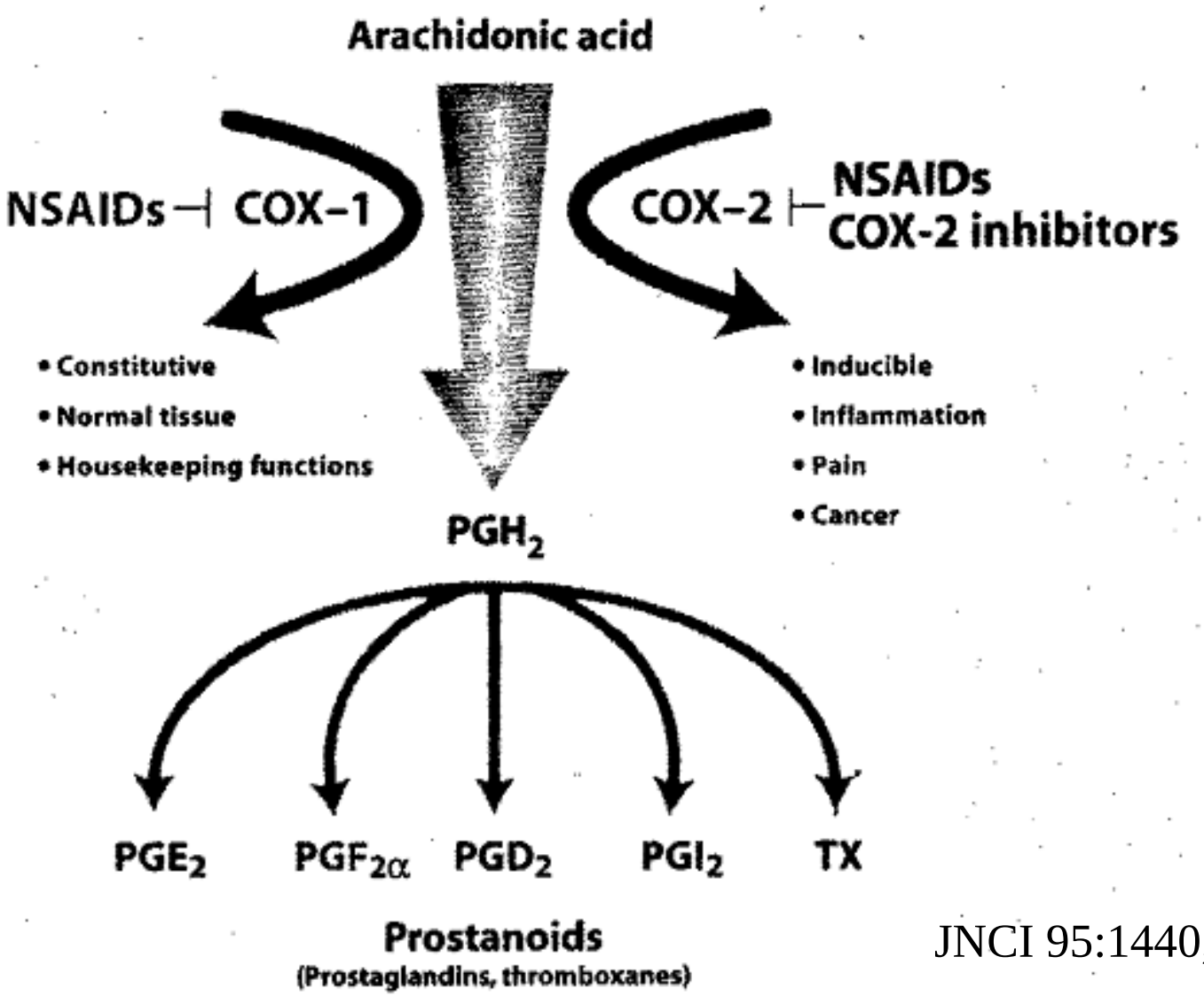
COX-2 inhibitor and irradiation

Saitama Cancer Center

Kunihiko Kobayashi MD, PhD

Synthesis of prostaglandins from arachidonic acid by cyclooxygenase (COX) enzymes

