8. **Cervical Cancer (cervix uteri)**

Introduction

In 1958 Sweden reported 890 new cases of cervical cancer. In 2000, despite a substantial increase in population, 448 new cases were diagnosed. The reduction in incidence observed in Sweden and several other developed countries is largely due to the screening programs, which in Sweden have been conducted regularly since the end of the 60s. Parallel to reduction of the incidence, a reduction in mortality was also observed. For some age groups the mortality decreased with 60 per cent. In contrast, the total treatment outcomes for all patients with invasive cervical cancer remain largely unchanged. The reason for that may be, that in spite of better treatment methods, screening programs might be more effective in detecting slower growing and less aggressive invasive cervical tumours. According to the latest results from the Cancer Registry in Sweden the 5-year survival rate for all stages was 66.7 per cent for women diagnosed 1964–66 and 69.7 per cent for women diagnosed 1993–95.

Histologically, squamous cell carcinoma is the most common malignant tumour in the cervix uteri and represents about 85 per cent of the cases. The other 15 per cent include adenocarcinoma and some small groups of mixed forms with benign or malignant squamous and adenoma cell components.

Staging is based on the International Federation for Gynecology and Obstetrics (FIGO) latest classification from 1986. Stages are determined following preoperative gynecologic examination under anaesthesia, fractionated curettage and radiological examination of the lungs and kidneys. During the last years through screening procedures and earlier diagnosis there has been a major shift toward early stages.

Summary of the earlier report, SBU 129/2

The synthesis of the literature on radiotherapy in the earlier report SBU 129/2 is based on 59 scientific articles, including 8 randomized studies, 1 prospective study, 36 retrospective studies and 14 others. These studies involve 34 024 patients.

Three main issues have been discussed in the earlier report.

1. The importance of radiotherapy in early stages, Ib and IIa.
2. The value of (or indication for) radiotherapy of the paraaortic lymph nodes.
3. Low versus high dose rate for local radiotherapy of cervical cancer.

Conclusions

- Due to favourable anatomy and exceptionally good radiation tolerance of nearby pelvic organs, particularly the uterus, radiotherapy has become the dominant treatment method for cervical cancer.
- Surgery alone is used at the early stages where small tumour volumes are involved.
- Further pathological findings, when cancer is more extensive than expected preoperatively, or when lymph node metastases are discovered, motivate postoperative radiotherapy even in early stages.
- There is general agreement that advanced cervical cancer should be treated by radiotherapy alone. Clinical trials are under way that combine radiotherapy and chemotherapy, and even surgery.
- Two different methods of intracavitary brachytherapy are currently in use, low dose and high dose rate (LDR, HDR) therapy. HDR therapy appears to be economically more favourable. The possibility of higher risk for late complications associated with HDR therapy has not been fully studied.

Discussion

The previous SBU report on Radiotherapy for Cancer was published 1996 but the literature was reviewed until 1994 and the conclusions presented in the previous report were valid in 1994. Radiotherapy alone

was the dominant treatment especially for advanced cervical cancer but even in the early cervical cancer radiotherapy played an important role. Radiotherapy could be used both preoperatively in bulky or large diameter tumours of the early stages and adjuvantly after surgery, when positive lymph nodes or more extensive tumour than expected was found at surgery.

Generally the choice of treatment has been based on an individual basis both in regard to patient characteristics as and to the institution where the treatment was performed.

Literature

The articles on which the conclusions in the SBU 129/2 report were based were classified and graded as follows (number of studies/number of patients).

	1 = High	2 = Moderate	3 = Low	Total
C	1/367	3/778	4/909	**8/2 054**
P	1/263	–	–	**1/263**
R	15/7 567	16/3 101	5/597	**36/11 265**
L	4/20 442	–	–	**4/20 442**
O	10	–	–	**10**
Total	**31/28 639**	**19/3 879**	**9/1 506**	**59/34 024**

Assessment of new literature

Search methods and selections

Computerized literature searches were performed in Medline for 1994–October 2001. The MeSH search term cervix neoplasms was used in combination with radiotherapy as a subheading, MeSH-term and text-word. Limitations to the following study designs were made: randomized controlled studies, other controlled studies and meta-analysis. A supplementary search was made in the Cochrane Library. As all the referees (Nina Einhorn, Claes Tropé, Mona Ridderheim, Karin Boman, Bengt Sorbe) are specialists in gynecological oncology and experts in all three gynecological tumour types, which were decided by the SBU to be reviewed, a joint meeting of all referees was organised in Stockholm to select relevant abstracts as well as relevant publications.

