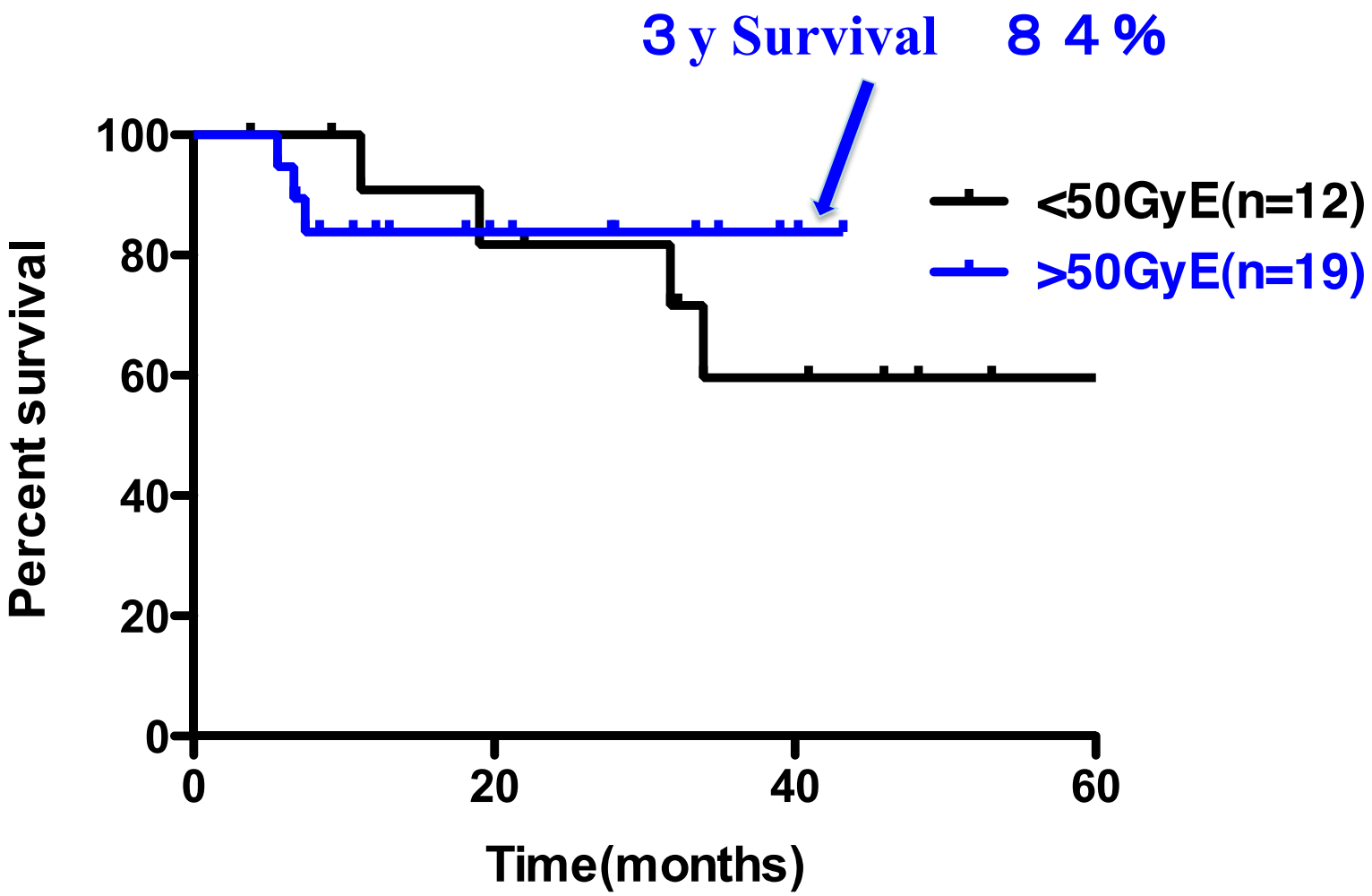


# Local Control Rates by total dose

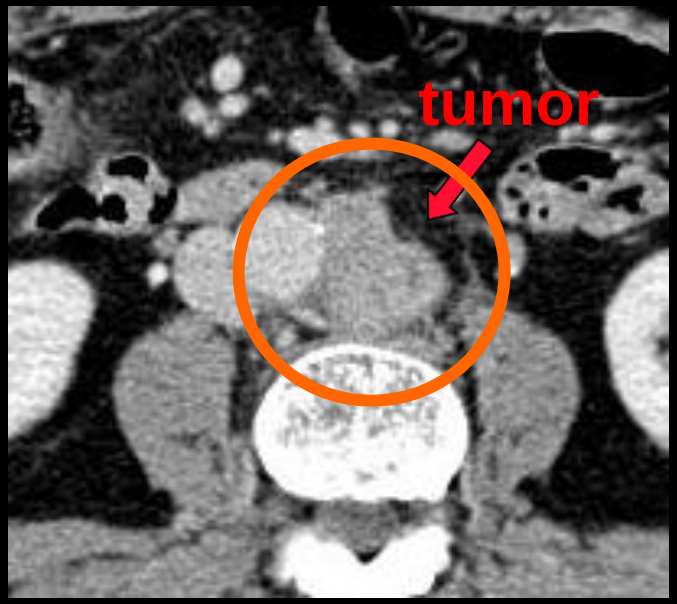
**Carbon-ion therapy for patients with para-aortic lymph node metastasis**



# Overall Survival Rates *by total dose*

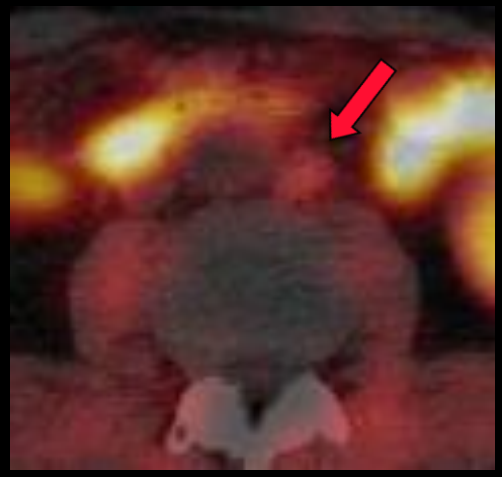


# Case : 85y Male 50.4GyE/12fr



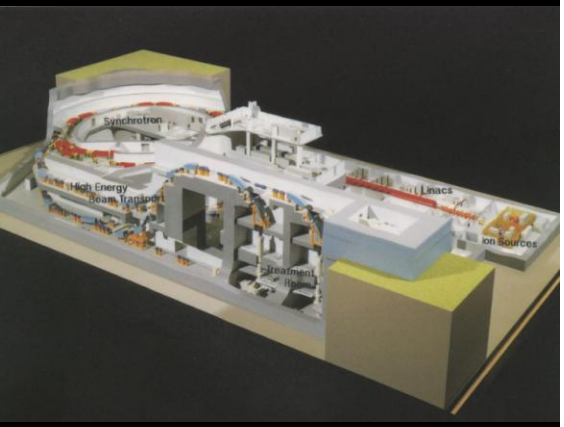

Before Treatment

24 months after Treatment

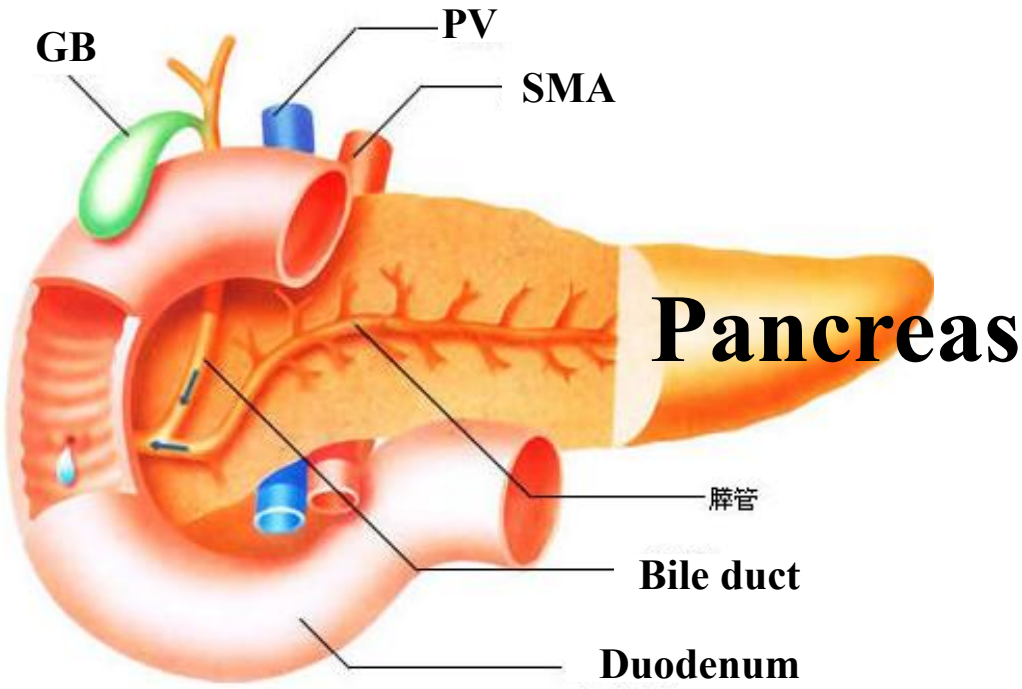



Before Treatment

2 months after Treatment

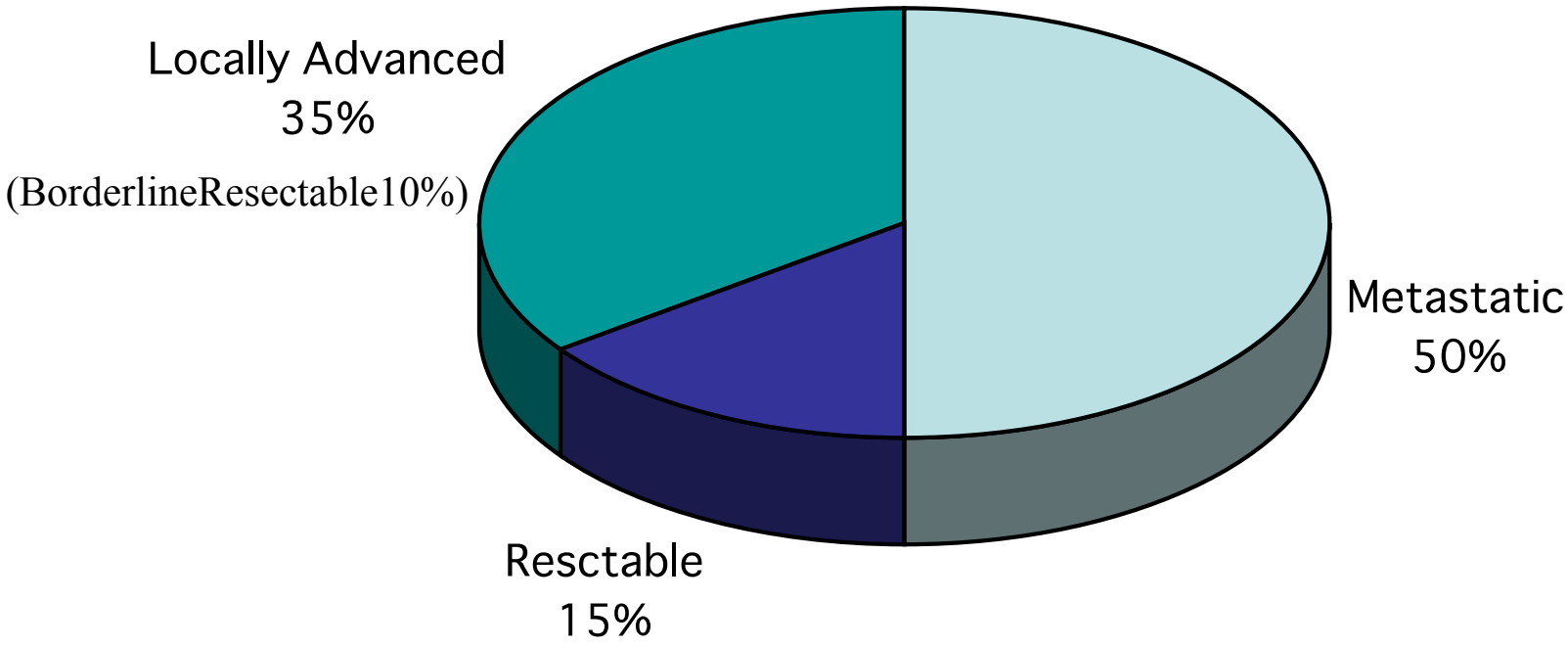



# Carbon-ion therapy for patients with Pancreas Cancer




Research Center of
Charged Particle Therapy
National Institute of
Radiological Sciences,

# Distribution of Pancreatic Cancers at Diagnosis



# Stage at Diagnosis and Prognosis

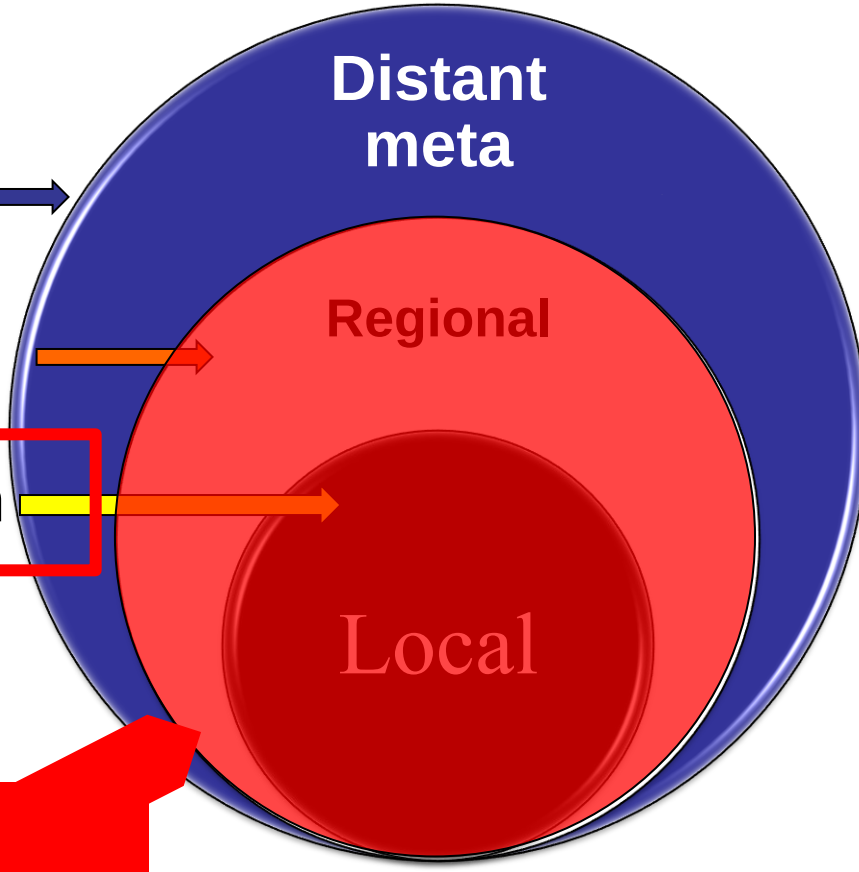
(Pancreas cancer)

| Stage | Median S | 1 y Surv | 2 y Surv |
|---|---|---|---|
| Operable | 11-18M | 20-50% | 18-42% |
| Locally advanced | 5-8M | 4-30% | |
| Metastases | 2.5-4M | 0-10% | |

| | 5-y Survival |
|---|---|
| Pancreas | 5% |
| Lung | 20% |
| All Cancer | 50% |

# Why pancreas cancer is resistant to conventional treatments？

1. Easy distant metastasis
2. Easy infiltration of neuroplexus
3. Large radioresistant cell fraction

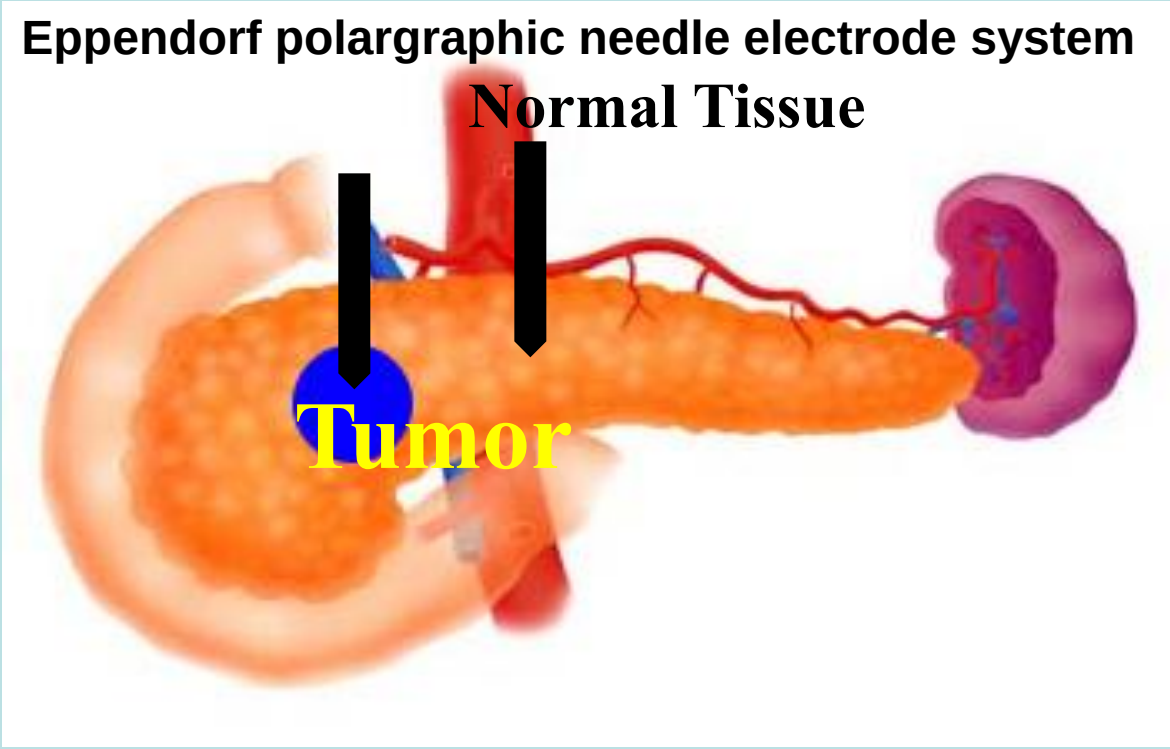



**Carbon-ion can be expected to control them.**

# $pO_2$ measurements in pancreatic tumors and normal pancreatic tissue

| Patient | Tumor | Normal Tissue |
|---|---|---|
| 1 | | |
| 2 | | |
| 3 | | |
| 4 | | |
| 5 | | |
| 6 | | |
| 7 | | |

