



# Comparison of photon therapy, brachytherapy and ion therapy in cervical cancer

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# Background

- Cervical cancer is the second most common cancer among women worldwide
- Estimated 468 000 new cases and 233 000 deaths in the year 2000

Survival rates vary between regions

- 69% in the North American Surveillance Epidemiology and End Results registry (SEER)
- 49% in developing countries

# Background

Human papillomavirus (HPV) :

- Primary cause
- > 90% of squamous cell cervical carcinomas contain HPV-DNA

Other risk factors:

- High number of sexual partners
- Sexual activity starting at young age (<16)
- History of genital warts
- Immunosuppression

# Background

Squamous cell carcinoma: most common histology  
~ 80-85%

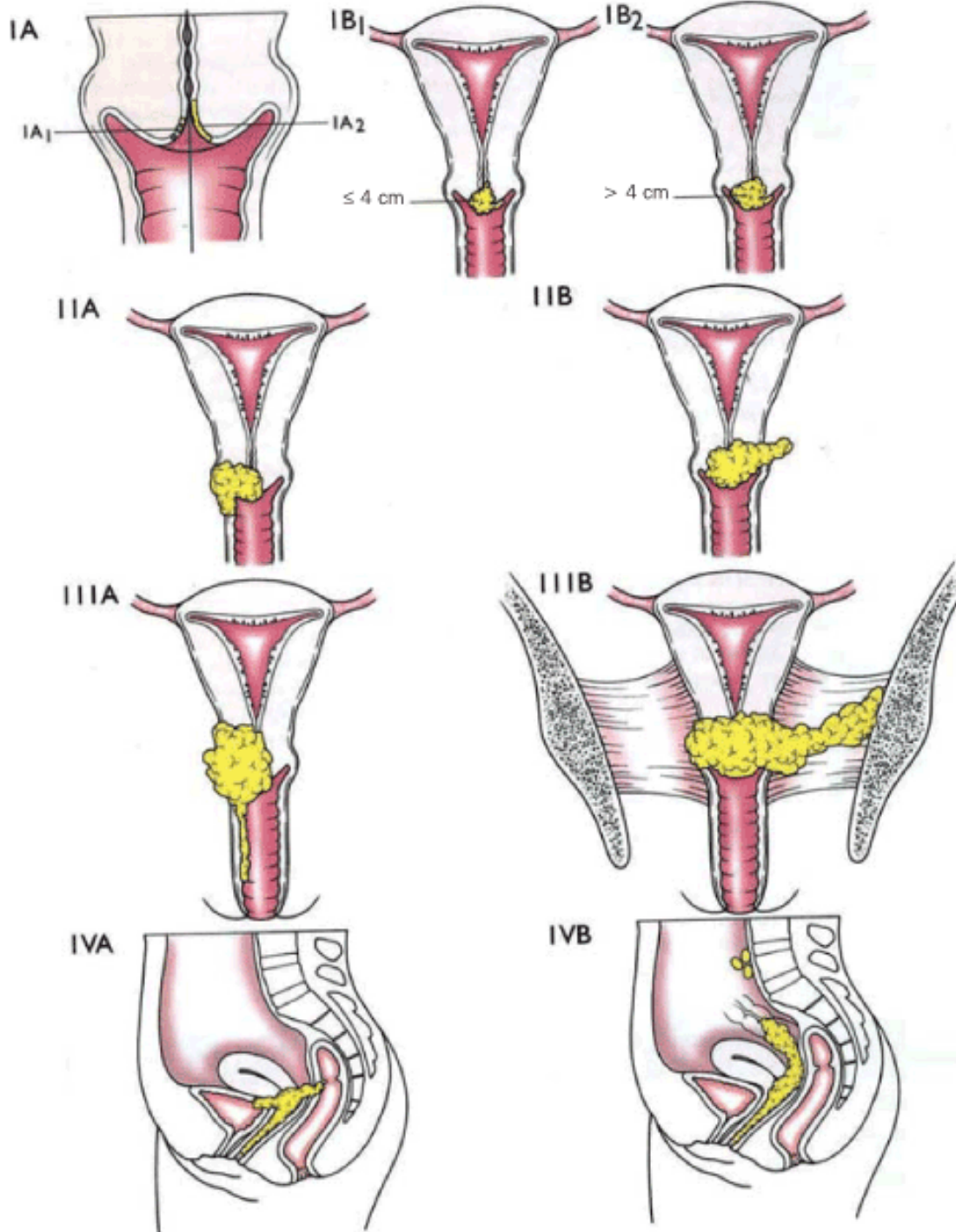
- Adenocarcinoma ~ 10%
- Adenosquamous carcinoma
- Clear cell carcinoma
- Adenocystic carcinoma mucoepidermoid carcinoma

