

A Systematic Overview of Radiation Therapy Effects in Uterine Cancer (Corpus Uteri)

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Acta Oncologica Vol. 42, No. 5/6, pp. 557–561, 2003

A systematic review of radiation therapy trials in several tumour types was performed by The Swedish Council of Technology Assessment in Health Care (SBU). The procedures for evaluation of the scientific literature are described separately (Acta Oncol 2003; 42: 357–365). This synthesis of the literature on radiation therapy for uterine cancer is based on data from one randomized study. Moreover, data from two prospective studies and seven retrospective studies were used. In total, 10 scientific articles are included, involving 3 446 patients. The results were compared with those of a similar overview from 1996 including 13 597 patients. The conclusions reached can be summarized as:

- There is fairly good evidence that there is no need for adjuvant radiotherapy in patients with good risk uterine cancer.
- There is fairly good evidence that adjuvant radiotherapy reduces the relapse rate in high-risk patients but has no impact on survival.
- There is substantial documentation showing that medically inoperable patients and patients with locally recurrent uterine cancer can be treated with radiotherapy alone with curative effect.

Received 7 May 2003

Accepted 3 June 2003

Endometrial cancer is the most common gynaecologic malignancy in Sweden. In the year 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% of cases occur before the age of 40 years. According to the latest results from the Cancer Registry of Sweden, the 5-year survival rate for all stages was 75.2% for women diagnosed in 1964–1966 and 83.4% for women diagnosed in 1993–1995.

The most common histopathological type of tumour is adenocarcinoma, representing 75% of all cases. Numerous observations suggest that endometrial cancer has a hormonal aetiology.

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 Gynaecology and Obstetrics) introduced surgical staging (peritoneal wash-

ings, total hysterectomy, pelvic and para-aortic lymph node sampling). This staging implies a primary operation excluding the use of preoperative radiotherapy. During the past two decades 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 sole treatment modality. Treatment has changed since the 80s and surgery is becoming the primary treatment for most for uterine cancer patients. Still, patients not suitable for primary surgery because of poor general condition or patients with advanced-stage tumours can be cured by radiotherapy. According to the latest Annual Report (volume 23), 72% of all patients are surgically staged.

According to the latest Annual Report, clear cell carcinomas and seropapillary carcinomas have the poorest prognosis of all histopathological subtypes, with 51.0% and 45.5% 5-year survival, respectively, which can be compared

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with a 76.3% overall survival for all uterine adenocarcinomas.

Lymph node 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, according to the latest Annual Report, about two-thirds of patients 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 2 randomized studies, 1 prospective study, 48 retrospective studies and 4 others. The studies included 13 597 patients.

Conclusions

- Endometrial cancer is a radiosensitive tumour. In early decades, when primary surgery was not used, 69% of the patients were cured by radiotherapy.
- During the 1970s it was shown that combined radiotherapy and surgery gave better results.
- There is agreement that patients with tumours in stage I should be treated with primary surgery. There is some controversy about whether patients with poorly differentiated tumours should be given preoperative radiotherapy.
- Radiotherapy alone can successfully be used in patients who are inoperable because of 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% to less than 1%. Patients with favourable prognostic factors have a low risk for vaginal metastases and withholding radiotherapy is therefore justified.
- Postoperative external radiotherapy improves survival in patients with unfavourable prognostic factors.
- It can be assumed that most patients with uterine cancer will continue to be referred for some form of radiotherapy.

Discussion

In 1986 FIGO decided that endometrial cancer should be surgically staged and therefore the procedures previously used for determination of tumour stage are no longer applicable. FIGO acknowledges that there is perhaps 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 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 of 1986, the policy of treatment in uterine cancer is changing and primary radiotherapy is being 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 sole treatment method.

Literature

The articles on which the conclusions in the previous 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
M	–	–	–	–
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

M = meta-analysis; C = controlled clinical trial; P = prospective trial; R = retrospective study; L = literature review; O = other studies.

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-analyses, epidemiologic studies such as case-control studies, cohort studies, prospective studies and retrospective studies. A supplementary search was made in the Cochrane Library.

Primarily, 82 Abstracts concerning uterine cancer were reviewed. Another two recently published studies were added, making a total of 84 Abstracts. 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