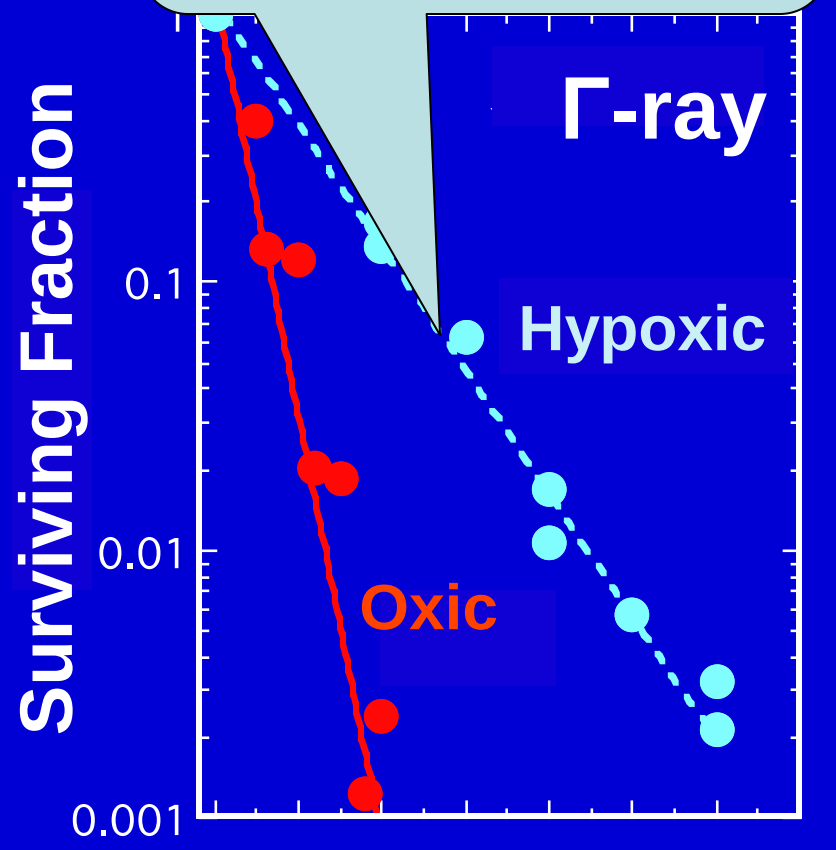
Eppendorf polargraphic needle electrode system



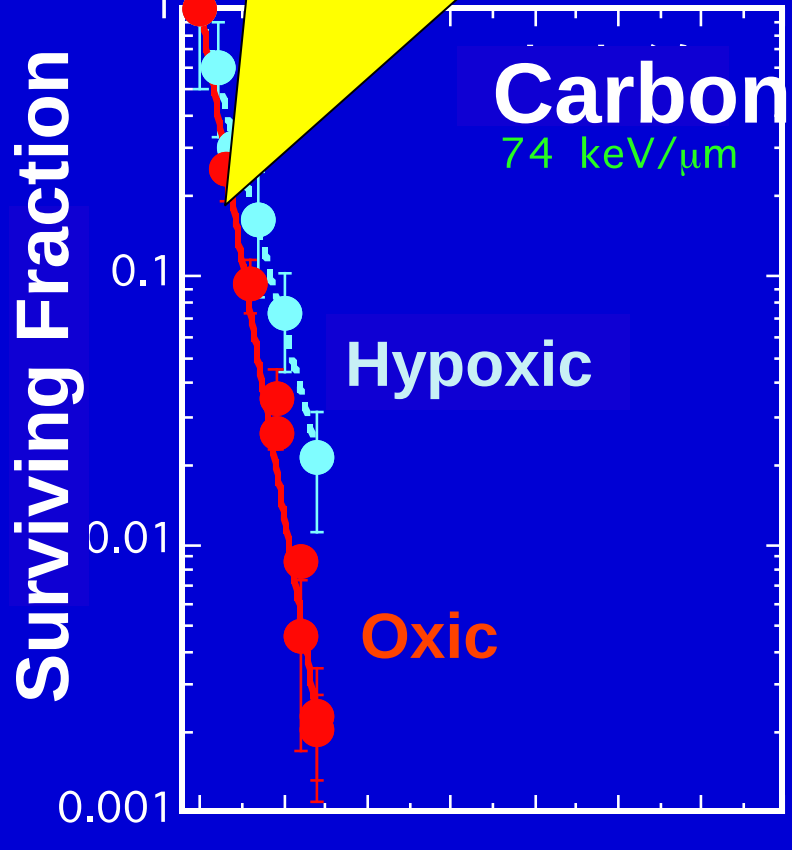

(Koong AC, IJROBP 48, 2000)

# Comparison of Oxygen effects for cytotoxic reactions of gamma-ray and carbon-ion beam

In gamma-ray hypoxic cells are radioresistant three times as much as oxic cells

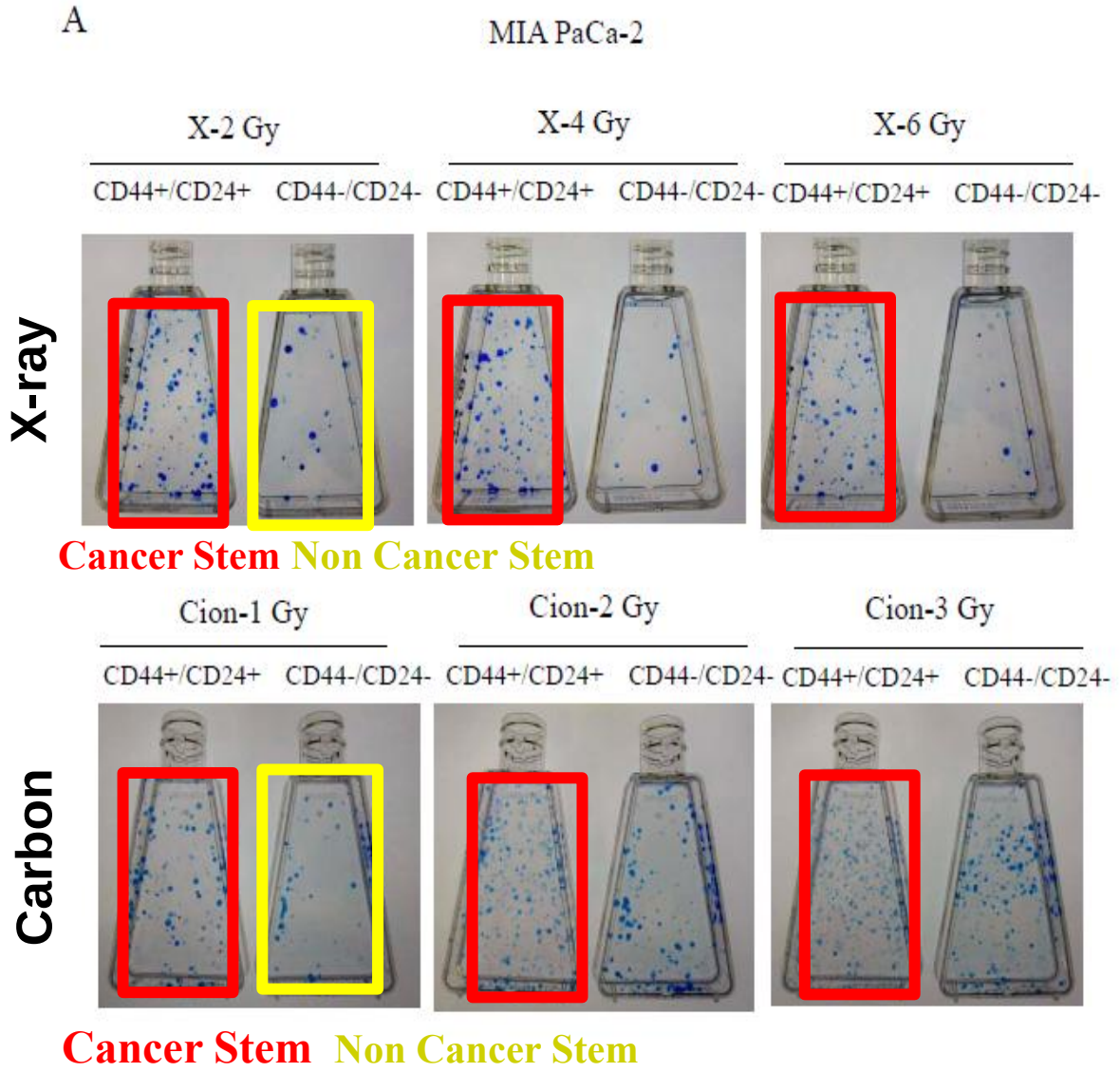


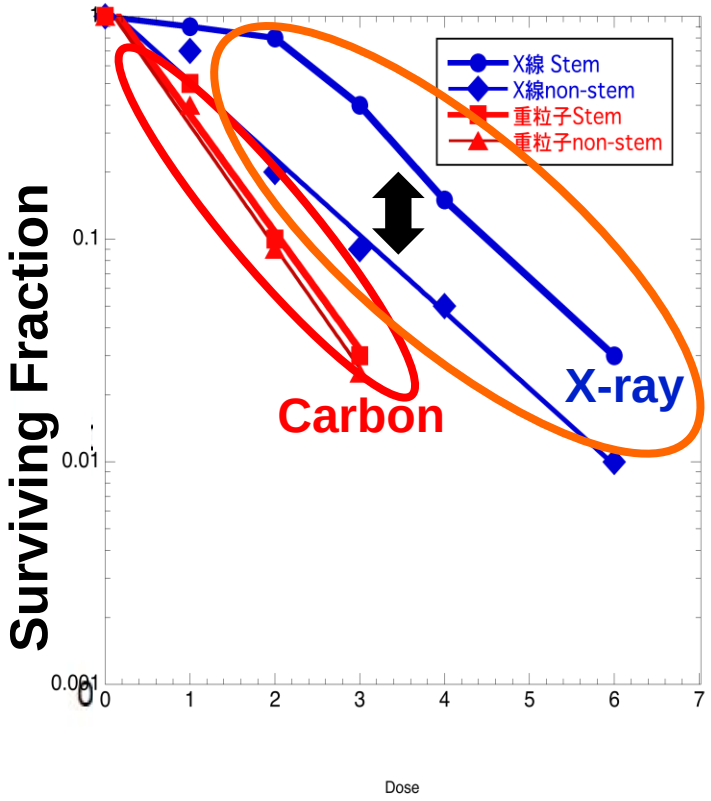

In carbon beam the sensitivities of oxic and hypoxic cells are almost same




By Dr. Koichi Ando

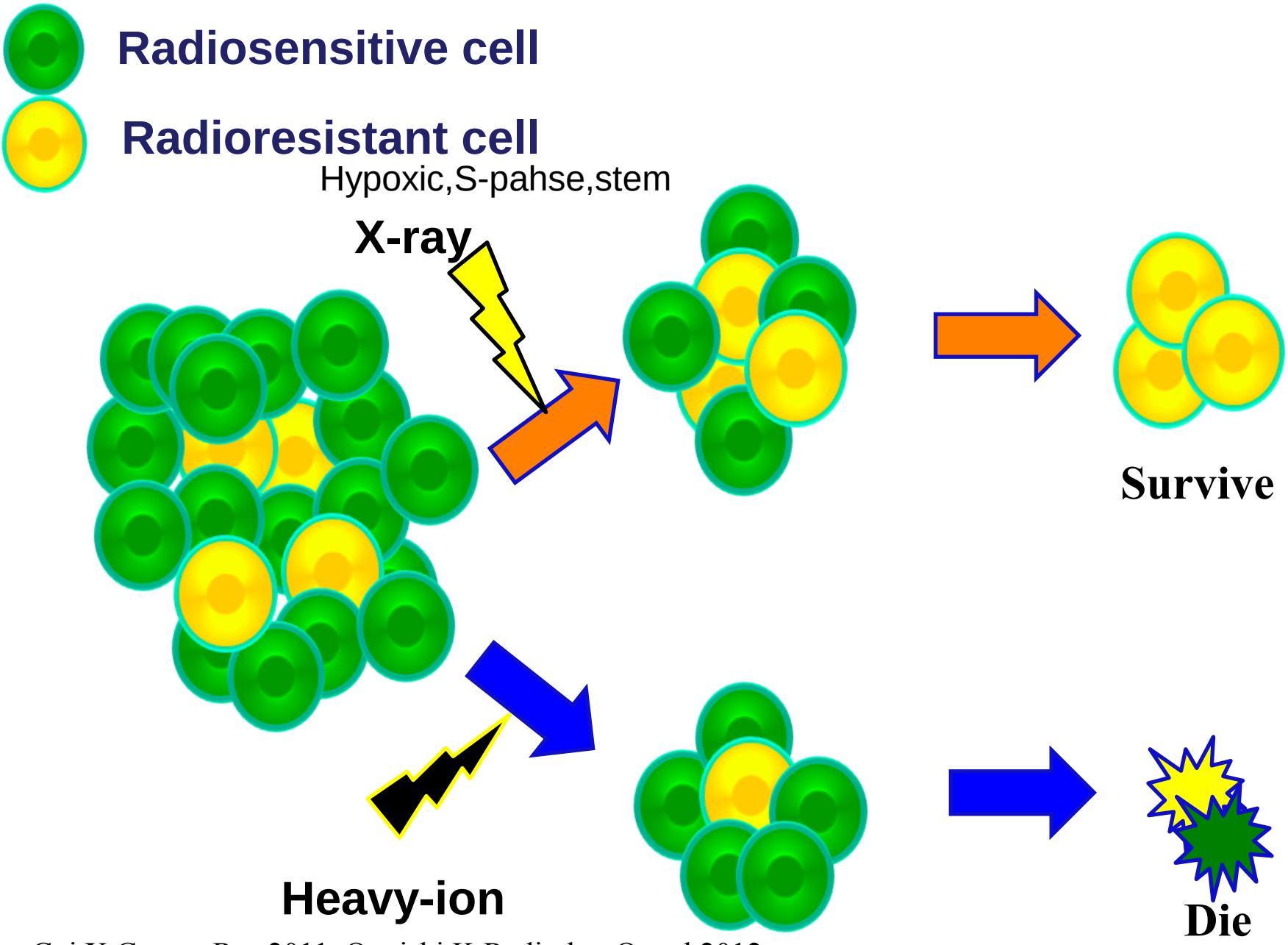
# Different Effects of Carbon ion beams and X-rays on Survival in Pancreatic Cancer Stem Cells




Cui X:Cancer Res 2011, Oonishi K:Radiother Oncol 2012

# The effects of cell killing by X-ray and Heavy-ion




Cui X:Cancer Res 2011, Oonishi K:Radiother Oncol 2012

# Why pancreas cancer is resistant to conventional treatments？

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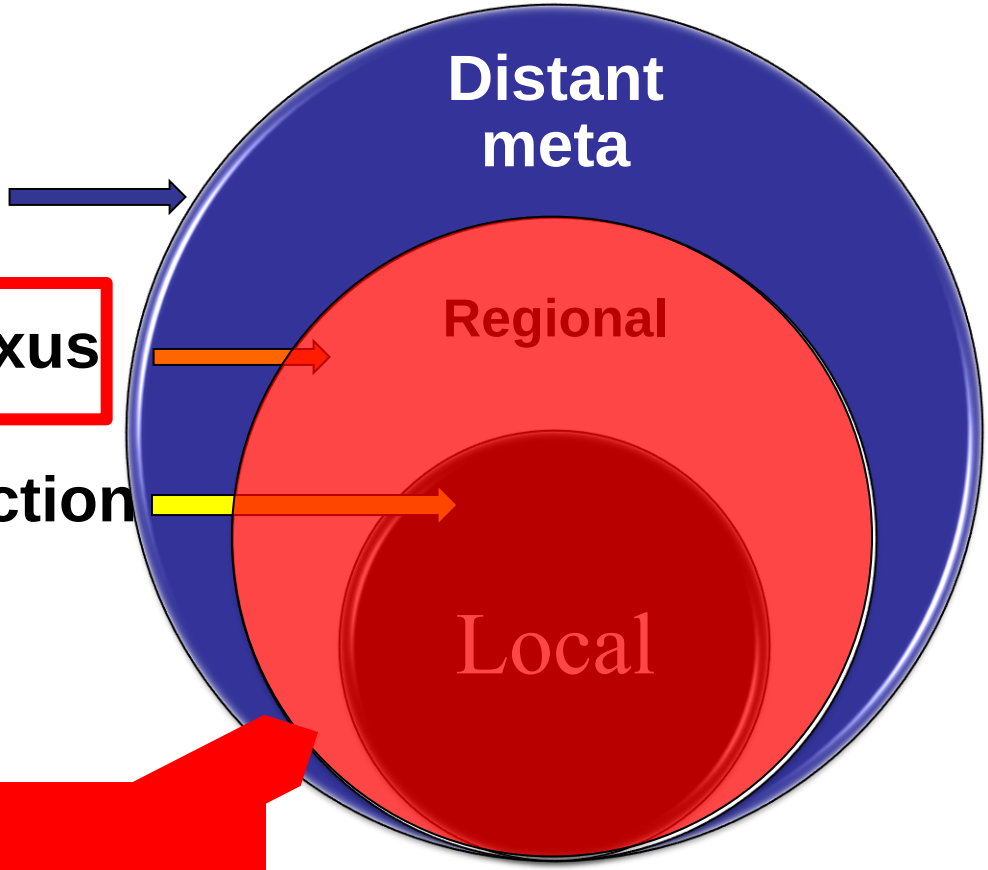
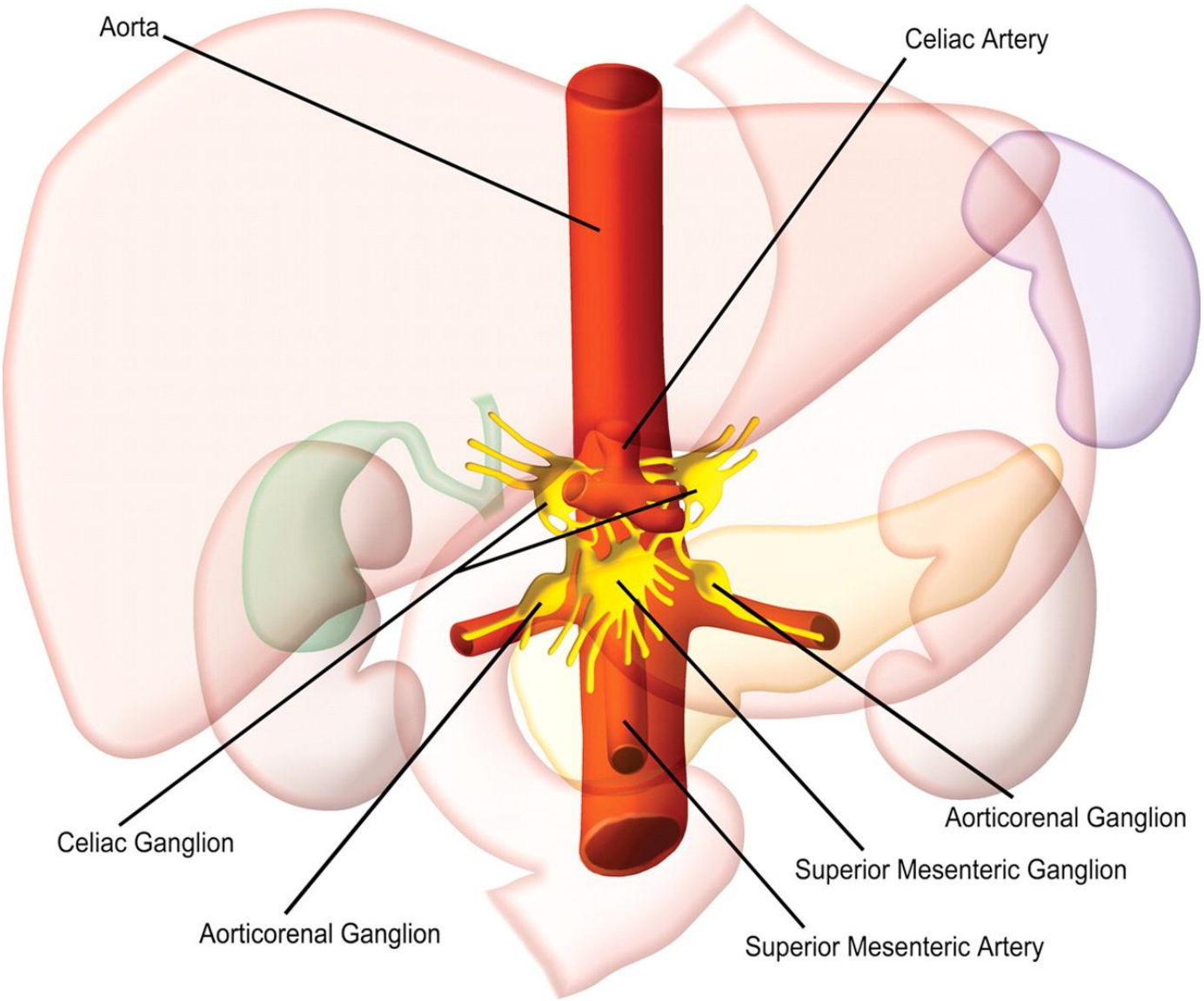



