9. **Uterine Cancer (Corpus uteri)**

Introduction

Endometrial cancer is the most common gynecologic malignancy in Sweden. In 2000, there were 1 292 newly diagnosed cases. The incidence is 22 per 100 000 women per year. The median age is 65 years. Only 1 per cent of the cases occur before the age of 40 years. According to the latest results from Cancer Registry of Sweden, the 5-year survival rate for all stages was 75.2 per cent for women diagnosed 1964–66 and 83.4 per cent for women diagnosed 1993–95.

The most common histopathological type of tumour is adenocarcinoma representing 75 per cent of all cases. Numerous observations suggest that endometrial cancer has a hormonal etiology.

Stage, grade, histopathological type and depth of myometrial invasion are the most important prognostic factors.

Until 1986 only clinical staging was applicable. In 1986 FIGO (International Federation for Gynecology and Obstetrics) introduced surgical staging (peritoneal washings, total hysterectomy, pelvic and paraaortic lymphnode sampling). This staging implies primary operation excluding the use of preoperative radiotherapy. During the recent two decades the clinical staging has been increasingly abandoned and replaced by primary surgery and surgical staging. This resulted in changes in treatment modalities. Previously radiotherapy was used extensively preoperatively or as the only treatment modality. Treatment has changed since the 80s and surgery is becoming the primary treatment for most of the uterine cancer patients. Still, patients not suitable for primary surgery because of poor general condition or patients with tumours in advanced stages can be cured by radiotherapy. According to the latest Annual Report (volume 23), 72 per cent of all patients are surgically staged.

According to the latest Annual Report, clear cell carcinomas and seropapillary carcinomas have the worst prognosis of all histopathological sub-

types with 51.0 per cent and 45.5 per cent 5-year survival respectively, which can be compared to 76.3 per cent overall survival for all uterine adenocarcinomas.

Lymph nodes involvement increases with myometrial invasion and tumour grade. There is an ongoing discussion concerning the surgical staging procedure, whether lymph node dissection or sampling should be used as a routine procedure. Postoperative radiotherapy is used extensively and about 2/3 of the patients according to the latest Annual Report are treated with postoperative irradiation.

Summary of the earlier report, SBU 129/2

The summary of the earlier report is based on 55 scientific articles including two randomized studies, one prospective study, 48 retrospective studies and four others. The studies included 13 597 patients

Conclusions

- Endometrial cancer is a radiosensitive tumour. In early decades, when primary surgery was not used, 69 per cent of the patients were cured by radiotherapy.
- During the 1970s it was shown, that combined radiotherapy and surgery gave better results.
- There is an agreement, that patients with tumours in stage I should be treated by primary surgery. There is a controversy, whether patients with poorly differentiated tumours should be given preoperative radiotherapy.
- Radiotherapy alone can successfully be used in patients, who are inoperable due to age, general condition or locally advanced cancer.
- Postoperative vaginal radiotherapy is used in most patients and reduces the percentage of patients who develop vaginal metastases, from 7–20 per cent to less than 1 per cent. Patients with favourable prognostic factors have low risk for vaginal metastases and withholding radiotherapy is justified.

- Postoperative external radiotherapy improves survival in patients with unfavourable prognostic factors.
- It can be expected that most patients with uterine cancer will continue to be referred to some form of radiotherapy.

Discussion

In 1986 FIGO decided that endometrial cancer should be surgically staged and therefore procedures previously used for determination of tumour stage are no longer applicable. FIGO acknowledges that there maybe is a small number of patients with uterine cancer, who will be treated primarily with radiotherapy and in those cases the clinical staging adopted by FIGO in 1971 should still apply. Surgical staging requires primary surgery with lymph node dissection or sampling. This procedure is especially believed to be of importance for patients with poor prognostic factors, e.g. tumours with grade 3 and deep myometrial invasion. As a result of the FIGO decision 1986, the policy of treatment in uterine cancer is changing and primary radiotherapy is becoming abandoned, especially in stage I, but also in stage II disease.

Unfortunately no randomized trials have been performed to evaluate the importance of primary radiotherapy in patients with poor prognostic factors.

In cases of advanced uterine carcinomas as well as in patients with bad general condition radiotherapy can be used as the only treatment method.

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	2/645	–	–	**2/645**
P	1/133	–	–	**1/133**
R	20/8 911	17/2 855	11/473	**48/12 239**
L	–	2	–	**2**
O	2/580	–	–	**2/580**
Total	**25/10 269**	**19/2 855**	**11/473**	**55/13 597**

Assessment of new literature

Search method and selection

Computerized literature searches were performed in Medline for 1994–October 2001. The MeSH search term endometrial neoplasms was used in combination with radiotherapy as a subheading, MeSH-term and textword. Limitations to the following study designs were made: randomized controlled studies, other controlled studies, meta-analysis, epidemiologic studies such as case-control studies, cohort studies, prospective studies and retrospective studies. A supplementary search was made in 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 and publications.