Primarily 72 abstracts concerning cervical cancer were received by the referees. Five more studies recently published were added, totally 77 abstracts. All abstracts as well as most of the publications were discussed by the referees and decision was made on further analysis of 34 publications, all randomized studies and one meta-analysis.

Reasons for exclusion of 42 abstracts and publications not selected for further analysis were:

Group		
A	10	reviews
B	10	short comments/editorials
C	8	basic science investigations
D	4	experimental phase I-II investigations (and comparisons with historical results)
E	4	studies with small patient material (pilot studies or interim analysis)
F	6	general topics not relevant to the aim of the study

Overview of new studies

Early stages (IB–IIB): Adjuvant radiotherapy after surgery alone or after surgery with adjuvant chemotherapy. Radiotherapy alone versus surgery alone or versus surgery with preoperative radiotherapy.

Overview 1 (after the list of references)

According to current opinion most women with stage IB–II cervix cancer can be treated successfully with radiotherapy whereas a careful selection of patients is necessary before planning primary radical surgery. Surgery has become primary treatment in premenopausal women with normal ovarian function and also in elderly women, who are medically operable, with FIGO stage IB–IIA tumours and a tumour diameter of 4 cm or smaller. Women with a tumour diameter >4 should be treated with radiotherapy with concomitant chemotherapy.

The literature shows:

- In one large randomized study of early stage cervical cancer adjuvant pelvic radiotherapy significantly improved DFS whereas no benefit was found in one small study.

- The addition of adjuvant radiotherapy to surgery and adjuvant chemotherapy has been investigated in one small randomized study and no improvement of DFS or OS was found.
- Radiotherapy has been compared to radical class III Piver surgery in one large randomized study and no difference in DFS or OS was found.
- Radiotherapy was compared to preoperative brachytherapy and surgery in a fairly small early study and a significantly improved OS was found in the surgically treated group. There was, however, an increased late toxicity in that group.

Radiotherapy with concomitant chemotherapy

Overview 2 (after the list of references)

The literature shows:

- During the last seven years data from nio randomized trials have been published, six of which showed a significant benefit with concomitant chemoradiotherapy, especially in early stages.
- A meta-analysis of all randomized trials comparing radiotherapy alone with combined chemoradiotherapy showed a significantly improved PFS and OS. It was concluded that the beneficial effect was greater in trials including a high proportion of patients with stage I and II carcinoma.

A consensus conference (1999) by the NCI has concluded that concomitant cisplatinum based chemotherapy and radiotherapy compared to radiotherapy alone gives better OS and DFS in patients with cervical cancer. However, this has only been shown for stage <III. There were not enough patients with advanced cervical cancer in the studies published, and no benefit demonstrated in stage III–IV carcinoma.

Radiotherapy with neoadjuvant chemotherapy

Overview 3 (after the list of references)

The literature shows:

- In four small randomized studies no improvement in DFS or OS was shown by the addition of neoadjuvant chemotherapy to radiotherapy

and in one fairly large study the addition of neoadjuvant chemotherapy had a negative effect on OS.

- In one small study in stage IIIB patients radiotherapy alone was compared to either neoadjuvant chemotherapy + radiotherapy or neoadjuvant chemotherapy followed by surgery and radiotherapy. An improved DFS and OS was found in the surgically treated group.

Different approaches in radiotherapy

Overview 4 (after the list of references)

The literature shows:

- Hyperfractionated radiotherapy has been compared to conventionally fractionated radiotherapy in a very small randomized study (15 patients in each treatment group) and a significantly better local tumour control was found.
- The importance of treatment volume, pelvis versus pelvis + paraaortic nodes, was studied in two trials. In one of the studies the radiotherapy was given postoperatively. The results in the two studies were conflicting. In the larger study a benefit in OS with extended radiotherapy was found while the smaller study found a worse cause-specific survival and a significantly increased toxicity with extended field radiotherapy after surgery.

Brachytherapy with low, median or high dose rate

Overview 5 (after the list of references)

The literature shows:

- Altogether six studies dealing with low, median and high dose rates brachytherapy have been published. Most of the studies are small.
- Low dose brachytherapy with a low dose rate (0.35–0.4 Gray/h) has the same efficacy and gives less complications compared to higher dose rate (0.73–0.8 Gray/h).
- There is no difference in efficacy or complication rate between brachytherapy with high dose rate 7.5 Gray/fraction and 6.0 Gray per fraction.

- One large randomized study has compared brachytherapy with low dose rate with brachytherapy with high dose rate. High dose rate brachytherapy gave the same local control rate but less rectal complications compared to low dose rate brachytherapy.