**Carbon-ion can be expected to control them.**

# Local recurrent sites after operation for Pancreatic cancer

| Recurrent sites | 140 cases |
|---|---|
| Neuroplexus | 120(86%) |
| Residual Pancreas | 28(20%) |

# Neuroplexus lesions around the Pancreas



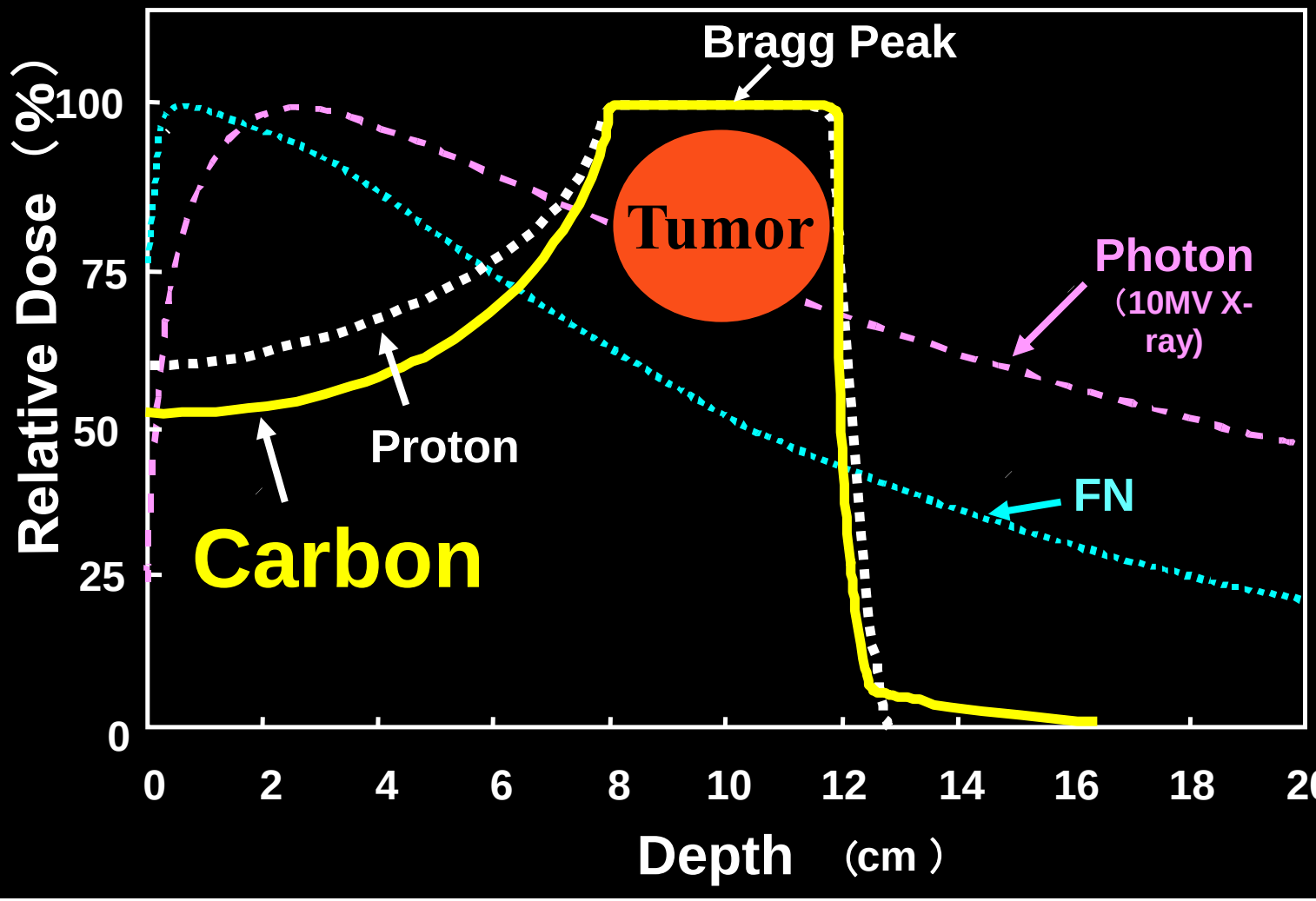

Spinal cord

# Dose Distribution

Case: 75y male

52.8 GyE/ 12fr

## Depth-Dose Distribution in Various Radiation




CTV : GTV+paraaortic area (celiac-SMA level), retroperitoneal area (Neuroplex

Respiratory Gating System

# Standard versus Extended lymphadenectomy Associated with pancreatoduodenectomy

| | Italy | | Johns Hopkins | | Mayo Clinic | | Japan | |
|---|---|---|---|---|---|---|---|---|
| | Stand | Extend | Stand | Extend | Stand | Extend | Stand | Extend |
| Numbe | | | | | | | | |
| Operat | | | | | | | | 7 |
| Transfu | | | | | | | | 4 |
| Numbe | | | | | | | | .1 |
| Compli | | | | | | | | % |
| Mortal | | | | | | | | 2%) |
| 3y-Surv | | | | | | | | |
| 5y-Surv | | | | | | | | |
| MST（M | | | | | | | | |
| | NS | | NS | | NS | | NS | |

**Dissected Lymphnodes by Standard Lymphadectomy**

**①Peripancreas**

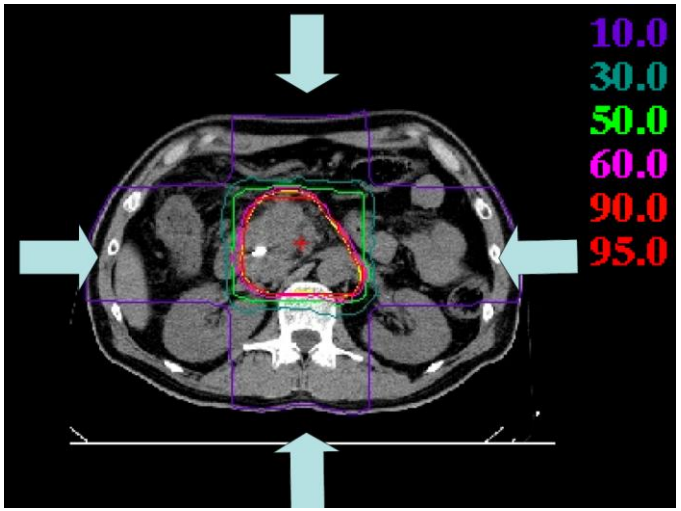
**②Celiac artery + Common hepatic artery**

**③SMA**

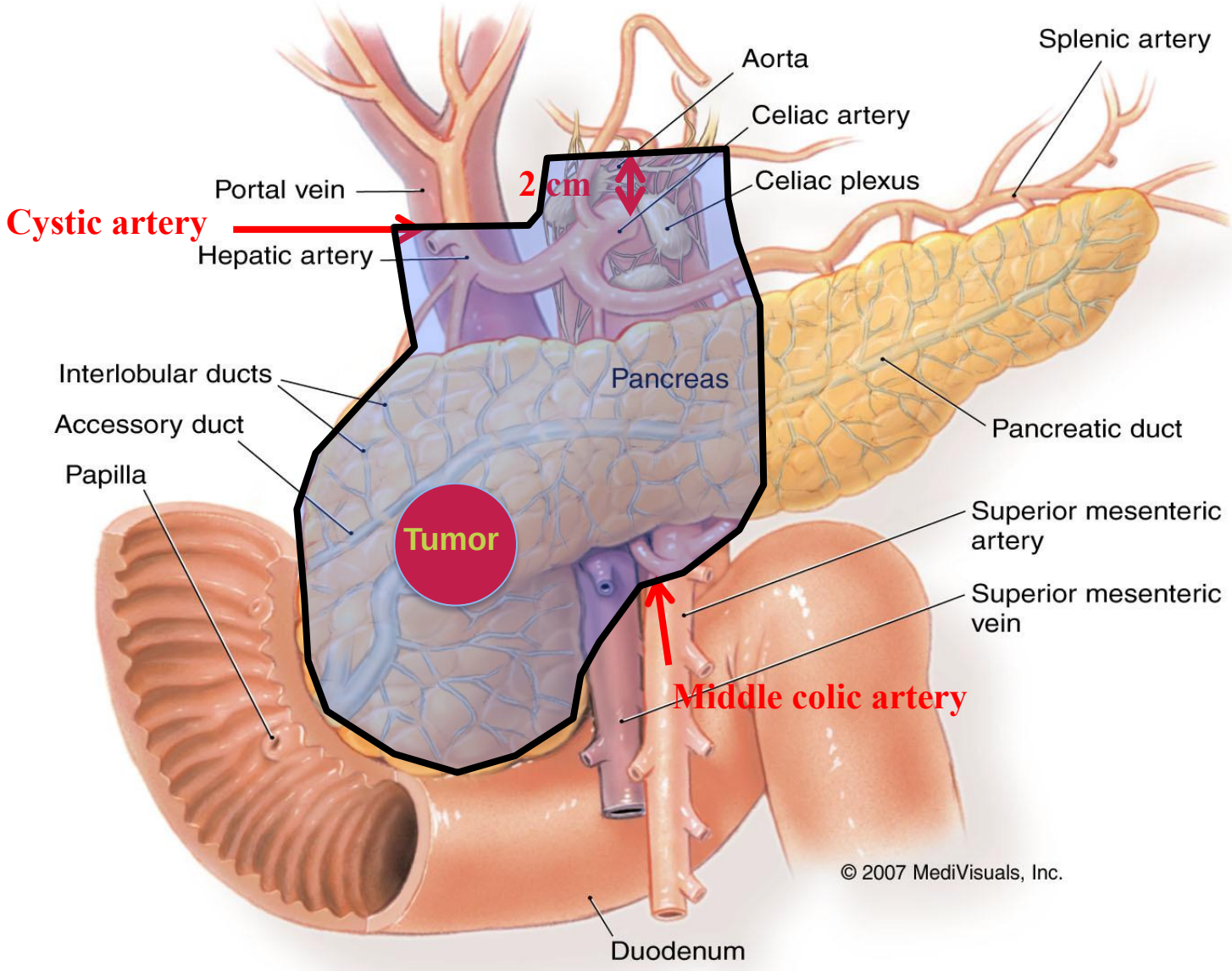
**④Hepatoduodenal ligament**

# Radiation Method

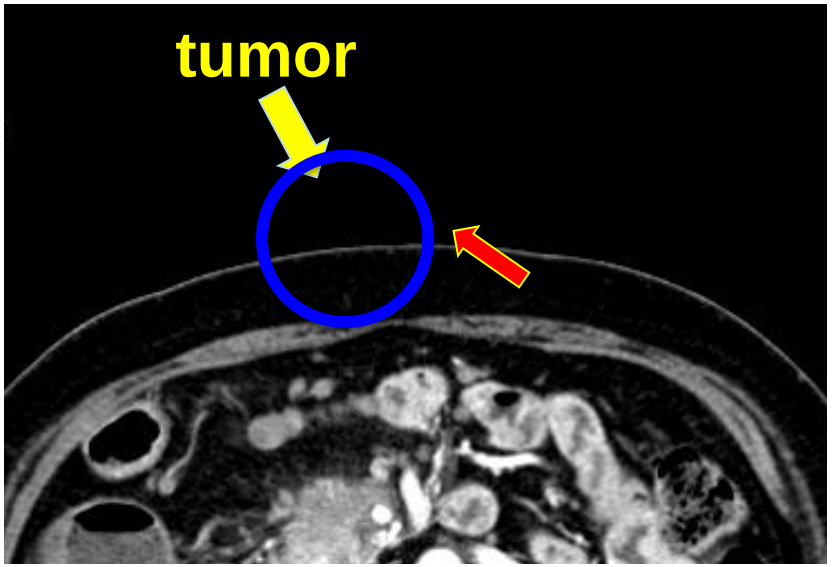
- 3-D Conformal Planning (2.5mm-thick CT Images)
- GTV : primary tumor and involved node
- CTV : GTV+Neuroplexus lesions(periarterial area : Celiac-SMA paraaorta)+Proximal LN
- PTV : CTV + 0.5cm (exclude GI)
- Respiratory Gating System
- Radiation Field : 4-field



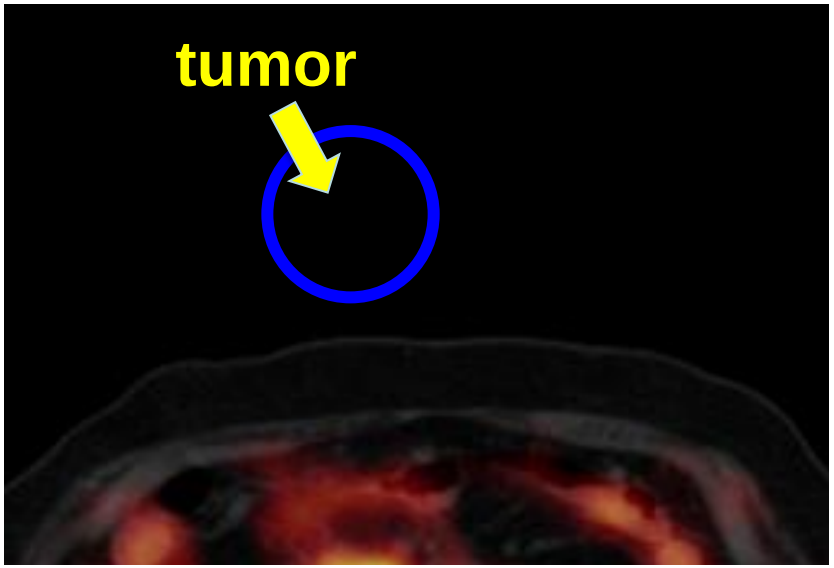
# Radiation Field for Pancreatic head cancer



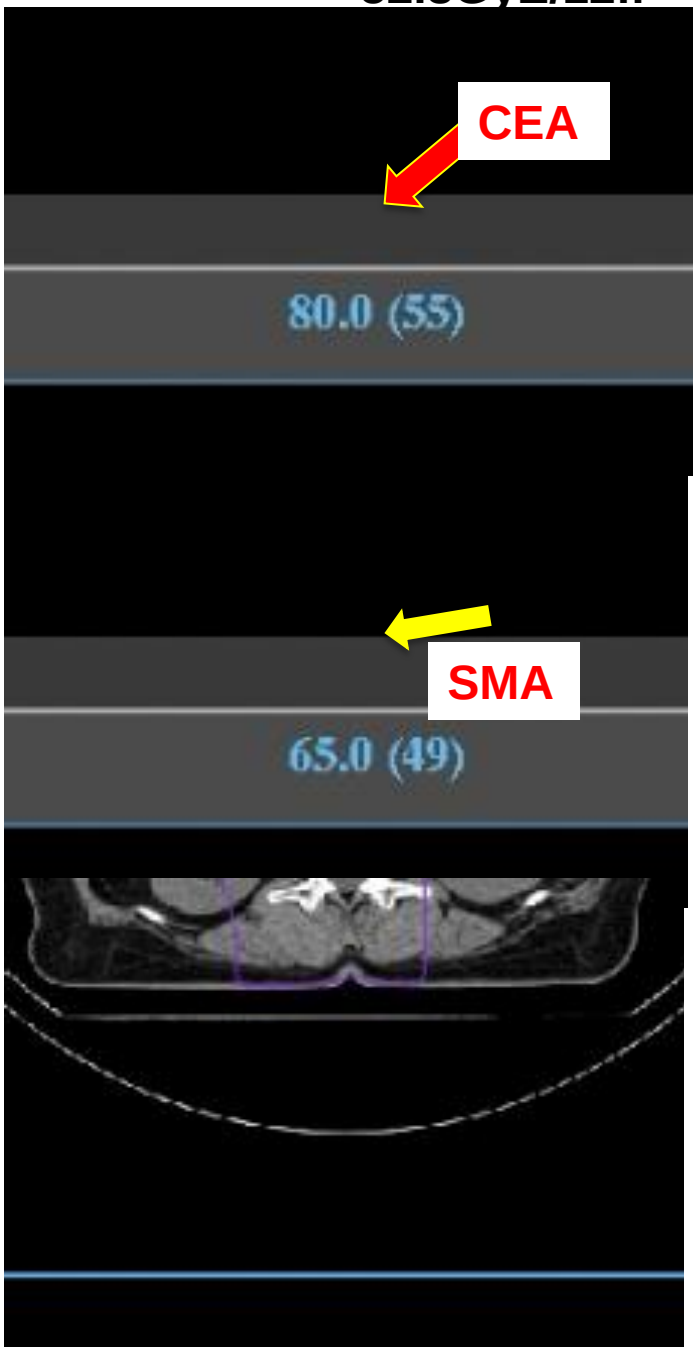
# Case: 63y Female Pancreatic head cancer 52.8GyE/12fr