# Work-up and staging

- Clinical staging is based on the **FIGO classification\*** at the time of the primary diagnosis
- **Is determined clinically on the basis of the size of the cervical tumour and its extension into adjacent structures**
- Results of CT, MRI or PET can still not be used for FIGO-staging (e.g. lymph node involvement)
- ...however, the information from such studies is used to assess more accurately extent of pelvic disease and lymph node metastasis, which may have impact on the choice of treatment ...

\*International Federation for Gynecology and Obstetrics

FIGO-  
Stages



# Prognostic factors

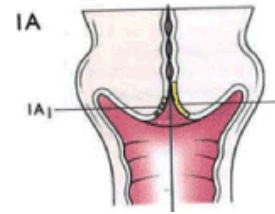
- FIGO stage
- Nodal involvement (particularly para-aortic)
- Age of the patient
- Anaemia
- etc

## Recurrent cervical cancer

- 90% of recurrences are identified within 3 years after initial diagnosis
  - Less than 5% of these patients survive 5 years
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# Limited disease

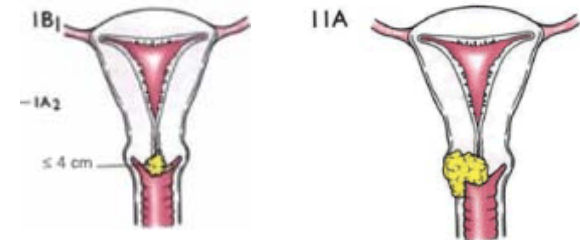
- FIGO stage **IA**: Surgery



- FIGO stage **IB1 + IIA** : **Surgery**

+ **adjuvant (chemo)radiotherapy** in case of poor prognostic pathological factors not assessable by presurgical staging like

- deep cervical stromal invasion
  - lymphovascular space invasion
  - positive vaginal or parametrial margins
  - microscopic lymph node involvement
- or **primary radiotherapy** in case of lymph node involvement

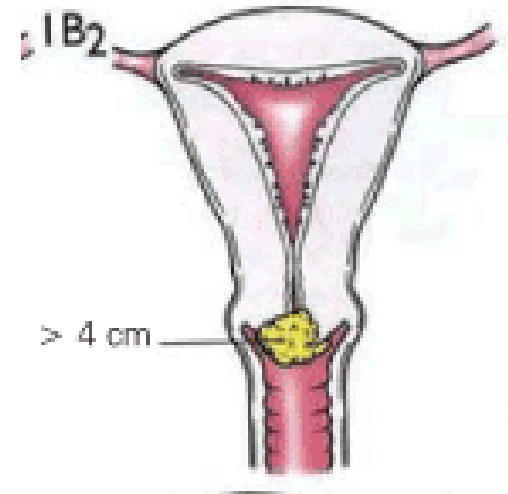




# Locally extended disease

## Stage **IB2**

- associated with higher frequency of pelvic and para-aortic lymph node metastasis



Different treatment options are available:

- **Primary radiotherapy** (with/without chemotherapy) or
- **Surgery** followed by **adjuvant radiotherapy** or
- in selected cases preoperative radiotherapy followed by hysterectomy

# Locally extended disease

## Stage IIB-IVA

Local control and cure with radical surgery alone is unlikely ...

Treatment of choice is **radiotherapy** with sufficient doses in appropriate volumes combined with chemotherapy in the majority of patients !

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However ...

- Radioresistant hypoxic tumour cells are relatively dominant in bulky tumours and may affect local control rate ...