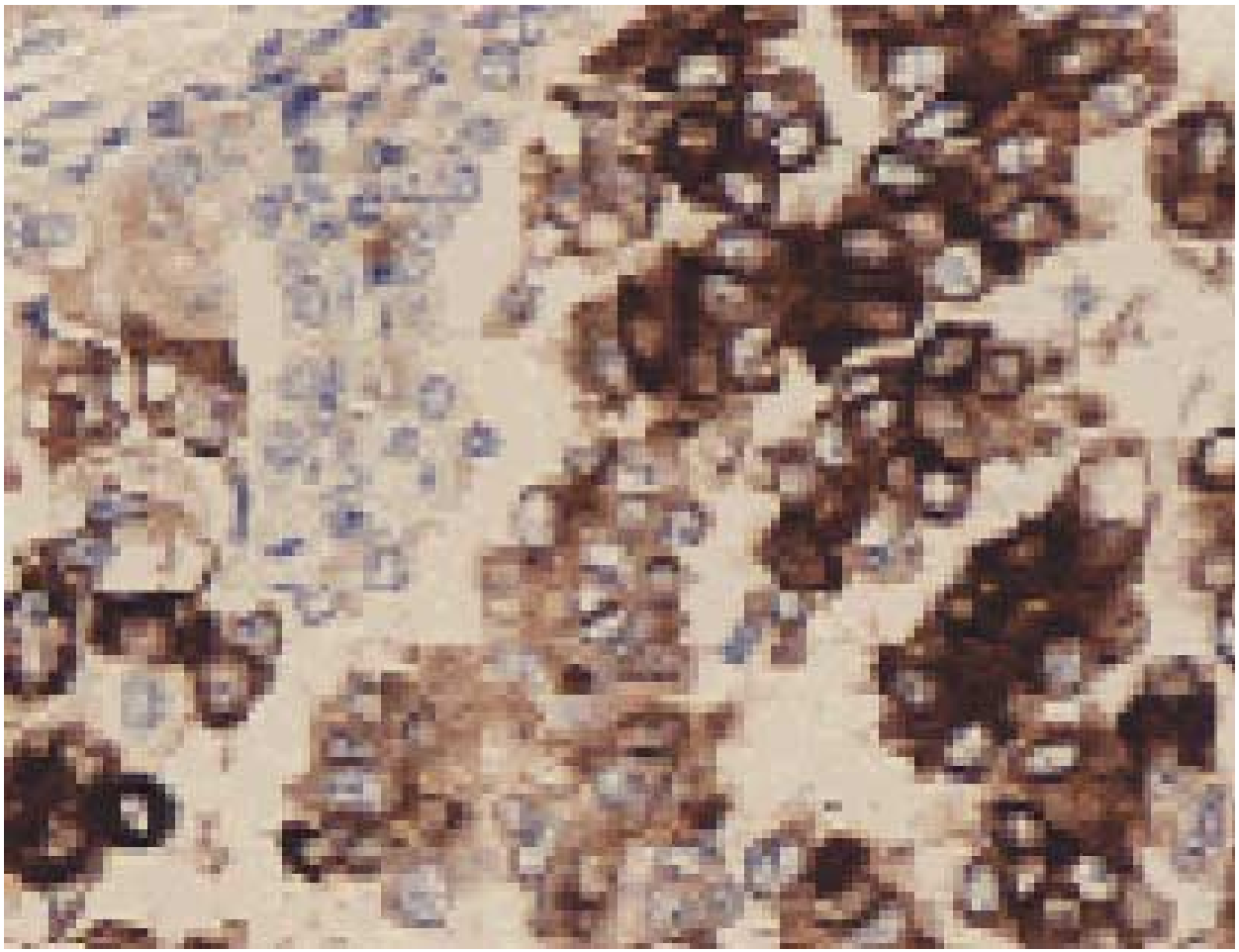


JNCI 95:1440, 2003

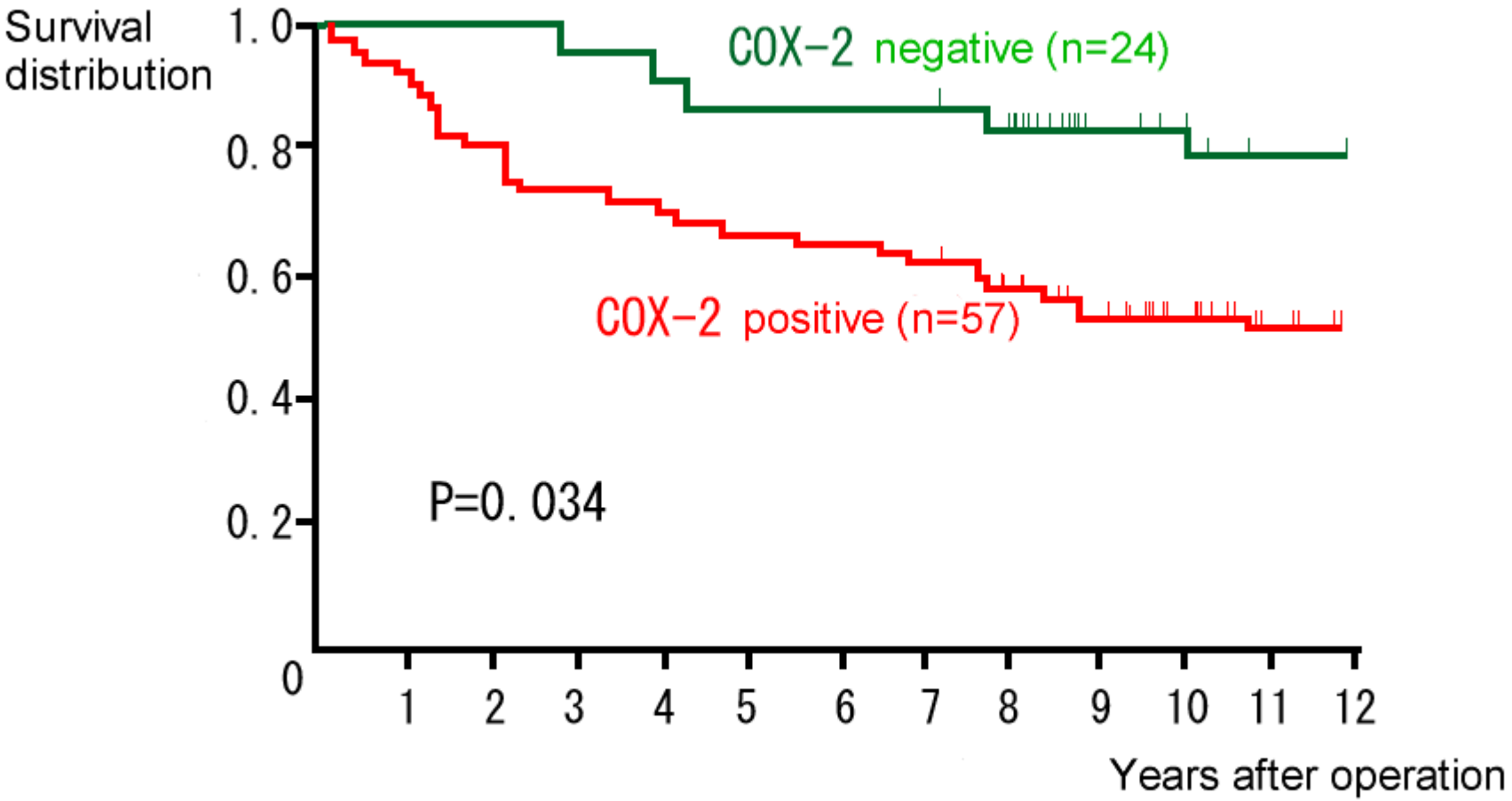
Difference between COX-1 and COX-2

	COX-1	COX-2
Structures (amino acids)	576	604
Their similarity	61%	
Gene location (chromosome)	No. 9	No. 1
Appearance	permanent	transient
Site	normal cells	inflammatory cells malignant tissue

COX-2 in NSCLC tissue



Prognosis of early stage adenocarcinoma of the lung



T.Hida Clinical Cancer Research Vol.5,1001-5,1999

COX-2 overexpression in various cancers

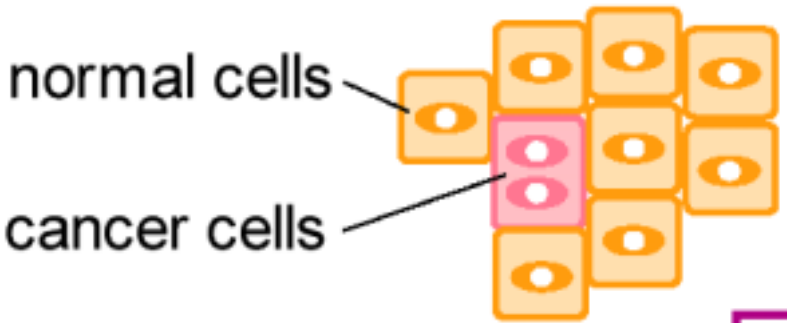
	Colorectal	Gastric	Esophageal	Pancreatic
% with Cox-2 overexpression	60-100	6-75	78-100	31-90

	Hepatic	Breast	NSCLC	SCLC
% with Cox-2 overexpression	31-90	29-89	30-95	none

	Prostate	Bladder	Cervical	Head & neck
% with Cox-2 overexpression	0-87	31-75	28-100	100