CT




FDG PET



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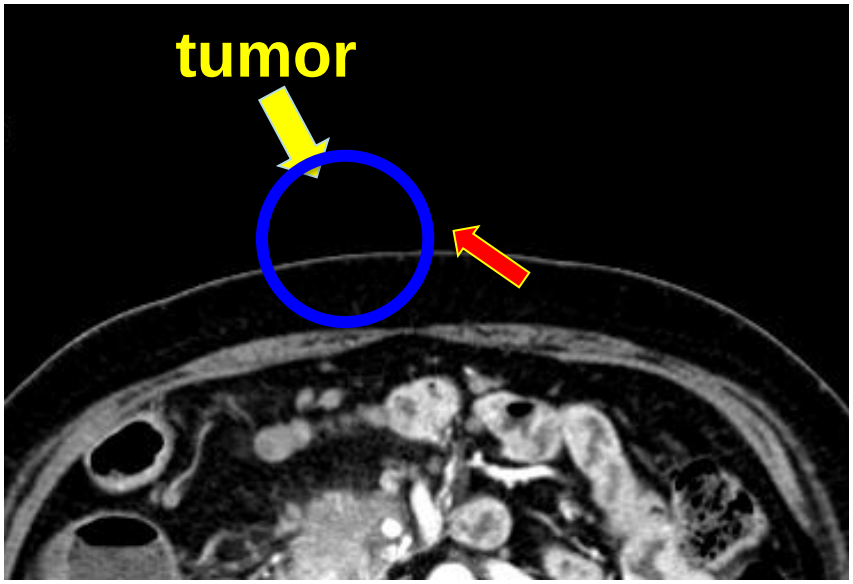
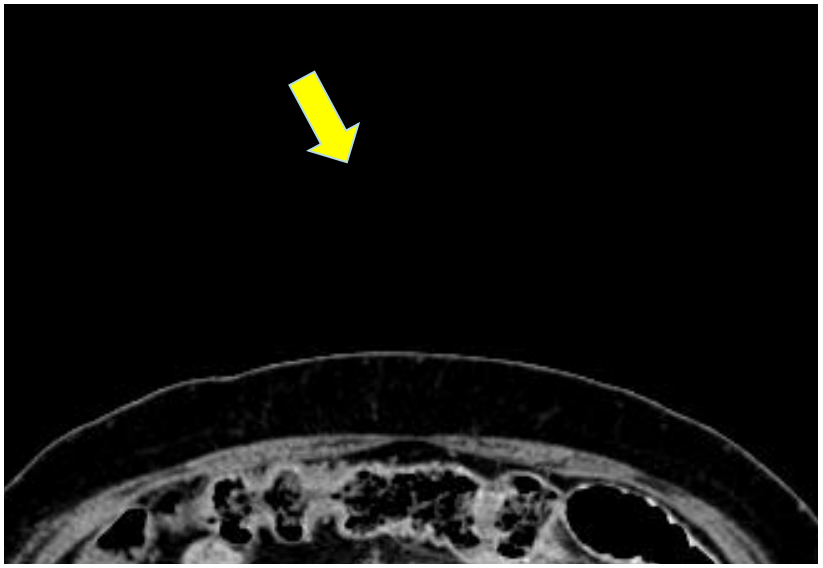
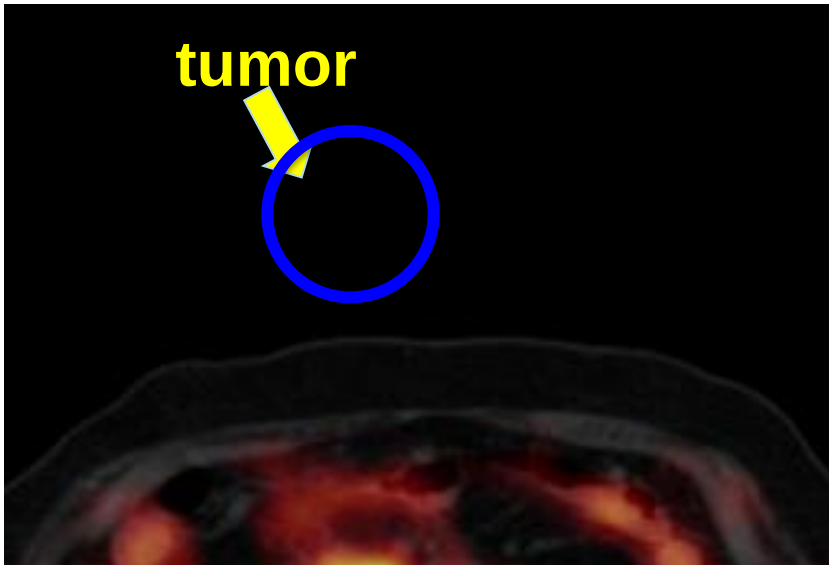



CT



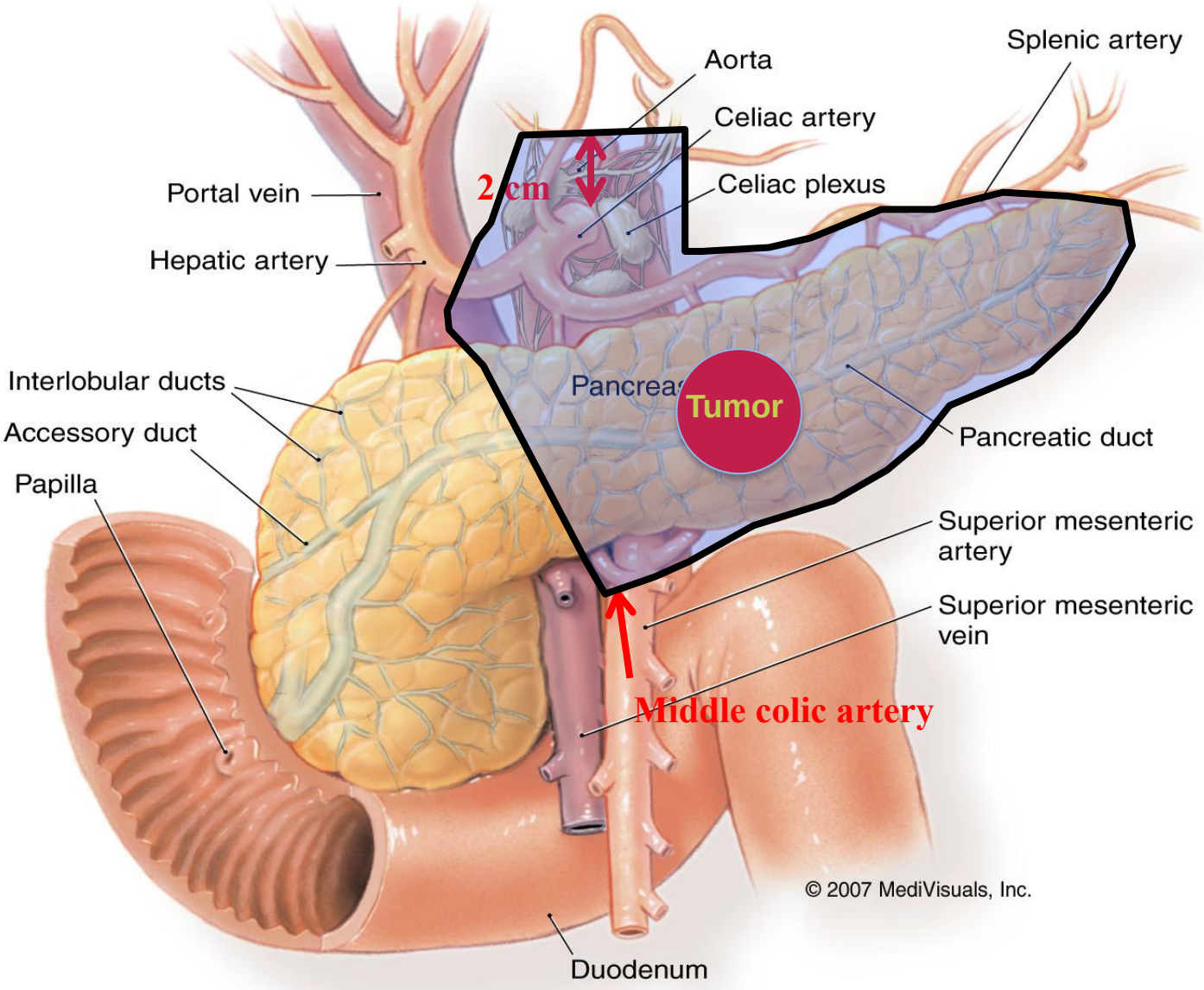
12 M after treatment



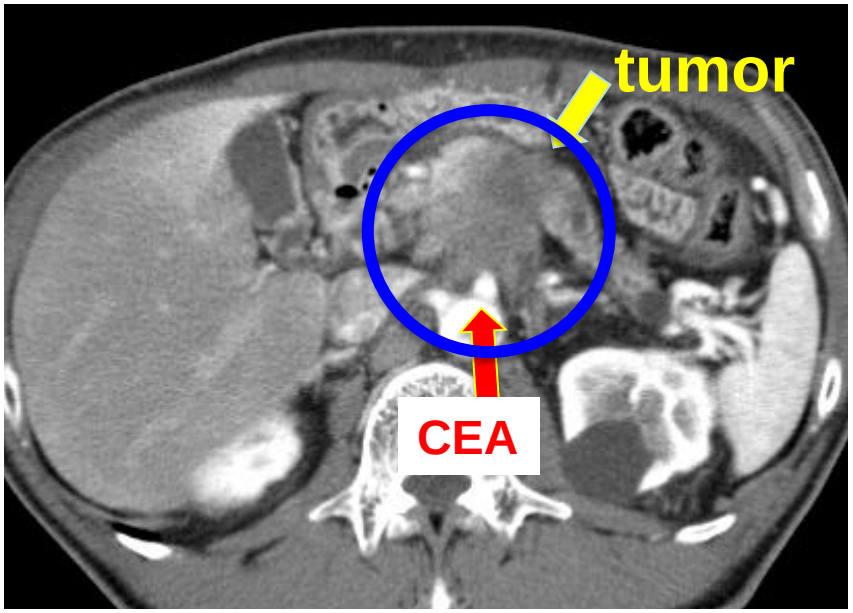

FDG PET

12 M after treatment

# Radiation Field for Pancreatic body cancer

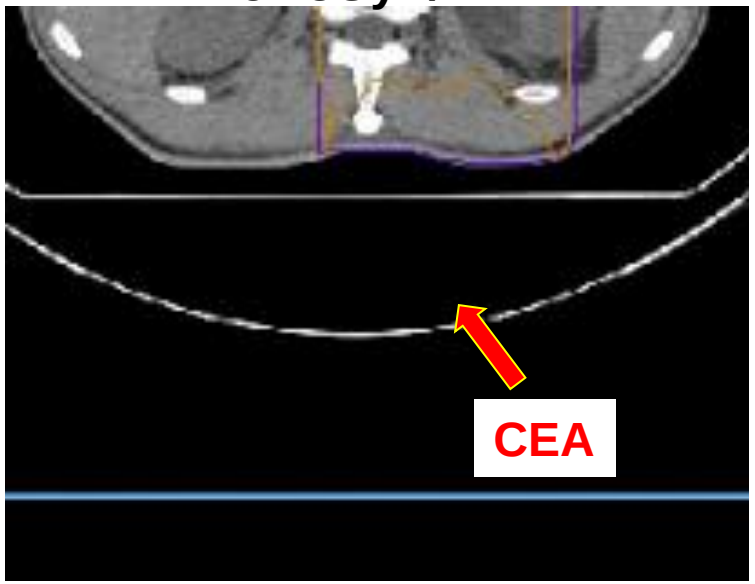


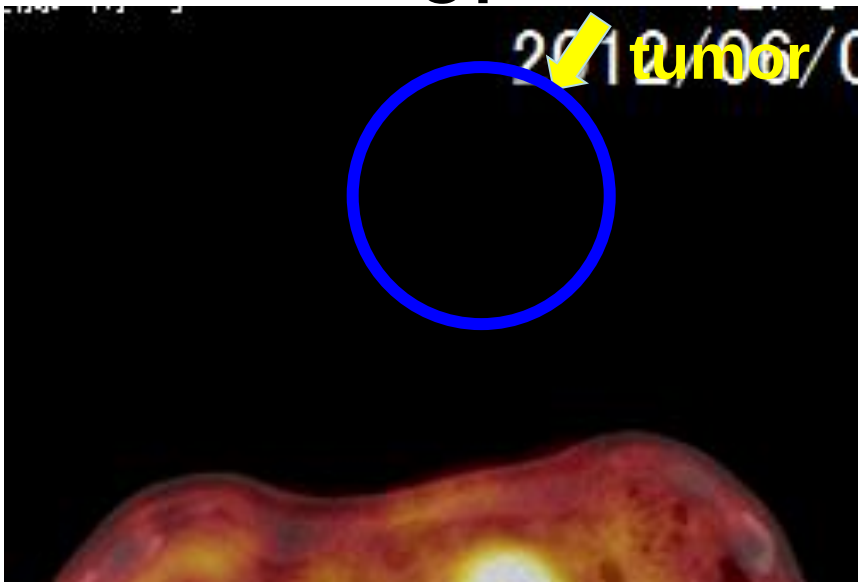
# Case: 56y Male Pancreatic body cancer



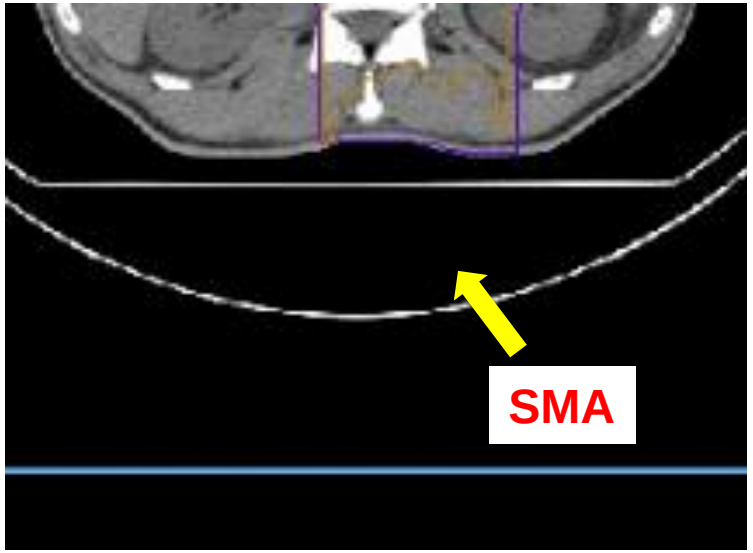

CT

52.8GyE/12fr




FDG PET



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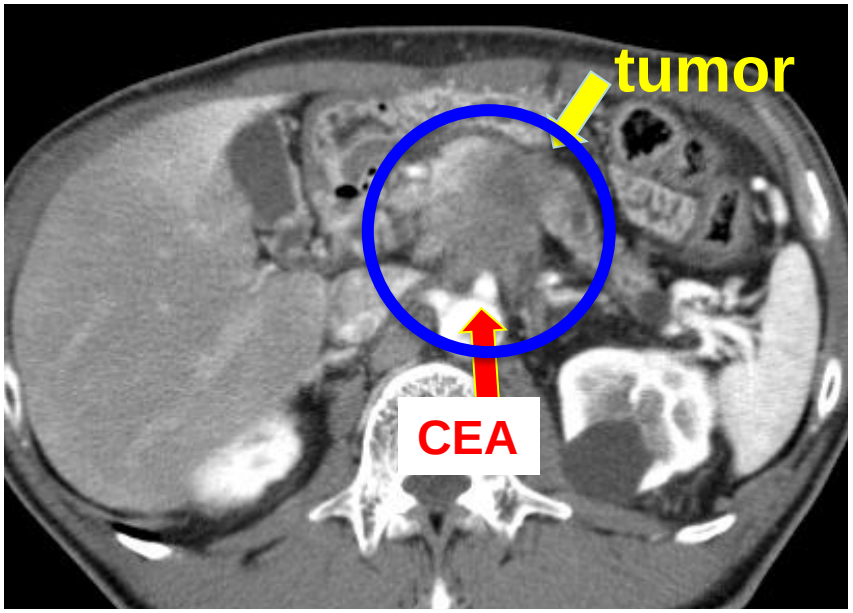
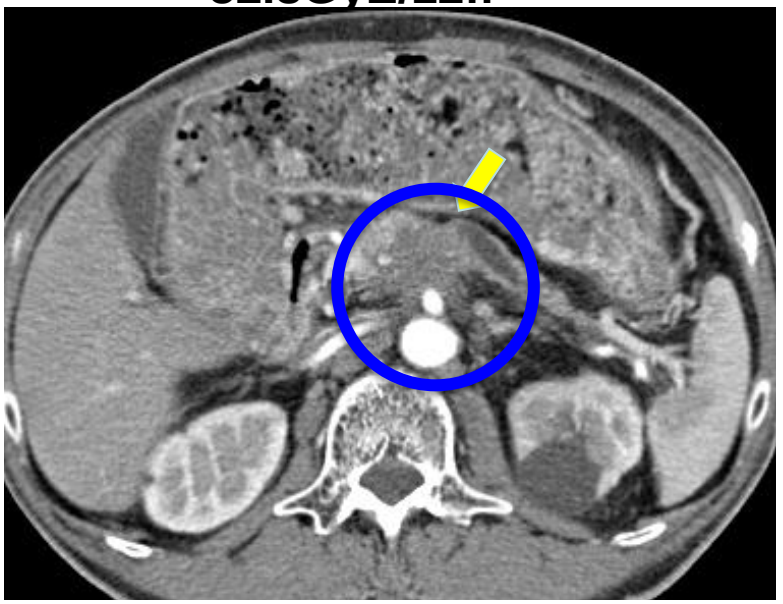
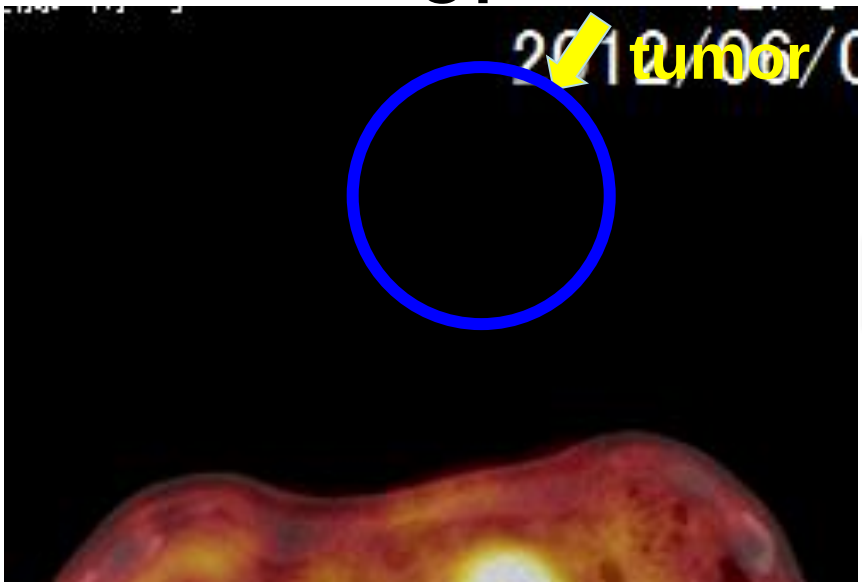



