e-session 571

Particle therapy in the treatment of gynaecological cancers

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Discussant: **Dr Domenica Lorusso**, Policlinico Universitario Gemelli, Roma, Italy

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National Center for Oncological Hadrontherapy

Disclosures

I have no actual or potential conflict of interest in relation to this presentation

Agenda

- Introduction: what is hadrontherapy?
- Rationale of hadrontherapy
- Current Evidence: role of hadrontherapy in gynecologycal maligniancies
- Conclusions: Take Home Messages

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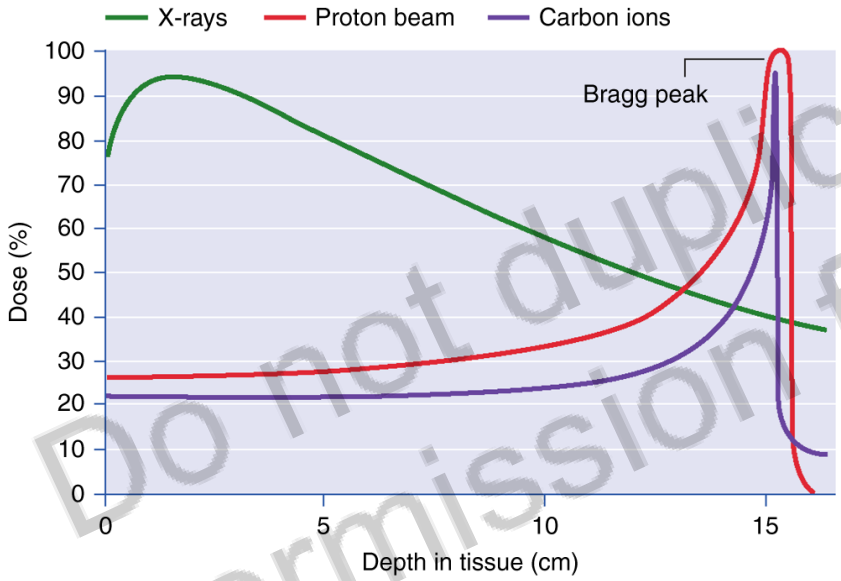
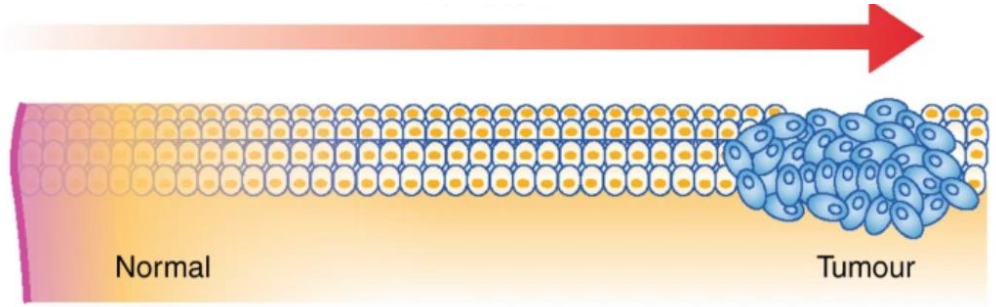
- Dosimetric hallmarks:



✓ **favourable depth–dose curve:**

- X-ray energy decreases exponentially with dose
- Hadrons deposit most of their initial energy close to the end of the range (Bragg peak) within the tumour target



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Introduction: what is hadrontherapy?

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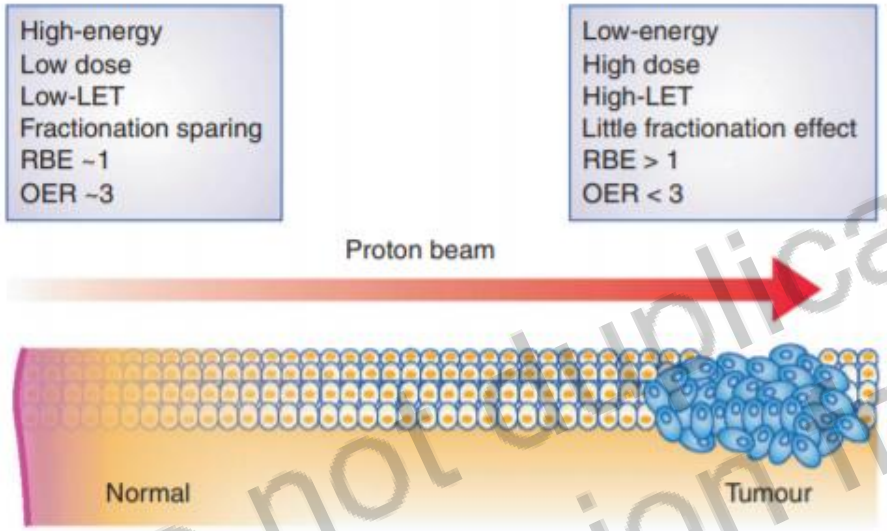

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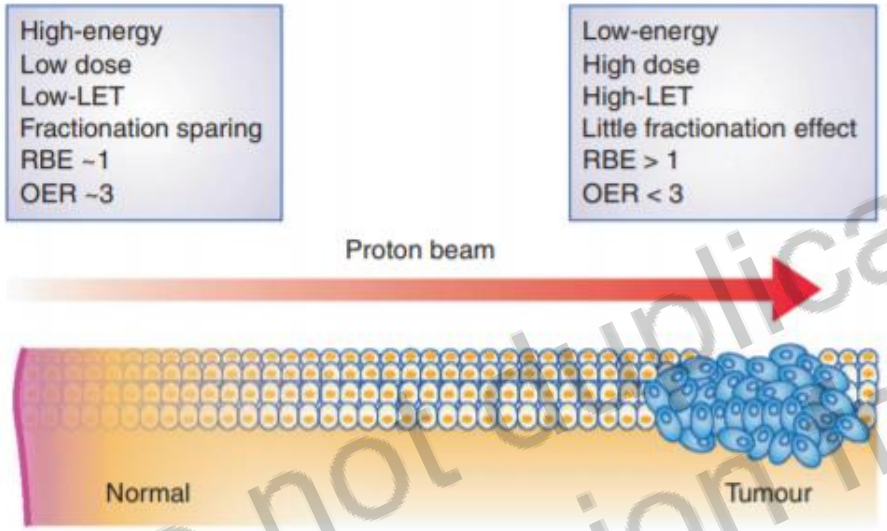

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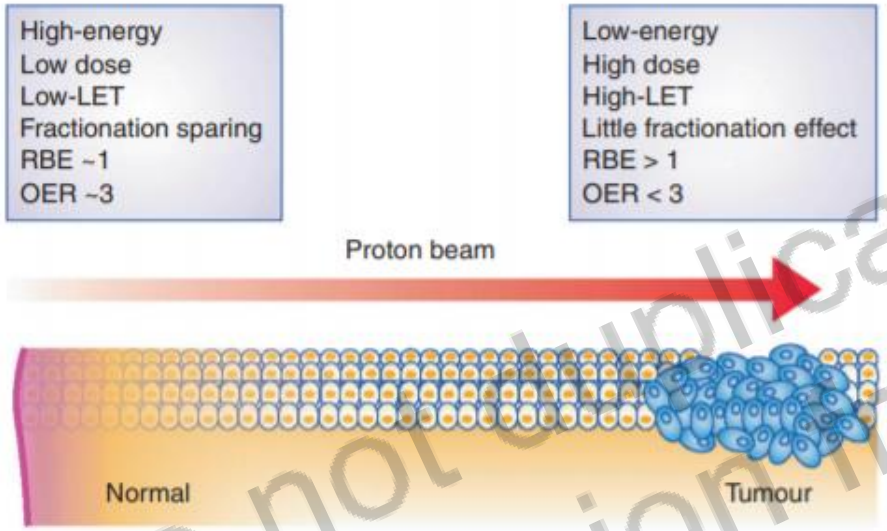

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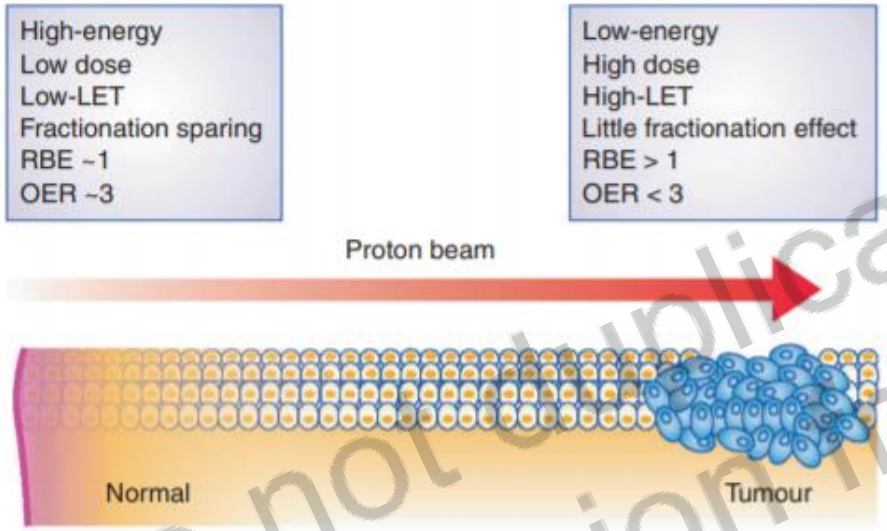

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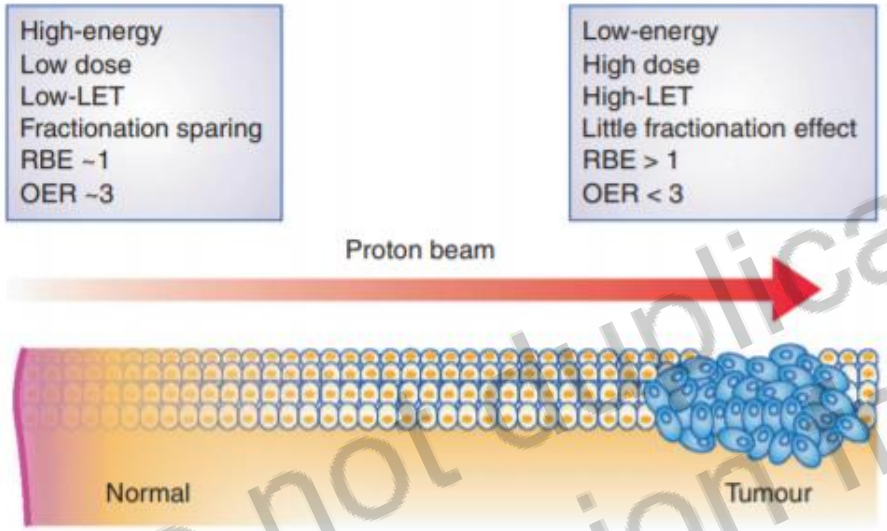

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- ✓ Reduced dependence on fractionation and cell-cycle stage (cells are most sensitive to irradiation during mitosis and in G2, less sensitive in G1, and least sensitive during the latter part of S phase)
- ✓ Reduced oxygen enhancement ratio **(OER)** in the tumour