JNCI 95:1440, 2003

COX-2 and tumorigenesis



COX-2 overexpression

↓

apoptosis ↓

↓

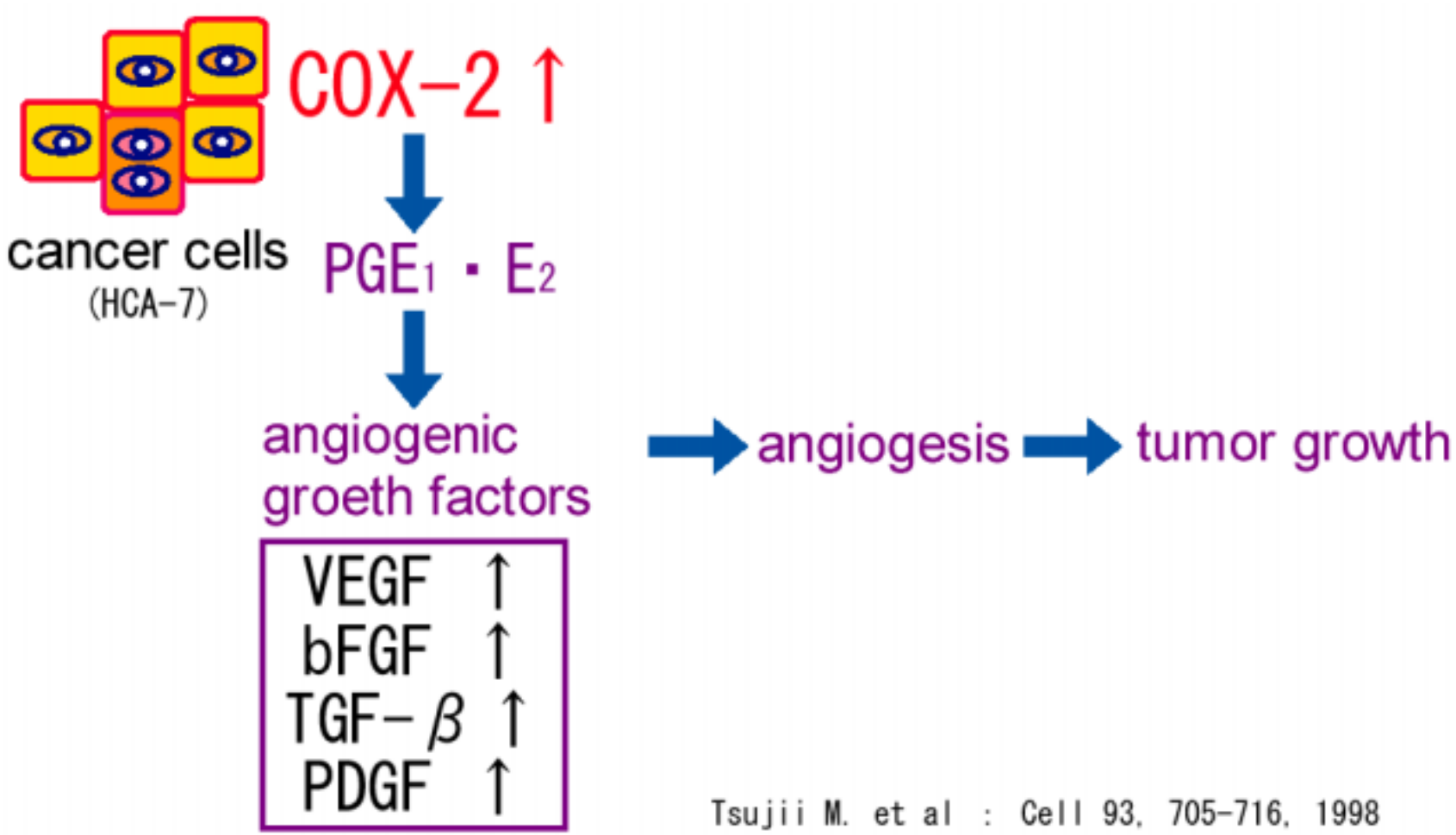
cell life ↑

↓

Storage of gene mutation

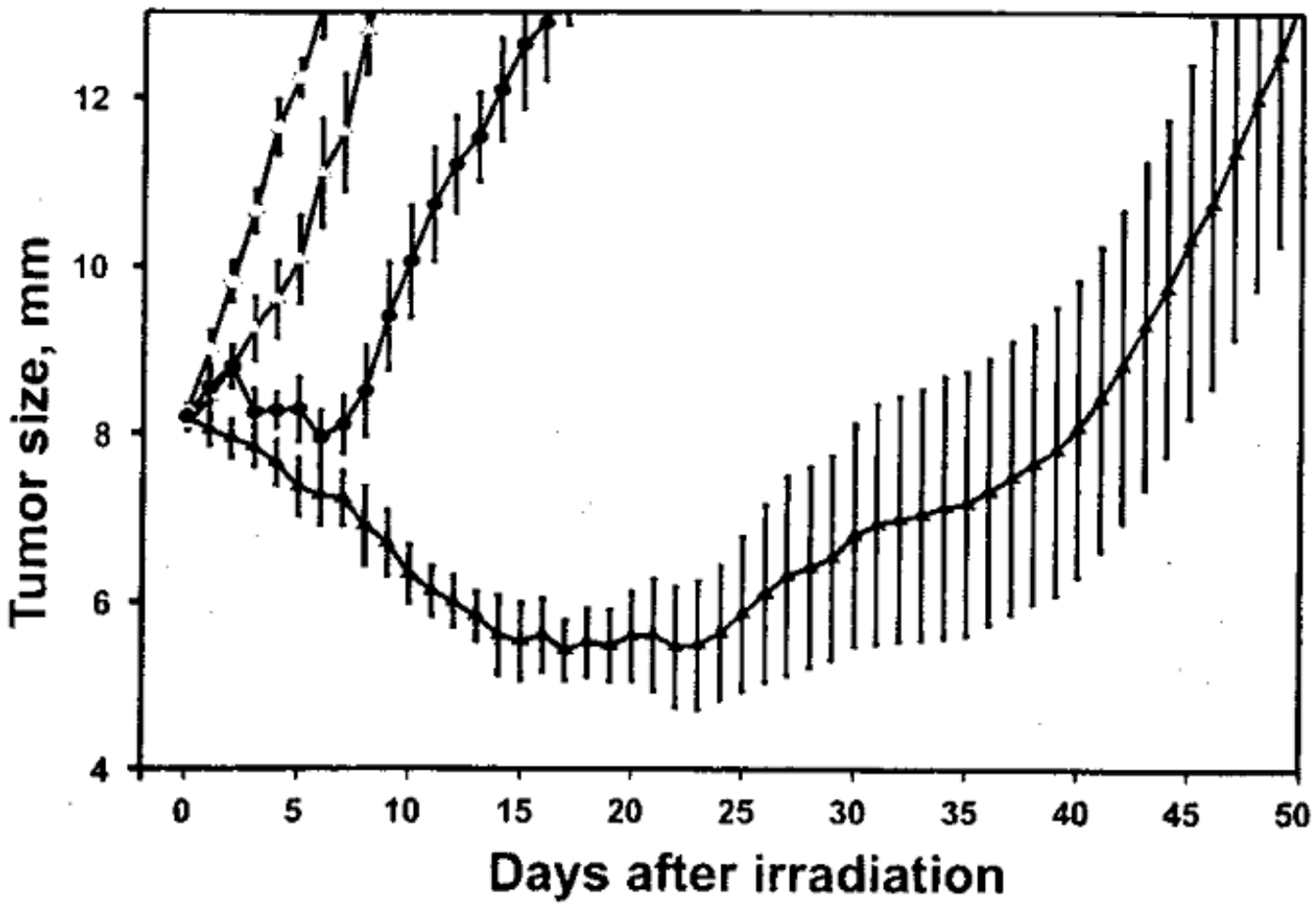
Tsujii M. et al : Cell 83, 493-501, 1995