CT

52.8GyE/12fr



12 M after treatment




FDG PET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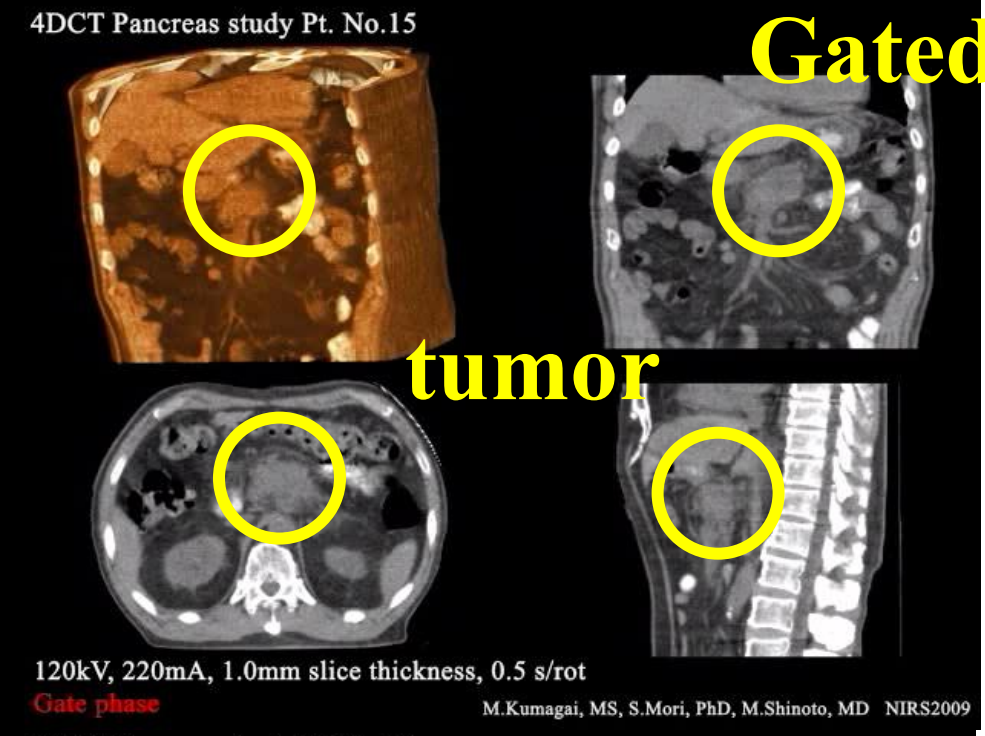
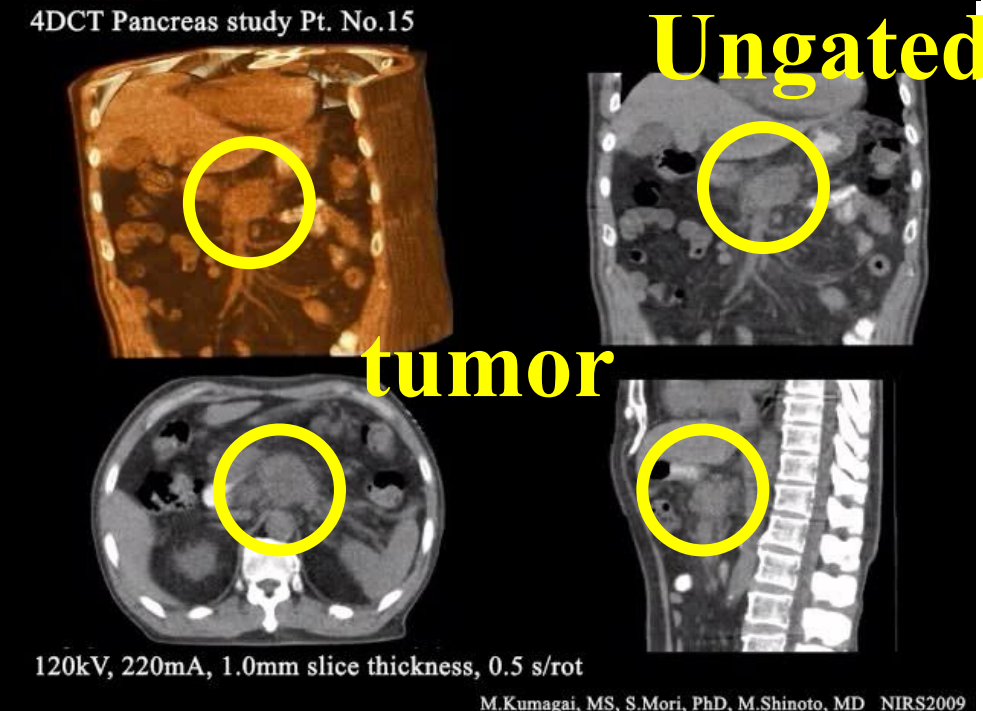
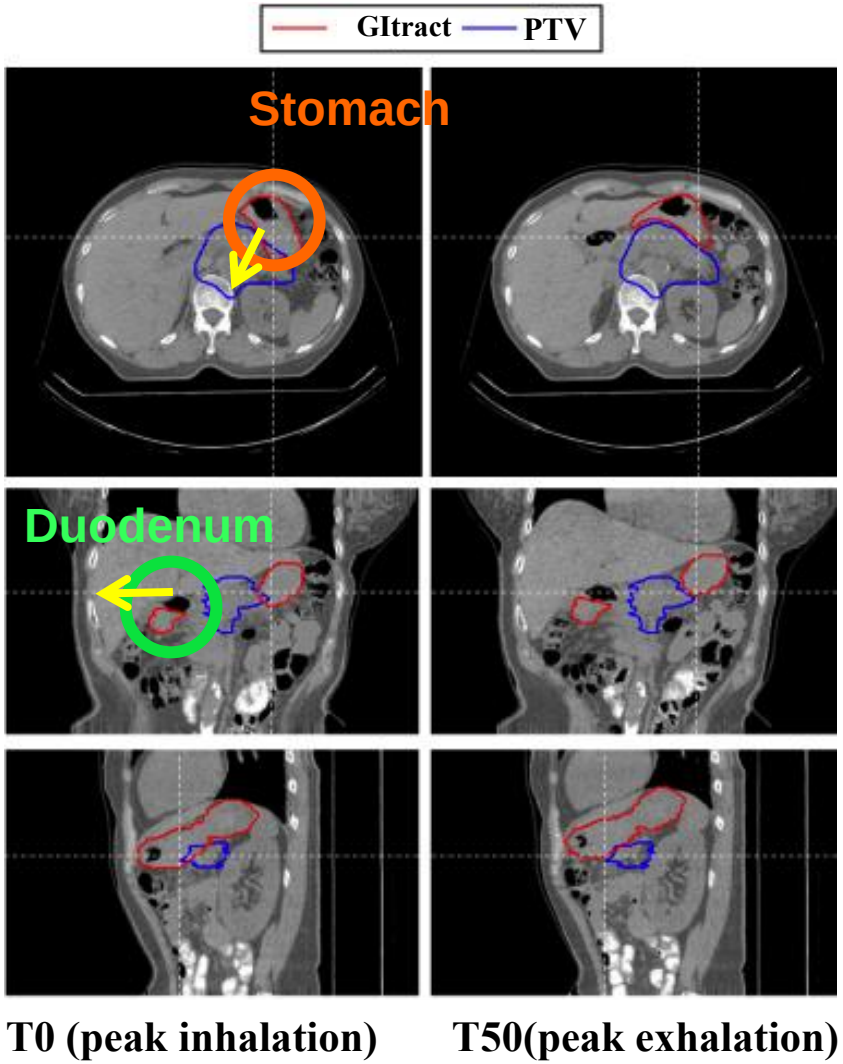



# Respiratory pattern using 4DCT scan



# NIRS Sequencing Trial: Schema

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 (year)

Phase I /II clinical trial
preoperative
(Protocol 9906)
16fr
22pts.

Phase I /II clinical trial
Short-course preoperative
(Protocol 0203)
8fr
26pts.

Phase I /II clinical trial
locally advanced
(Protocol 0204)
12fr
47pts.

Phase I /II clinical trial
GEM+Carbon
(Protocol 0513)
12fr
72pts.

# Treatment Data

| Dose Level (GyE/12Fr/3weeks) | # of patients |
|---|---|
| 38.4GyE | 7 |
| 40.8GyE | 4 |
| 43.2GyE | 7 |
| 45.6GyE | 5 |
| 48.0GyE | 7 |
| 50.4GyE | 13 |
| 52.8GyE | 3 |

**GyE** = carbon physical dose x relative biological effectiveness(RBE)

# Toxicities of Chemoradiotherapy for locally advanced Pancreas cancer

| | Year | n | Treatment | Dose | ≧G3Toxicities | | |
|---|---|---|---|---|---|---|---|
| | | | | | All | GI | Blood |
| | | | | | 23% | | |
| | | | | | | 57% | 52% |
| | | | | | | 22% | 24% |
| | | | | | | 26% | 31% |
| **NIRS** | 2010 | **46** | **CIRT** | **45.6-52.8 GyE** | **17%** | 17% | **0%** |

**Carbon-ion radiotherapy demonstrated low rates of severe toxicities**

# At 45.6GyE or higher dose Carbon-ion radiotherapy provided good local control

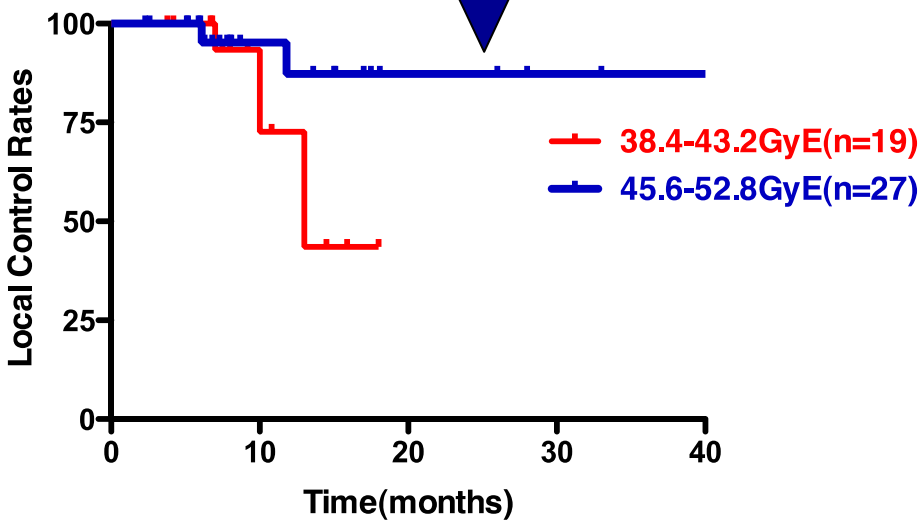
PC

mo

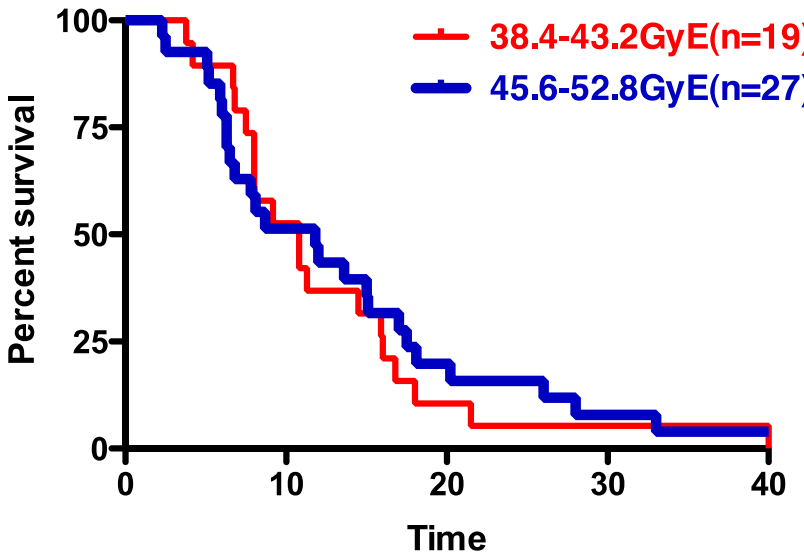
%

%

Lo ntrol




Overall Survival

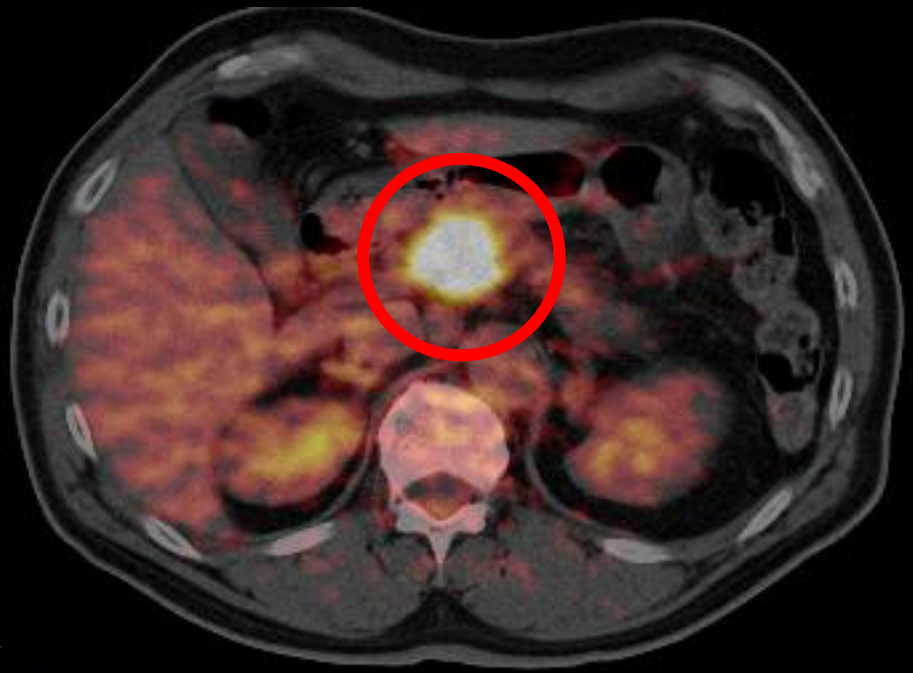


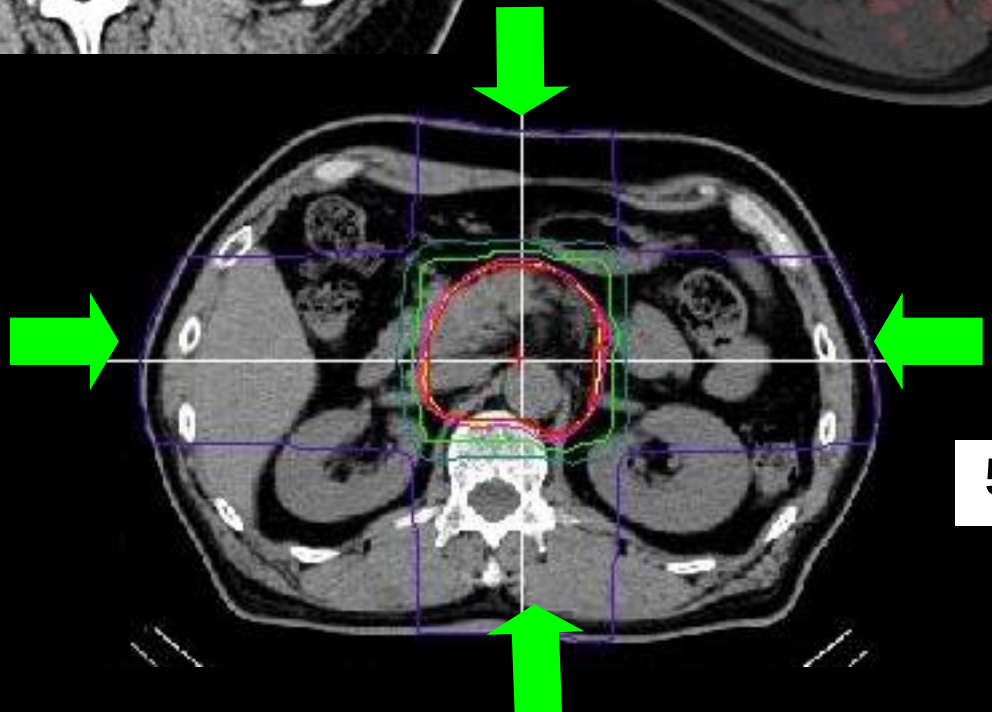
# Chemoradiation Therapy for locally advanced PC

| | Year | n | Treatment | Dose | Local Control | Survival | |
|---|---|---|---|---|---|---|---|
| | | | | | | 1yr | 1.5yr |
| ECOG | 1985 | 47 | 5FU+RT | 40Gy | 68% | 32% | 11% |
| | | 44 | 5FU | - | 68% | 26% | 21% |
| Crane CH | 2002 | 61 | 5FU+RT | 30Gy | 46% | 28% | 7% |
| | | 34 | GEM+RT | 30Gy | 45% | 42% | 12% |
| Okusaka T | 2004 | 42 | GEM+RT | 50.4Gy | 94% | 28% | 25% |
| Murphy JM | 2007 | 74 | GEM+RT | 20-42Gy | 74% | 46% | 24% |
| **NIRS** | 2012 | **46** | **CIRT** | **45.6-52.8 GyE** | **87%** | **47%** | **26%** |