Radiotherapy – response modifiers

Overview 6 (after the list of references)

The literature shows:

- One randomized study investigated the effect of radiation in hyperbaric oxygen. No difference was found in comparison to radiation in air.
- Two trials, where the benefit of radiosensitizing agents were studied, are reported. No benefit was found.

Radiotherapy with different kinds of concomitant chemotherapy

Overview 7 (after the list of references)

The literature shows:

- Two recent large studies have compared radiochemotherapy including cisplatin to radiochemotherapy with hydroxy-urea. Both studies showed significantly improved survival when cisplatin was used as concomitant chemotherapy.

Literature

The articles that appear in the reference list were classified and graded as follows:

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients).*

	1 = High	**2 = Moderate**	**3 = Low**	**Total**
M	1/3 611	–	–	**1/3 611**
C	10/3 584	4/1 105	20/2 845	**34/4 341**
Total	**11/5 293**	**4/1 105**	**20/1 554**	**35/7 952**

* Since some patients can be included in several reports, the sums of the totals are lower than the sums of the numbers given within the table.

Conclusions and comments

- There are limited scientific data supporting that postoperative pelvic radiotherapy improves diseasefree survival in early cervical cancer. No firm conclusion can be drawn. (*Pro:* 28[C1], *con:* 12[C3]).
- There is a moderate scientific evidence that external beam radiotherapy combined with brachytherapy gives a similar diseasefree and overall survival as radical hysterectomy in early cervical cancer. (14[C1]).
- There is a strong scientific evidence that concomitant radiochemotherapy improves diseasefree and overall survival compared to radiotherapy alone in early cervical cancer. (7[M1]).
- NCI have recently published an announcement stating that cisplatinum based chemotherapy should be used concomitant with radiotherapy in cervical cancer. No solid documentation for this statement can be found concerning locally advanced stages (>IIB). (7[M1], 25[C1], 34[C1]).
- There is a strong scientific evidence that cisplatinum based chemotherapy given concomitantly with radiotherapy is superior to concomitant chemotherapy with hydroxyurea. (25[C1], 34[C1]).
- There is no scientific evidence that neoadjuvant chemotherapy followed by radiotherapy improves diseasefree or overall survival compared to radiotherapy alone inpatients with localized cervical cancer. (15([C3], 29[C3], 11[C2], 3[C3], 31[C2]).
- There is a moderate scientific evidence that high dose rate brachytherapy gives the same local control rate but less rectal complications compared to low dose rate brachytherapy. (21[C1]).

In the decision of optimal therapy for patients with cervical cancer clinical and tumour related factors should be taken account of, such as age, menopausal status, general medical condition, tumour stage, tumour size.

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Overview 1 *Cervix cancer, early stages (IB–IIB). Adjuvant radiotherapy after surgery alone or after surgery with adjuvant chemotherapy. Radiotherapy alone versus surgery alone or versus surgery with preoperative radiotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Sedlis 1999 [27] C	Value of adjuvant RT **A:** Surgery + RT 46 Gy/23 fr or 50.4 Gy/28 fr **B:** Surgery alone	1988–95 St IB A 137pts B 140 pts
Lahousen 1999 [12] C	Adjuvant RT vs adjuvant CHT **A:** Surgery + RT 56.8 Gy/26 fr **B:** Surgery + CHTadj (Cp + Bleo) **C:** Surgery only	1989–95 St IB–IIB A 24 pts B 28 pts C 24 pts
Curtin 1996 [4] C	Value of RT in addition to surgery + CHT **A:** Surgery + CHTadj (Cp + Bleo) + RT 45 Gy/20 fr **B:** Surgery + CHTadj as A	1987–94 St IB–IIA, high risk (T >4 cm, deep parametrial invasion, + paraaortic or pelvic nodes). A 45 pts B 44 pts
Landoni 1997 [14] C	Radiotherapy vs surgery **A:** EBRT 40 –50 Gy to pelvis + BRT (LDR, Ce137) to total dose 70–90 Gy to point A **B:** Surgery only (radical hysterectomy Piver Class III)	1986–91 St IB–IIA A 171 pts B 172 pts
Sundför 1996 [29] C	Radiotherapy vs surgery + BRT **A:** EBRT 40 Gy/24–26 fr + BRT 66–70 Gy to point A **B:** Preop. BRT as A + surgery	1968–80 Stage IIA–IIB A 70 pts B 72 pts

Adj: adjuvant; BRT: brachytherapy; Bleo: bleomycin; CHT: chemotherapy; Cp: cisplatin; DFS: disease free survival; EBRT: external beam radiotherapy; LDR: low dose rate; ns: not significant; OS: overall survival; pts: patient(s); RT: radiotherapy; y: year(s)