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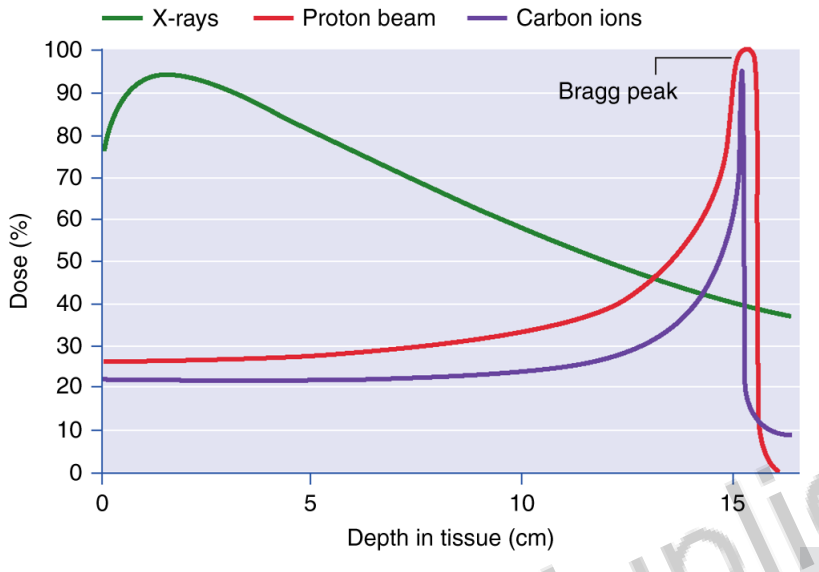
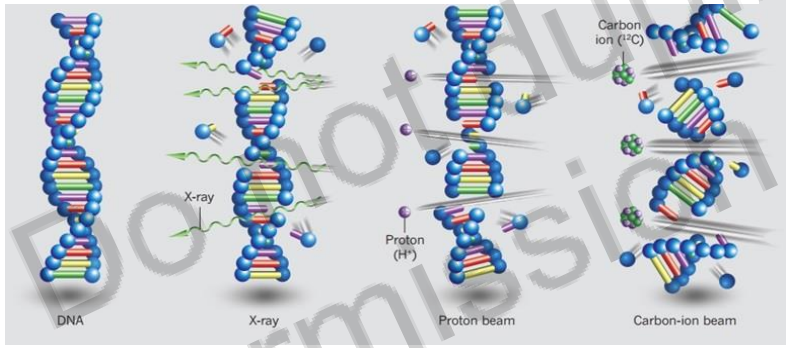
Rationale of hadrontherapy





- Normal tissue sparing, higher dose to tumor
- Effectiveness to hypoxic and radioresistent tumors

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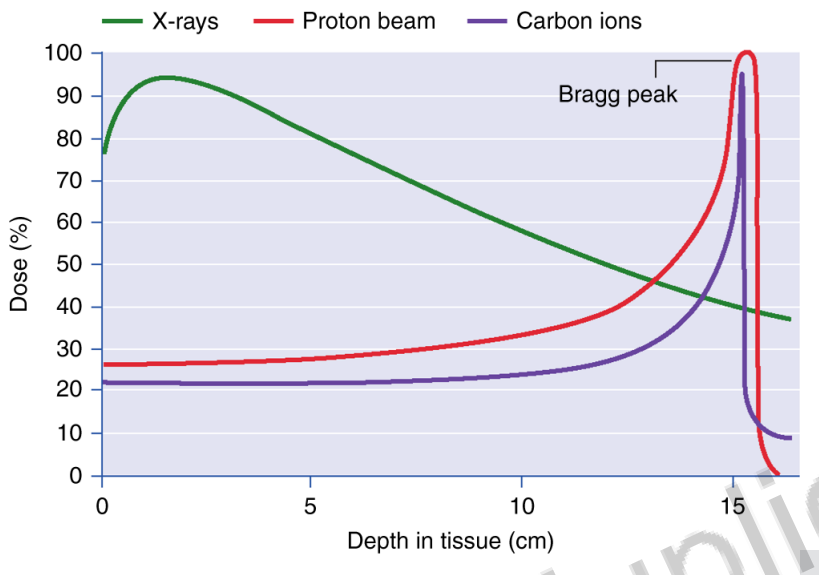

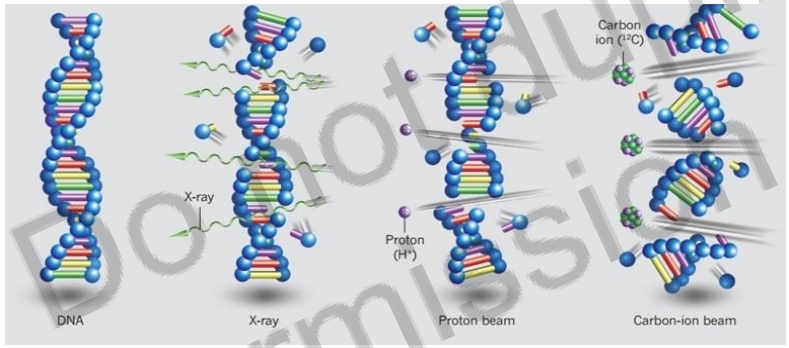

- Normal tissue sparing, higher dose to tumor:
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suitable for tumors close to radiation-sensitive organs (bowel, spinal cord, brain…), slow-growing tumors, oxygen-poor tumors or local recurrences after photon beam radiotherapy

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Rationale of hadrontherapy

- **Cervical adenocarcinoma** is relatively radioresistant compare to squamous cell carcinoma with poorer OS and LC results under conventional chemoradiotherapy
  - ✓ 5-y Locoregional failure rate ≥ 30% (pelvis is the main site of relapses)
  - ✓ 5.y OS rate: 20.3% (especially for III, IVA)

- **Primary gynecological melanomas** rare, radio-chemoresistant and aggressive cancers
  - ✓ 5-year OS of 37-50% for vulvar, 13-32% for vaginal, and approximately 10% for cervical melanoma

- **Inoperable endometrial carcinoma** in patients unfit for BT
  - ✓ 3-10% medically inoperable and unfit for BT

- **Recurrence in-field**

Grigsby PW et al. 1988 ;Gien LT et al 2010; Gadducci A et 2018,Wang et al 2019 ,Lee MY et al 2015.

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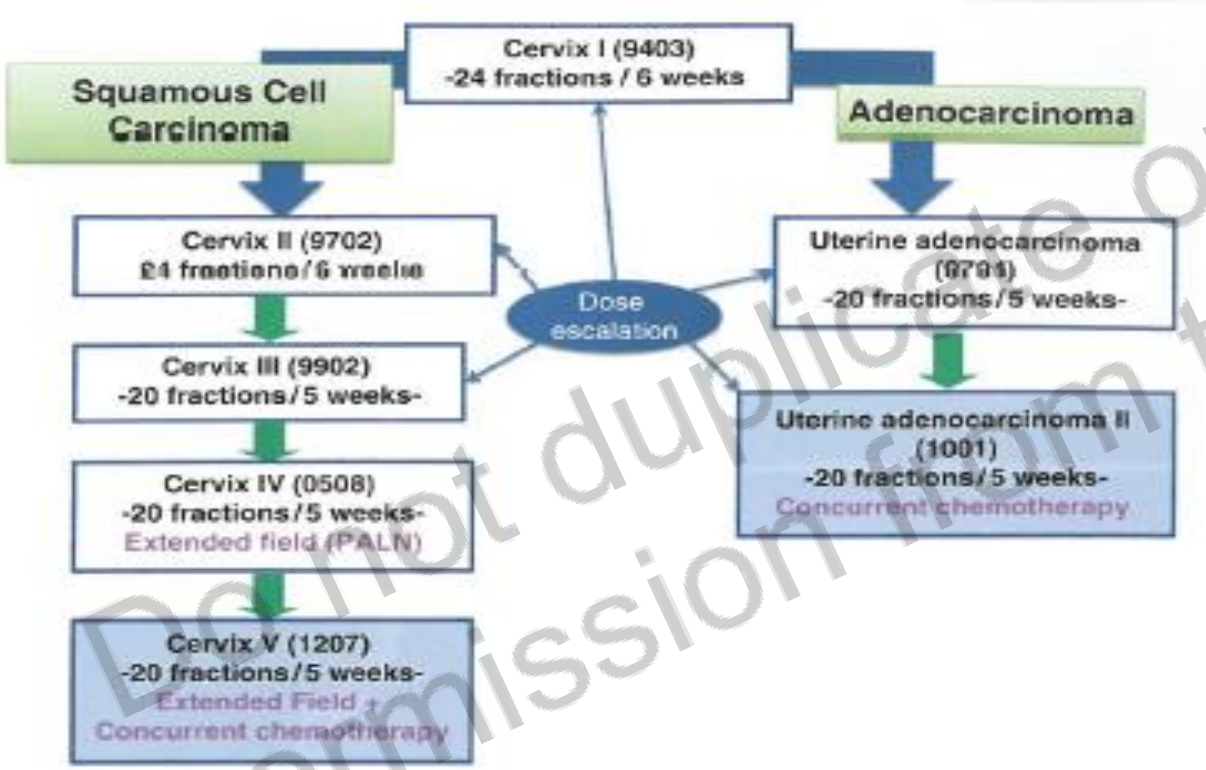
Current Evidence: role of hadrontherapy in gynecologycal maligniancies

- In 1994 at NIRS (Japan), clinical trials of the use of CIRT for locally advanced cervical cancer started



- ✓ **PROTOCOL 9403:** first study that demonstrates advantages in LC for very advanced disease (probably for hypoxic tissues)
- ✓ **PROTOCOL 9403&9702:** phase I and II dose escalation study that demonstrates that maximum tolerance dose to rectum of 60 GyE
- ✓ In all studies:
  - ✓ Total dose ranged from 52.8 GyE to 74.4 GyE
  - ✓ Whole pelvic irradiation (GTV + elective nodes irradiation)
  - ✓ Good LC with poor systemic control that lead to combo treatment **(Protocol 1207 and 1001)**

Current Evidence: role of hadrontherapy in gynecologycal maligniancies

- **PROTOCOL 9902:** dose escalation study

No. of patients	22
Follow-up, range (median) (mo)	7.6–134.8 (47.3)
Age, range (mean) (y)	31–80 (58.0)
Performance status	
0–1	21
2	1
Stage	
IIB	1
IIIB	18
IVA	3
Lymph node status	
Negative	14
Positive	8
Tumor size (cm), range (median)	4.0–12.0 (6.2)
<5.0	1
5.0–6.9	14
≥7.0	7

- ✓ Total dose to the cervical tumor: 64.0–72.0 GyE for 20 fractions
- ✓ **OTT** ranged from 32 to 37 days, **with a median of 36 days**
- ✓ Median follow-up durations for all patients: 47 months
- ✓ Median follow-up for **surviving patients: 116 months**

Wakatsuki M et al Dose-escalation study of carbon ion radiotherapy for locally advanced squamous cell carcinoma of the uterine cervix (9902). Gynecol Oncol. 2014 Jan;132(1):87-92.