# Case 1: 66y Male

Pbh 35mm×25mm Stage Ⅳa
TS2,N0,S+,RP+,CH-,DU-,PV+A+





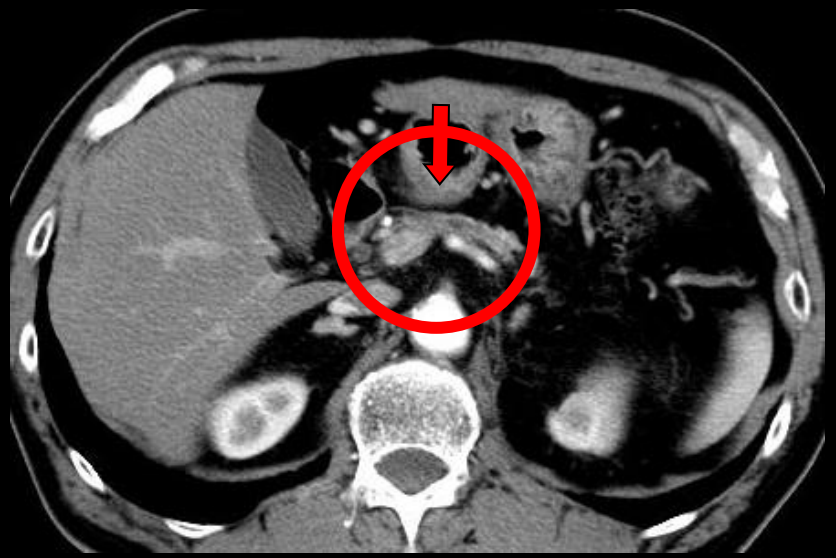
50.4GyE / 12fr

# Case 1: 66y Male

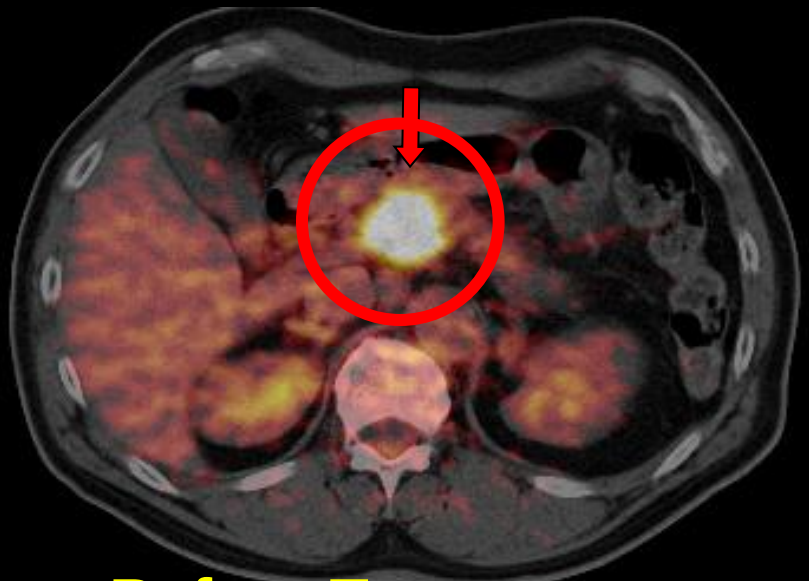
50.4GyE / 12fr

Alive at 70M after treatment

Before Treatment



40M after treatment



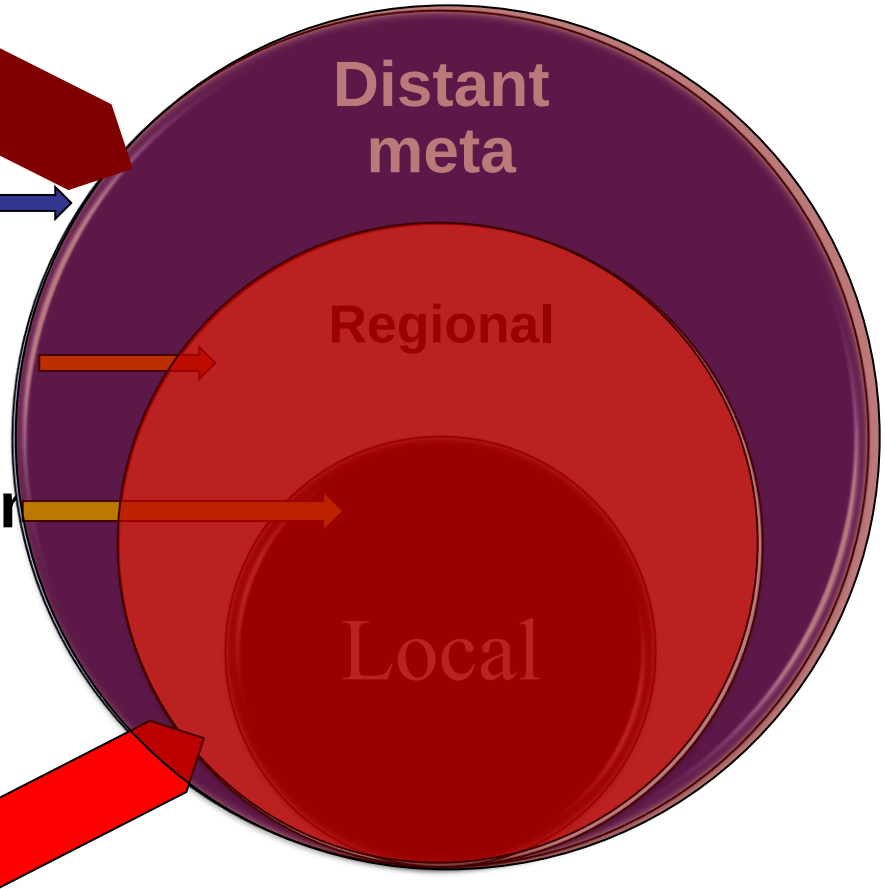
Before Treatment

6M after treatment

# Why pancreas cancer is resistant to conventional treatments？

**Chemotherapy**

1. Easy distant metastasis
2. Easy infiltration of neuroplexus
3. Large radioresistant cell fraction




**Carbon-ion can control them.**

# NIRS Sequencing Trial: Schema

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012
(year)

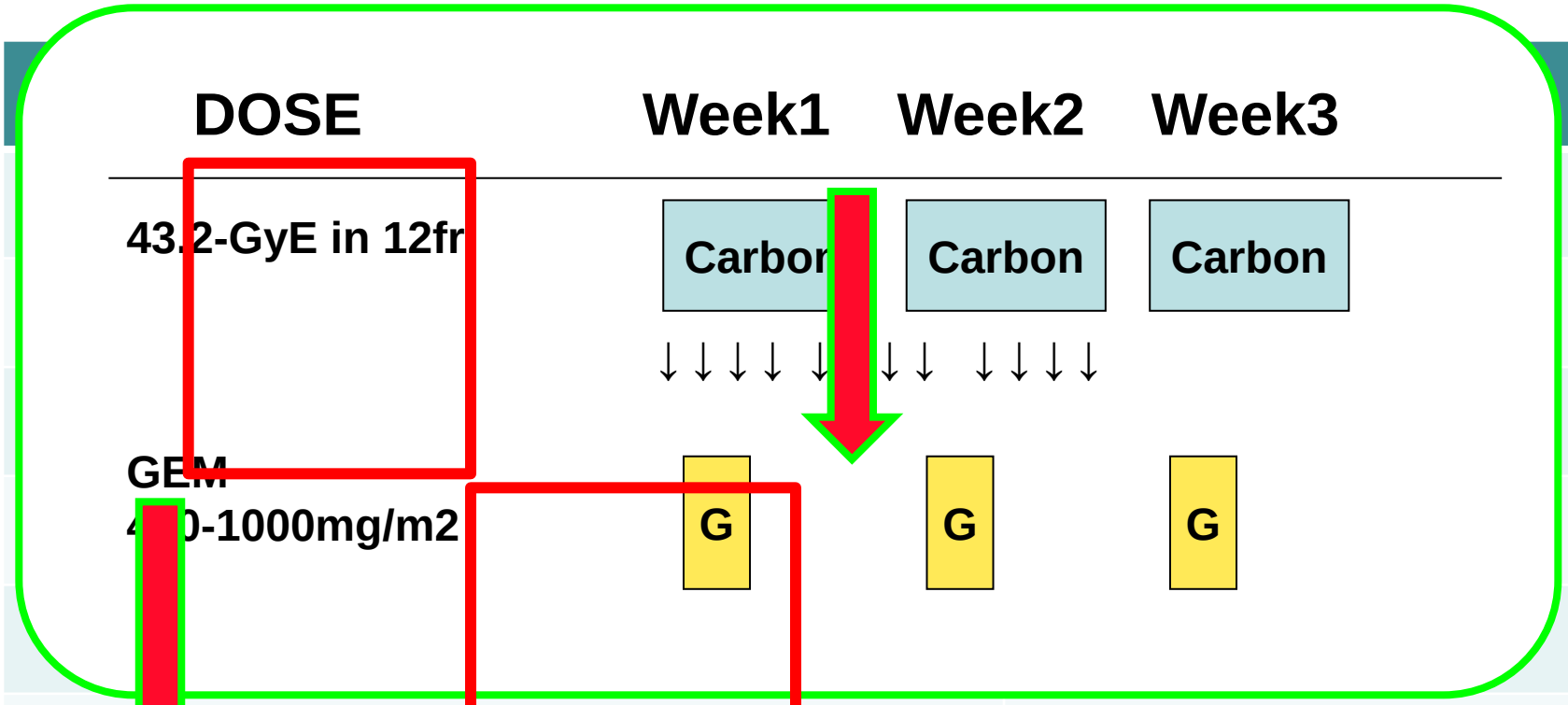
Phase I /II clinical trial
preoperative
(Protocol 9906)
16fr
22pts.

Phase I /II clinical trial
Short-course preoperative
(Protocol 0203)
8fr
26pts.

Phase I /II clinical trial
locally advanced
(Protocol 0204)
12fr
47pts.

Phase I /II clinical trial
GEM+Carbon
(Protocol 0513)
12fr
72pts.

# Dose escalation




| | | |
|---|---|---|
| 50.4GyE | 1000mg/m² | 11 |
| 52.8GyE | 1000mg/m² | 11 |
| 55.2GyE | 1000mg/m² | 5 |

# Comparison with Radiation Dose by Biological Effective Dose

| Total Dose | Fraction Number | Dose/fraction | BED3.0 | BED10 |
|---|---|---|---|---|
| 38.4GyE | 12 | 3.2 | 79.4 | 50.7 |
| 40.8GyE | 12 | 3.4 | 87.0 | 54.7 |
| 43.2GyE | 12 | 3.6 | 95.0 | 58.8 |
| 45.6GyE | 12 | 3.8 | 103.4 | 62.9 |
| 48.0GyE | 12 | 4.0 | 112.0 | 67.2 |
| 50.4GyE | 12 | 4.2 | 121.0 | 71.6 |
| 52.8GyE | 12 | 4.4 | 130.2 | 76.0 |
| 55.2GyE | 12 | 4.6 | 138.4 | 80.5 |
| 82.0GyE | 41 | 2.0 | 136.7 | 98.4 |
| 66.0GyE | 33 | 2.0 | 118.8 | 79.2 |

# DLT by total dose

| Total Dose | n | DLT * | | Toxicity |
|---|---|---|---|---|
| | | − | + | |
| 43.2GyE・400mg/m$^2$ | 6 | 6 | 0 | |
| 43.2GyE・700mg/m$^2$ | 6 | 6 | 0 | |
| 43.2GyE・1000mg/m$^2$ | 12 | 10 | 2 | **Neutropenia G4** |
| 45.6GyE・1000mg/m$^2$ | 6 | 6 | 0 | |
| 48.0GyE・1000mg/m$^2$ | 8 | 7 | 1 | **Infection G3** |
| 50.4GyE・1000mg/m$^2$ | 11 | 11 | 0 | |
| 52.8GyE・1000mg/m$^2$ | 11 | 11 | 0 | |
| 55.2GyE・1000mg/m$^2$ | 11 | 11 | 0 | |

**＊DLT : dose limiting toxicity:** ≧G4 haematological toxicities
≧G3 non-haematological toxicities
(excluding nausea, anorexia, dehydration)

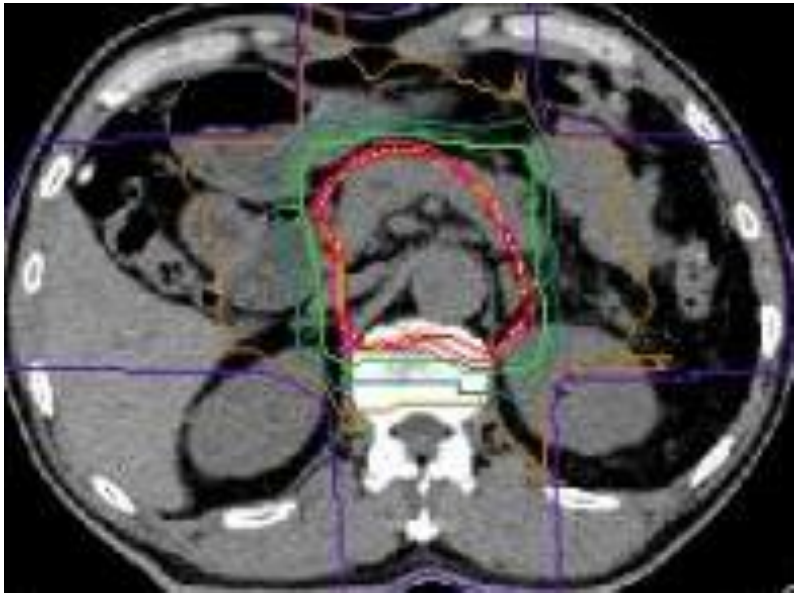
# Upper gastrointestinal acute and late Grade2-3 toxicity by total dose

| Carbon・GEM | n | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|
| 43.2GyE・400・700・1000mg/m² | 24 | 24 | 0 | 0 | 0 | 0 | 0 |
| 45.6GyE・1000mg/m² | 7 | 7 | 1 | 0 | 0 | 0 | 0 |
| 48.0GyE・1000mg/m² | 8 | 8 | 1 | 0 | 0 | 0 | 0 |
| 50.4GyE・1000mg/m² | 11 | 10 | 0 | 1 | 1 | 0 | 0 |
| 52.8GyE・1000mg/m² | 11 | 10 | 1 | 3 | 0 | 0 | 0 |
| 55.2GyE・1000mg/m² | 10 | 5 | 0 | 5 | 0 | 0 | 0 |

**Grade 1** : Asymptomati
**Grade 2** : Symptomatic; altered GI function
**Grade 3** : Symptomatic and severely altered GI; IV fluids, tube feedings, or TPNindicated ≥24 hrs