Results			Conclusion/Comments
Act.	**DFS%**	**OS% at 2 y**	Adjuvant pelvic radiotherapy significantly improves DFS. 7% grade >3 urin. bladder or rectal toxicity in group A. Interim analysis. Important question. **C1**
A	88	89	
B	79	82	
	p=0.008	Sign not evaluated	
Act.	**DFS% at 4 y**		Adjuvant CHT or RT do not improve DFS. Low power. **C3**
A	79		
B	64		
C	58		
ns			
Median follow-up 36 m			Radiotherapy did not improve DFS in high risk early stage pts. Poor study design. Low power. Trial closed too early due to poor accrual. 72/89 pts evaluable: major protocol violation 12 pts; lost to follow-up 5 pts. **C3**
Act.	**DFS%**	**OS%**	
A	78	74	
B	80	84	
ns ns			
Act.	**DFS%**	**OS% at 5 y**	No difference in OS between surgery and radiotherapy in early stages of cervical cancer. Relapse treatment with RT after surgery (group B) leads to severe urological complications. **C1**
A	74	83	
B	74	83	
	ns	ns	
	OS%		Significant difference in OS between radiotherapy compared with brachytherapy + surgery in stage IIA– IIB. Both surgery and RT changed during the long study time. **C2**
	5 y	**10 y** **20 y**	
A	72	69 68	
B	87	84 81	
	p=0.01		
Lymphedema only in gr B. More severe urin. bladder and rectal complications in gr B. One patient in gr A and 2 pts in gr B died of complications.			

Overview 2 *Cervix Cancer Radiotherapy with concomitant chemotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Green RT 2001 [7] M	Value of concomitant CHT **A:** RT **B:** RT + CHTco CHTco= cisplatin, in the majority of pts.	All known randomized trials performed (17 published, 2 unpublished) 1981–2000 St I–IV (68% in st I–II) 3 611 pts
Onishi 2000 [19] C	Value of concomitant intraarterial CHT **A:** EBRT 50 Gy/25 fr to pelvis + BRT 24 Gy to point A **B:** RT as A + CHT i.a. (Cp)	1988–98 St IIIA, B, IVA A 15 pts B 18 pts
Keys 1999 [10] C	Value of concomitant CHT **A:** EBRT + BRT 75 Gy to point A **B:** RT as A + CHTco (Cp) Radical hysterectomy was performed in both groups	1992–97 St IB, >4 cm A 186 pts B 183 pts
Morris 1999 [17] C	Value of concomitant CHT **A:** RT 45 Gy to pelvis and paraaortic nodes **B:** RT 45 Gy to pelvis + CHTco (Cp)	1990–97 St IB–IVA A 193 pts B 193 pts 30% of pts st III–IVA
Tseng 1997 [32] C	Value of concomitant CHT **A:** RT **B:** RT+ CHTco (Cp + V + Bleo)	1990–95 St IIB–IIIB A 62 pts B 60 pts Toxicity sign increased in gr B (36.7%) vs gr A (17.7%) p=0.02

Adj: adjuvant; Bleo: bleomycin; BRT: brachytherapy; CHT: chemotherapy; co: concomitant; Cp: cisplatin; d: dat(s); DFS: disease free survival; EBRT: external beam radiotherapy; Epi; epirubicin; 5Fu: 5-fluorouracil; fr: fraction(s); HRT: hyperfractionated radiotherapy; m: months; Mito: mitomycin; neoadj: neoadjuvant; NR: not reported; OS: overall survival; PFS: progressionfree survival; pts: patient(s); RT: radiotherapy; V: vincristine; y: year(s)

Results	Conclusion/Comments
Median follow-up 3 y **PFS% OS%** A 47 40 B 63 52 p <0.0001 p <0.0001 In group B sign. more grade 3–4 hematological toxicity.	Well performed meta-analysis. Concomitant CHT and improve OS and PFS in this selected patient material. A greater beneficial effect was seen in st I and II pts. **M1**
OS% at 2 y **OS% at 5 y** A 75 50 B 54.5 ns 44.4 ns Sign. more bowel toxicity grade 3–4 (2 deaths) in group B.	Small patient groups. 3 different CHT delivery ways. Low doses of radiotherapy. **C3**
Act. **DFS%** **OS% at 4 y** A 63 74 B 79 85 p <0.001 p=0.008	Concomitant RT + CHT reduced the risk of recurrence in stage I bulky cervical cancer. Higher complication rate for RT + CHT group. Well planned and performed study. **C1**
Act. **DFS%** **OS% at 5 y** A 40 58 B 67 73 p <0.001 p=0.004 Increased hematological side-effects in group B.	A subgroup analysis showed no sign diff in OS or DFS in pts st III–IV, but too few pts to draw any conclusion. Important conclusion for stage I–II with improved OS with RT + concomitant CHT. RT not similar in the two groups (extended fields in gr A). **C1**
Act. **DFS%** **OS% at 3 y** A 53 65 B 51.7 62 ns ns	RT + concomitant CHT did not improve OS or DFS but increased toxicity. Low RT-dose. Low power. **C3**