Primarily 82 abstracts concerning uterine cancer were reviewed by the referees. Two more studies recently published were added, in all 84 abstracts. All abstracts as well as most of the publications were discussed by the referees and decision was made on further analysis of 10 publications and one abstract. The reasons for the exclusion of 73 abstracts and publications not selected for further analysis were:

Group		
A	5	reviews
B	44	general topics not relevant to the aim of the study
C	21	studies with small number of patients (less than 100) or selected patient series
D	3	interim analysis

Of 10 publications and one abstract analysed only two represented randomized clinical trials.

The abstract was not included in classification and grading.

Overview of new studies

Radiotherapy in early stages (I–II) disease

Overview 1 (after the list of references)

The literature shows that:

- In patients with favourable prognostic factors (stage I, grade 1, myometrial invasion <50 per cent, age below 60 years) there is no indication for postoperative radiotherapy. With surgery alone disease free survival is about 95 per cent.
- Postoperative radiotherapy in stage I reduces locoregional recurrence rate significantly compared to surgery alone but has no impact on overall survival.
- The only randomized trial reported on postoperative external radiotherapy in patients stage I, with unfavourable prognostic factors (grade 3, myometrial invasion >50 per cent, clear cell carcionoma), shows a significantly reduced local recurrence rate but no survival benefit compared to surgery alone. There is a great need for more randomized studies.

Radiotherapy in inoperable or recurrent uterine cancer

Overview 2 (after the list of references)

The literature shows that:

- Patients with uterine cancer, not operable due to bad medical conditions, can be treated with radiotherapy alone with a five years survival of 60 per cent.

Literature

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
C	1/715	–	–	**1/715**
P	2/1 025	–	–	**2/1 025**
R	2/500	3/602	2/604	**7/1 706**
Total	**5/2 240**	**3/602**	**2/604**	**10/3 446**

Conclusions and comments

Primary surgery for operable uterine cancer has become routine treatment since the introduction of surgical staging.

- There is a fairly good evidence that there is no need for adjuvant radiotherapy in patients with good risk uterine cancer. ([6]R3, [10]P1).
- There is a fairly good evidence that adjuvant radiotherapy reduces the relapse rate in high risk patients but has no impact on survival. ([3]C1).
- There is a substantial documentation showing that medically inoperable patients and patients with locally recurrent uterine cancer can be treated with radiotherapy alone with curative effect. ([1]R3, [4]R2, [7]R1, [8]R1).

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Overview 1 *Uterine cancer. Radiotherapy in early stage (I, II) disease.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Creutzberg 2000 [3] C	Value of adj RT in high risk pts **A:** Surgery + RT, 46 Gy **B:** Surgery only Not complete surgical staging (acc to FIGO)	1990–97 St I, high risk pts (gr 1, >50% m.i.; grade 2 and 3) A 354 pts B 361 pts
Greven 1998 [5] R	Value of vaginal BRT after EBRT **A:** Surgery + EBRT, 45 Gy **B:** Surgery + EBRT, 45 Gy + BRT, 17–50 Gy Complete surgical staging (acc to FIGO)	1983–93 St I, II A 173 pts B 97 pts
Irwin 1998 [6] R	EBRT vs EBRT + BRT vs BRT as adj therapy **A:** Surgery **B:** Surgery + EBRT, 40–41 Gy **C:** Surgery + EBRT same as B + BRT **D:** Surgery + BRT Complete surgical staging (acc to FIGO)	1984–88 St I, all risk groups A 228 pts B 97 pts C 217 pts D 8 pts
Roberts 1998 [11] C	Value of adj RT in intermediate risk pts **A:** Surgery **B:** Surgery + RT, 50 Gy Complete surgical staging (acc to FIGO)	Stage IB, IC, IIA, IIB, intermediate risk pts A 200 pts B 190 pts
Paulsen 1996 [10] P	No adj. RT to low risk patients Not complete surgical staging (acc to FIGO)	1986–88 St I, low risk (grade 1 and 2, <50% myometrial invasion) 641 pts

BRT: brachytherapy; CSS: cancer specific survival; DFS: disease free survival; EBRT: external beam radiotherapy; LRR: local recurrence rate; mgh: milligramhours; m.i.: myometrial invasion; NED: no evidence of disease; ns: no significant; OS: overall survival; PFI: progressionfree interval; pts: patient(s); RT (in this overview RT/EBRT denotes radiotherapy to pelvis, unless the target volume is otherwise specified): radiotherapy; y: year(s);