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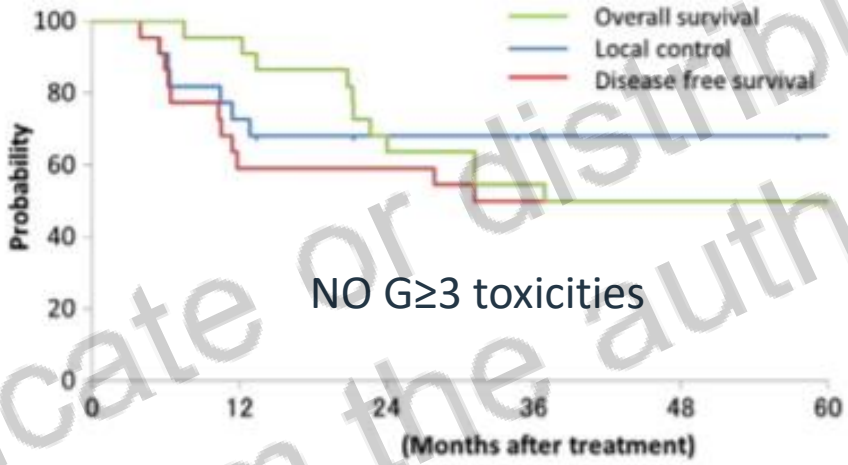

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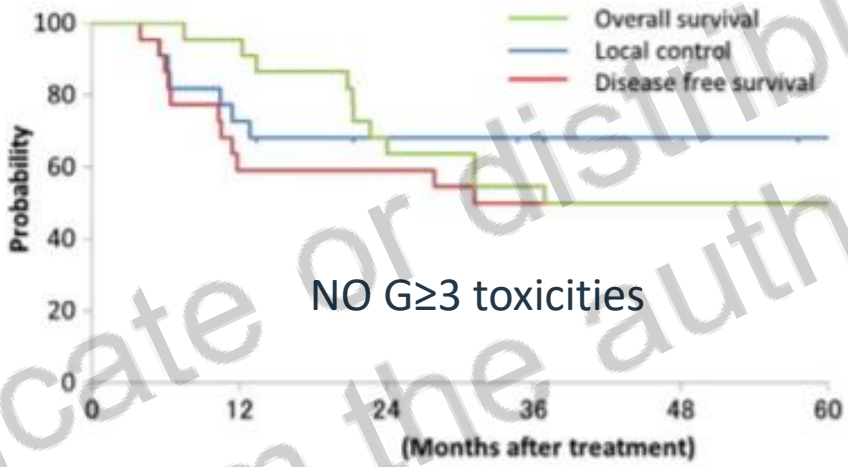

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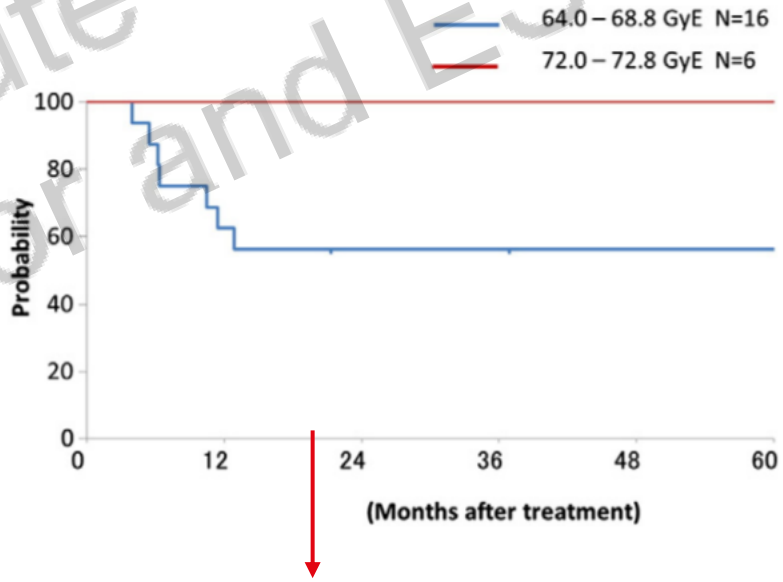

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(p = 0.069)

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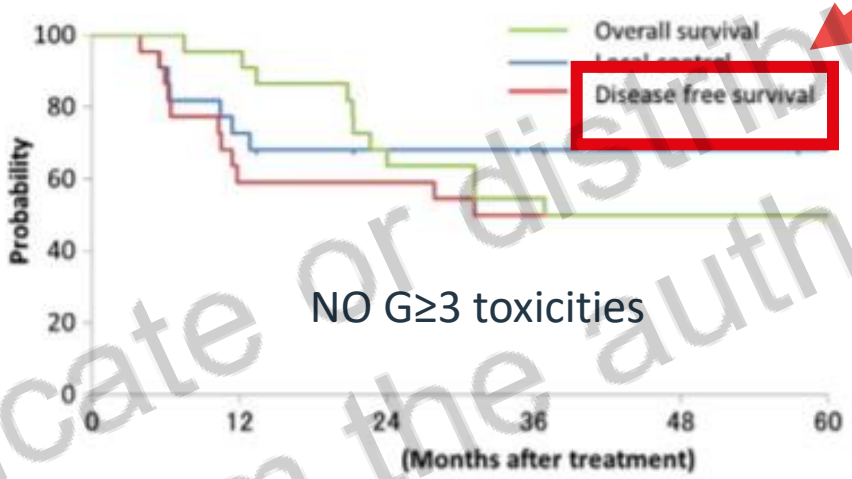

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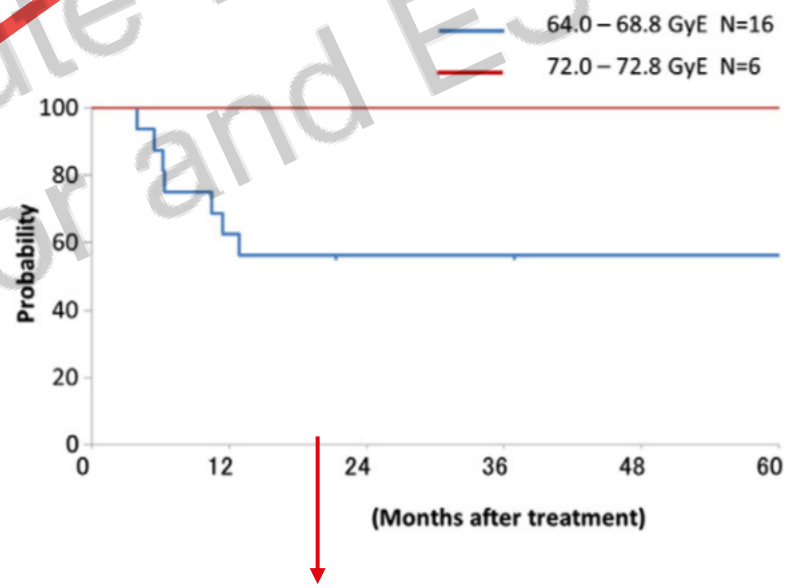

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- **PROTOCOL 0508: extended field RT study**

No. of patients		26
Follow-up	range (median) (mo)	8–85 (38)
Age	range (mean) (y)	32–78 (59)
Performance status	0–1	26
Stage (FIGO)	IIB	13
	IIIB	11
	IVA	2
Pelvic lymph node status	Negative	6
	Positive	20
Tumor size	range (cm) (median)	4.0–10.0 (6.1)
	< 5.0	7
	5.0–6.9	13
	≥ 7.0	6

- ✓ Pelvis + para-aortic nodes: 39.0 GyE/13 fx, additional 15.0 GyE/5 fx to GTV and surrounding tissues; local boost up to 18.0 GyE /2 fx
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Wakatsuki M et al Clinical trial of prophylactic extended-field carbon-ion radiotherapy for locally advanced uterine cervical cancer (protocol 0508). PLoS One. 2015 May 20;10(5):e0127587

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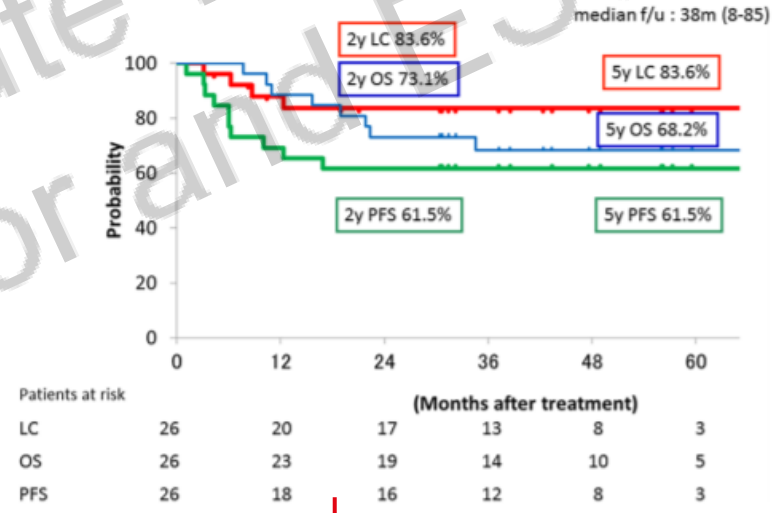

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- ✓ No concurrent chemotherapy
- ✓ Unsatisfactory OS-PFS
- ✓ 26.9% of the patients developed distant failure

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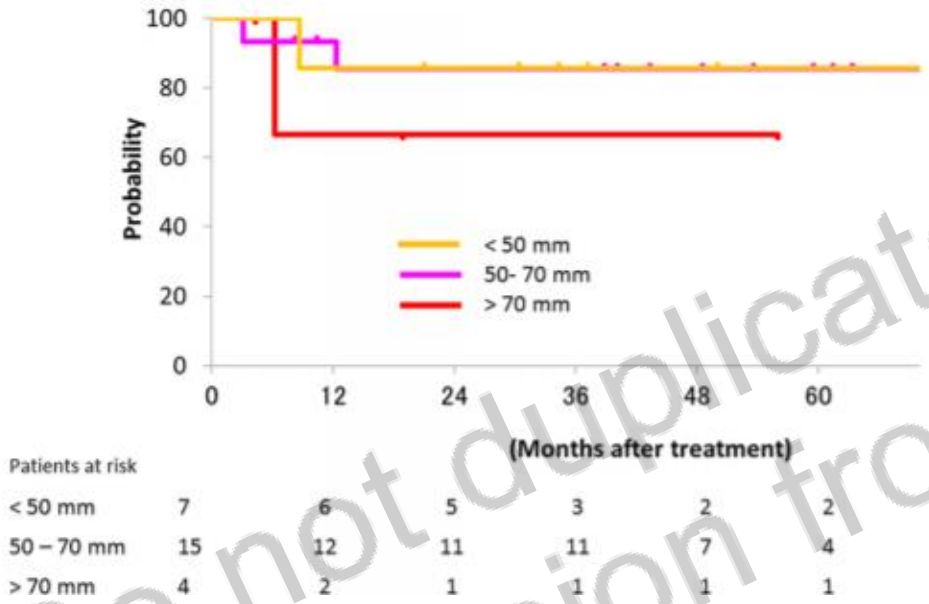

- ✓ **Protocols 9702 and 9902**: the PALN failure rate was 25.0% and in pelvic lymph node-positive patients, PALN failure was seen at a high rate of 44.4%
- ✓ **Protocol 0508:**
  - 1/26 patients developed PALN failure
  - cumulative PALN failure rate was 5.3% (95%CI: 0–- 15.3%)
  - better control for smaller GTV
    - 2-year and 5-year local control rate for < 50 mm, 50–70 mm, and > 70 mm were 86%, 86% and 67%

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Current Evidence: role of hadrontherapy in gynecologycal maligniancies