The table continues on the next page

Overview 2 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Thomas 1998 [31] C	RT vs HRT ± concomitant CHT **A:** RT 50 Gy/25 fr **B:** RT as A + CHTco (5Fu) **C:** HRT 52.8 Gy/33fr/2fr/d **D:** RT as C + CHTco (5Fu)	1987–1995 Pts stratified in 3 strata: I: St IB, IIA, IIBM (medial parametrial involv.), 99 pts II: St II BL (lateral parametrial involv.) –IIIB (with unilat. pelvic wall involv.), 105 pts III: St IIIB (with bilat pelvic wall involv.) –IV, 17 pts Only stratum I and all pts evaluated.
Peters 2000 [23] C	Value of concomitant CHT Radical surgery in all pts + **A:** RT 49.3 Gy, 4 field technique **B:** RT as A + CHTco (5Fu) Pts with positive iliac nodes received 45 Gy to paraaortic nodes.	1991–1996 St IA–IIA, high risk pts, A 116 pts B 127 pts St IB–IIB A 127 pts
Pearcey 2000 [22] C	Value of concomitant CHT **A:** RT 50 Gy **B:** RT + CHTco (Cp)	B 126 pts
Wong 1999 [35] C	Value of concomitant CHT **A:** EBRT 40 Gy + BRT 85–90 Gy to point A **B:** RT as A + CHTco (Epi)	1987–93 St I, II, III A 110 pts B 110 pts
Lorvidhaya 1995 [16]	Comparision of different schedules of CHT **A:** RT 50 Gy/25 fr **B:** RT as A + CHTadj (5Fu) **C:** RT as A + CHTco (Mito + 5Fu) **D:** RT as A + CHTco (Mito + 5Fu) + CHTadj (5Fu)	1988–92 St IIB, IIIB, IVA A 170 pts B 149 pts C 159 pts D 153 pts

Results	Conclusion/Comments
Median follow-up 59 m Act. **DFS% at 5 y** All pts Stratum I A 45 39 B 61 76 p = 0.05 C 53 58 D 58 65 ns ns	RT + concomitant CHT was beneficial only for early stages. Low power, too many arms. Closed too early due to poor accrual. **C3**
PFS% OS% at 4 y A 63 61 B 80 p=0.007 71 p=0.003 Grade 3–4 hemotological and gastrointestinal toxicity sign more in group B.	Concomitant CHT improves PFS and OS for high risk early stage patients. RT not well described, otherwise well performed trial. **C1**
OS% at 5 y A 56 B 59 ns	No difference in survival with RT + concomitant CHT compared with RT alone. **C1**
Median follow-up 77 m **DFS% OS%** A 75 NR B 85 NR p= 0.02 p= 0.04 Sign. more gr 3–4 hematological toxicity in group B.	Sign better DFS and OS in group B. Sign. higher rate of distant metastases in group A. Stage II and III not reported separately. Poor description of RT technique. **C3**
Act. **DFS% at 5 y** A 42 B 58 C 62 D 64 A vs B, C and D p=0.003	Interim analysis. RT not well described. Toxicity not described. **C3**

Overview 3 *Cervix Cancer Radiotherapy with neoadjuvant chemotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Leborgne 1997 [15]	Value of neoadjuvant CHT **A:** EBRT + BRT 75–80 Gy **B:** CHT neoadj (Cp + V + Bleo) + RT as A	1987–90 St IB–IVA A 49 pts B 48 pts
Sundför 1996 [28] C	Value of neoadjuvant CHT **A:** RT 64.8 Gy/1.8 Gy/fr **B:** CHT neoadj (5Fu) + RT as A	1989–92 St IIIB-IVA A 47 pts B 47 pts
Tattersall 1995 [30] C	Value of neoadjuvant CHT **A:** EBRT 40–55 Gy + BRT 30–35 Gy to point A **B:** CHT neoadj (Epi + Cp) + RT as A	1989–93 St IIB–IVA A 131 pts B 129 pts
Kumar 1994 [11] C	Value of neoadjuvant CHT **A:** EBRT 50 Gy/25 fr + BRT 30 Gy to point A **B:** CHT neoadj (Bleo + If + Cp) + RT as A	1990–92 St IIB–IVA A 88 pts B 89 pts
Chiara 1994 [3] C	Value of neoadjuvant + adjuvant CHT **A:** EBRT 40 Gy + BRT 25–40 Gy **B:** CHTneoadj (Cp) + RT as A + CHT adj (Cp)	1989–91 St IIB–III A 29 pts B 32 pts
Sardi 1996 [26] C	Value of neoadjuvant CHT or neoadj CHT + surgery **A:** EBRT 50–60 Gy + BRT 25–35 Gy **B:** CHT neoadj (Cp + V + Bleo) + RT as A **C:** CHT neoadj + surgery + RT as A	1988–92 St IIIB A 53 pts B 52 pts C 50 pts

