



BrachyNext

Working Together to Shape the Future of
Brachytherapy



Re-irradiation Using HDR Interstitial Brachytherapy for Locally Recurrent Cervical Cancer

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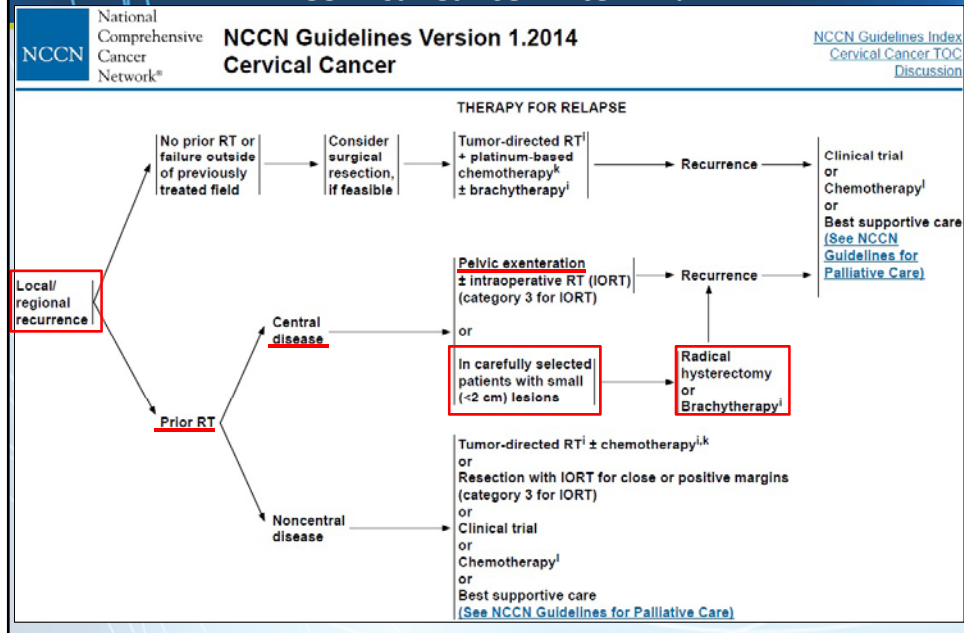
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Disclosure

Yasuo Yoshioka, MD, does not have any financial relationships or products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.



What Can We Do for Recurrent Cervical Cancer After RT?



Japanese Guidelines Are Less Aggressive...

- (1) Best supportive care
- (2) May consider palliative chemotherapy
- (3) May consider pelvic exenteration or hysterectomy
- (4) Re-irradiation should not be the first choice

Personal translation of “子宮頸癌治療ガイドライン2011年版 (in Japanese)”

CQ 27

照射野内再発に対して推奨される治療は？

推奨

- ① 緩和医療を原則とする (グレードC1)。
- ② 照射野内再発では奏効率が低いことを念頭に、症状緩和を目的とした化学療法も考慮される (グレードC1)。
- ③ 腫瘍断端、子宮頸部の中央再発に対しては、術前評価を十分に行ったうえで、骨盤除腫瘍術や子宮全摘出術も考慮される (グレードC1)。
- ④ 再照射は第一選択とはならない (グレードC2)。



Summary of Surgery

– from Japanese Guidelines

1. Pelvic exenteration

- 5-year overall survival: 37~66%,¹⁻⁴ expecting long-term survival
- Severe complication: 45~65%¹⁻⁶
- Peri-operative mortality: 2~14%¹⁻⁶
- Need strict indication according to each institution

2. Radical hysterectomy

- 5-year overall survival: 49~72%^{7,8} (cases w/o pelvic wall invasion)
- Severe complication: >40%
- Some report good results using total hysterectomy⁹
- Relatively less invasive than pelvic exenteration, but need IC