COX-2 and tumor angiogenesis



Tsujii M. et al : Cell 93, 705-716, 1998
D'Haens : Gut 35, 1728-1733, 1994

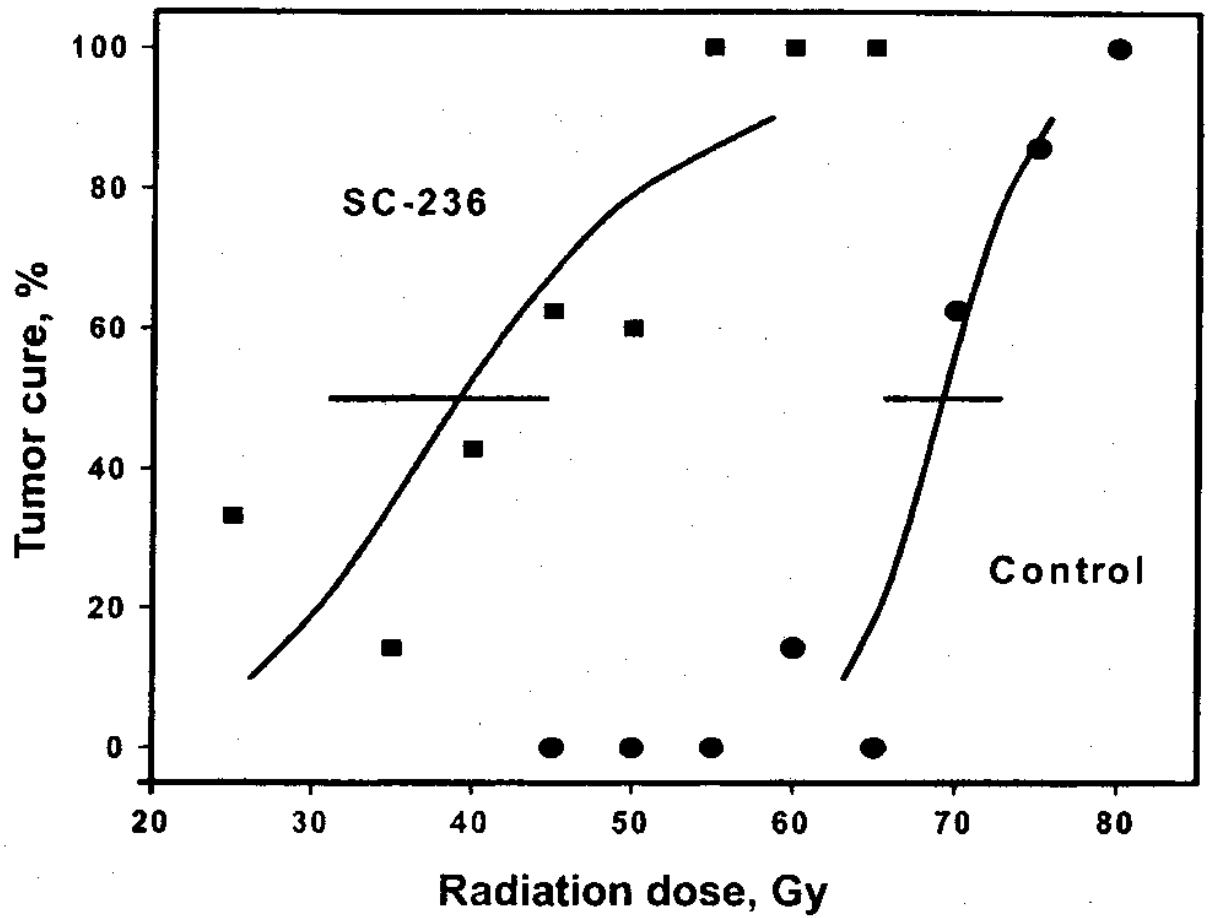
COX-2 expression and radiotherapy ①



○:control, △:SC-’236, ●:irradiation, ▲: SC-’236+ irradiation

PASCO 43:483, 2002

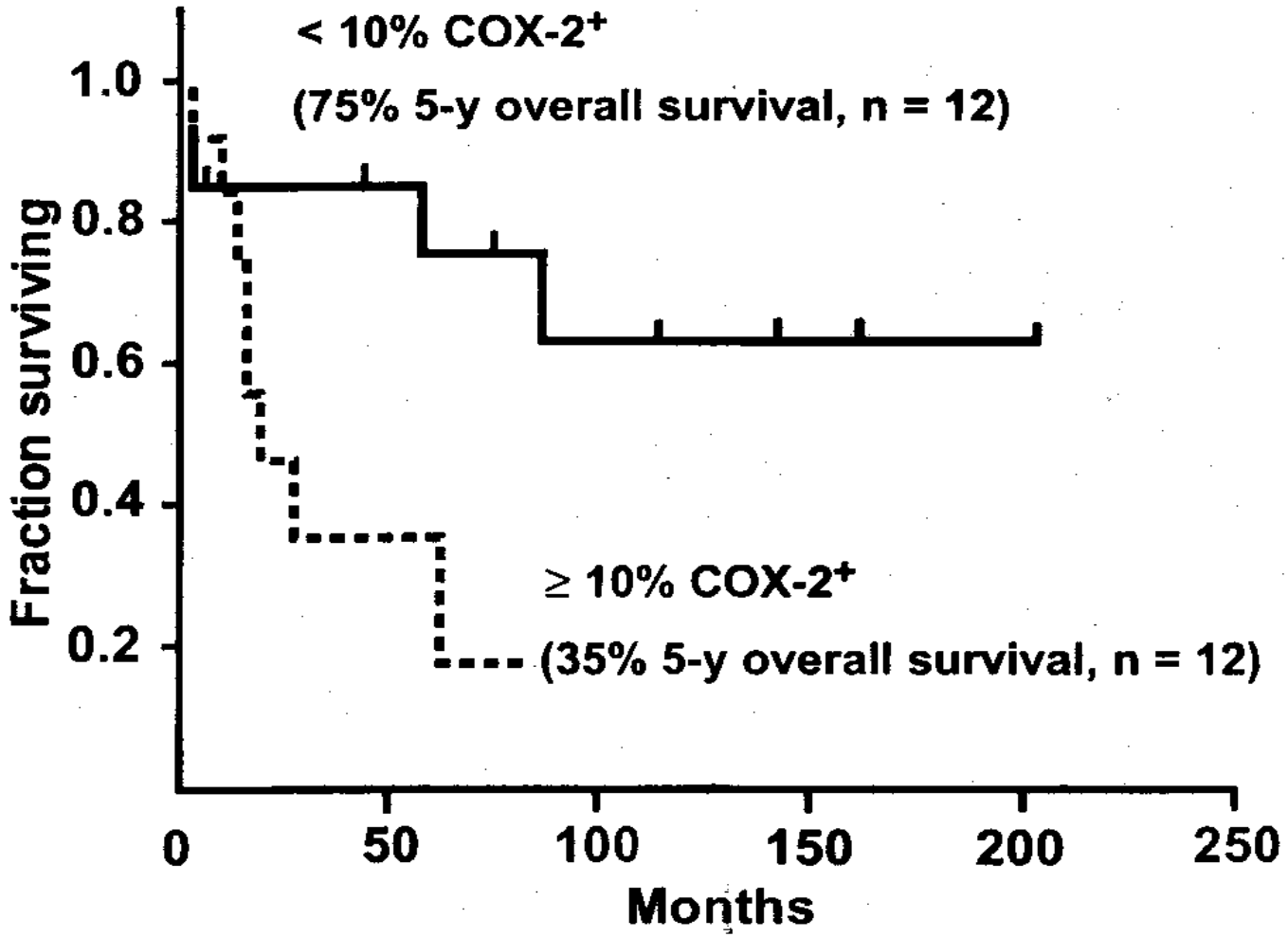
COX-2 expression and radiotherapy ②



■: SC-’236+ irradiation, ●:irradiation

PASCO 43:483, 2002

COX-2 expression and radiotherapy ③



Int J Radiat Oncol Biol Phys 49:1213, 2001

COX-2 expression and radiotherapy ④

- Mechanism of radiation potentiation by COX-2 inhibitors-

- Ionizing radiation increases expression of COX-2 and the synthesis of PGs in both normal and tumor cells.
- Induction of apoptosis
  - in the normal tissue, in turn, avoiding necrosis
  - in the tumor tissue
- Inhibition of angiogenesis
  - in the normal tissue, in turn, avoiding inflamation
  - in the tumor tissue

A COX-2 inhibitor

- meloxicam (Mobic®) -

Development of NSAIDs

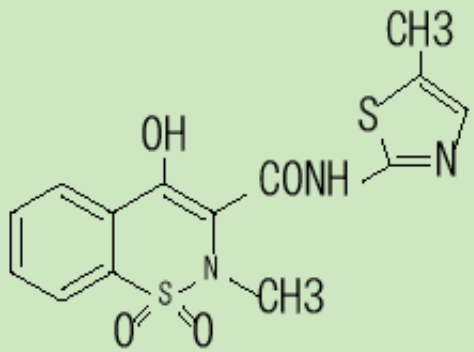
- The 1st period (1897-1985):Standard NSAID
  - In 1897, aspirin was developed.
  - In 1971, mechanism of NSAID was clarified by Vane.

  ✧aspirin, indomethacin, diclofenac etc.
- The 2nd period (1986-1993):Prodrug
  - In 1991, COX-1 and COX-2 were found.

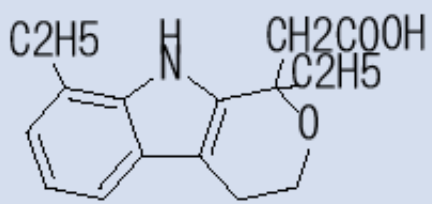
  ✧loxoprofen, etc.
- The 3rd period (1994-):Selective COX-2 inhibitor
  - In 1994, the COX theory was proposed by Vane.

  ✧Meloxicam, etodolac, celecoxib etc.