Adj: adjuvant; Bleo: bleomycin; BRT: brachytherapy; CHT: chemotherapy; co: concomitant; Cp: cisplatin; d: dat(s); DFS: disease free survival; EBRT: external beam radiotherapy; Epi; epirubicin; 5Fu: 5-fluorouracil; fr: fraction(s); HRT: hyperfractionated radiotherapy; If: ifosfamide; LRC: locoregional control; LFR: local failure rate; m: months; Mito: mitomycin; neoadj: neoadjuvant; NR: not reported; OS: overall survival; PFS: progressionfree survival; pts: patient(s); RT: radiotherapy; V: vincristine; y: year(s)

Results	Conclusion/Comments
Median follow-up 43 m **LRC%** **DFS% at 43 m** A 68 49 B 65 ns 38 ns	Neoadjuvant chemotherapy does not improve DFS. Low power. Low dose radiotherapy. **C3**
Median follow-up 4 y **DFS%** **OS%** A 45 61 B 39 60 ns ns	Low power. No conclusion can be drawn. **C3**
Median follow-up 1.3 y **LFR%** **OS%*** A 16 70 B 26 50 p=0.003 p=0.02	OS worse with neoadjuvant chemotherapy. RT not well described but well designed and performed trial. *Figures for OS are estimated from survival curves. Short follow-up, no later update has been published. **C2**
Act. **DFS%** **OS% at 32 m** A 67 43 B 69 ns 38 ns 2 pts died after the 1st CHT course in group B.	No difference in OS or DFS between RT alone and neoadjuvant CHT + RT. Short follow-up. RT related toxicity not well described. **C2**
Act. **PFS%** **OS% at 3 y** A 72.4 83 B 59.3 ns 72 ns	No improvement in pelvic control and survival with neoadjuvant CHT + RT compared with RT. Low power. **C3**
DFS% **OS% at 4 y** A 28 37 B 45 53 C 65 63 p=0.005 p=0.005	Surgery gives the best results after neoadjuvant chemotherapy. Selected patient material. Low power. One patient died of trombocytopenia in group C. 3 pts had Bleo induced lungtoxicity. 1 rectovaginal fistula in group B. **C3**

Overview 4 *Cervix Cancer different approaches in radiotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Viswanathan 1999 [34] C	Value of hyperfractionated RT **A:** RT 50 Gy/25 fr **B:** HRT 60 Gy/50 fr/2 fr/d	1989–94 St IIB–IIIB A 15 pts B 15 pts
Rotman 1995 [25] C	Benefit of extended field RT **A:** RT 40–50 Gy/1.6–1.8 Gy/fr to pelvis + BRT 40–50 Gy **B:** RT 44–45 Gy/1.6 Gy/fr to pelvis + paraaortic nodes + BRT as A	1979–86 St IB–IIB A 167 pts B 170 pts
Chatani 1995 [1] C	Small field vs large field RT ± surgery **A:** EBRT 30 Gy to pelvis **B:** EBRT 30 Gy to pelvis + 45 Gy to paraaortic nodes **C:** Surgery + RT as A **D:** Surgery + RT as B BRT was given in all groups: 30 Gy to point A (Manchester technique)	1986–90 St IB–IIB A 18 pts B 18 pts C 30 pts D 27 pts

BRT: brachytherapy; CSS: causespecific survival; d: day(s); DFS: disease free survival; fr: fraction(s); EBRT: external beam radiotherapy; HDR: high dose rate; HRT: hyperfractionated radiotherapy; OS: overall survival; pts: patient(s); RT: radiotherapy; y: year(s)

Results	Conclusion/Comments
Tumour control % at 5 y A 49 B 68 p=0.05 2 pts in group A vs 9 pts in group B had grade 3–4 bowel complications, p=0.02.	Hyperfractionation gives better tumour control but increases bowel toxicity. Very small and heterogenous material with many drop outs **C3**
DFS% **OS% at 10 y** A 40 44 B 42 55 ns p=0.02 One pt in group A vs 4 pts in group B died of RT complications.	Improved OS with pelvic + paraaortic irradiation in stage IB–IIB cervical carcinoma. Well performed trial. **C1**
CSS% at 3 y A 89 B 57 C 86 D 70 ns Sign more bowel complications in group B and D, p<0.025.	Few patients. High complication rate in groups B and D. **C3**