- **PROTOCOL 9704 : adenocarcinoma of the uterine cervix**

Characteristic	Cases of Analysis for Toxicity (No. of Analyses for Efficacy)
Cases of uterine cervix	58 (55)
Age (median)	28-85 y (59 y)
Histology	
Adenocarcinoma	45 (42)
Adenosquamous carcinoma	13 (13)
FIGO stage	
IIB	20 (20)
IIIB	35 (33)
IVA	3 (2)
Tumor size (median)	3.0-11.8 cm (5.5 cm)
<5 cm	19 (17)
≤5 cm to >7 cm	29 (28)
≤7 cm	10 (10)
Lymph node	
N1	27 (24)
N0	31 (31)
Dose (C-ion RT)	
62.4 GyE/20 fractions	4 (3)
64.8 GyE/20 fractions	4 (4)
68.0 GyE/20 fractions	10 (10)
71.2 GyE/20 fractions	23 (21)
74.4 GyE/20 fractions	17 (17)

5-y-LC: 54.5%
5-y-OS: 38.1%

vs

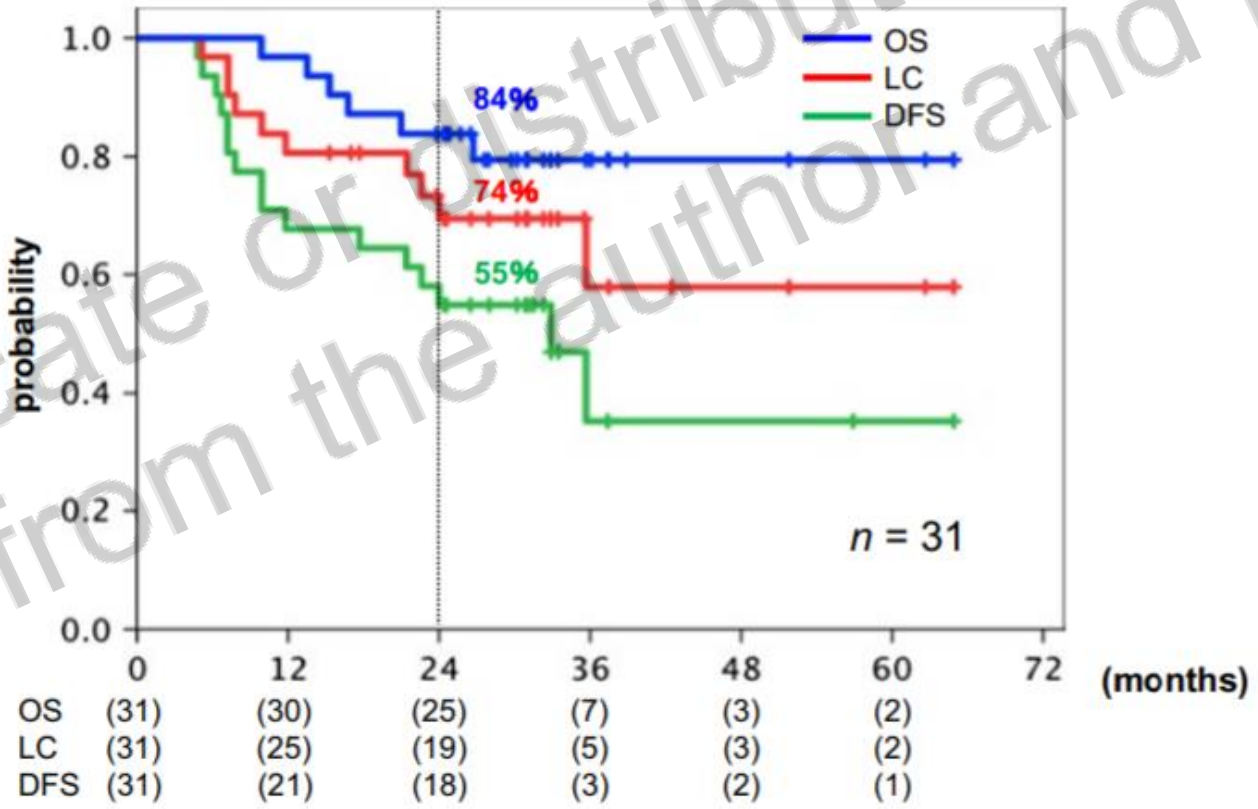
Authors	stage	n.pts	RT	OS	LC
Grigsby et al	III	12	RT	25% (5y)	33% (5y)
Eifel et al	III	61	RT	35% (2-y); 26% (5 y)	46% (5y)
Niibe et al	IIIB	61	RT/RCT	22% (5y)	36% (5y)
Huang et al	III	28	RT/RCT	29% (5y)	58% (5y)

Wakatsuki M et al Clinical outcomes of carbon ion radiotherapy for locally advanced adenocarcinoma of the uterine cervix in phase 1/2 clinical trial (protocol 9704). Cancer. 2014

Current Evidence: role of hadrontherapy in gynecologycal maligniancies

- **PROTOCOL 1001: concurrent chemotherapy**

Characteristics	No. of patients enrolled (No. of patients analyzed)
Cases of uterine cervix	33 (31)
Age [median], years	26–70 [47] (26–70 [47])
Histology	
Mucinous adenocarcinoma	17 (17)
Endometrioid adenocarcinoma	7 (6)
Clear cell carcinoma	3 (3)
Adenosquamous carcinoma	6 (5)
UICC TNM stage	
II B	20 (19)
III B	10 (9)
IVA	3 (3)
Tumor size [median], cm	3.0–9.7 [5.2] (3.0–9.7 [5.4])
<5 cm	13 (12)
≤5 cm to >7 cm	12 (11)
≤7 cm	8 (8)
Pelvic LN metastasis	
Yes	14 (12)
No	19 (19)
Dose of C-ion RT	
68.0 Gy (RBE) in 20 fractions	3 (3)
71.2 Gy (RBE) in 20 fractions	3 (3)
74.4 Gy (RBE) in 20 fractions	27 (25)
No. of weekly CDDP administration	
0 time	2 (0)
3 times	1 (1)
4 times	6 (6)
5 times	24 (24)



Okonogi N et al Clinical outcomes of carbon ion radiotherapy with concurrent chemotherapy for locally advanced uterine cervical adenocarcinoma in a phase 1/2 clinical trial (Protocol 1001). Cancer Med. 2018 Feb;7(2):351-359

Current Evidence: role of hadrontherapy in gynecologycal maligniancies

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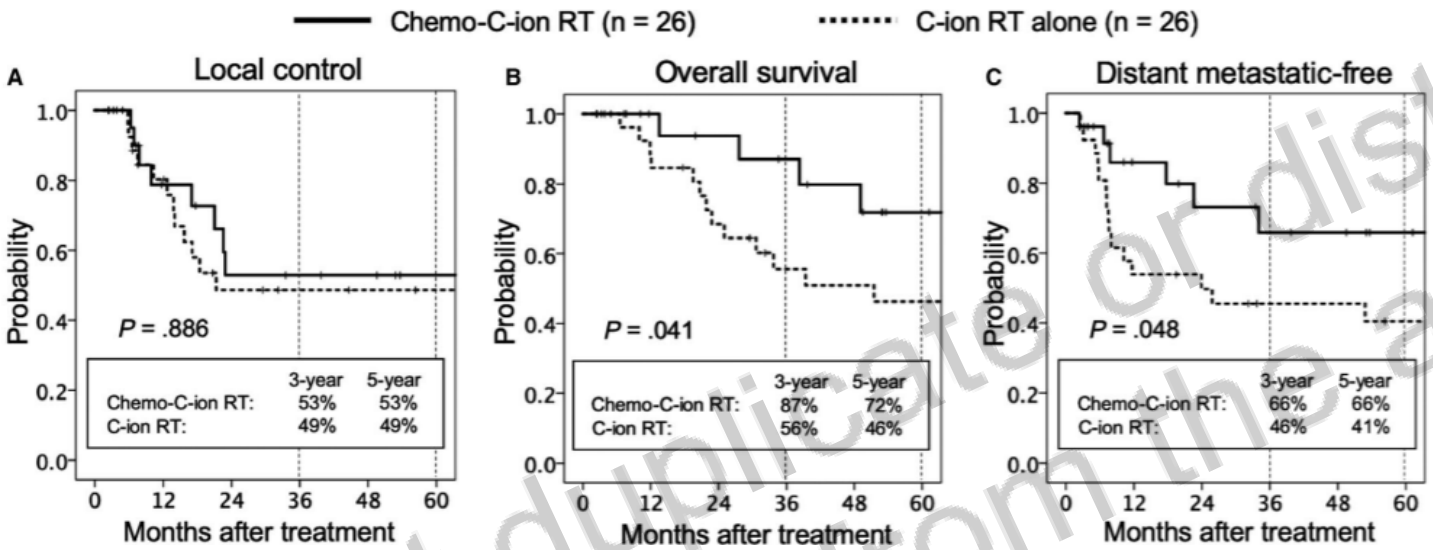

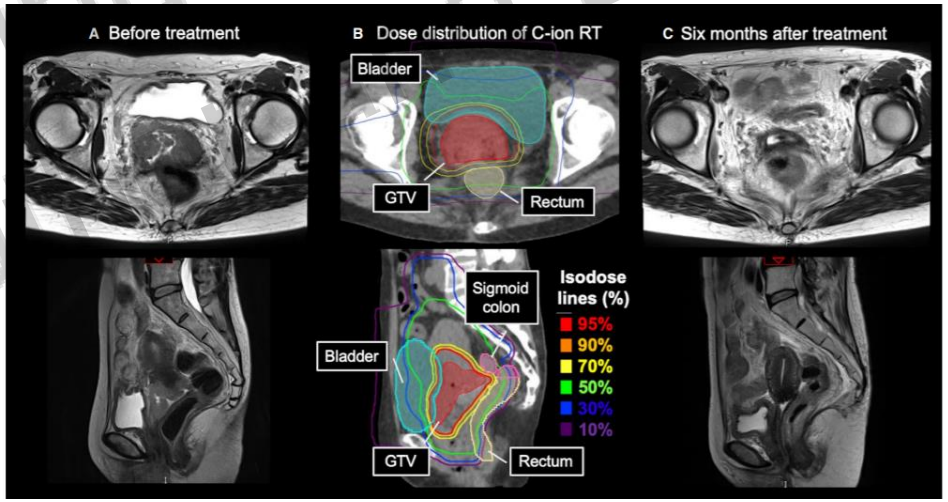

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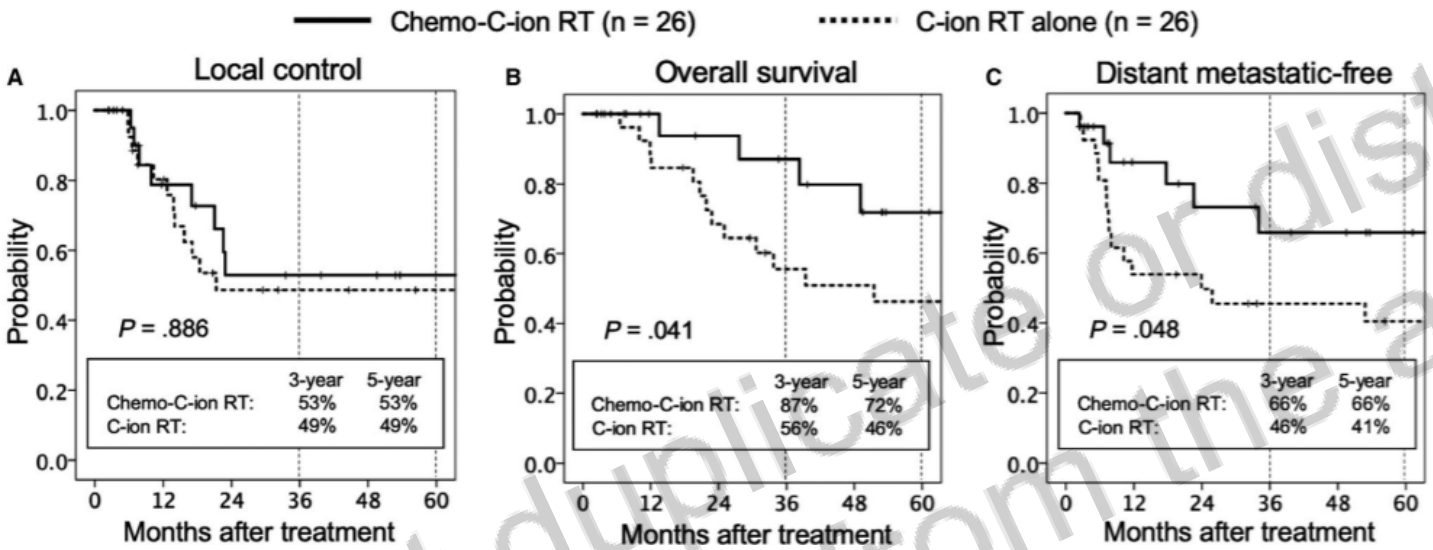