Results	Conclusion/Comments
Act. **OS%** **LRR% at 5 y** A 81 4 B 85 ns 14 p=0.001	Well performed trial. Adjuvant RT had no impact on OS. Relapses in vagina could be effectively treated with RT in 85%. **C1**
follow-up median 5 y **Pelvic control rate %** A 96 B 94 ns	The authors conclusion: vaginal BRT unnessesary when external therapy is given. **R2**
OS% **DFS% at 5 y** A 90 84 B 79 77 C 82 ns 77 ns 12 pts had grade 3–4 bowel complications in group C.	Very selected patent material. Distant metastases occured more frequently in pts who got adj RT. No difference in LRR or OS between the groups. **R3**
Act. **OS% at 3 y** A 89 B 96 ns	Local recurrence in 12 pts gr A, 3 pts gr B. As secondary treatment successful, no difference in OS. Abstract.
OS% **DFS% at 5 y** 96 93 Vaginal recurrence rate 7%. 15/17 pts with vaginal recurrence alive NED 5 y after salvage treatment.	Adjuvant therapy is not needed for low risk patients as secondary treatment can cure most of vaginal recurrencies. **P1**

The table continues on the next page

Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Carey 1995 [2] P	Treatment outcome in low and high risk pts **A:** Low risk Surgery **B:** High risk Surgery + RT, 40–45 Gy Not complete surgical staging (acc to FIGO)	1982–86 St I A 227 pts: gr 1–2, < 50% m.i.; B 157 pts: gr 1–2, > 50% m.i.; gr 3
Fishman 1996 [4] Case control Study R	Treatment outcome: inoperable and operable pts **A:** BRT, inoperable pts **B:** Surgery BRT= Heyman paching, 6000–12 600 mgh	1975–92 St I–II A 54 pts, medically inoperable B 108 pts St I mean age in group A 76 years mean age in group B 70 years St II mean age in group A 70 years mean age in group B 66.5 years
Maingon 1996 [9] R	Preoperative radiotherapy Preop. BRT to pts with low risk. Preop. BRT + EBRT, 40 Gy to pts with high risk.	1972–93 St I–II 83 pts with low risk (grade 1, 2, no cervical involvement) 87 pts with high risk (grade 3, cervical involvement)

Results	Conclusion/Comments
DFS% at 5 y A 95 B 81	No need for RT in low risk patients. Severe or life-treatening late RT-related side-effects in 6 pts in gr B. **P1**
Act. **CSS% OS% at 5 y** Stage I A 80 30 B 98 88 Stage II A 88 24 B 100 85 Medium survival, m: Stage I Stage II A 37 50 B 75 79	The difference in survival for inoperable and operable patients is due to intercurrent diseases. RT alone is a well tolerated and effective treatment for medically in operable pts.
OS% DFS% St IA 83 82 St IB 79 79 St II 83 81 OS at 5 y: low risk 82% high risk 83%	Randomized studies are needed to establish if preoperative RT has any place in treatment of operable uterine cancer. **R2**

Overview 2 *Uterine cancer. Radiotherapy in inoperable or recurrent uterine cancer.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Kucera 1998 [8] R	HDR BRT alone in medically inoperable patients HDRBRT: 34 Gy to uterus 7 Gy to vagina	1981–92 St I 220 pts, medically inoperable
Knocke 1997 [7] R	BRT alone in inoperable patients	1981–92 St I–III 280 pts
Ackerman 1996 [1] R	RT in recurrent uterine cancer RT: 55–65 Gy	1983–89 54 pts Previous treatment: Surgery alone 32 pts Surgery + adj RT 22 pts

Adj: adjuvant; BRT: brachytherapy; DFS: disease free survival; HDR BRT: high dose rate brachytherapy; OS: overall survival; pts: patient(s); RT (in this overview RT/EBRT denotes radiotherapy to pelvis, unless the target volume is otherwise specified): radiotherapy; y: year(s)

Results	Conclusion/Comments
OS% DFS% at 5 y 57.7 85.4 The calculated risk for severe late complications was 4.6% at 5 y.	In stage I radiotherapy can give high DFS in inoperable patients. Interesting material of RT alone for pts with severe medical conditions. High mortality in intercurrent diseases. **R1**
OS% DFS% at 5 y 52 76 The calculated risk for severe late complications was 5.2% at 5 y.	High DFS with RT alone in inoperable patients. Well performed retrospective analysis. **R1**
DFS% at 5 y 38	Local recurrence in uterine cancer can be successfully treated with RT. Authors conclusion is, that by routine adjuvant RT to low risk patients only 3–4% gain in survival. **R3**