Case 1

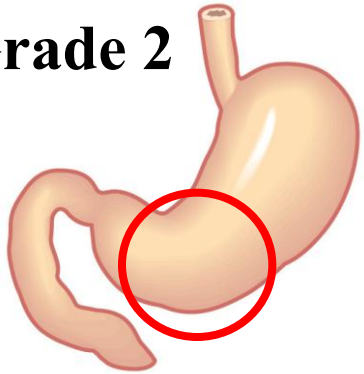
Dose distribution



0513-67 71y Male

55.2GyE・1000mg/m$^2$

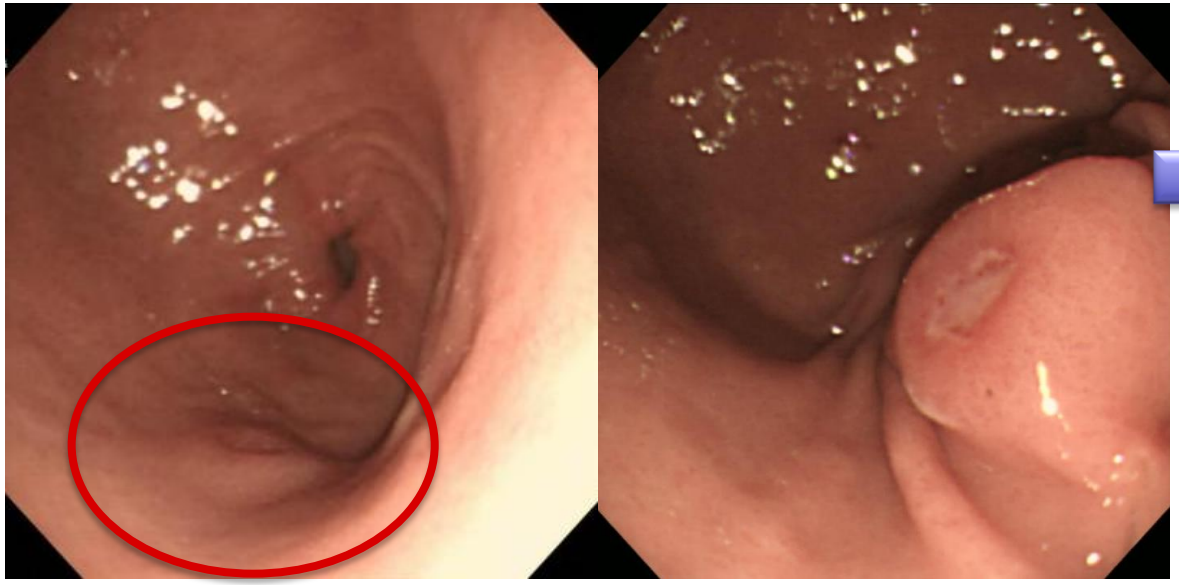
Gastric Ulcer Grade 2



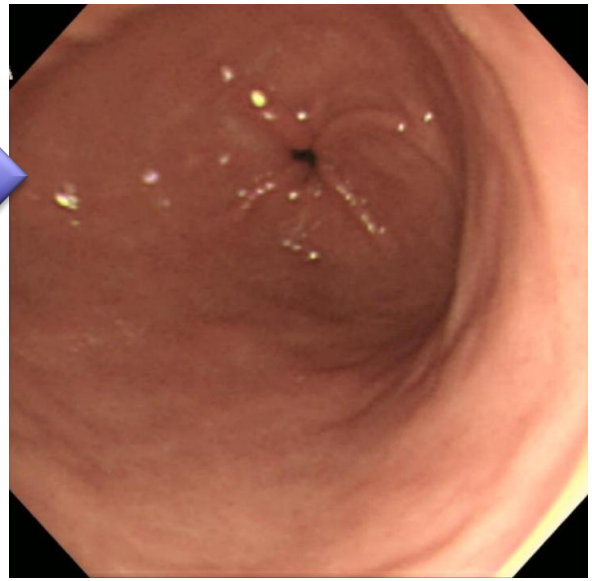
Light Abdominal Pain

PPI for 2months

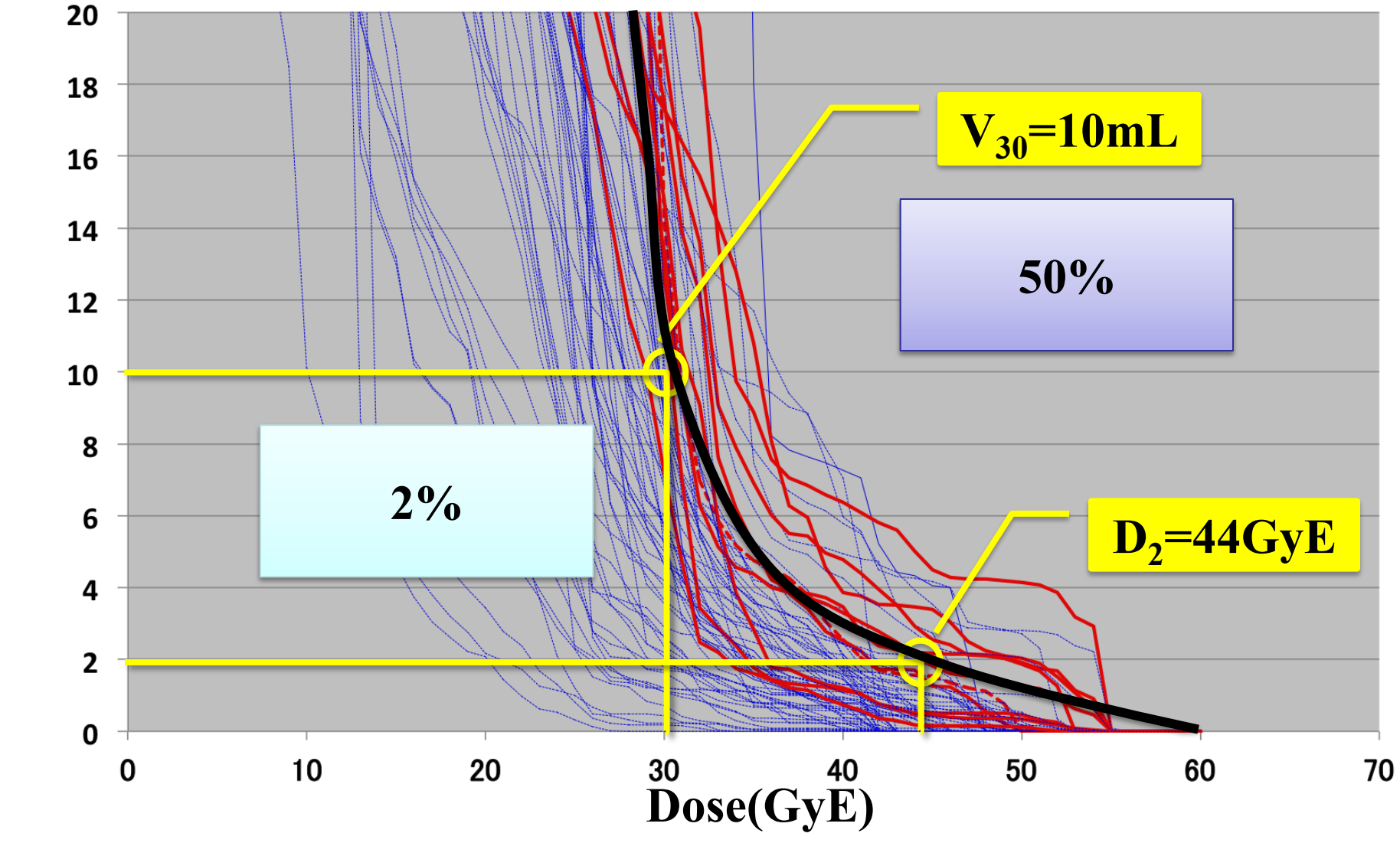
1 month after CIRT



3M after CIRT



# DVH for all the patients with pancreatic cancer



# Correlation between upper gastrointestinal acute Grade2-3 toxicity and V30 and D2

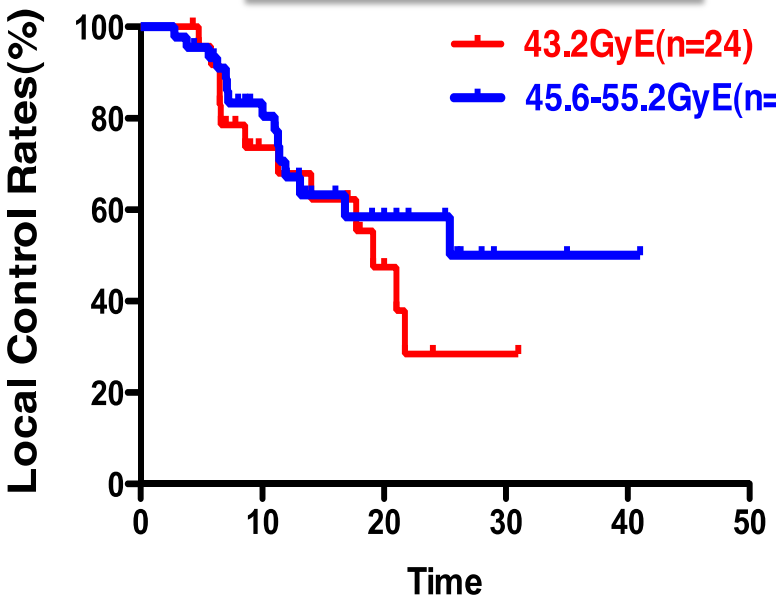
（%: incidence of upper gastrointestinal acute Grade2-3 toxicity ）

| | D2≧44 | D2<44 | Total |
|---|---|---|---|
| V30≧10mL | 5/10(50%) | 4/13(31%) | 9/23 |
| V30<10mL | 0/1(0%) | 1/47(2%) | 1/48 |
| Total | 5/11 | 5/60 | 10/71 |

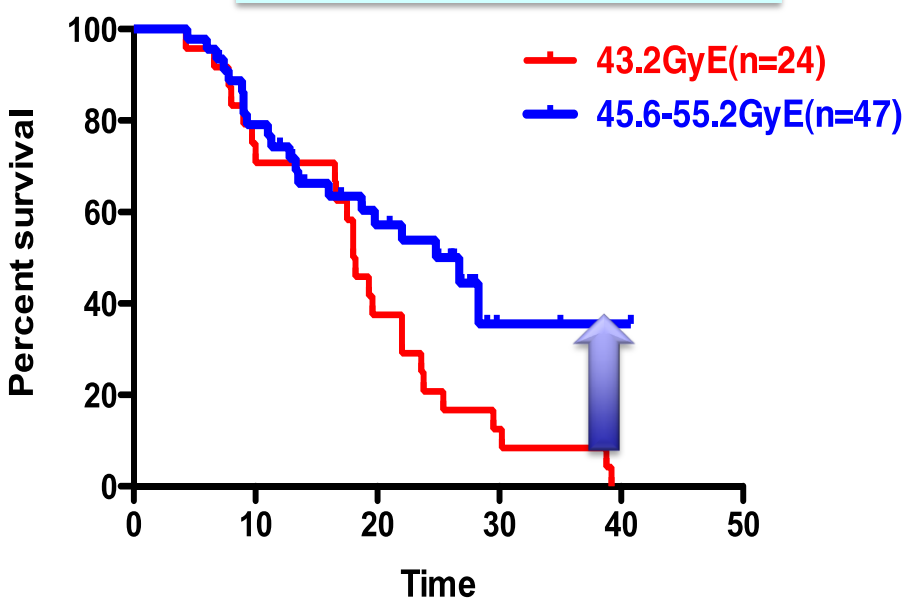
# GEM+CIRT for locally advanced

| | Total dose | n | 12mo | 24mo |
|---|---|---|---|---|
| Local Control | 45.6GyE< | 47 | 67% | 58% |
| | 43.2GyE | 24 | 68% | 28% |
| Overall Survival | 45.6GyE< | 47 | 74% | 54% |
| | 43.2GyE | 24 | 71% | 21% |

## Local Control




## Overall Survival



# GEM+CIRT for locally advanced

| | Year | n | Treatment | Dose | Survival | |
|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr |
| ECOG | 2008 | 34 | GEM+RT | 50.4Gy | 50% | 12% |
| | | 37 | GEM | - | 32% | 4% |
| Ishii | 2010 | 50 | GEM | - | 64% | 14% |
| Sudo | 2011 | 34 | S-1+RT | 50.4Gy | 71% | 25% |
| Small | 2011 | 28 | GEM+BZ*+ RT | 36Gy/15fr. | 45% | 17% |
| Schellenberg | 2011 | 20 | GEM+SBRT | 25Gy/1fr. | 50% | 20% |
| **NIRS** | | **47** | **GEM+CIRT** | **45.6-55.2 GyE** | **74%** | **54%** |

***Bevacizumab**

# NIRS Sequencing Trial: Schema

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 (year)

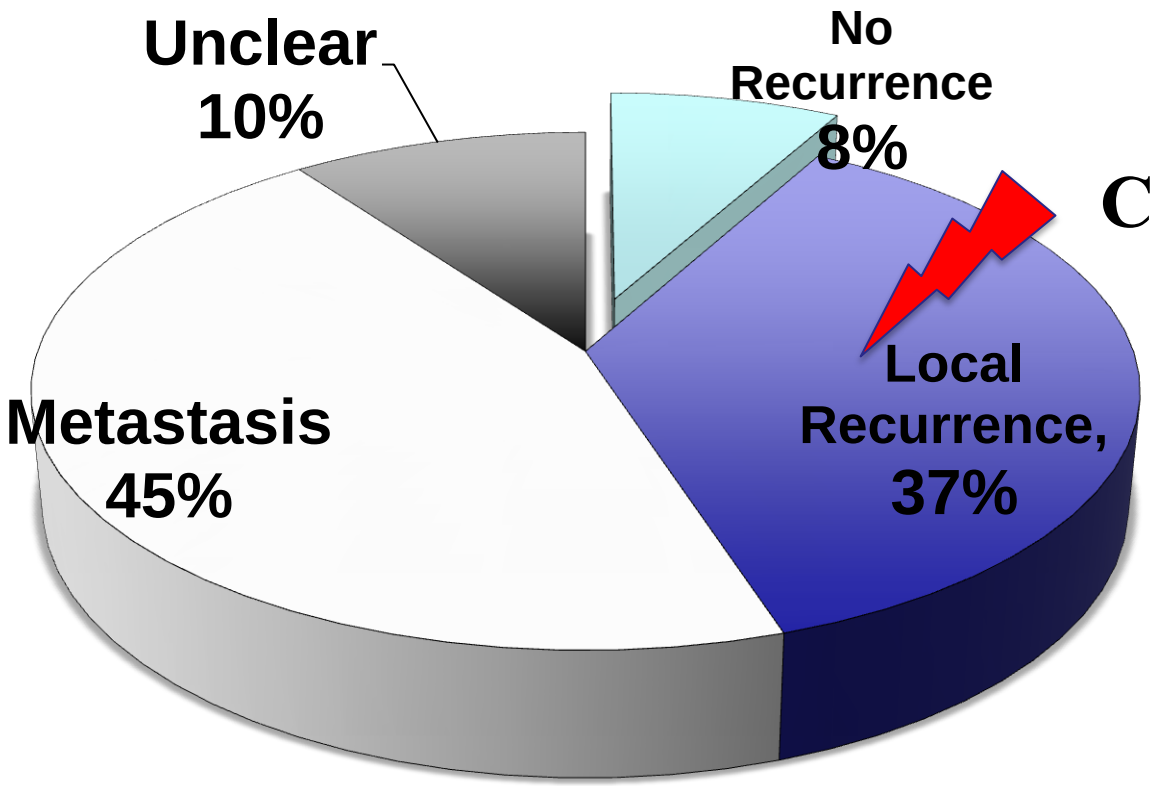
Phase I /II clinical trial
preoperative
(Protocol 9906)
16fr
22pts.

Phase I /II clinical trial
Short-course preoperative
(Protocol 0203)
8fr
26pts.

Phase I /II clinical trial
locally advanced
(Protocol 0204)
12fr
47pts.

Phase I /II clinical trial
GEM+Carbon
(Protocol 0513)
12fr
42pts.

# Patterns of failure after resection




**Oettle et al, JAMA 2007**

# What is the common frequency of positive margins?

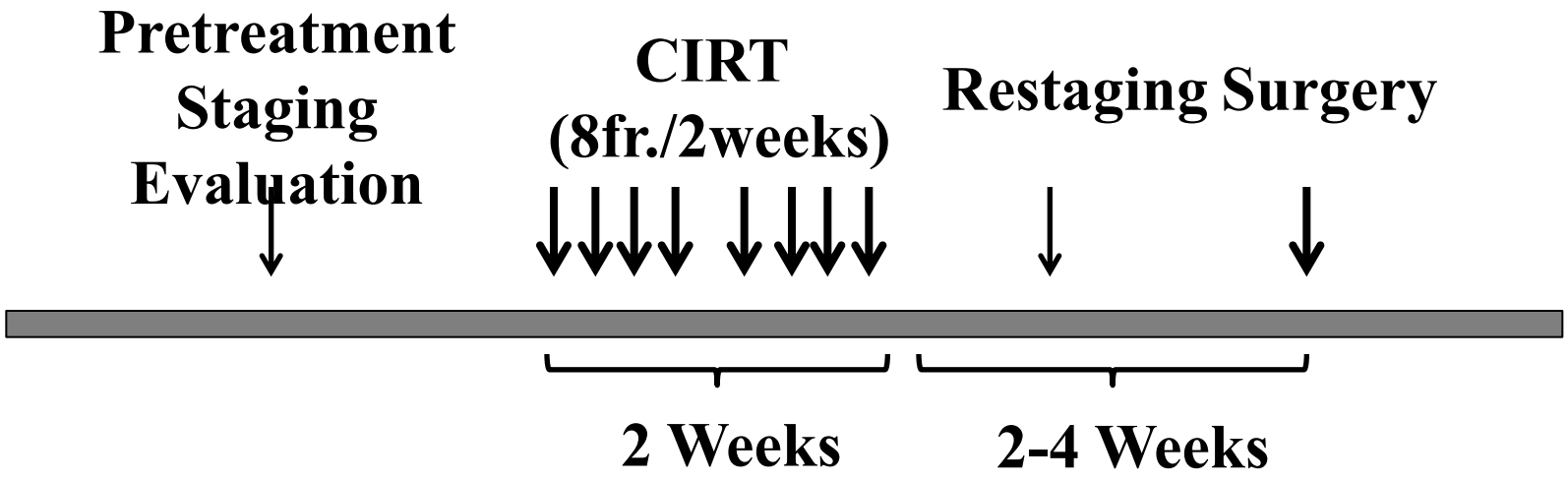
- ESPAC1: 101/541(18.7%)
- RTOG 9704: 140/445(34%)

## Pathologically positive margins

| Site | SMA | SMV | Ret | Panc | b.d. | HA |
|---|---|---|---|---|---|---|
| Number (n=53) | 22 (42%) | 16 (30%) | 19 (36%) | 8 (15%) | 3 | 1 |

Pingpank et al: JGISurg 5: 2: 121, 2001

# Schedule of CIRT and surgery




**Surgery was performed within 4 weeks from the completion of CIRT**

# Patient Characteristics

**Apr. 2003-Feb. 2011**

| **Patient Data** | | |
|---|---|---|
| Number of Patients | | 26 |
| | Male : Female | 15 : 11 |
| Median Age (Range) | | 66 (40-79) |
| Tumor Location | head | 17 |
| | body-tail | 7 |
| | head-body-tail | 2 |
| Clinical Stage (UICC 6th) | IIA | 14 |
| | IIB | 12 |
| Surgery | pancreatoduodenectomy | 15 |
| | distal pancreatectomy | 5 |
| | total pancreatectomy | 1 |
| | bypass | 2 |
| | no surgery | 3 |

**resection rate 81%**

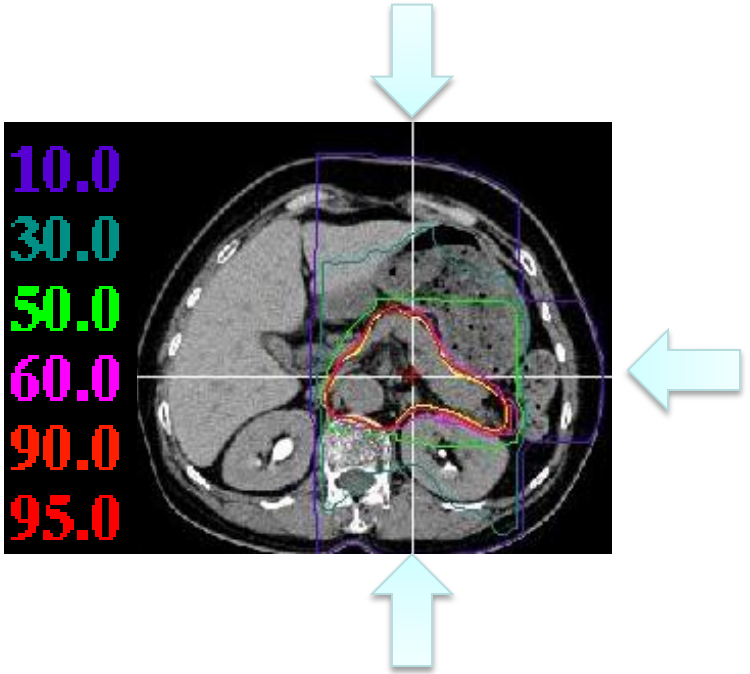
# Dose escalation

| Dose Level (CIRT) | # of patients | # of patients with resection |
|---|---|---|
| 30.0GyE | 6 | 3 |
| 31.6GyE | 4 | 3 |
| 33.6GyE | 3 | 3 |
| 35.2GyE | 6 | 6 |
| 36.8GyE | 7 | 6 |

# Radiation Method

- 3-D Conformal Planning (2.5mm-thick CT Images)
- GTV : primary tumor and involved node
- CTV : GTV+Neuroplexus lesions(periarterial area : Celiac-SMA )+regional LN

- PTV : CTV + 0.5cm (exclude
- Respiratory Gating System
- Radiation Field : 3-field