Overview 5 *Cervix cancer. Brachytherapy with low, median or high dose rate.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Patel 1998 [20] P Study I C Study II	BRT LDR vs BRT MDR **Study I** not randomized RT same in all groups + BRT : **A:** LDR to 35.0 Gy **B:** MDR to 30.6 Gy (-12,5%) **C:** MDR to 24,5 Gy (-30%) **Study II** randomized RT (same as in study I) + BRT: **A:** MDR to 28.0 Gy (-20%) **B:** MDR to 24,5 Gy (-30%)	Stage IIB–III Study I A 173 pts B 87 pts C 86 pts Study II A 92 pts B 88 pts
El-Baradie 1997 [6] C	BRT HDR vs MDR St I–II **A:** HDR 32.0 Gy **B:** MDR 35.6 Gy St III **A:** HDR 30.0 Gy **B:** MDR 34.0 Gy St IV **A:** HDR 22.5 Gy **B:** MDR 25.5 Gy	1991–93 St I–IV A 22 pts B 23 pts
Chatani 1994 [2] C	BRT-HDR, different fraction dose **A:** BRT-HDR 6 Gy/fr, 22.5–37.5 Gy to point A **B:** BRT-HDR 7.5 Gy/fr, 18–36 Gy to point A EBRT 10–40 Gy to pelvis was given in both groups.	1986–90 St I–IV A 83 pts B 82 pts
Haie-Meder 1994 [9] C	BRT-LDR, different dose rates **A:** BRT-LDR 0.4 Gy/h, 60 Gy **B:** BRT-LDR 0.8 Gy/h, 60 Gy Radical hysterectomy + bilateral pelvin lymphadenoectomy in all pts. When positive nodes EBRT 45 Gy with central shield was given.	1985–88 St I–IIA A 102 pts B 102 pts

BRT: brachytherapy; CSS: causespecific survival; DFS: disease free survival; fr: fraction(s);
EBRT: external beam radiotherapy; HDR: high dose rate; HRT: hyperfractionated radiotherapy;
LC: local control; LDR: low dose rate; MDR: medium dose rate; NR: not reported, OS: overall survival;
PFS: progressionfree survival; pts: patient(s); RT: radiotherapy; y: year(s)

Results	Conclusion/Comments
Study I Act **LC%** **Urin. bladder + rectal at 5 y morbidity >grade 3, %** A 63.4 5.3 B 70.5 12.5 p<0.05 C 71.7 ns 7.7 Study II at 3 y A 74.8 9.3 B 66.6 ns 6.4 pNR	This report includes 2 studies. Study I is not randomized, historical controls (LDR pts). Study II is randomized. No sign difference between differents dose levels in local control. When increased dose rate is used, a reduction of 30% of the dose is recommended. **C2**
LC% **OS%, at 3 y** A 67 62 B 74 ns 68 ns No difference in complication rate (urin. bladder, rectal) between groups at 3 y.	No difference in OS or LC between high dose and medium dose rate. Few patients. Short observation time. Important question. **C3**
CSS% at 5 y St I St II St III St IV A 100 82 62 22 B 93 85 52 31 ns No difference in complication rate	In group B (higher dose/fr) shorter treatment time and no increase in complication rate. **C3**
Complication rate % A 63 B 75 p=0.03 No difference in OS	Lower dose rate gives the same OS and less complications. Badly described paper. Only 2 years observation in spite that the work was done 1985–88 and was published 1994. **C3**

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Overview 5 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Lambin 1994 [13] C	BRT-LDR, different dose rates **A:** BRT-LDR 0.38 Gy/h, 60 Gy **B:** BRT-LDR 0.73 Gy/h, 60 Gy In both groups a Wertheim operation was performed.	1985–88 St I–II A 79 pts B 76 pts
Patel 1994 [21] C	BRT-LDR vs BRT-HDR **A:** BRT-LDR 0.55–0.65 Gy/h, 35–75 Gy to point A **B:** BRT-HDR 1.3–1.6 Gy/min, 10–38 Gy to point A In both groups EBRT 35–45 Gy to pelvis.	1986–89 St I–III A 246 pts B 236 pts