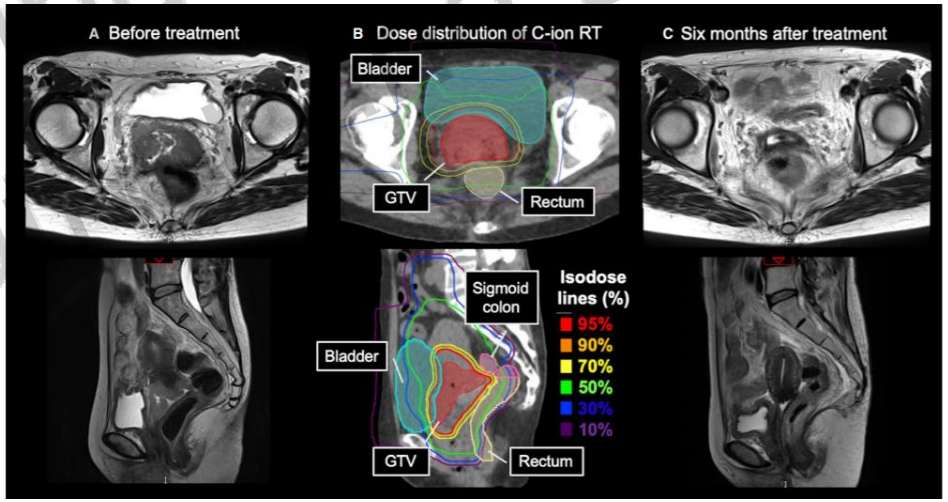

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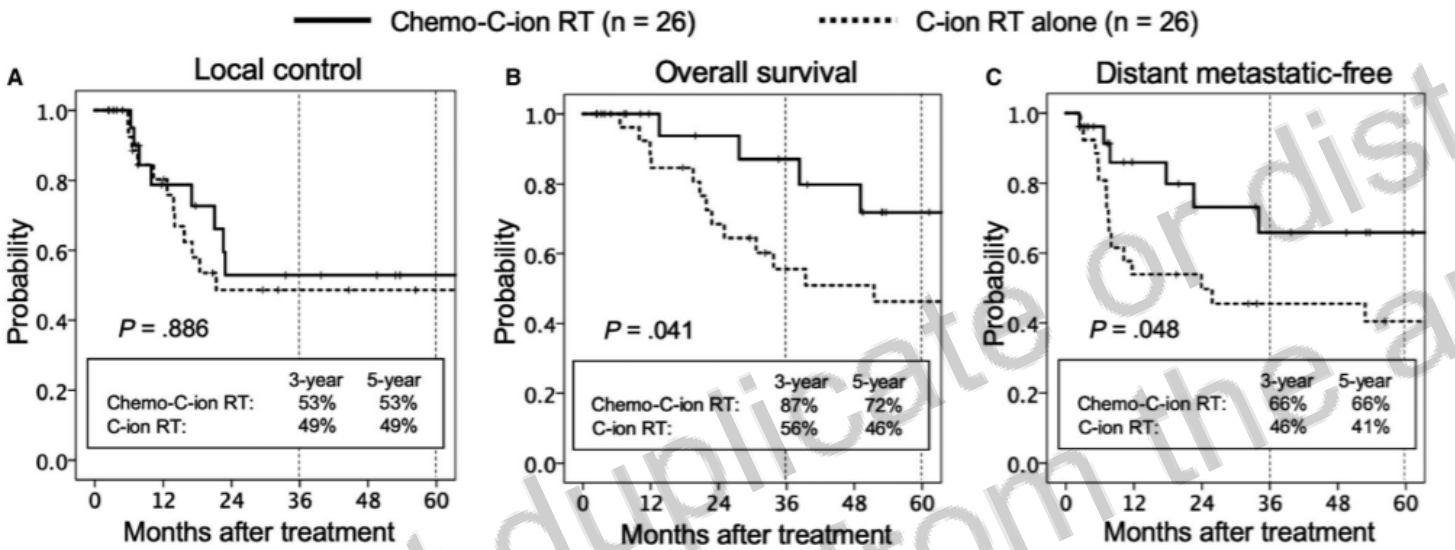

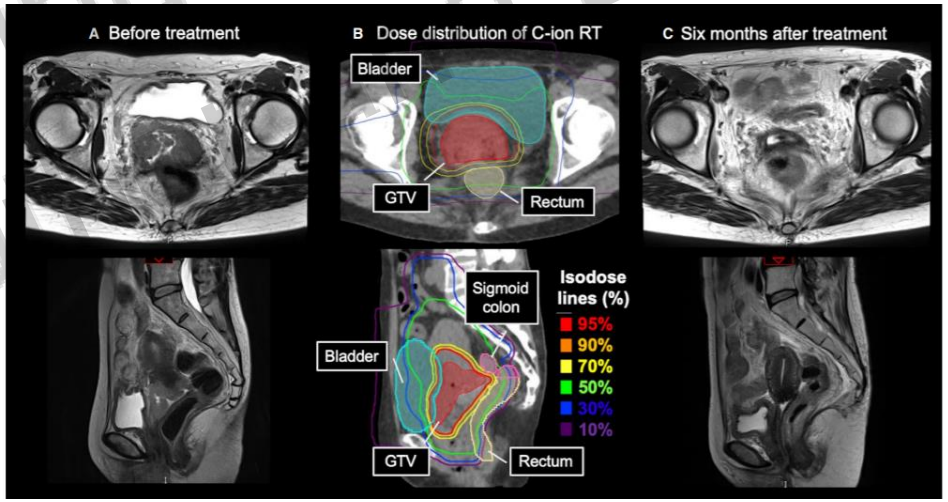

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Current Evidence: role of hadrontherapy in gynecologycal maligniancies

- Mucosal Malignant Melanoma of the lower genital tract are really rare and aggressive malignancies with a 5-year OS of 37–50% for vulvar, 13–32% for vaginal, and approximately 10% for cervical melanoma

Gadducci A, Carinelli S, Guerrieri ME, Aletti GD. Melanoma of the lower genital tract: Prognostic factors and treatment modalities. Gynecol Oncol. 2018 Jul;150(1):180-189. doi: 10.1016/j.ygyno.2018.04.56

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- Radiotherapy can be used in the adjuvant setting, in patients with positive surgical margins or histologically positive nodes

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Current Evidence: role of hadrontherapy in gynecologycal maligniancies

- Mucosal Malignant Melanoma and CIRT

Characteristics	Number of Patients	%
Age (median), years	51–88 (71)	
Tumor site		
Vagina	22	60
Vulva	12	32
Cervix uterus	3	8
Prior treatment		
Surgery	9	24
Chemotherapy	3	8
None	25	68
T stage (including recurrent T stage)		
T1	8	22
T2	21	56
T3	8	22
Tumor size in maximal diameter		
≤30 mm	29	78
>30 mm	8	22
Lymph node metastasis		
Positive	5	14
Negative	32	86
The reason for inoperableness		
Medically inoprerable	27	73
Patient's refusal	10	27
Total dose of C-ion RT		
57.6 Gy (RBE) in 16 fractions	35	95
64.0 Gy (RBE) in 16 fractions	2	5
Adjuvant therapy		
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Nivolumab	1	3
None	27	73

- Retrospective analysis of 37 patients
- Median follow-up periods: 23 months (range: 5–103 months) for all patients and 53 months (range: 16–103 months) for survivors

Murata H et al Long-Term Outcomes of Carbon-Ion Radiotherapy for Malignant Gynecological Melanoma. Cancers (Basel). 2019 Apr 4;11(4)

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- **35 pts up to a total dose of 57.6 GyE in 16 fractions**

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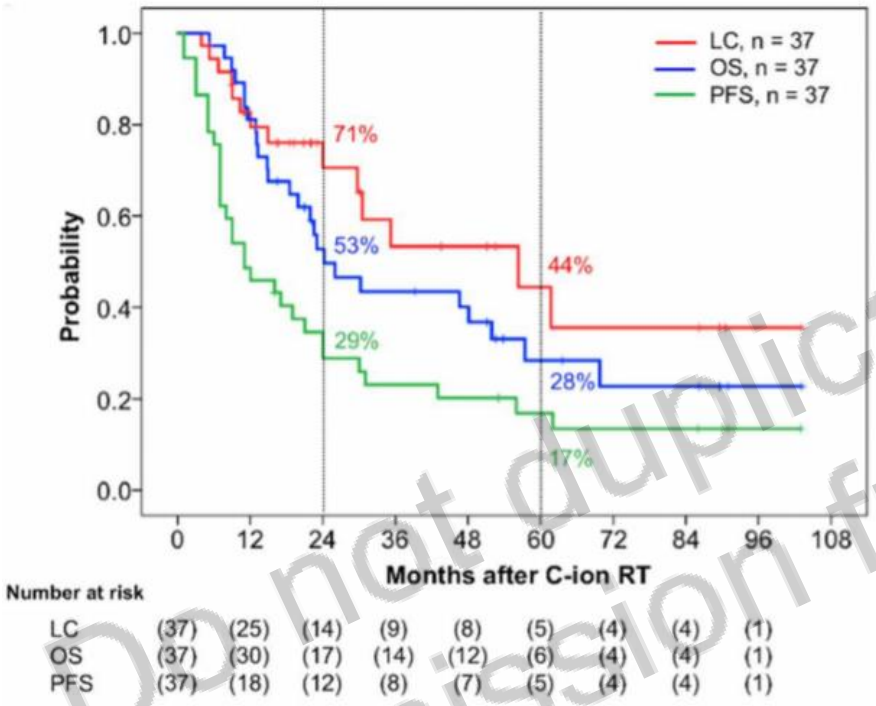