# Overview - Radiotherapy

## Conventional radiotherapy (Photons + brachytherapy)

- Definitive Radiotherapy
  - of limited disease
  - of locally extended disease
- Adjuvant conventional radiotherapy following surgery

## Ion therapy

- Proton therapy
  - Carbon ion therapy
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# Conventional radiotherapy

## Definitive Radiotherapy of limited disease

Treatment consists of a combination of external radiotherapy and brachytherapy

- Mean 5-year survival for stage IB is 85% \*
- Mean 5-year survival for IIA is 78% \*

# Conventional radiotherapy

## Definitive Radiotherapy of limited disease

- \*Local control rate is excellent with 90% (Stage IB) and 83% (Stage IIA)
- Probably due to patient selection, in stage II B survival varies from 50% to 76% as well as local control from 60-87%

# Conventional radiotherapy

## Definitive Radiotherapy of locally extended disease

- Treatment consists of external radiotherapy, brachytherapy, more recently combined with chemotherapy
- \*The mean 5-year **local control rate** is
  - ~ 77% (Stage IIB)
  - 44-66% (Stage IIIB)
  - ~ 20% (Stage IVA).

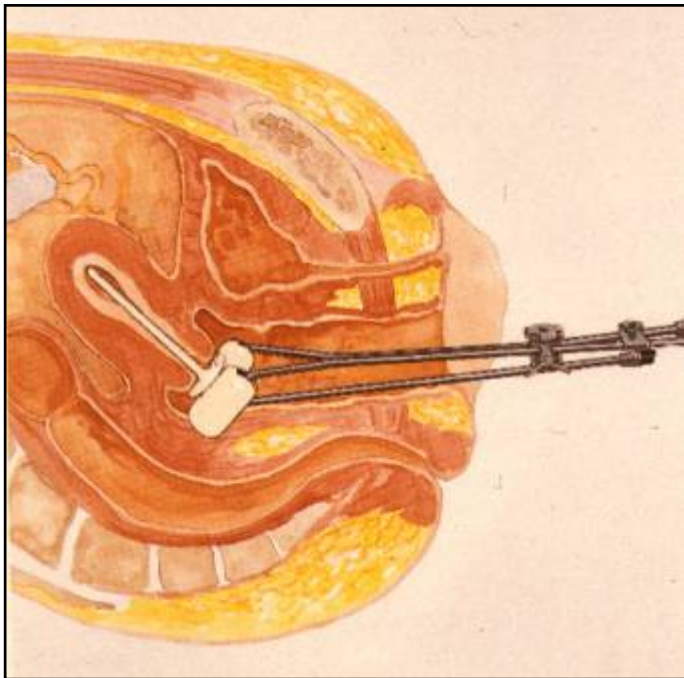
# Conventional radiotherapy

## Definitive Radiotherapy of locally extended disease

- The mean 5-year survival varies
  - 65-70% (Stage IIB)
  - 34-52% (Stage III B)
  - 0-19% (Stage IV)



# Brachytherapy



## *HDR vs. LDR brachytherapy*

Studies comparing LDR and HDR brachytherapy showed overall no significant difference in local control and survival rate

# Adjuvant conventional radiotherapy following surgery

Sedlis A. et al.

- significant reduction of local recurrence by using adjuvant radiotherapy in patients with stage IB cervical cancer (27.8% vs. 15.3%) as compared to surgery alone,
- however on the risk of significantly increased side effects ...

# Adjuvant conventional radiotherapy following surgery

Pieterse QD et al.

- Patients with localized early-stage cervical cancer and **adverse risk factors** like  
tumour size  $\geq 4$  cm,  
invasion  $\geq 15$  mm,  
capillary lymphatic space involvement  
benefit from postoperative radiotherapy with  
a 5-year disease free survival of **85% vs. 43%**