Results	Conclusion/Comments
Higher complication rate for higher dose rate. p=0.03. Higher tumour sterilization rate for lower dose rate. p=0.07	Lower dose rate recommended. Poorly described trial. **C3**
LC% at 5 y **Rectal toxicity, gr 1–4 %** A 79.7 19.9 B 75.8 ns 6.4 p=0.001 No difference in serious rectal toxicity (grade 3–4) between the groups. OS at 5 y no sign difference.	Well performed trial with important question. HDR BRT caused less rectal complications than LDR BRT. **C1**

Overview 6 *Cervix cancer. Radiotherapy – response modifiers.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Dische 1999 [5] C	Benefit of oxygenation **A:** EBRT 40 Gy/10 fr + hyperbar O2 **B:** EBRT 45 Gy/10 fr + hyperbar O2 **C:** EBRT 58 Gy/10 fr + hyperbar O2 BRT 20 Gy to point A given in all groups.	1971–80 St IIB St III A 68 pts 70 pts B 22 pts 23 pts C 83 pts 54 pts A hemoglobin value >12 g/L was required at RT start.
Grigsby 1999 [8] C	Value of radiosensitizer **A:** EBRT 46 Gy to pelvis + 10 Gy to paraaortic nodes **B:** EBRT as A + misonidazol (400 mg/m2/d) BRT 30 Gy to point A (Fletcher) given in both groups.	1980–84 St IIB–IVA A 61 pts B 59 pts
Okkan 1996 [18]	Value of radiosensitizer **A:** EBRT 42.5–44 Gy **B:** EBRT as A + ornidazole BRT 21.66 Gy to point A given in both groups.	1982–87 St IIB, IIIB A 38 pts B 38 pts

BRT: brachytherapy; d: day(s); DFS: disease free survival; fr: fraction(s); EBRT: external beam radiotherapy; HRT: hyperfractionated radiotherapy; LC: local control; OS: overall survival; PFS: progressionfree survival; pts: patient(s); RT: radiotherapy; y: year(s)

Results	Conclusion/Comments
Median follow-up 13.2 y No difference in survival or loco regional control.	Poor study design. Poor RT. Inclusion criteria and treatment change during study time. At dose level 45 Gy + O2 there was an increased late RT-related morbidity. **C3**
PFS% **OS%, at 5 y** A 22 30 B 29 ns 30	No difference in OS or PFS or toxicity between groups with or without misonidazole. The trial was closed too early due to poor accrual. **C3**
Act **LC%** **DFS% at 10 y** Stage III A 15 8 B 54 p=0.04 37 p=0.05 All pts A 50 B 61 ns	No difference LC and DFS for the whole treatment group but for stage III significant difference. No difference in RT-related late toxicity between groups. Low RT doses, few patients. Ornidazole doses changed during treatment. **C3**

Overview 7 *Cervix cancer. Radiotherapy with different kinds of concomitant chemotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Rose 1999 [24] C	Value of concomitant CHT including cisplatin **A:** EBRT + BRT + CHTco (Cp) **B:** RT as A + CHTco (Cp + 5Fu + Hu) **C:** RT as A + CHTco (Hu) RT: EBRT 40.8 Gy/24 fr or 51 Gy /30 fr BRT 30–40 Gy to point A	1992–97 St IIB–IV A 176 pts B 173 pts C 177 pts
Whitney 1999 [33] C	Value of concomitant CHT including cisplatin **A:** EBRT + BRT + CHTco (Cp + 5Fu) **B:** RT as A + CHTco (Hu) EBRT: 40.8 Gy to pelvis BRT: 40 Gy to point A	1986–90 St IIB–IV (62% St II B) All pts without intra-abdominal spread. A 177 pts B 191 pts

BRT: brachytherapy; Co: concomitant; CHT: chemotherapy; Cp: cisplatin; DFS: disease free survival; EBRT: external beam radiotherapy; fr: fraction(s); 5Fu: 5-fluorouracil; Hu: hydroxyurea; m: month(s); OS: overall survival; pts: patient(s); RR: relative risk; RT: radiotherapy; y: year(s);

Results	Conclusion/Comments
Median follow-up 35 m **OS%** A 66 A vs C p=0.004 B 67 B vs C p=0.002 C 50 RR of disease progression or death: Gr A 0.57, gr B 0.55 as compared with gr C. Hematological toxicity sign. more in gr B and C vs A.	Concomitant CHT including cisplatin improves OS and PFS. Low RT-dose. Long treatment time. **C1**
Median follow-up 8.7 y **DFS%** **OS%** A 57 55 B 41 43 p=0.03 p=0.02 Median survival time not reached in gr A, 59.8 m in gr B.	Grade 3–4 leukopenia 6% in gr A, 46% in gr B. No sign. difference in gastrointestinal toxicity, gr 3–4, between groups, (A 8%, B 4%). **C1**