Overview 1

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

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results			Conclusion/comments
Creutzberg 2000 (3) C	Value of adj. RT in high-risk pts A: Surgery + RT, 46 Gy B: Surgery only Not complete surgical staging (according to FIGO)	1990–1997 St I, high-risk pts (gr 1, > 50% m. i.; grade 2 and 3) A: 354 pts B: 361 pts	Act. A B	OS% 81 85 ns	LRR%, at 5 y 4 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% of cases. C1
Greven 1998 (8) R	Value of vaginal BRT after EBRT A: Surgery + EBRT, 45 Gy B: Surgery + EBRT, 45 Gy + BRT, 17–50 Gy Complete surgical staging (according to FIGO)	1983–1993 St I, II A: 173 pts B: 97 pts	Follow-up median 5 y Pelvic control rate% A: 96 B: 94 ns			The authors' conclusion: vaginal BRT unnecessary when external therapy is given. R2
Irwin 1998 (1) 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 (according to FIGO)	1984–1988 St I, all risk groups A: 228 pts B: 97 pts C: 217 pts D: 8 pts	A B C	OS% 90 79 82 ns	DFS%, at 5 y 84 77 77 ns	Highly selected pt material. Distant metastases occurred more frequently in pts who were given adj. RT. No difference in LRR or OS between the groups. R3
Roberts 1998 (9) C	Value of adj. RT in intermediate-risk pts A: Surgery B: Surgery + RT, 50 Gy Complete surgical staging (according to FIGO)	Stage IB, IC, IIA, IIB, intermediate-risk pts A: 200 pts B: 190 pts	Act. A B	OC% at 3 y 89 96 ns		Local recurrence in 12 pts gr A, 3 pts gr B. As secondary treatment successful, no difference in OS. Abstract
Paulsen 1996 (2) P	No adj. RT to low-risk patients Not complete surgical staging (according to FIGO)	1986–1988 St I, low risk (grade 1 and 2, < 50% myometrial invasion) 641 pts		OS% 96	DFS%, at 5 y 93	Adjuvant therapy is not needed for low-risk patients, as secondary treatment can cure most vaginal recurrences. P1
Carey 1995 (10) 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 (according to FIGO)	1982–1986 St I A: 227 pts: gr 1–2, < 50% m.i.; B: 157 pts: gr 1–2, > 50% m.i.; gr 3	A B	DFS% at 5 y 95 81		No need for RT in low-risk patients. Severe or life-threatening late RT-related side effects in 6 pts in gr B. P1
Fishman 1996 (5) Case control Study R	Treatment outcome: inoperable and operable pts A: BRT, inoperable pts B: Surgery BRT = Heyman patching, 6000–12 600 mgh	1975–1992 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	Act. Stage I A B Stage II A B Medium survival, m: Stage I Stage II A B	CSS% 80 98 88 88 100 37 75	OS% at 5 y 30 88 24 85 50 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 inoperable pts. R2

Overview 1 (Continued)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Maingon 1996 (11) R	Preoperative radiotherapy Preop. BRT to pts with low risk Preop. BRT+EBRT, 40 Gy to pts with high risk	1972–1993 St I–II 83 pts with low risk (grade 1, 2, no cervical involvement) 87 pts with high risk (grade 3, cervical involvement)	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 whether preoperative RT has any place in the treatment of operable uterine cancer. R2

Abbreviations: BRT = brachytherapy; CSS = cancer-specific survival; DFS = disease-free survival; EBRT = external beam radiotherapy; LRR = local recurrence rate; mgh = milligram hours; m.i. = myometrial invasion; NED = no evidence of disease; ns = not significant; OS = overall survival; PFI = progression-free interval; pts = patient(s); RT (in this overview RT/EBRT denotes radiotherapy to the pelvis, unless the target volume is otherwise specified) = radiotherapy; y = year(s).

C 21 Studies with a small number of patients (less than 100) or selected patient series

D 3 Interim analyses

Of 10 publications and one Abstract analysed, only 2 represented randomized clinical trials. The Abstract was not included in classification and grading.

OVERVIEW OF NEW STUDIES

Radiotherapy in early stages (I–II)

See Overview 1 for a description of the trials, trial results and conclusion

The literature shows that:

- In patients with favourable prognostic factors (stage I, grade 1, myometrial invasion < 50%, age below 60

years) there is no indication for postoperative radiotherapy. With surgery alone, disease-free survival is about 95%.

- 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 stage I patients with unfavourable prognostic factors (grade 3, myometrial invasion > 50%, clear cell carcinoma) shows a significantly reduced local recurrence rate but no survival benefit compared to surgery alone. More randomized studies are greatly needed.

Radiotherapy in inoperable or recurrent uterine cancer

See Overview 2 for a description of the trials, trial results and conclusion

Overview 2

Uterine cancer. Radiotherapy in inoperable or recurrent endometrial cancer

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Kucera 1998 (7) R	HDR BRT alone in medically inoperable patients HDRBRT: 34 Gy to uterus 7 Gy to vagina	1981–1992 St I 220 pts, medically inoperable	OS% DFS%, at 5 y 57 85 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
Knocke 1997 (6) R	BRT alone in inoperable patients	1981–92 St I–III 280 pts	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
Ackerman 1996 (4) R	RT in recurrent uterine cancer RT: 55–65 Gy	1983–1989 54 pts Previous treatment: Surgery alone: 32 pts Surgery + adj. RT: 22 pts	DFS%, at 5 y 38	Local recurrence in uterine cancer can be successfully treated with RT. Authors' conclusion is that with routine adjuvant RT to low-risk patients, there is only a 3–4% gain in survival. R3

Abbreviations: 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 the pelvis, unless the target volume is otherwise specified) = radiotherapy; y = year(s).

The literature shows that:

- Patients with uterine cancer, not operable owing to bad medical condition, can be treated with radiotherapy alone with a 5-year survival of 60%.

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 fairly good evidence to suggest that there is no need for adjuvant radiotherapy in patients with good risk uterine cancer ((1) R3, (2) P1).

There is fairly good evidence that adjuvant radiotherapy reduces the relapse rate in high-risk patients but has no impact on survival ((3) C1).

There is substantial documentation showing that medically inoperable patients and patients with locally recurrent uterine cancer can be treated with radiotherapy alone with curative effect ((4) R3, (5) R2, (6) R1, (7) R1).

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