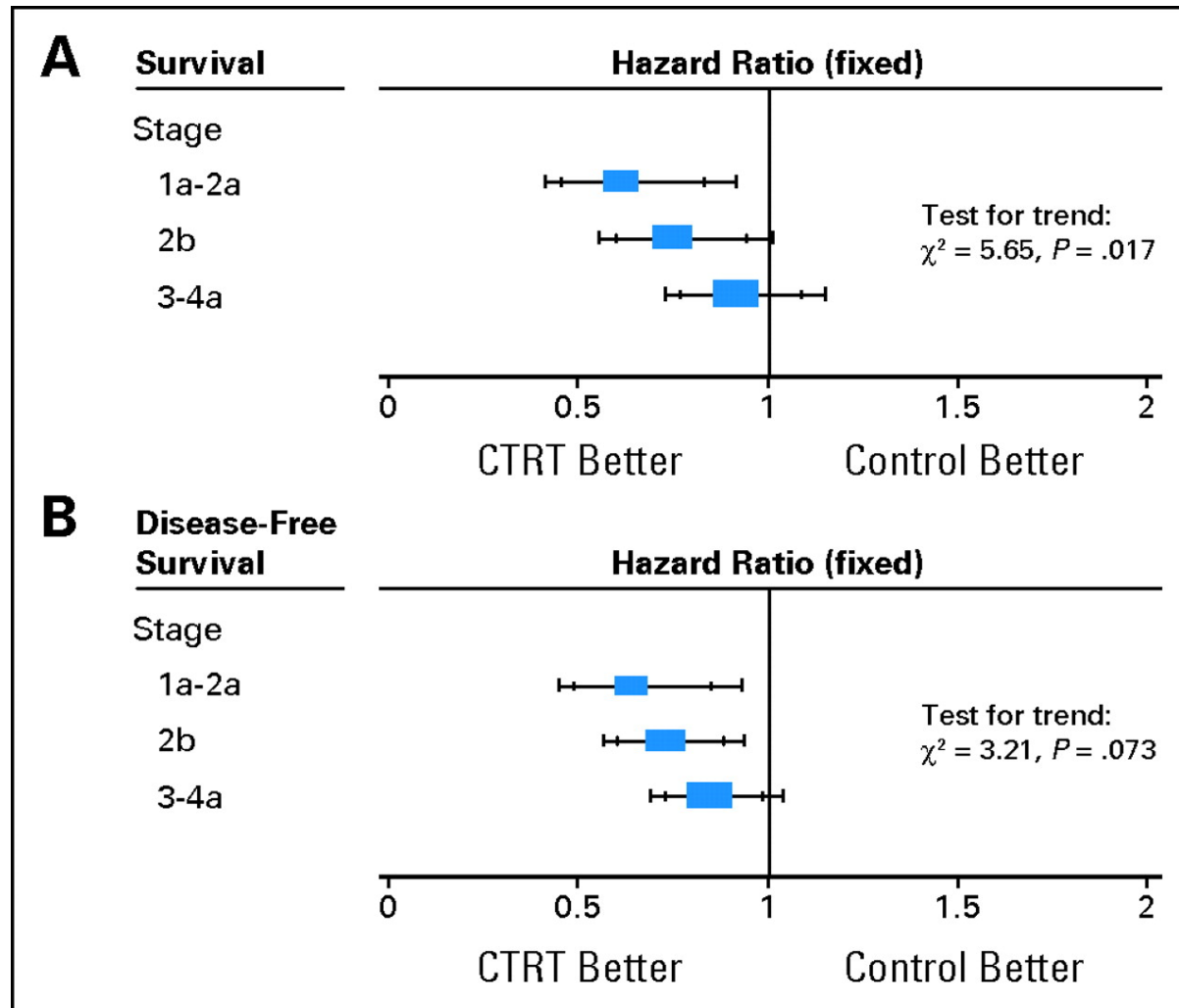
\* Pieterse QD et al. Int J Gyn Cancer 2006;16:112-8.

## Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials

*Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration*

- 6% improvement in 5-year survival with radiochemotherapy vs. radiotherapy alone ( $p > 0.001$ )
- Reduction of local and distant recurrences and progression
- Improvement of disease free survival
- Increased hematologic and GI toxicity

Fig 2. (A) Survival and (B) disease-free survival by tumor stage (main group of 13 trials only)



Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, J Clin Oncol; 26:5802-5812 2008

# Proton therapy

- Data from Tsukuba/Japan are available, which were reported in 1991<sup>1</sup> and updated 2003<sup>2</sup>
- A total of 25 patients ineligible for intracavitary brachytherapy received a combination of external photon and proton beams radiotherapy

<sup>1</sup> Arimoto T, et al. Cancer 1991; 68:79-83.

<sup>2</sup> Kagei K, et al. Int J Radiat Oncol Biol Phys 2003; 55:1265-71.

# Proton therapy

## Treatment regimen

- Photon therapy (50.4 Gy/1.8 Gy) to the pelvis and the tumour was delivered via anterior-posterior fields with or without central shielding of the cervix and paracervical region
- Proton therapy to the tumour was delivered in 3 or 4 fractions weekly with doses per fraction varying from 2,5 to 4 Gy due to limited availability of beam time
- Median combined tumor dose: 86 Gy (range, 71-101 Gy).