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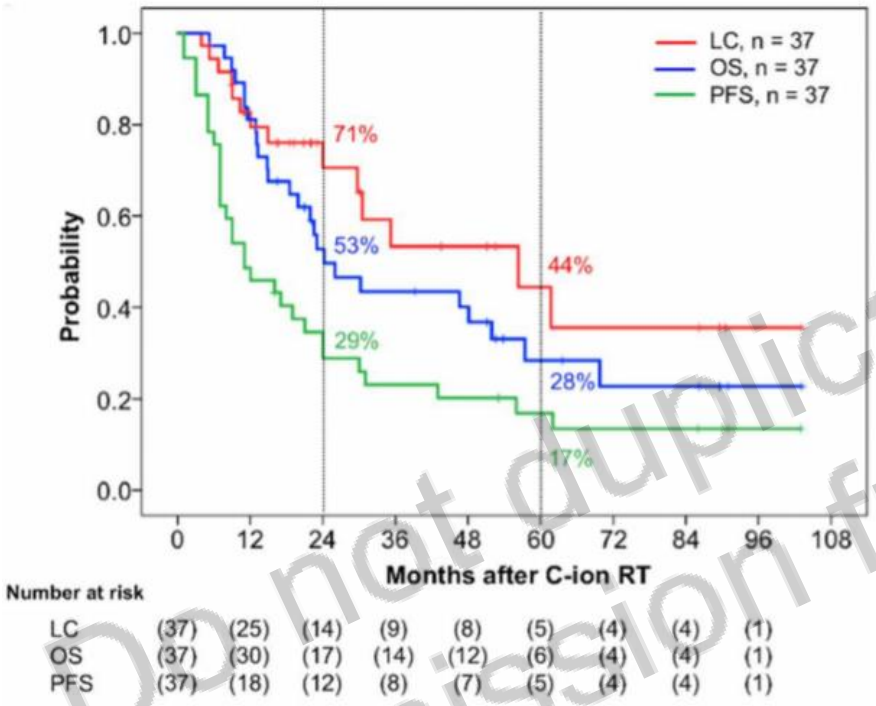

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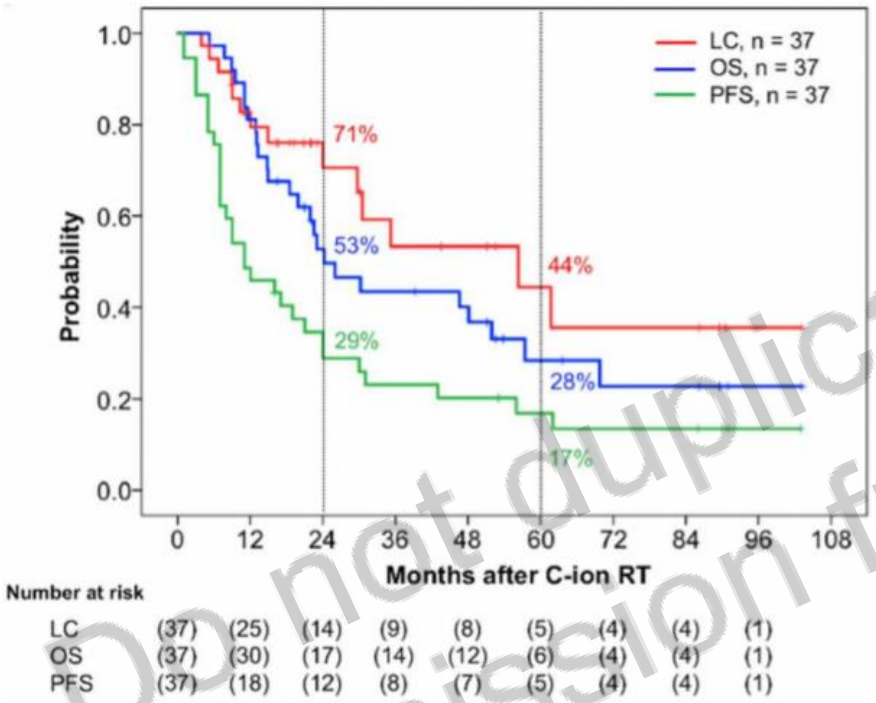

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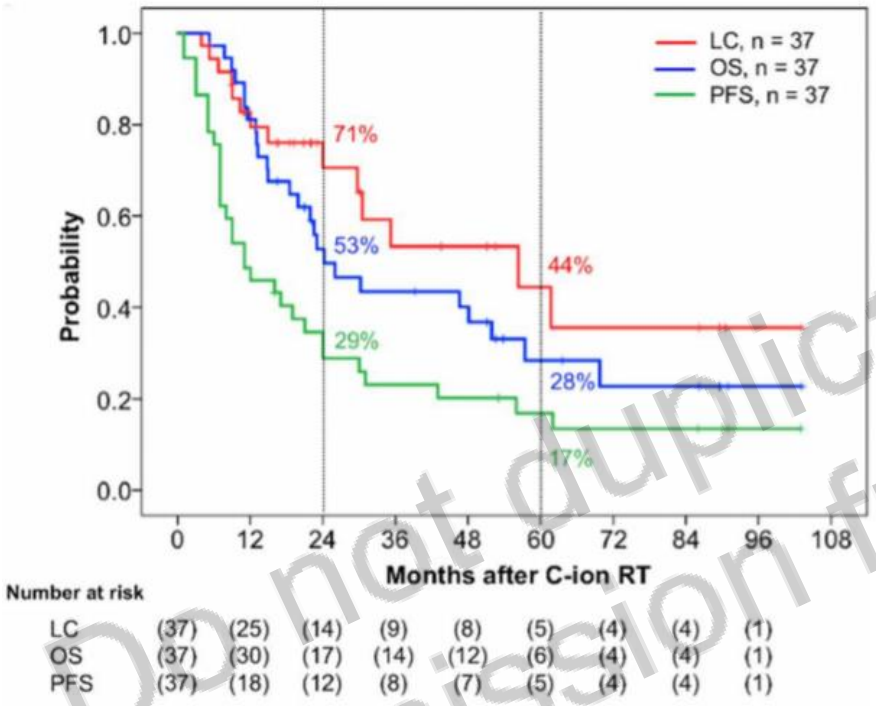

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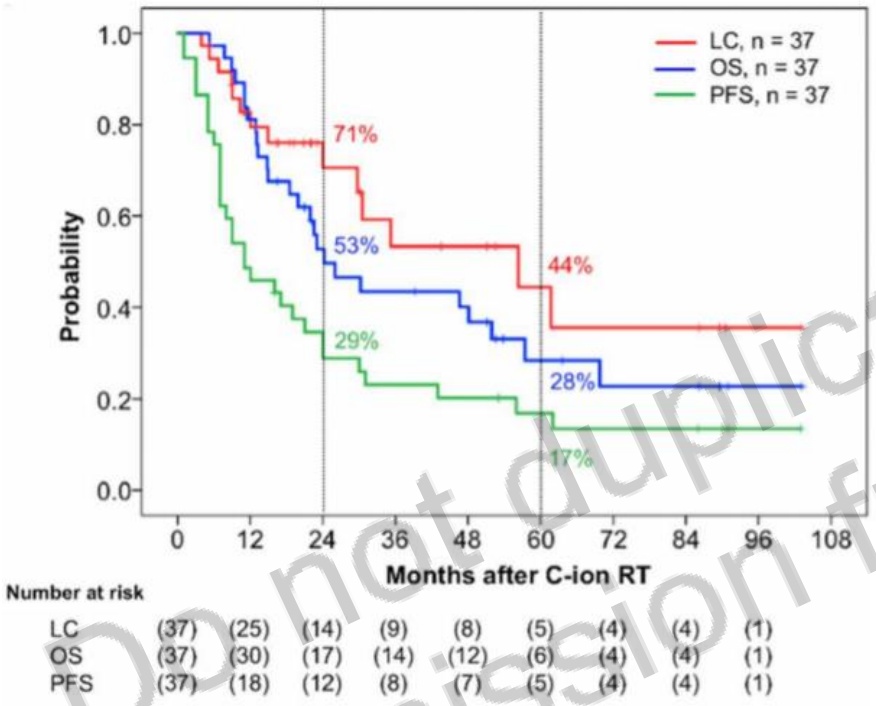

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- Promising **2-y LC and 2-y 0S**
- Acceptable toxicity rate

Acute Toxicity	CTCAE v.4 Scoring				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4–5
Dermatitis/mucositis	2	18	14	3	0
Genitourinary toxicity	28	9	0	0	0
Lower gastrointestinal toxicity	17	14	6	0	0
Late toxicity	**RTOG/EORTC Scoring**				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4–5
Dermatitis/mucositis	28	9	0	0	0
Genitourinary toxicity	30	3	4	0	0
Lower gastrointestinal toxicity	29	5	3	0	0

Murata H et al Long-Term Outcomes of Carbon-Ion Radiotherapy for Malignant Gynecological Melanoma. Cancers (Basel). 2019 Apr 4;11(4)

Current Evidence: role of hadrontherapy in gynecologycal maligniancies

- Mucosal Malignant Melanoma and CIRT

Factor	No. of Patients	LC		PFS		OS		DM	
		2-Year (%)	*p*-Value	2-Year (%)	*p*-Value	2-Year (%)	*p*-Value	2-Year (%)	*p*-Value
Age (years)			0.213		0.617		0.983		0.041
<71	17	49.7		17.6		57.0		52.9	
≥71	20	89.2		39.4		43.3		40.1	
Prior treatment			0.468		0.547		0.564		0.242
No	12	69.4		30.5		53.5		37.6	
Yes	25	72.2		25.0		50.0		58.3	
T stage (including recurrence)			0.974		0.953		0.877		0.903
T1–2	29	65.4		26.6		53.7		48.0	
T3	8	87.5		37.5		37.5		37.5	
Tumor diameter			0.337		0.418		0.304		0.320
≤30 mm	29	73.9		33.4		57.2		46.3	
>30 mm	8	60.0		12.5		37.5		37.5	
LN metastasis			0.320		0.248		0.069		0.206
Positive	5	60.0		0.0		40.0		80.0	
Negative	32	73.0		40.4		54.9		39.1	
Adjuvant chemotherapy			0.535		0.142		0.382		0.796
No	27	65.8		20.4		53.8		43.4	
Yes	10	80.0		50.0		50.0		50.0	
Tumor response within 6 months after commencing C-ion RT			0.535		0.923		0.818		0.826
CR	19	77.7		23.7		61.5		43.2	
Non-CR	18	61.6		33.3		43.2		45.8	
Primary site			N.S.		N.S.		N.S.		N.S.
Vagina	22	73.4		26.5		55.2		53.0	
Vulva	12	76.4		33.3		58.3		33.3	
Cervix uterus	3	33.3		33.3		33.3		33.3	

- None of the factors examined significantly influenced LC, PFS, and OS in univariate analysis