1) Rutledge FN, et al. Am J Obstet Gynecol 1977;129:881-92
 2) Terán-Porcayo MA, et al. Med Oncol 2006;23:219-23
 3) Marnitz S, et al. Gynecol Oncol 2006;103:1023-30
 4) Jurado M, et al. Gynecol Oncol 2010;116:38-43
 5) Shingleton HM, et al. Obstet Gynecol 1989;73:1027-34

6) Kasamatsu T, et al. Int J Gynecol Obstet 2005;89:39-44
 7) Coleman RL, et al. Gynecol Oncol 1994;55:29-35
 8) Maneo A, et al. Int J Gynecol Cancer 1999;9:295-301
 9) Ota T, et al. Br J Cancer 2008;99:1216-20

Summary of Re-irradiation

– from Japanese Guidelines

- Methods: EBRT, ICBT, ISBT
- Local control rate: 64~92%^{1,2}
- 5-year overall survival: 4~40%²⁻⁵
- Severe complication: 38~66%^{1,3,5}
- ISBT may be good for a smaller tumor or for a recurrence after >5 years³⁻⁶
- ISBT should be performed at an experienced center
- Re-irradiation should not be the first choice for in-field recurrence

EBRT: external beam radiotherapy
 ICBT: intracavitary brachytherapy
 ISBT: interstitial brachytherapy

1) Rusell AH, et al. Gynecol Oncol 1987;27:226-32
 2) Sommers GM, et al. Gynecol Oncol 1989;35:150-5
 3) Jones TK Jr, et al. Radiology 1970;95:167-74
 4) Randall ME, et al. Gynecol Oncol 1993;48:23-31
 5) Xiang-E W, et al. Gynecol Oncol 1998;69:125-9
 6) Brabham JG, et al. Am J Clin Oncol 2009;32:417-22



Summary of Chemotherapy

– from Japanese Guidelines

- Treatment goal is to improve QOL by relief of symptoms
- Response rate is as low as 30~33%¹⁻³ (compare with 60~75% for out-of-field recurrence)
- In informed consent, best supportive care should also be notified as an important option

1) Pectasides D, et al. Int J Gynecol Cancer 2009;19:777-81

2) Benjapibal M, et al. Oncology 2007;72:33-8

3) Kosmas C, et al. Br J Cancer 2009;101:1059-65

Aim

To examine:

1. Effectiveness of chemotherapy
2. Effectiveness and safety of radiation therapy
3. Effectiveness and safety of surgery

in the treatment of in-field recurrence
of uterine cervical cancer,

and to propose a possible strategy for the
management of this difficult clinical problem.



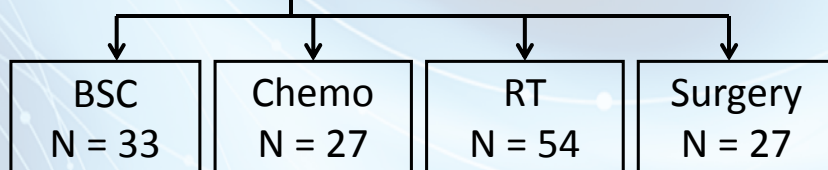
Patients and Methods – Osaka Study

275 patients who developed recurrence
in the prior RT field
between 1997 Apr. and 2012 Apr.

Excluded

- Simultaneous out-of-field recurrence
- Treated at other hospitals
- Second cancer
- Not enough data

In-field recurrence



Patient Characteristics

(Note that a significant selection bias exists)

		BSC N = 33	Chemo N = 27	RT N = 54	Surgery N = 27
Age	Median (range)	72 (32-90)	52 (18-73)	55 (30-83)	59 (28-77)
FIGO stage	I-II	14	14	41	13
	III-IV	19	13	13	14
Histology	SCC	28	20	33	17
	Non SCC	5	7	21	10
DFI (months)	≤6	14	11	15	16
	7-24	13	15	25	7
	25≤	6	1	14	4
PS	0-1	26	26	54	27
	2	7	1	0	0
No. of recurrences	Single	22	15	52	24
	Multiple	11	12	2	3
Tumor size (mm)	Median (range)	30 (1-120)	30 (10-80)	25 (1-80)	40 (5-70)