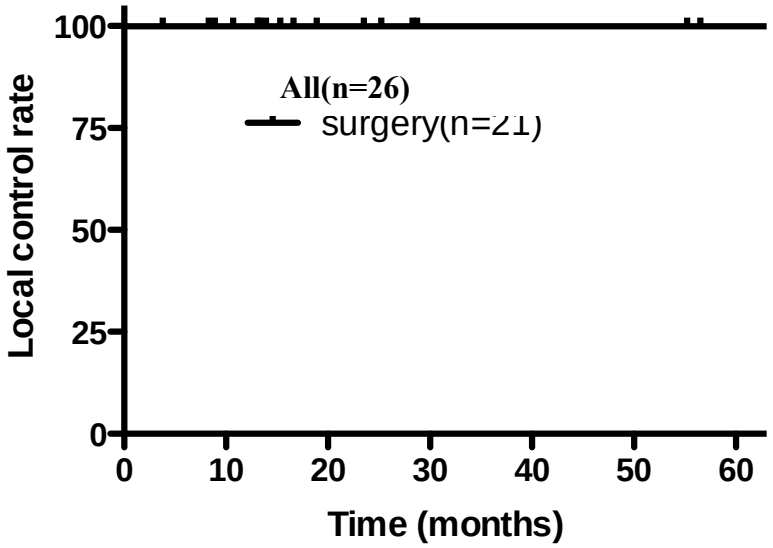
# Acute and Late toxicity

| | Acute toxicities (NCI-CTC) | | | | | | Late toxicities (RTOG/EORTC) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | G0 | G1 | G2 | G3 | G4 | n | G0 | G1 | G2 | G3 | G4 |
| skin | 26 | 26 | 0 | 0 | 0 | 0 | 26 | 26 | 0 | 0 | 0 | 0 |
| GI | 26 | 25 | 1 | 0 | 0 | 0 | 26 | 26 | 0 | 0 | 0 | 0 |
| Liver | 26 | 25 | 0 | 0 | 1 | 0 | 26 | 26 | 0 | 0 | 0 | 0 |
| Portal Vein | 26 | 26 | 0 | 0 | 0 | 0 | 26 | 25 | 0 | 0 | 0 | 1 |
| Leakage | 26 | 26 | 0 | 0 | 0 | 0 | 26 | 26 | 0 | 0 | 0 | 0 |

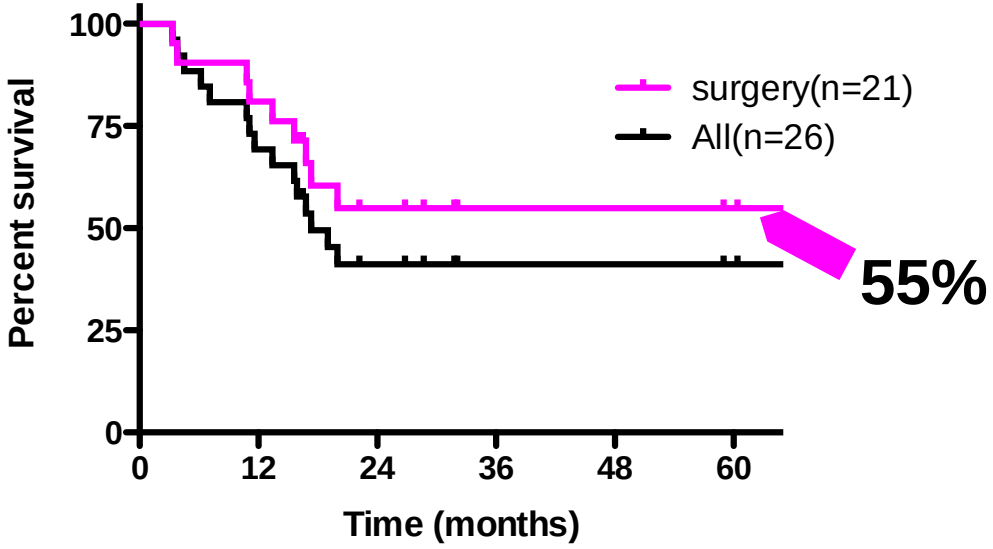
Shinoto M, Cancer, 111, 45-51, 2012

# Preoperative CIRT

## Local Control




## Overall Survival



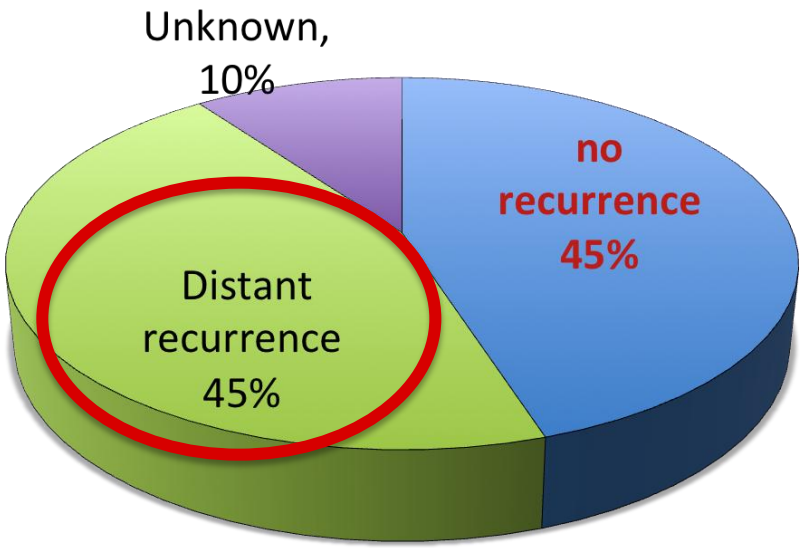

Shinoto M, Cancer, 111, 45-51, 2012

# Preoperative CIRT

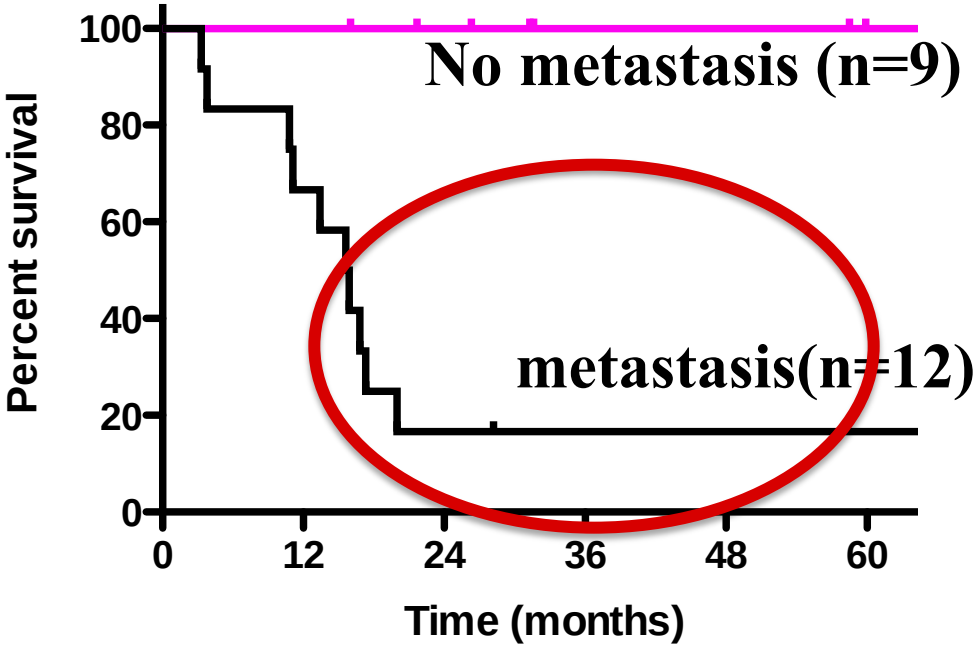
| | year | n | treatment | Local recurrence | Survival | |
|---|---|---|---|---|---|---|
| | | | | | 1-yr | 5-yr |
| Moutardier[1)] | 2004 | 40 | CRT+surgery | - | 80% | 30% |
| CONKO-001[2)] | 2007 | 161 | surgery only | 41% | 73% | 12% |
| | | 133 | surgery+GEM | 34% | 73% | 23% |
| Varadhachary[3)] | 2008 | 52 | CRT+surgery | 25% | 98% | 32% |
| Le Scodan[4)] | 2009 | 26 | CRT+surgery | - | 48% | 25% |
| **NIRS** | | **21** | **CIRT+surgery** | **0%** | **81%** | **55%** |

# Preoperative CIRT

## Failure pattern after surgery

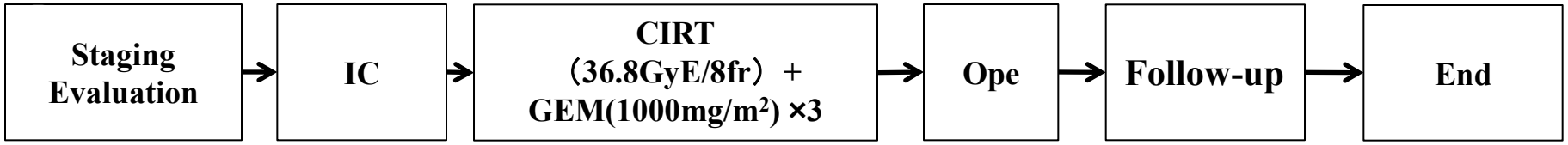


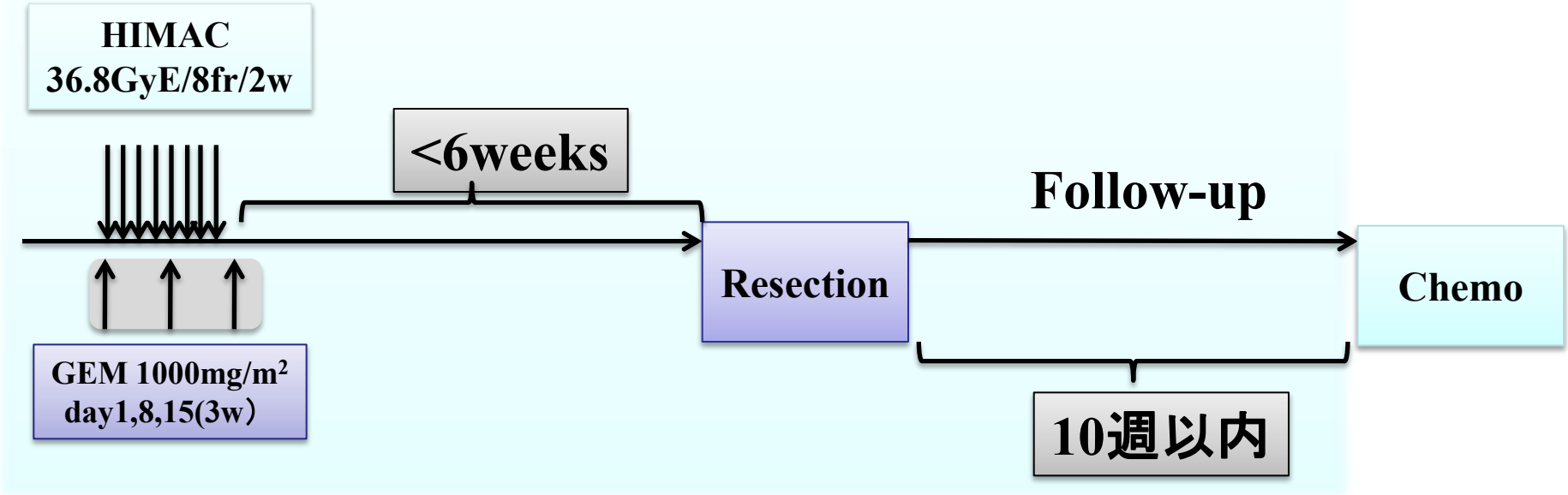

## Overall Survival



# A phase I/II clinical trial of carbon ion radiotherapy and concurrent gemcitabine chemotherapy for patients with preoperative pancreatic cancer

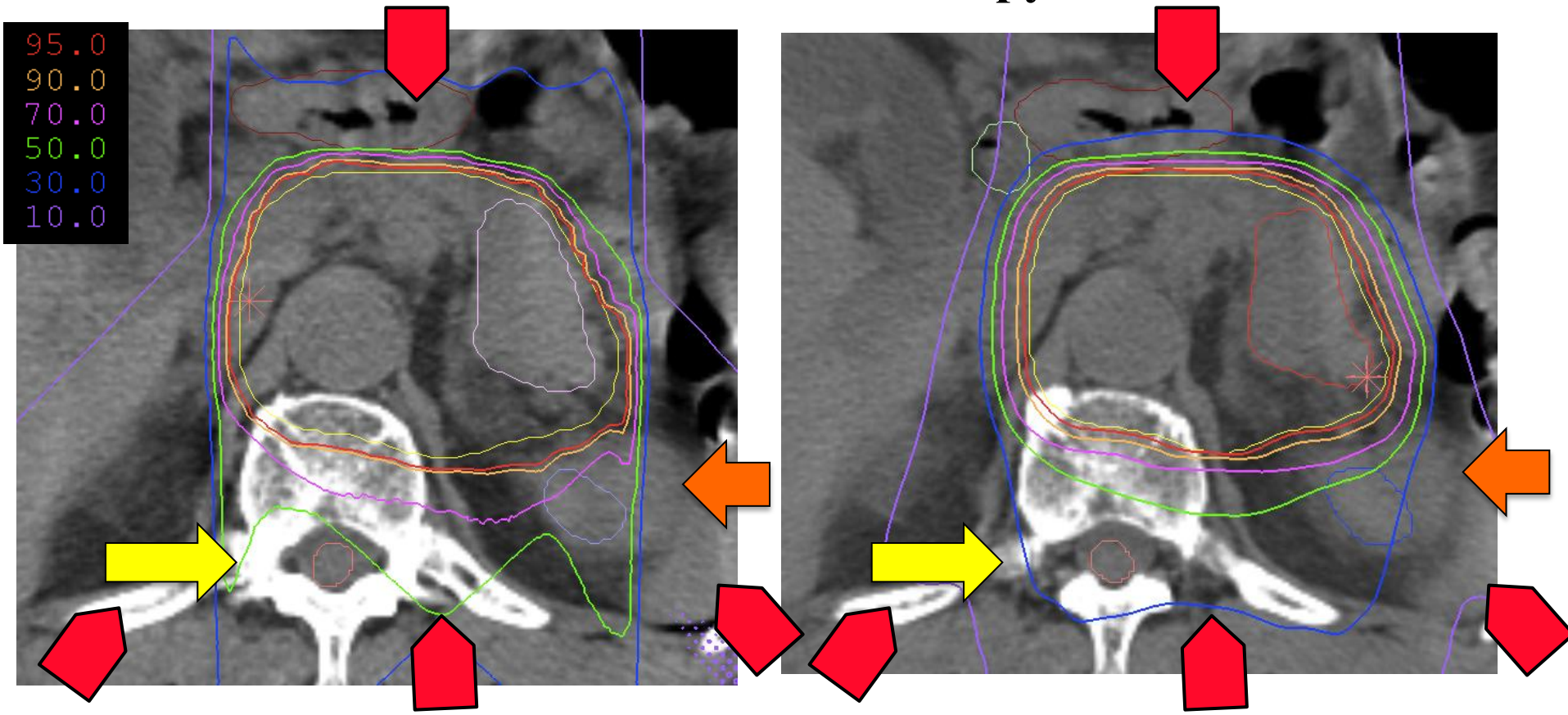
# Schema for New Protocol



# Difference between Broad Beam and Scanning Beam

## Dose Distribution of Carbon-ion radiotherapy for Pancreatic cancer




## Broad Beam

**Wobbler Method**

**with bolus&collimator**

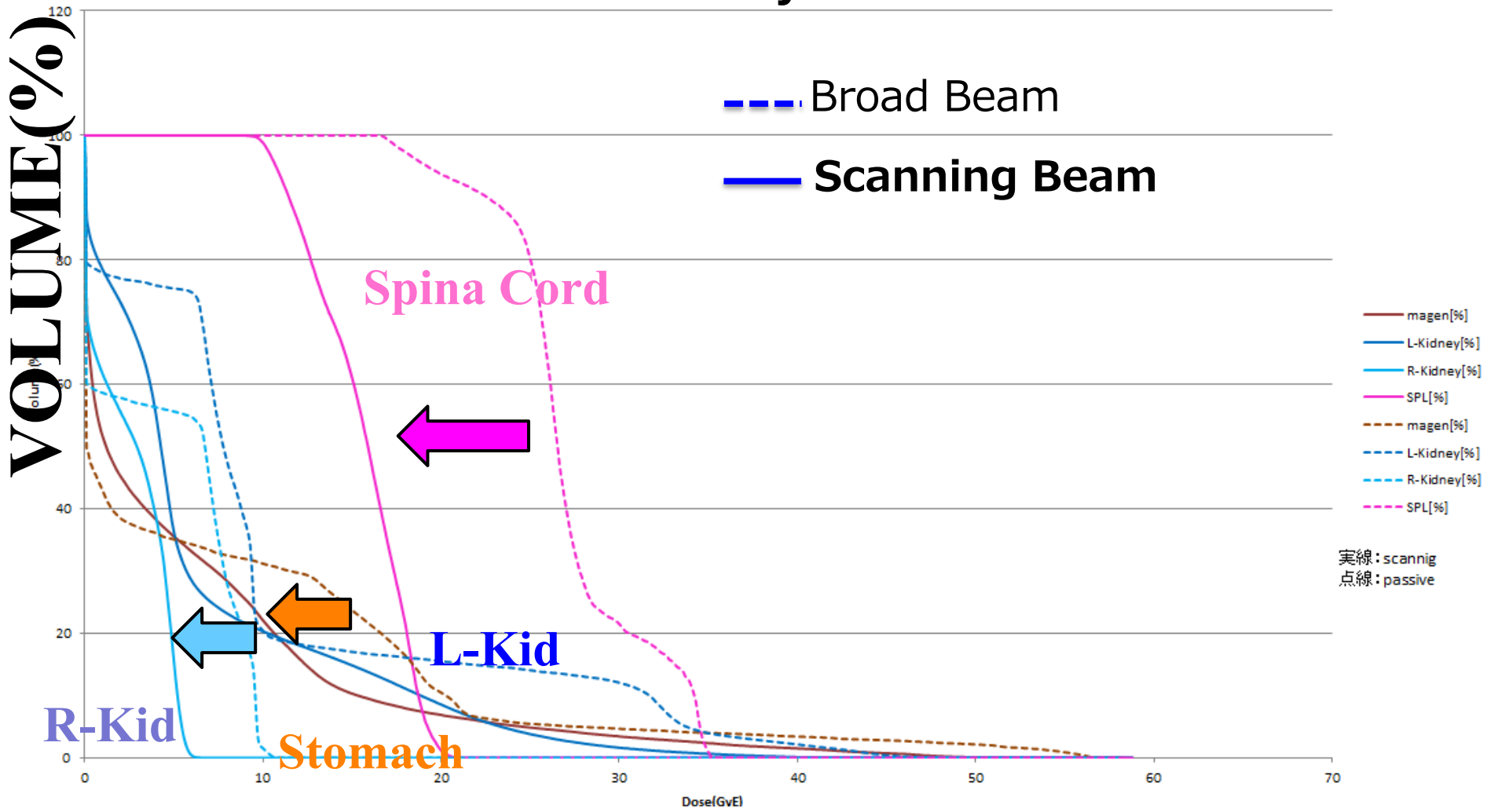
## Scanning Beam

**Scanning Method**

**without bolus&collimator**

# Difference between Broad Beam and Scanning Beam

## （DVH; dose-volume histogram）
## 55.2GyE/12Fr



# Conclusion

**Carbon ion radiotherapy very well improved tumor control and survival rate of Locally Recurrent Rectal Cancer**

**and**

**Pancreas Cancer**

**with acceptable morbidity in the surrounding normal tissues.**

# Japanese Pub for cats