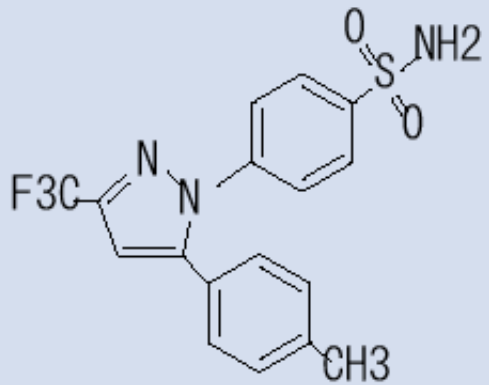
Selective COX-2 inhibitors



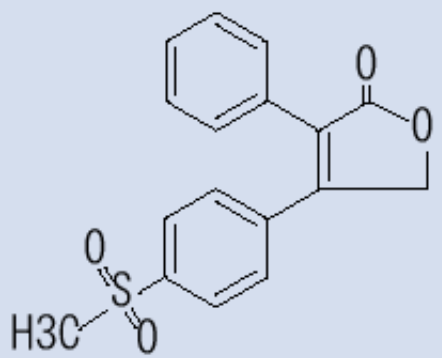
meloxicam



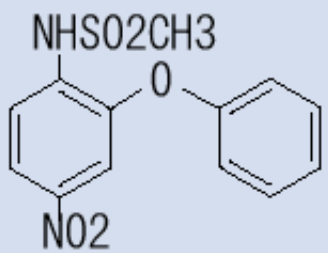
etodolac



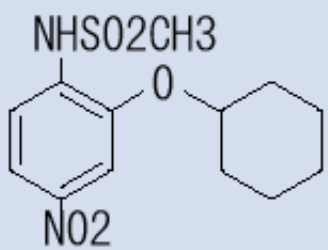
celecoxib



rofecoxib

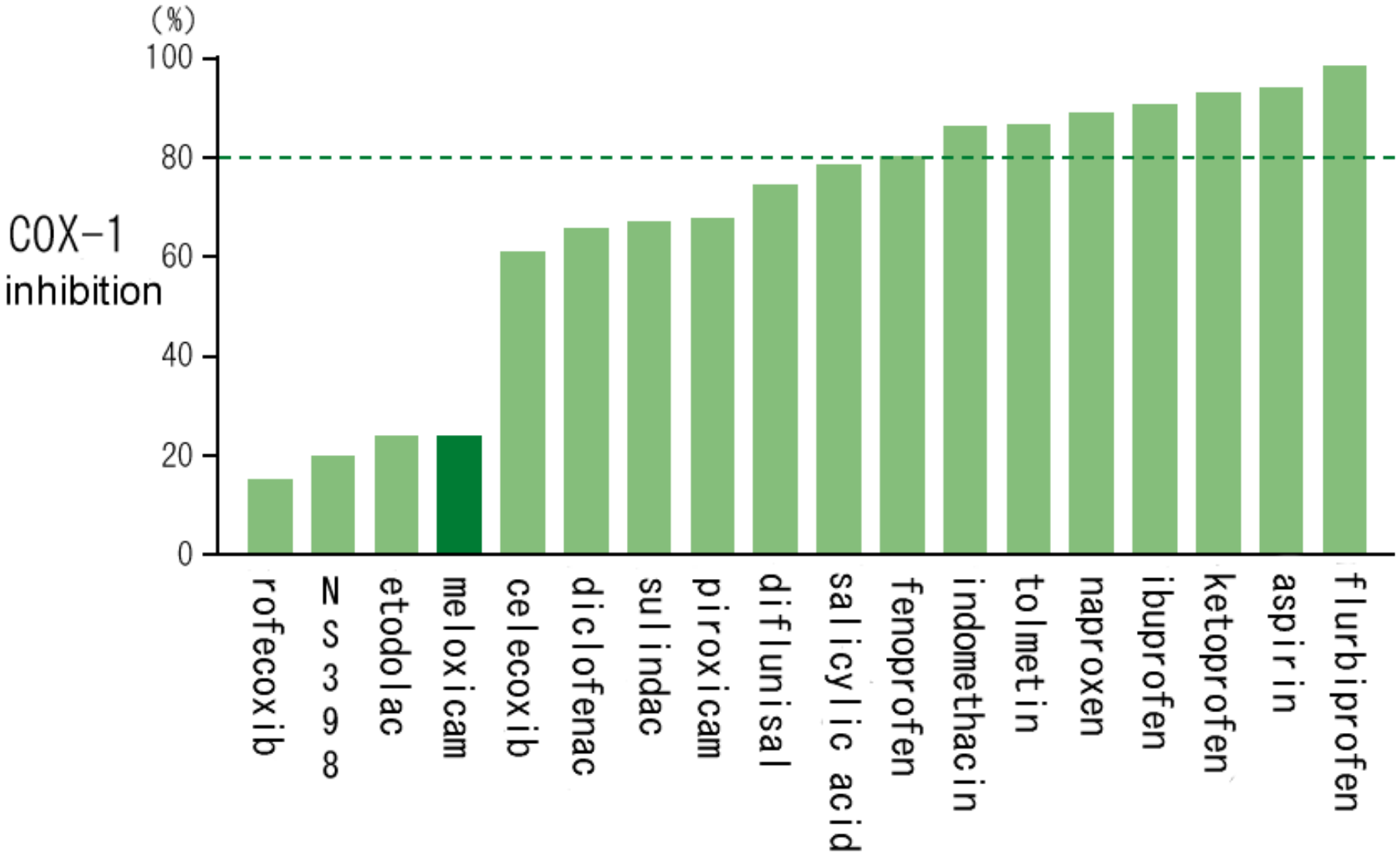


nimesulide



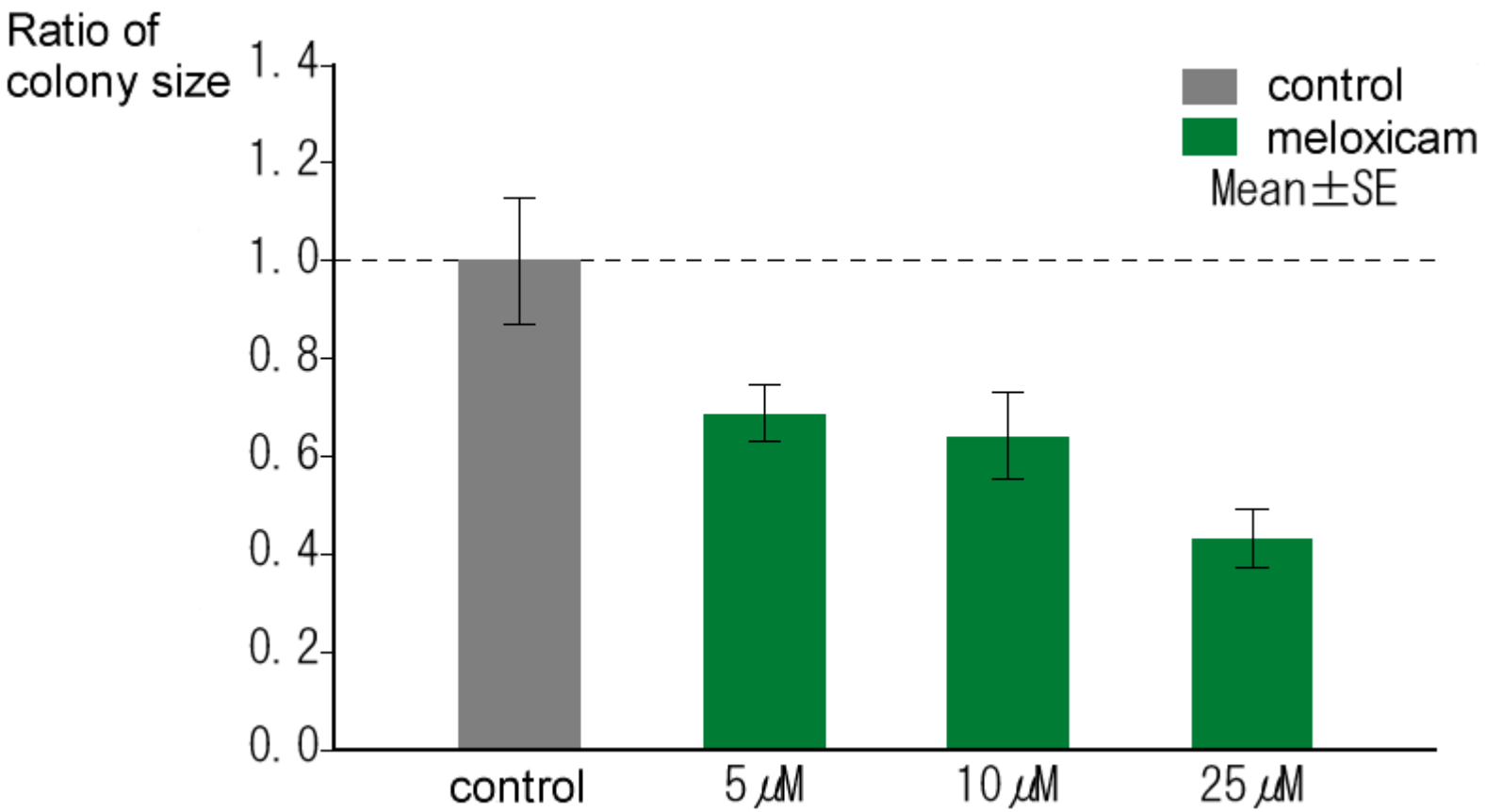