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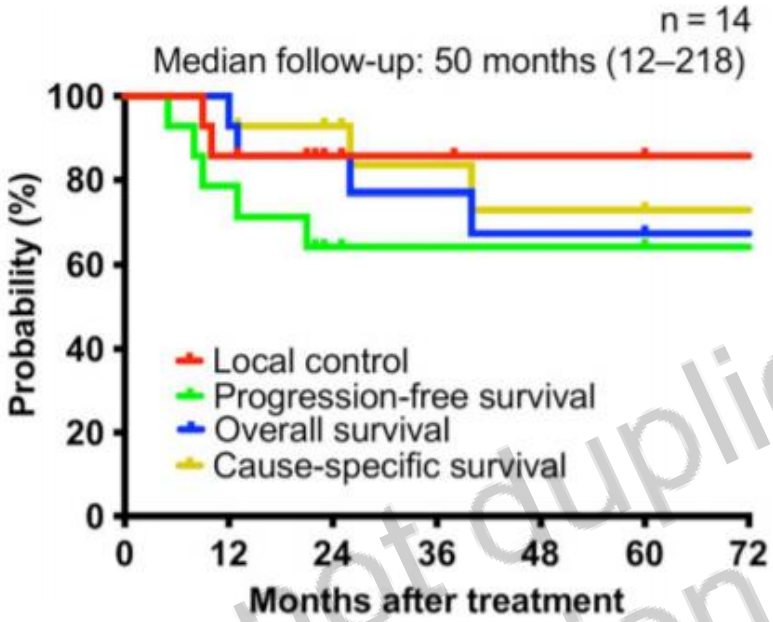
- None of the factors examined significantly influenced LC, PFS, and OS in univariate analysis
- Age was associated with the rate of distant metastasis: **younger group (age < 71 years) showed a higher incidence of distant metastasis than the elderly group (age ≥ 71 years) (p = 0.041)**

Murata H et al Long-Term Outcomes of Carbon-Ion Radiotherapy for Malignant Gynecological Melanoma. Cancers (Basel). 2019 Apr 4;11(4)

Current Evidence: role of hadrontherapy in gynecologycal maligniancies

- Inoperable endometrial cancer



- pooled analysis of data from two trials
- 14 patients with stage ≤IIIC endometrial carcinoma
- medically inoperable because of comorbidities, age, or refusal of surgery
- total dose to the tumor was 62.4–74.4 GyE

Irie D et al Carbon-ion radiotherapy for inoperable endometrial carcinoma. J Radiat Res. 2018 May 1;59(3):309-315.

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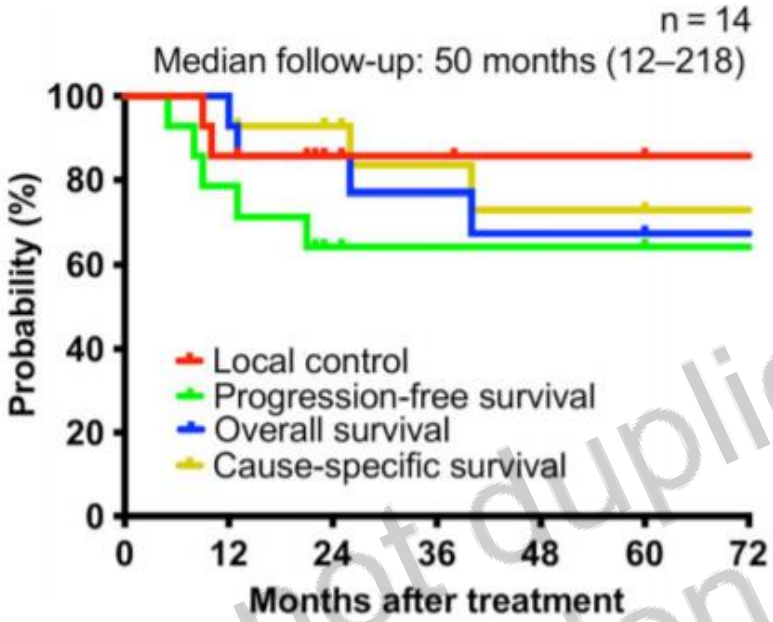

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Table 3. Tumor response at 6 months after carbon-ion radiotherapy

Total dose [Gy (RBE)]	No.	Complete response	Partial response	Stable disease	Progressive disease
62.4	2	1	1	0	0
64.8	1	0	1	0	0
68.0	3	1	1	1	0
71.2	3	3	0	0	0
74.4	5	5	0	0	0
Total	14	10	3	1	0

- ✓ 2/6 patients receiving 62.4–68.0 GyE achieved CR
- ✓ 8/8 patients receiving 71.2–74.4 GyE achieved CR

(P = 0.015)

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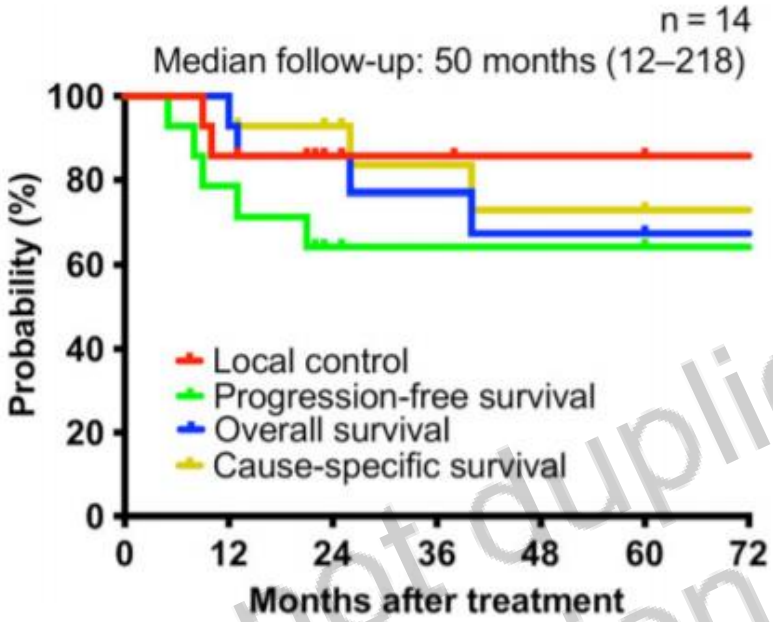
Current Evidence: role of hadrontherapy in gynecologycal maligniancies

- Inoperable endometrial cancer



- pooled analysis of data from two trials
- 14 patients with stage ≤IIIC endometrial carcinoma
- medically inoperable because of comorbidities, age, or refusal of surgery
- total dose to the tumor was 62.4–74.4 GyE

Table 3. Tumor response at 6 months after carbon-ion radiotherapy

Total dose [Gy (RBE)]	No.	Complete response	Partial response	Stable disease	Progressive disease
62.4	2	1	1	0	0
64.8	1	0	1	0	0
68.0	3	1	1	1	0
71.2	3	3	0	0	0
74.4	5	5	0	0	0
Total	14	10	3	1	0

- ✓ 2/6 patients receiving 62.4–68.0 GyE achieved CR
- ✓ 8/8 patients receiving 71.2–74.4 GyE achieved CR

(P = 0.015)

No patient developed Grade 3 or higher acute or late toxicity.

Irie D et al Carbon-ion radiotherapy for inoperable endometrial carcinoma. J Radiat Res. 2018 May 1;59(3):309-315.

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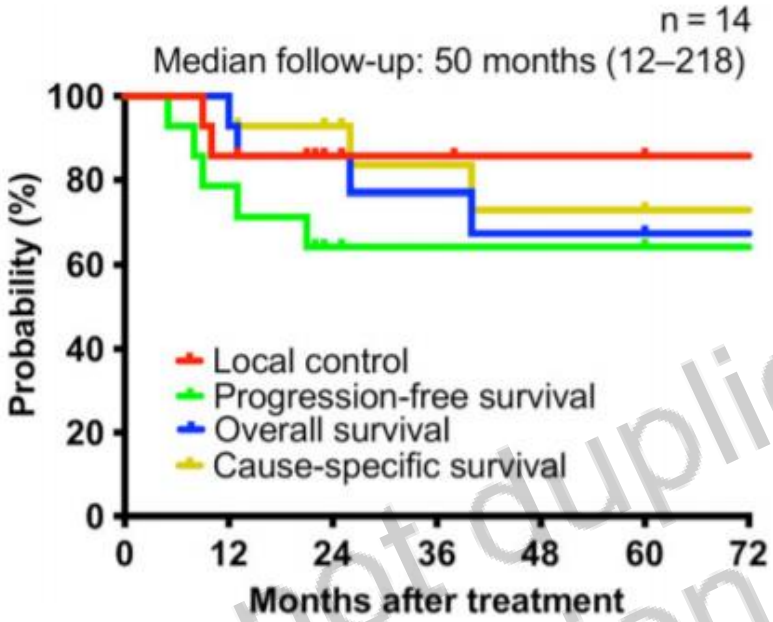

5-y LC: 86%
5 y- PFS: 64%
5 y- OS : 68%

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- Re-irradiation for recurrence

- Retrospective series of **16 cases**
- **Unresectable** recurrence at the edge of the previously irradiated field
- Median age 57 years (range=35-79 years)
- Median **tumor size was 27 mm** (range=14-80 mm)
- Total dose range: **48-57.6 GyE**

Case	Primary site, Stage	Histology	Initial treatment	Dose of prior RT	Duration of prior RT to C-ion RT (months)	Tumor size (mm)	Dose of C-ion RT	Recurrence
1	Cervical cancer, T2bN1M0	Squamous cell carcinoma	CCRT	50 Gy/25 fr.	26	33	48 Gy (RBE)/12 fr.	NER
2	Cervical cancer, T2aN0M0	Squamous cell carcinoma	RT alone	50 Gy/25 fr.	25	28	48 Gy (RBE)/12 fr.	NER
3	Endometrial cancer, T1N0M0	Endometrioid adenocarcinoma	Surgery	50 Gy/25 fr.	68	25	48 Gy (RBE)/12 fr.	NER
4	Cervical cancer, T4N0M0	Squamous cell carcinoma	CCRT	50 Gy/25 fr.	26	14	48 Gy (RBE)/12 fr.	LN metastasis
5	Cervical cancer, T1b1N0M0	Squamous cell carcinoma	Surgery	66 Gy/33 fr.	11	33	52.8 Gy (RBE)/12 fr.	NER
6	Endometrial cancer, T3aN0M0	Carcinosarcoma	Surgery	60 Gy/30 fr.	12	20	57.6 Gy (RBE)/12 fr.	LN metastasis
7	Cervical cancer, T3bN1M0	Squamous cell carcinoma	Surgery	50 Gy/25 fr.	17	15	52.8 Gy (RBE)/12 fr.	Local recurrence, LN and Lung metastases
8	Cervical cancer, T2bN1M0	Squamous cell carcinoma	CCRT	50.6 Gy/27 fr.	33	24	57.6 Gy (RBE)/12 fr.	LN metastasis
9	Endometrial cancer, T3bN1M0	Endometrioid adenocarcinoma	Surgery	50 Gy/25 fr.	20	80	57.6 Gy (RBE)/16 fr.	Local recurrence
10	Cervical cancer, T2aN0M0	Squamous cell carcinoma	CCRT	46 Gy/23 fr.	77	30	52.8 Gy (RBE)/12 fr.	NER
11	Ovarian cancer, T1bN0M0	Serous adenocarcinoma	Surgery	56 Gy/28 fr.	40	18	52.8 Gy (RBE)/12 fr.	Lung metastasis
12	Endometrial cancer, T3aN0M0	Endometrioid adenocarcinoma	Surgery	50 Gy/25 fr.	130	22	52.8 Gy (RBE)/12 fr.	NER
13	Endometrial cancer, T1bN0M0	Small cell carcinoma	Surgery	54 Gy/27 fr.	17	75	52.8 Gy (RBE)/12 fr.	Lung metastasis
14	Cervical cancer, T1bN0M0	Mucinous adenocarcinoma	Surgery	50.4 Gy/28 fr.	21	38	57.6 Gy (RBE)/12 fr.	NER
15	Endometrial cancer, T1bN0M0	Endometrioid adenocarcinoma	Surgery	58.6 Gy/32 fr.	29	42	52.8 Gy (RBE)/12 fr.	Liver metastasis
16	Cervical cancer, T1bN1M0	Squamous cell carcinoma	Surgery	50 Gy/25 fr.	64	20	52.8 Gy (RBE)/12 fr.	NER

CCRT, Concurrent chemoradiotherapy; C-ion RT, carbon-ion radiotherapy; fr., fractions; LN, lymph node; NER, no evidence of recurrence; RT, radiotherapy.