(DFI: disease-free interval between initial treatment and recurrence, PS: performance status)

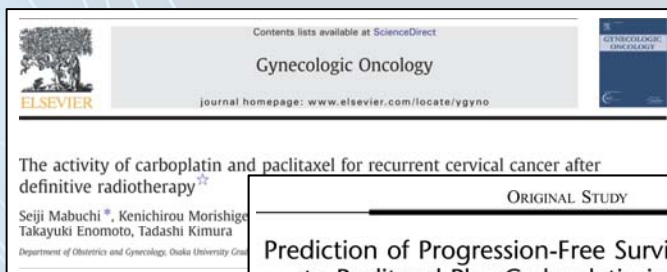


1. Chemotherapy
2. Radiation Therapy (Brachytherapy)
3. Surgery



Chemotherapy Strategy at Osaka University Hospital for Recurrent Cervical Cancer

1990s-2006: Platinum-based chemotherapy (Non-Taxane)
2007~: Carboplatin + Paclitaxel (TC)



Prediction of Progression-Free Survival and Response to Paclitaxel Plus Carboplatin in Patients With Recurrent or Advanced Cervical Cancer

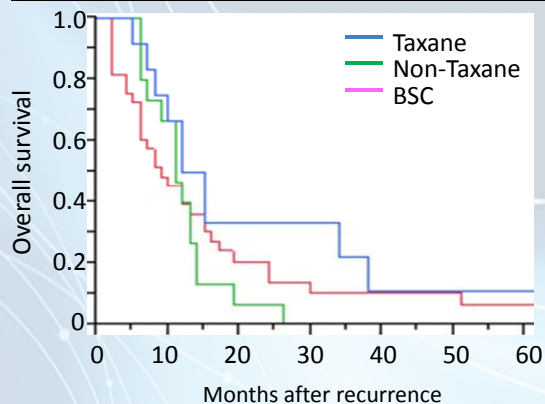
Takeshi Hisamatsu, MD,* Seiji Mabuchi, MD, PhD,* Kiyoshi Yoshino, MD, PhD,*
Masami Fujita, MD, PhD,* Takayuki Enomoto, MD, PhD,*
Toshimitsu Hamasaki, PhD,† and Tadashi Kimura, MD, PhD*

Mabuchi S, et al. Gynecol Oncol. 2009;113:200-4., Int J Gynecol Cancer. 2012;22:623-9.



Chemotherapy for In-Field Recurrence (n = 27)

(All regimens were platinum-based)	n	Regimens
Non-taxane-containing regimen	15	CDDP/CDGP +/- 5FU
Taxane-containing regimen	12	TC/TP/TEC



Log-rank test

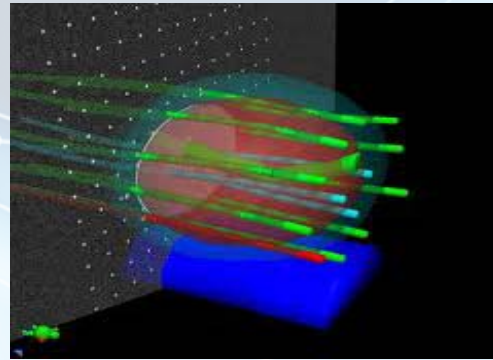
	P-value
Taxane vs non-taxane	0.063
Non-taxane vs BSC	0.678
Taxane vs BSC	0.902

Short Summary of Chemotherapy for In-Field Recurrent Cervical Cancer

Short-term survival is improved
by Platinum-Taxane regimen,
but long-term survival is NOT expected.