# Proton therapy

- Acute reactions were insignificant, two patients suffered from grade 4 toxicity of the intestine or urinary bladder
- 10-year survival rate was 89% (Stage IIB) and 40% (Stage IIIB/IVA)
- 5-year local control rates were also encouraging **with 100% in Stage IIB and 61% in stage IIIB/IVA**
- The data, however, have to be viewed with caution because patient numbers are small



# Carbon ion therapy

- The existence of hypoxic cells is well recognized as one of the major factors affecting resistance against radiotherapy and local failure <sup>1-3</sup>
- Bulky tumours are considered to have a large fraction of hypoxic tumour

<sup>1</sup> Fyles AW, et al. Radiother Oncol 1998;48:149-56

<sup>2</sup> Hockel M, et al. Cancer Res 1996;56:4509-15

<sup>3</sup> Knocke TH, et al. Radiother Oncol 1999;53:99-104

# Carbon ion therapy

<sup>1</sup>Nakano T et al. published important data on the radiobiological aspects of carbon beam therapy on cervical cancer

- Intratumoral pO<sub>2</sub> measurements were performed in 79 women with stage IIIB bulky and stage IVA cervical cancer
- In those 30 patients treated with photon beams the survival rate of patients with hypoxic and oxygenated tumors differed significantly
- In contrast to that, following carbon ion therapy no significant prognostic difference between hypoxic and oxygenated tumors was obtained

<sup>1</sup> Nakano T, et al. Clin Cancer Res 2006;12:2185-2190

# Carbon ion therapy

- Phase I/II dose escalation studies using carbon ion beams for bulky stage IIIB and stage IVA cervical tumors were performed at Chiba <sup>1,2</sup>
- The patients received 16 fractions to the whole pelvis and 8 fractions of local boost given once daily, 4 days a week

<sup>1</sup> Nakano T, et al. Cancer J Sci Am 1999;5:362-9.

<sup>2</sup> Kato S, et al. Int J Radiat Oncol Biol Phys 2006;65:388-97.

# Carbon ion therapy

- In the first study (**Protocol 9403**) the total doses ranged from 52.8 to 72 GyE with 2.2-3.0 GyE per fraction
- In the second study (**Prot 9702**) the dose to the whole pelvis was fixed at 44.8 GyE (2.8 GyE per fraction)
- and additional 24 or 28 GyE were given to the cervical tumor up to a total dose of 68.8 or 72.8 GyE

# Carbon ion therapy

- In the early period (Protocol 9403) severe gastrointestinal side effects occurred (RTOG/EORTC Grade 4 in 7 patients) with patients requiring surgical intervention
- An adaptation of the irradiation technique and limitation of the dose to the intestine to 60GyE resulted in improved safety

# Carbon ion therapy

The 5-year local control rate for patients was

- 45% in Protocol 9403
- 79% in Protocol 9702
- When the total dose was  $\geq 62.4$  GyE, local tumor control was favourable in those with tumor diameter  $> 6$  cm

# Carbon ion therapy

Despite encouraging local control rates

**the rate of distant metastasis remained high**

... and additional chemotherapy should be further explored

- Up to now patient numbers are small, however, carbon ion therapy for advanced cervical cancer implicitly needs further investigations

# Conclusions



## Conclusion: Definitive radiotherapy in limited disease

- Primary radiotherapy for stage I-II cervical cancer offers cure rates equivalent to those with radical hysterectomy

## Conclusion: Definitive radiotherapy in locally extensive disease

- Improved local control rates for stage IIIB and IVA cervical cancer would be desirable in many cases ...

## Conclusion: Adjuvant radiotherapy following surgery

- Postoperative radiotherapy in cases of histopathological risk factors is correlated with better survival
- ... however in part correlated with increased toxicity compared to primary radiotherapy alone

# Conclusion – Proton Therapy

- Data is scarce
  - Could be treatment of choice for patients in whom brachytherapy cannot be performed regardless of reasons
  - Treatment option in recurrent tumours of the lateral pelvic wall, which cannot be treated sufficiently by brachytherapy
  - Might offer advantages in case of unfavourable pelvic anatomy to reduce morbidity for instance for the rectum.
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# Conclusion – Carbon Ion Therapy

- Was found to be effective in locally advanced cervical cancer in initial dose-escalation trials
- Especially very advanced bulky stage IIIB-IVA patients successfully achieved local control and good prognosis
- **Recent data from Chiba strongly suggest that the biological advantages of high LET particles may effectively overcome radiation-resistant anoxic cells of bulky tumors**
- ~~Further prospective studies are urgently needed~~