NS-398

COX-1 inhibition when blocking COX-2



Warner T. D. et al : Proc Natl Acad Sci 96, 7563-7568, 1999

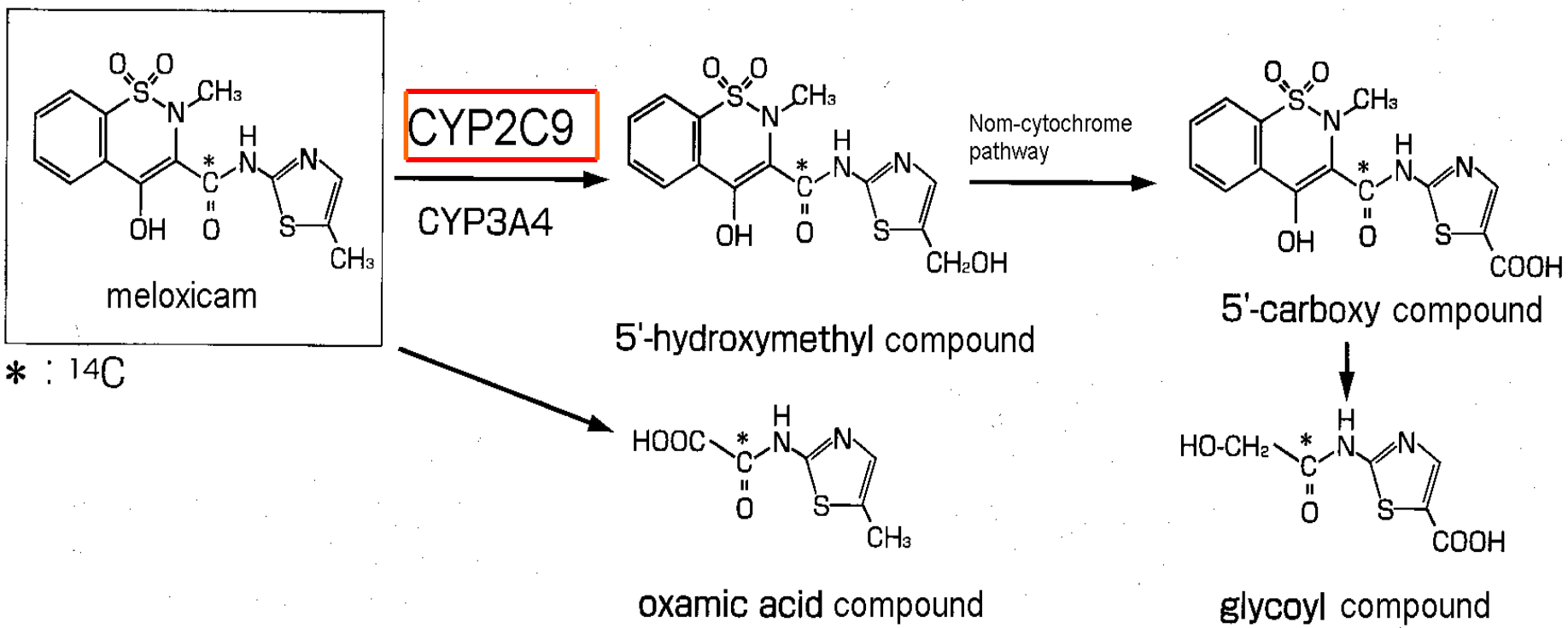
Antitumor activity of meloxicam



Ratio of colony size of colon carcinoma cells (Moser-S)

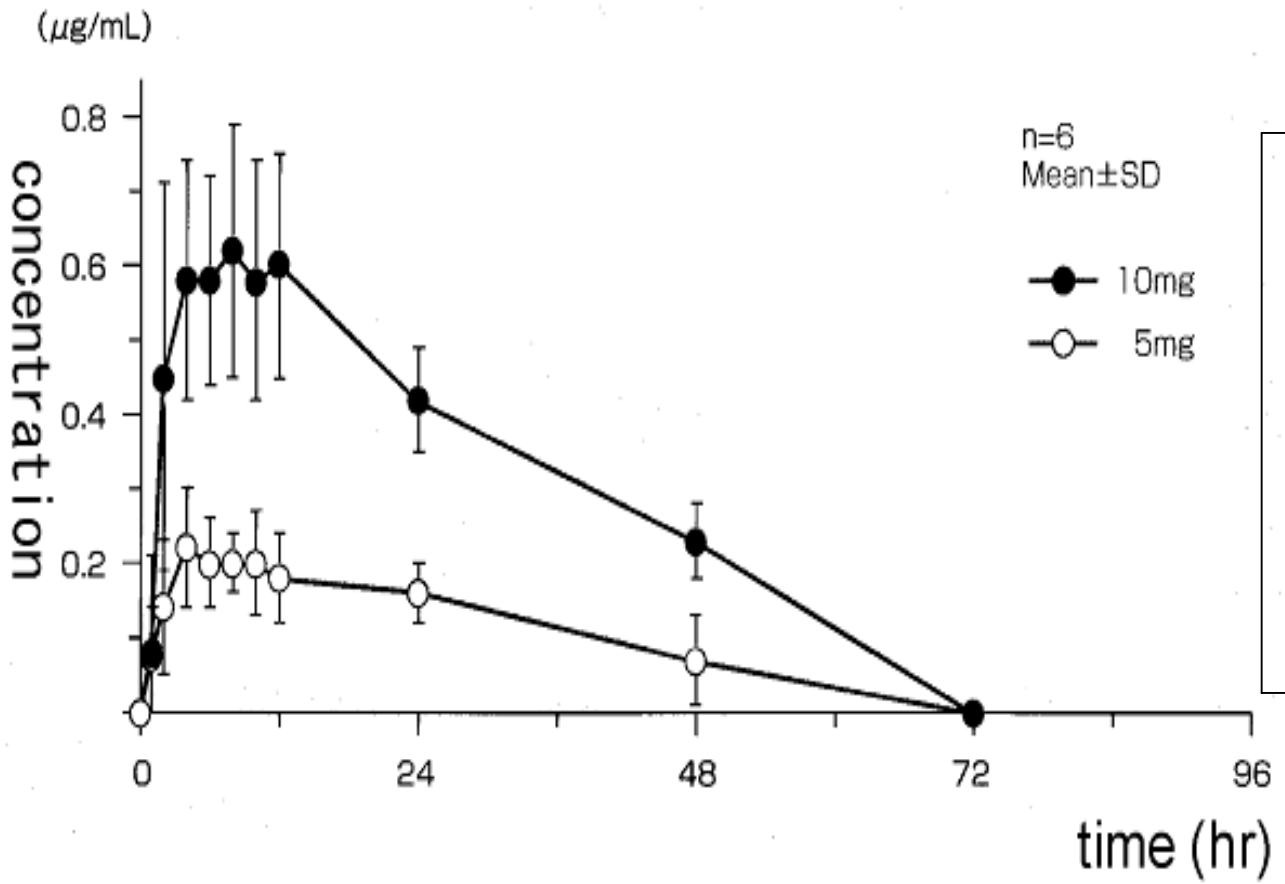
Goldman A. P. et al ：Carcinogenesis 19 (12), 2195-2199, 1998