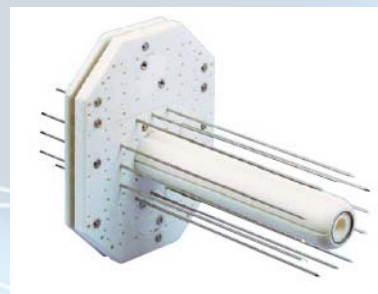
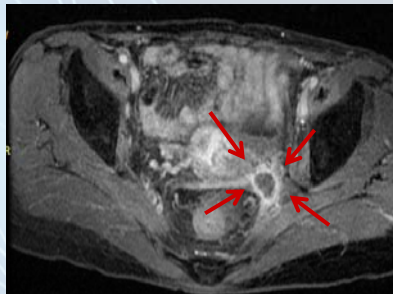


1. Chemotherapy
2. Radiation Therapy (Brachytherapy)
3. Surgery



“HDR Brachytherapy Alone” – Salvage RT Policy for In-Field Recurrent Cervical Cancer at Osaka University Hospital

Brachytherapy	N = 54
Intracavitary	3
Interstitial	51



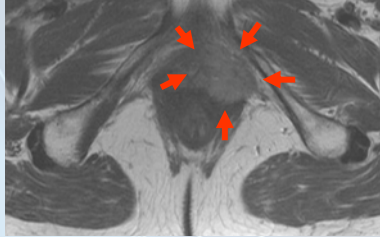
From 1995, we treat central recurrence of cervical cancer after RT, using high-dose-rate interstitial or intracavitary brachytherapy alone at Osaka University Hospital.

Inoue T, et al. J Brachytherapy Int 1999;15:161-7

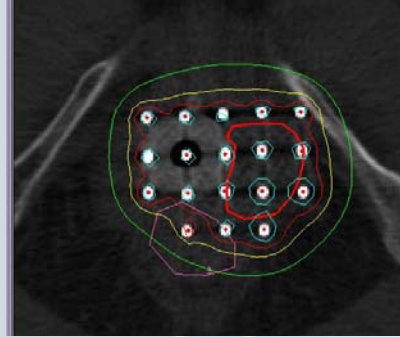
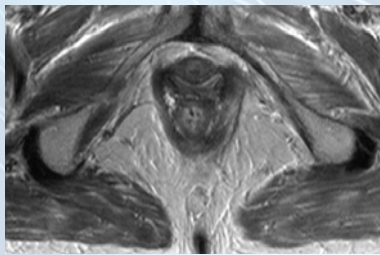


HDR-ISBT – Our Technique

70s, vaginal wall recurrence

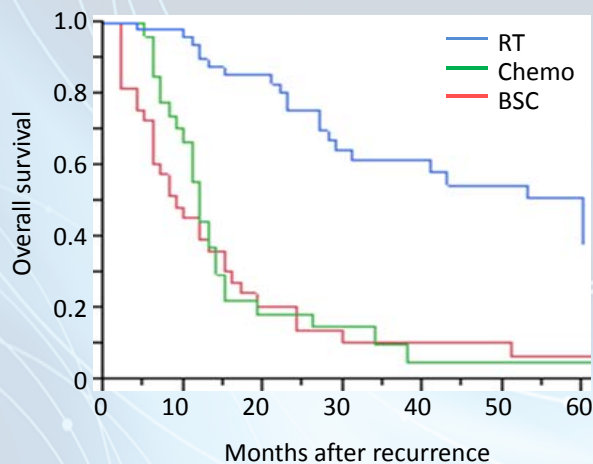


↓ 42 Gy/7 fractions/4 days



- Metallic needles placed via perineum
- Under epidural anesthesia
- Guidance of TRUS (transrectal ultrasonography) and a template
- CT-based treatment planning
- Dwell positions selected in the delineated target
- Dwell times optimized

Radiation Therapy for In-Field Recurrence in Comparison to Chemo or BSC (Osaka Univ.)