Shiba S et al Clinical Impact of Re-irradiation with Carbon-ion Radiotherapy for Lymph Node Recurrence of Gynecological Cancers. Anticancer Res. 2017 Oct;37(10):5577-5583

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Organs involved	G0	G1	G2	G3	G4
Gastrointestinal tract	14	2	0	0	0
Urinary tract	15	1	0	0	0
Leg edema	15	0	1	0	0
Lower extremity nerve	14	2	0	0	0

RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

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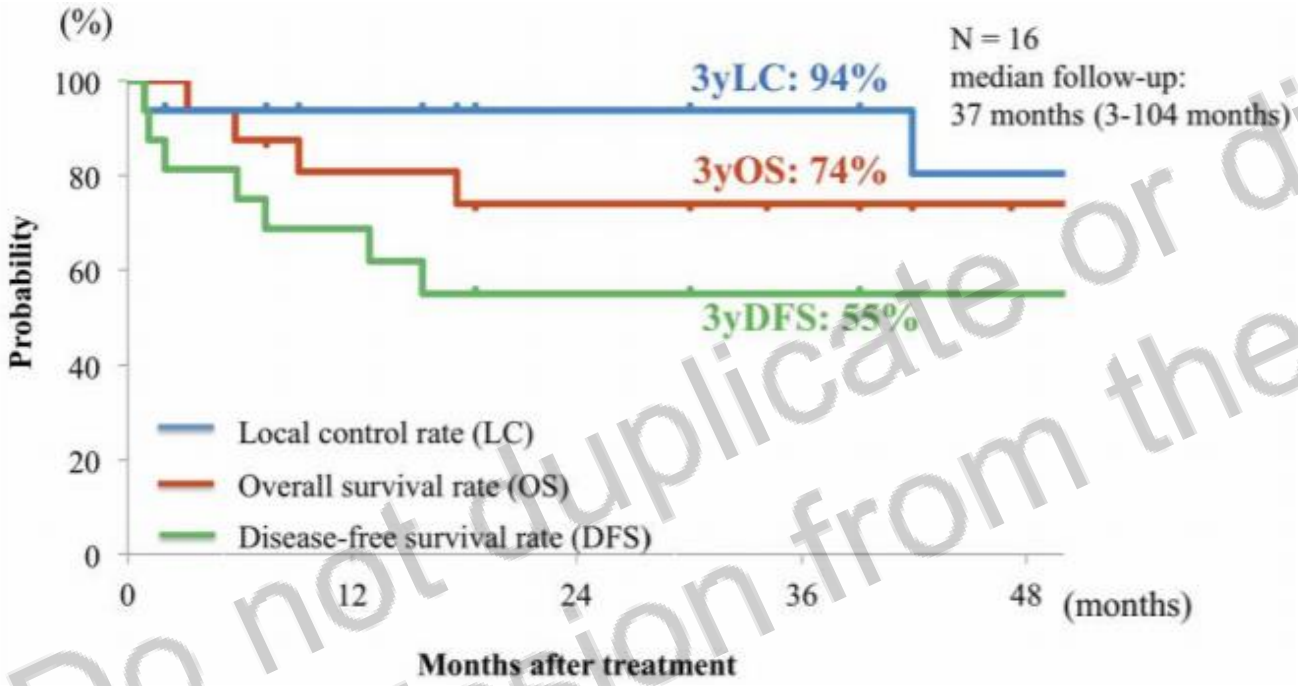

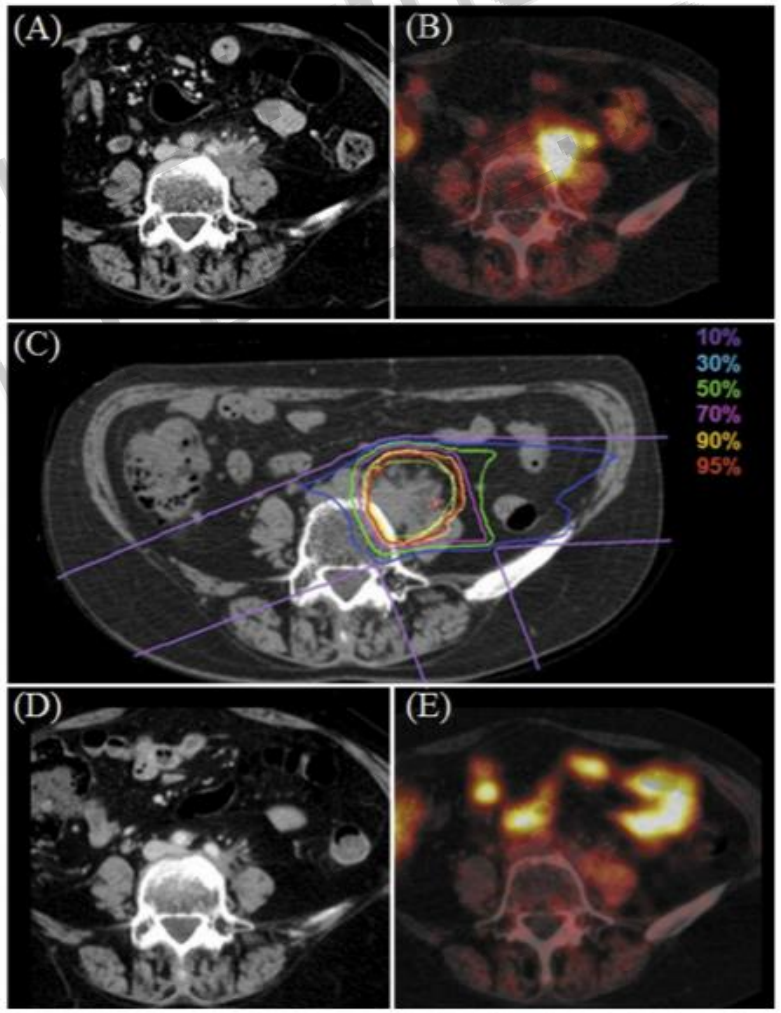

Two patients had local recurrence, and 7 patients had distant metastases

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Agenda

- Introduction: what is hadrontherapy?
- Rationale of hadrontherapy
- Current Evidence: role of hadrontherapy in gynecologycal maligniancies
- Conclusions: Take Home Messages

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- For locally advanced cervical cancer CIRT provides good outcome in patients receiving pelvic CIRT, prophylactic extended-field CIRT and concurrent chemotherapy
- CIRT seems to improve outcome in adenocarcinoma cervical cancer compared to photon beam RT
- **Prospective and randomized clinical trials are warranted!**

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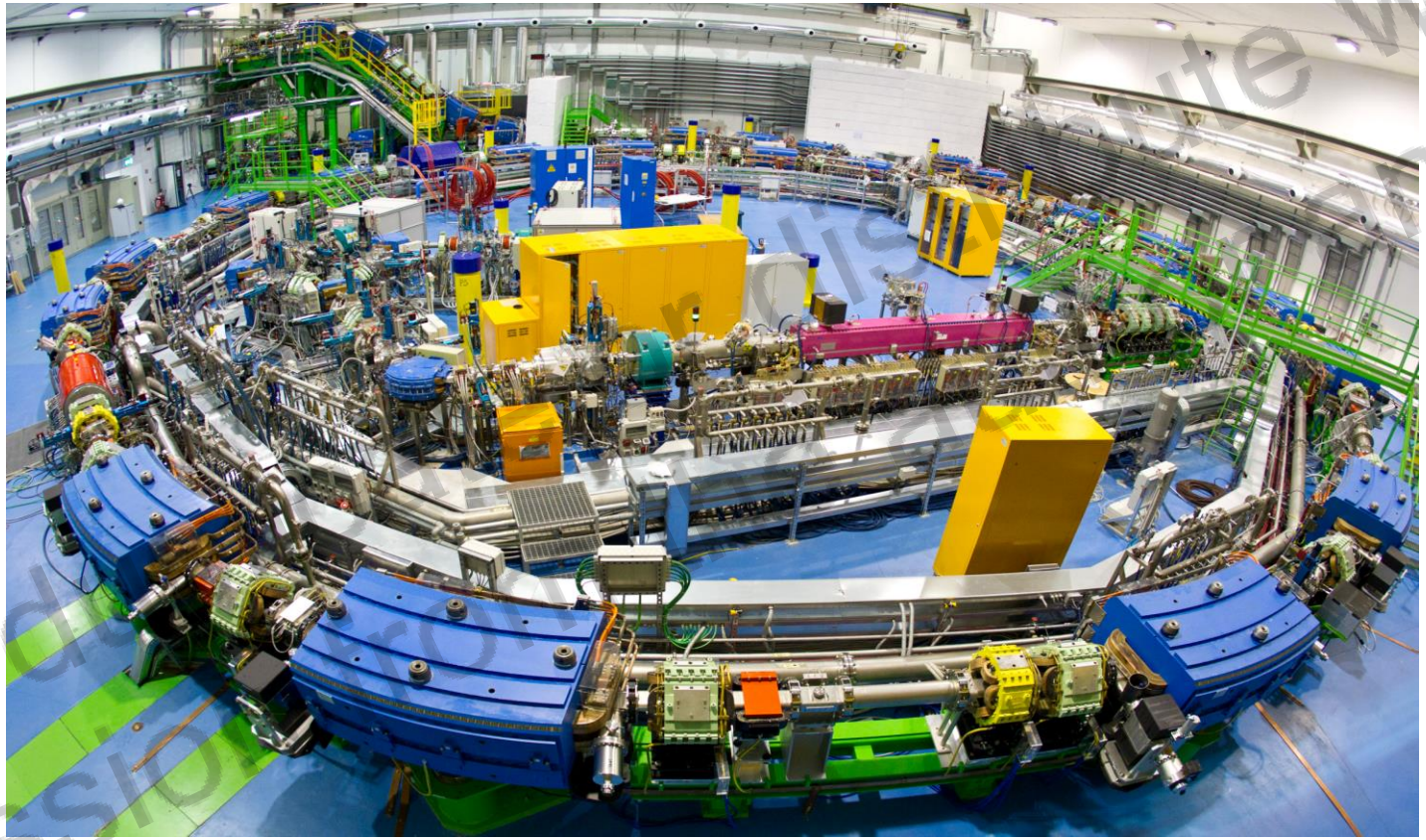
- For their radiobiological and ballistic hallmarks re-irradiation with CIRT could meet expectations as a curative treatment option
- A strong collaboration between Researchers and Physicians treating rare and radioresistant histologies as well as difficult-to-cure patients is of utmost importance to make a step forward in the treatment of these diseases

Thank you for your attention



"True progress is when the advantages of new technology are available for all"

H. Ford