Metabolic pathway of meloxicam



Pharmacokinetics of meloxicam

- Single dosing -



10 mg p.o. dosing

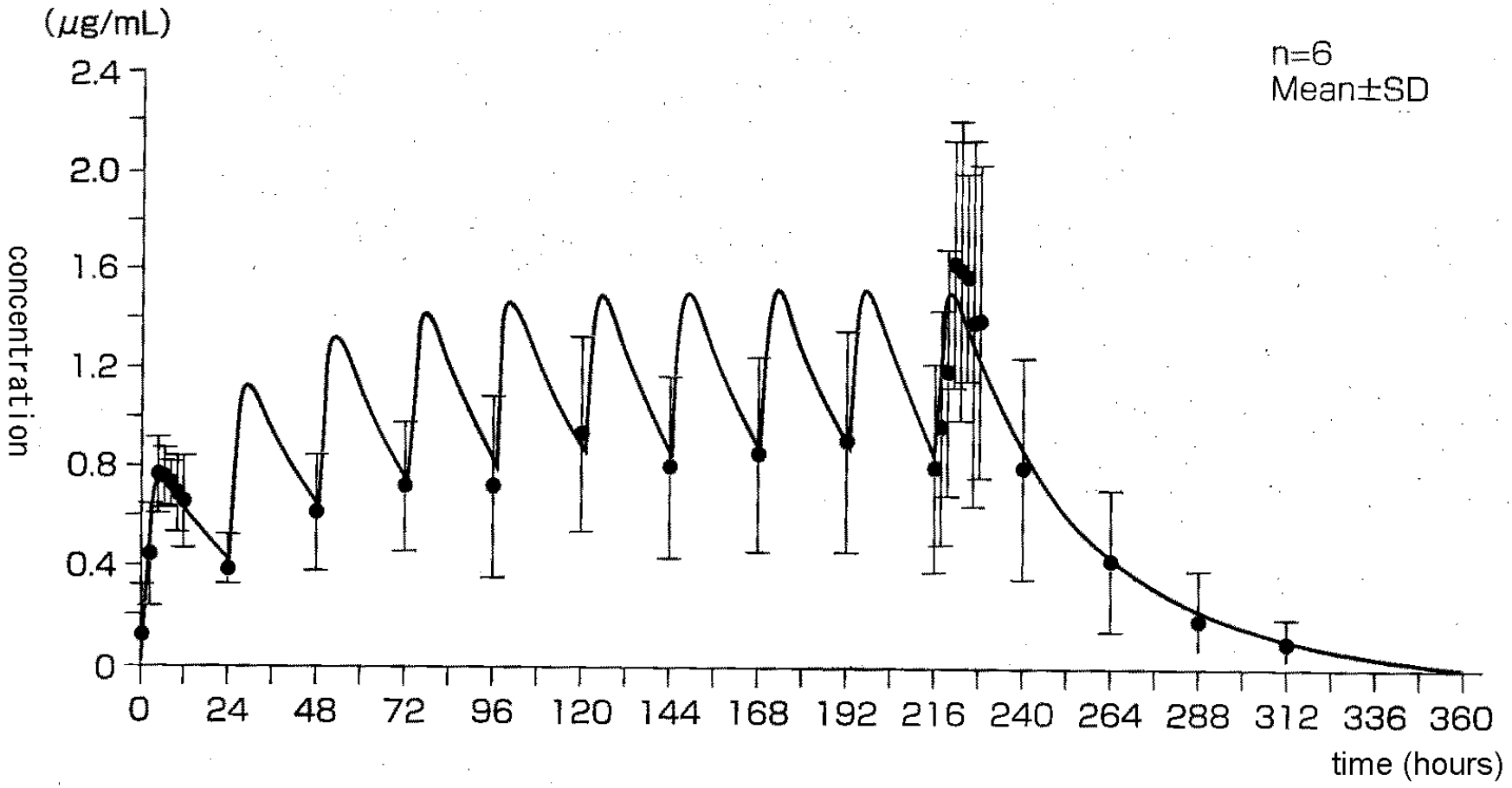
Cmax (μg/mL)
0.72±0.20

T1/2 (hr)
27.6±7.30

AUC0-168 (μg h/mL)
22.8±3.61

Pharmacokinetics of meloxicam

- Multiple dosing -



Side effects of meloxicam

	meloxicam 15mg (n=1590)	**piroxicam 20mg (n=689)**
GI side effcets	1.7%	4.9%*
Skin reaction	6.2%	4.4%
AST, ALT ↑	7.4%	6.3%
BUN, Cr ↑	0.4%	0.9%

A proposed clinical study using Meloxicam (Mobic®)

Daiichi pharmaceutical company in Japan will give us a grant. Meloxicam will be freely given to the patients entered in this clinical trial

Clinical trials combining celecoxib and radiation therapy

Phase	Diagnosis	Treatment	Group
II	NSCLC I/II	Celecoxib+RT	RTOG
I/II	NSCLC IIB-IIIB	Celecoxib+RT	RTOG
II	NSCLC III	Celecoxib+CBDCA/TXL/RT	VCC
II	NSCLC inope I/II	Celecoxib+RT	VCC
II	NSCLC recurrent	Celecoxib+taxane/RT	VCC
I	NSCLC inope	Celecoxib dose ↑ + RT	MDACC
I/II	Esophageal ca.	Celecoxib+CDDP/FU/RT	MDACC
II	Esophageal ca.	Celecoxib+CDDP/FU/RT	HOG
II	Cervical ca. locally advanced	Celecoxib+CDDP/FU/RT	RTOG

JNCI 95:1440, 2003

Possible clinical trials combining meloxicam and radiation therapy

Phase	Diagnosis	Treatment
I	Cervix & head and neck ca.	Meloxicam dose↑+CDDP/RT
II	Cervical ca. locally advanced	Meloxicam+CDDP/RT
II	Head and neck ca. locally ad.	Meloxicam+CDDP/RT
R. II	Cervical ca. locally advanced	Meloxicam+CDDP/RT
R. II	Head and neck ca. locally ad.	Meloxicam+CDDP/RT
R. III	Cervical ca. locally advanced	Meloxicam+CDDP/RT
R. III	Head and neck ca. locally ad.	Meloxicam+CDDP/RT

R.:randomized

A phase I study using Meloxicam (Mobic®)

- Locally advanced cervical cancer or head and neck cancer (n=6 x each dose)
- Meloxicam 15, 20, 25, 30mg/day+CDDP/RT
  - According to phase I study of CDDP/RT for cervical or head & neck cancers, the doses of CDDP and RT will be decided.
- Primary end point: Side effect
- Secondary end point: Response, (Survival time), (QOL)

A phase II study using Meloxicam (Mobic®)

- Locally advanced cervical cancer (n=30-100), or
  Locally advanced head and neck cancer (n=30-100)
- Meloxicam 15mg/day+CDDP/RT
  - According to phase I study of CDDP/RT for cervical or head & neck cancers, the doses of CDDP and RT will be decided.
- Primary end point: Response
- Secondary end point: Survival time, Side effects, (QOL)

A randomized phase II study using Meloxicam (Mobic®)

- Locally advanced cervical cancer (n=30-40 x 2), or
  Locally advanced head and neck cancer (n=30-40x2)
- Meloxicam 15mg/day+CDDP/RT
  - According to phase I study of CDDP/RT for cervical or head & neck cancers, the doses of CDDP and RT will be decided.
- Primary end point: Response, Side effects
- Secondary end point: Survival time, QOL
  - QOL investigation will be easily done by Care Notebook.

A randomized phase III study using Meloxicam (Mobic®)

- Locally advanced cervical cancer (n=100x2), and/or
  Locally advanced head and neck cancer (n=100x2)
- Meloxicam 15mg/day+CDDP/RT
  - According to phase I study of CDDP/RT for cervical or head & neck cancers, the doses of CDDP and RT will be decided.
- Primary end point: Survival time
- Secondary end point: Response, QOL, Side effects
  - QOL investigation will be easily done by Care Notebook.

Which trial do you recommend? ①

- **Meloxicam, a COX-2 inhibitor, is considered to have both antitumor effects for head/neck cancer and cervical cancer and protective effects for the oral mucosa and the rectal mucosa, respectively, indicating that the aim of clinical studies must focus on both response/survival and side effects/QOL.**
- **Safty for meloxicam at a dose of 15mg/day has been already established. Meloxicam at a dose of 15mg/day reduces inflamatory pain such as RA, indicating that this dose inhibits COX-2. These indicates no need of phase I study.**
- **Single arm phase II study cannot prove the benefit of COX-2 inhibitor at all. This study needs the control arm.**
- **Randomized phase III study is the best, but this needs a lot of patients.**

Which trial do you recommend? ②

	Phase	Diagnosis	Treatment
	I	Cervix & head and neck ca.	Meloxicam dose↑+CDDP/RT
	II	Cervical ca. locally advanced	Meloxicam+CDDP/RT
	II	Head and neck ca. locally ad.	Meloxicam+CDDP/RT
✓	R. II	Cervical ca. locally advanced	Meloxicam+CDDP/RT
✓	R. II	Head and neck ca. locally ad.	Meloxicam+CDDP/RT
	R. III	Cervical ca. locally advanced	Meloxicam+CDDP/RT
	R. III	Head and neck ca. locally ad.	Meloxicam+CDDP/RT

R.:randomized

A randomized phase II study using Meloxicam (Mobic®)

- This study will be an optional study in our group.
- The protocol using patients with cervical cancer will be proposed.