Log-rank test

	P-value
RT vs BSC	<0.001
RT vs Chemo	<0.001



What We Learned From Our ISBT Results

TABLE 2. Treatment Outcomes

Local control	
CR	31
PR	9
SD	8
PD	4
Response rate*	76.9%
Survival after recurrence (months)	
Median (range)	32 (4–156)
Severe late toxicity	
Patients with grade 3/4 toxicities	13 (25%)
Rectovaginal fistula	2
Vesicovaginal fistula	3
Vesicovaginal fistula plus rectovaginal fistula	4
Hematuria	2
Bowel obstruction	1
Genital skin ulceration	1

*Response rate indicates the proportion of patients who showed CR or PR to ISBT.
PD, progressive disease.

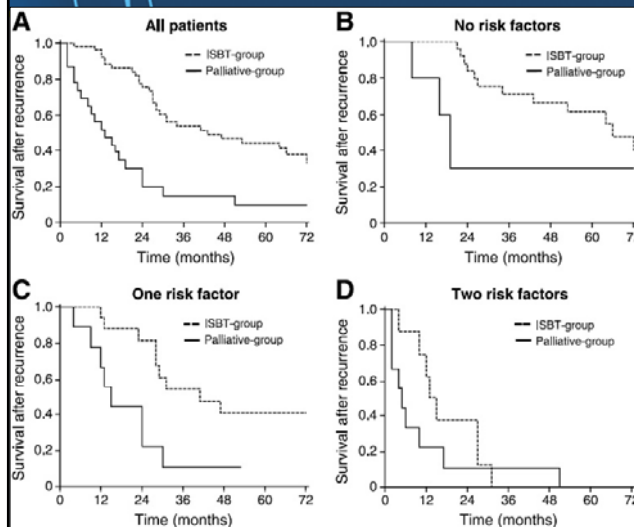
77% response rate
(CR + PR)

25% severe late toxicity
(G3-4)

2.7-year median
survival
(after recurrence)

Mabuchi S, et al. Int J Gynecol
Cancer 2014;24:141-8

What We Learned From Our ISBT Results



Mabuchi S, et al.
Int J Gynecol Cancer 2014;24:141-8

Multivariate analysis
identified
(1) DFI ≤ 6 mo
and
(2) tumor size ≥ 40 mm
as poor prognostic factors
(DFI: disease-free interval)

We classified into
3 groups: no factor,
1 risk factor,
2 risk factors

Patients with 2 risk
factors showed a
similar survival to
BSC patients



Short Summary of RT (Brachytherapy) for In-Field Recurrent Cervical Cancer

1. RT has the possibility to improve long-term survival, but 25% of patients encounter severe late toxicity
2. RT is less effective to those patients with a short disease-free interval (between initial treatment and recurrence), or to those with a larger tumor

1. Chemotherapy
2. Radiation Therapy (Brachytherapy)
3. Surgery





Surgery for In-Field Recurrence: Safety

Operative procedure	No. of patients	Operation time (m)	Blood loss (g)	Complication Grade 3-4
Lymph-adenectomy	2	147.5 (55-240)	260 (20-500)	0
Total abdominal hysterectomy	9	194.0 (75-325)	632.2 (100-2420)	2
(Semi-) radical hysterectomy	11	439.5 (155-729)	1651.6 (400-4000)	0
Total pelvic exenteration	5	715.0 (500-925)	3240 (1520-5400)	2

- No perioperative death
- 4 cases (14.8%) developed Grade 3-4 complications
- No relation between complication and operative procedure

Surgery for In-Field Recurrence: Safety

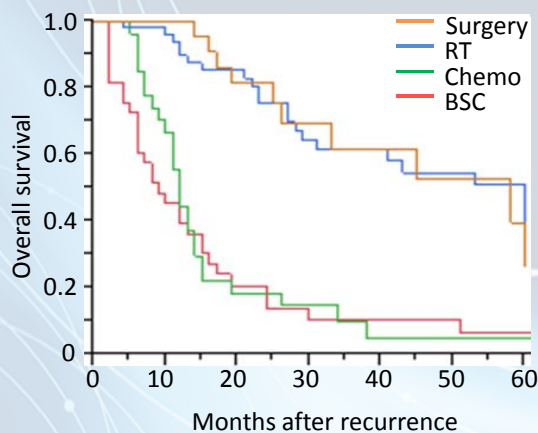
Details of Grade 3-4 complications

Complication event	Surgery	Age	DFI	Time of event	Treatment
Rectovaginal plus vesicovaginal fistula	TAH	69	3	4 mo	Urinary diversion and colostomy
Rectovaginal fistula	TAH	71	8	2 mo	Observation
Anastomotic leak	PE (P)	59	2	3 wk	Healed
Ureteral fistula	PE (AP)	28	18	4 mo	Healed

DFI: disease-free interval between initial treatment and recurrence



Surgery for In-Field Recurrence: Effectiveness



Log-rank test

	<i>P</i> -value
Surgery vs BSC	<0.0001
Surgery vs Chemo	<0.0001
Surgery vs RT	0.859

Short Summary of Surgery for In-Field Recurrent Cervical Cancer

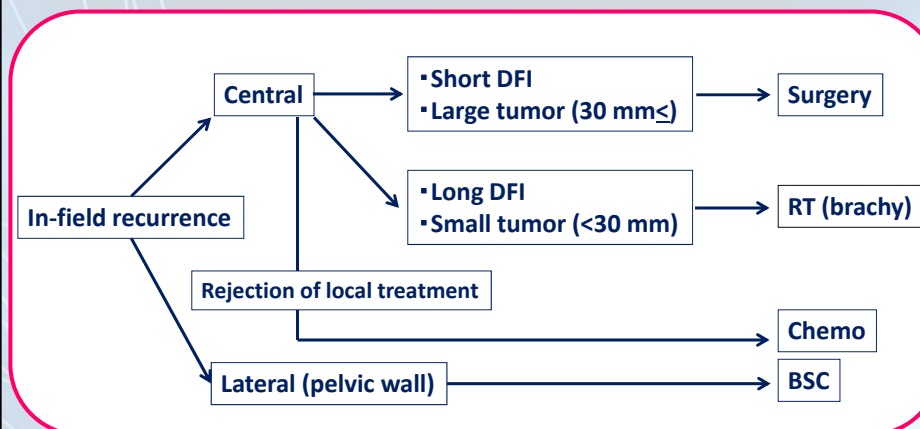
1. Surgery has the possibility to improve long-term survival
2. Surgery has the possibility of severe complications, and therefore needs fully informed consent
3. Surgery may require enough experience considering its technical difficulty in performing within the fibrotic (hard) tissue



Limitations – of Osaka study, but also of many other literatures

1. A retrospective, single-institution study
2. A small number of patients
3. Not enough follow-up period
4. Heavy selection bias exists (generally, smaller tumor, better PS: Re-irradiation > surgery > chemo > BSC)
5. Variation of procedures and experience

Conclusions: Proposal of a Treatment Strategy for In-Field Recurrent Cervical Cancer



* Performance status should be taken into consideration

* Complication should be fully informed enough in surgery or RT



Acknowledgements

Special thanks to:

Dr. Seiji Mabuchi (Gynecologic oncologist)

Dr. Fumiaki Isohashi (Radiation oncologist)

Prof. Tadashi Kimura (Director of Obstetrics & Gynecology)

Prof. Kazuhiko Ogawa (Director of Radiation Oncology)

and other staff at Osaka University Hospital



Osaka-jou (Osaka Castle)



Taiyo-no-Tou
(Tower of the
Sun)

If time remains...

Tips & Tricks for Interstitial Brachytherapy



Take CT one day before implant, with a template attached but without needles, and make a plan of needle positions