A randomized phase II study using Meloxicam (Mobic®) – draft -

A randomized phase II study - **Aim**

Determine the efficacy of meloxicam on concurrent chemoradiotherapy using cisplatin in patients with locally advanced cervical cancer

Primary endpoint:	Response
	Side effects
Secondary endpoint:	Survival time
	QOL

A randomized phase II study -Entry criteria

1. Squamous cell carcinoma of the uterine cervix
2. Stage IIB (≧4 cm in diameter) and IIIB disease (FIGO 1994)
3. Age; 20-70 years
4. PS; WHO 0-2
5. No prior chemotherapy, radiotherapy, and surgery to the pelvis
6. Life expectancy; longer than 6 months
7. Measurable disease
8. Adequate bone marrow, hepatic, and renal functions;
   - WBC≧3000/mm^3
   - Hb≧10g/dl
   - Platelet≧100,000/mm^3
   - Total bilirubin≦1.5mg/dl
   - AST/ALT≦2 times upper limit of normal
   - Serum creatinine≦1.5mg/dl
9. Written informed consent

A randomized phase II study **-Exclusion criteria**

1. Severe concomitant illness
2. History of other malignancies within the past 5 years except basal cell carcinoma or squamous cell carcinoma in-situ of the skin
3. **Tumor with infiltration of lower 1/3 of the vagina**
4. Patients who are pregnant or lactating
5. Patients planned for surgery following radiotherapy

A randomized phase II study -Entry & randomize

Ensure to meet the entry criteria, informed consent

↓

Entry

↓

randomize（block randomization：institution）

↓ ↓

Arm 1: **ChemoRT with meloxicam**	**Arm 2:** **without it**

A randomized phase II study –Treatment ①

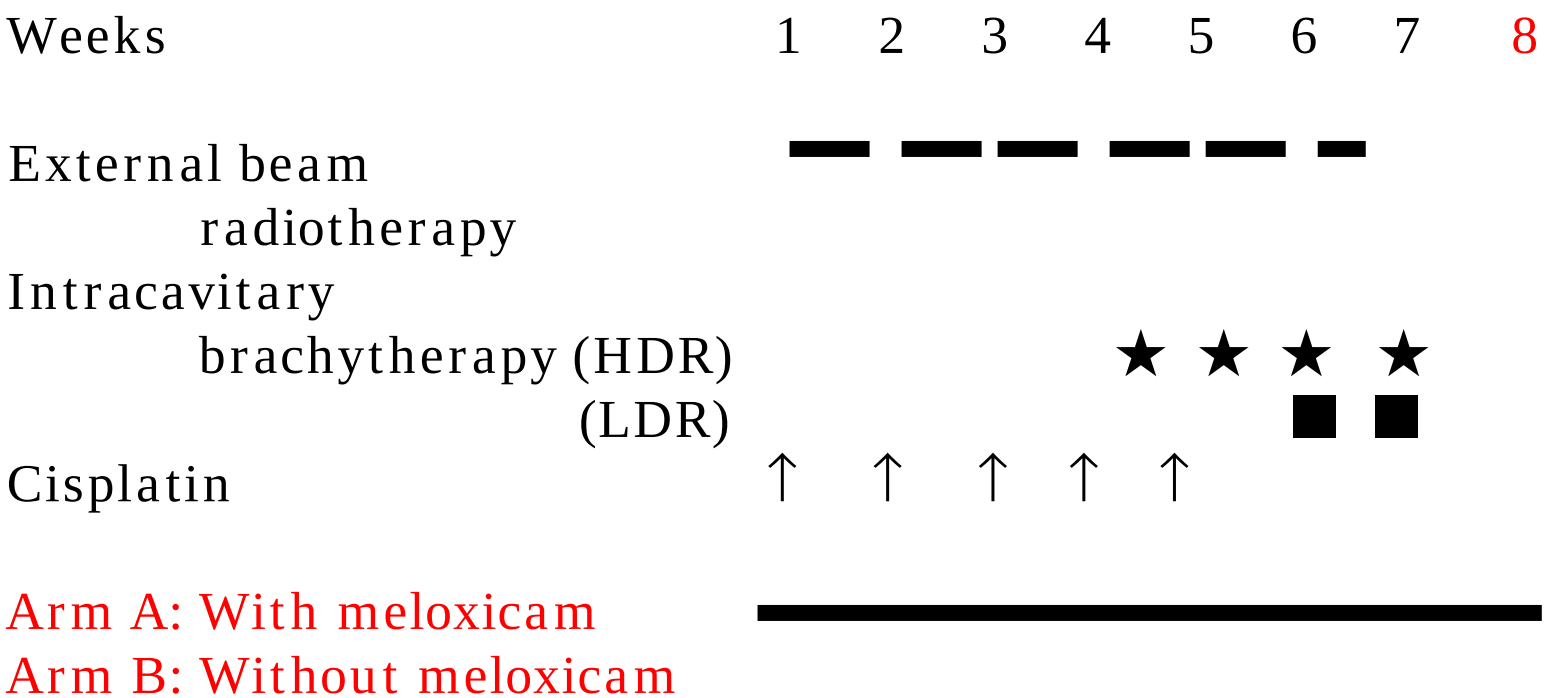
Arm 1: ChemoRT with meloxicam	Arm 2: without it
meloxicam p.o. For 8 weeks (from day –1 to day 56), 15 mg/bogy/day p.o. 1 x m	none (Prophylactic use of NSAID is prohibited.)

↓ ↓

＜ weekly CDDP and concurrent irradiation ＞

CDDP 40mg/m2/weekly x 5 with hydration of 2000mL.
Concurrent RT

A randomized phase II study –Treatment ②



A randomized phase II study –Treatment ④

- **External beam radiotherapy**

Fractionation schedule: 1.8—2.0 Gy/fraction, 5 fractions/week
Total dose: approximately 50 Gy
Whole pelvis 30-40Gy, Central shielding 20-10 Gy
10-15Gy of boost irradiation to the bulky parametrial disease or gross lymph node metastases is allowed.

- **Intracavitary brachytherapy**

HDR treatment: 24-28 Gy / 4 fractions (6-7 Gy/fraction)
LDR treatment: 30-40 Gy/ 1-2 fractions

- Chemotherapy
  - Cisplatin 40 mg/m^2 d.i.v. weekly, week 1-week 5
- COX-2 inhibitor
  - With meloxicam: For 8 weeks (from day –1 to day 56), 15 mg/day p.o. 1x m
  - Without meloxicam: Prophylactic use of NSAID or COX-2 inhibitor is prohibited

A randomized phase II study –Treatment ③

In case of

S-Cr>=2.0 mg/dl ⇛ Withhold CDDP

WBC<3,000 /mm3 ⇛ Withhold CDDP

Pl <75,000 /mm3 ⇛ Withhold CDDP

Gastric ulcer ⇛ Withhold meloxicam

Grade ≥3 nonhematological toxicities

⇛ Withhold CDDP+RT

Grade 4 hematological toxicities

⇛ Withhold CDDP+RT

PSR 3 or 4 ⇛ Withhold CDDP+RT

A randomized phase II study -Evaluation

- Plain pelvic MR or enhanced CT scan before the treatment, and after completion of RT
  - Response
- Evaluation of acute toxicities by NCI CTC up to 90 days from the beginning of the treatment and late toxicities
  - Side effects
- QOL evaluation before the treatment, at the end of RT, 1 year and 2 years after the treatment
  - QOL
- Follow up at least for 2 years
  - Survival

A randomized phase II study -Evaluation

Plain pelvic MR or enhanced CT scan

- Before the treatment and at the end of the treatment
- The same test (CT/MR) before and after the treatment should be performed.
- **For two times of testing, about 400 US dollars per person will be given to the institution joined the study except for Japanese institutions from the grunt.**

- Please discuss about this matter.
  - We consider that only single type (MR) of scan should be employed --- .

A randomized phase II study -Evaluation

QOL evaluation

- before the treatment, at the end of RT, 1 year and 2 years after the treatment
- Using a validated QOL questionnaire, Care Notebook
- Paying some money to the patient when answering Care Notebook, to avoid low return rate of the questionnaire

A randomized phase II study -Cost

- Meloxicam 15mg x 56 days
  - About 100 US dollars (but no cost in control)
- Two times of plain pelvic MR for response
  - About 400 US dollars
- Evaluation of acute and late side effects
  - No cost
- Four times of QOL evaluation
  - 5 US dollars x 4 times = 20 US dollars
- Follow up at least for 2 years
  - No cost

↓

✧**500 US dollars per person will be given to the institution joined the study except for Japanese institutions from the grunt.**
✧**Minimum number of patients is 4 in one institution joined the study.**