External radiotherapy increases the risk of death from early stage endometrial cancer

PM Tebeu[1,5], GY Popowski[2], HM Verkooijen[3], F Ludicke[4], M Usel[3], C Bouchardy[3], AL Major[1,4]

Departments of [1]Obstetrics and Gynaecology University Hospitals (UH) Geneva, UH [5] Yaounde, Cameroon,

[2]Radiation Oncology UH Geneva

[3] Geneva Cancer Registry,

[4] Fondation pour Recherches Medicales, Geneva

Epidemiology of endometrial cancer

- 15-20 new cases per 100 000 women each year
- Fourth cancer in women after breast, lung and colon
- First genital tract cancer in developed countries
- Third genital tract cancer in developing countries

FIGO 1971

Stage I:	Ia (less than 8 cm)
	Ib (8 cm and more)
Stage II:	Corpus + cervix
Stage III:	Outside uterus
Stage IV:	IVa (bladder / rectal mucosa)
	IVb : distal

1988 FIGO

Stage I:	Ia (epithelial invasion only) Ib (myometral invasion <50%) Ic (myometral invasion >=50%)
Stage II:	corpus + cervix IIa (glands) IIb (stroma)
Stage III:	IIIa (serosa, adnex, peritoneal cytology) IIIb (vagina) IIIc (nodes)
Stage IV:	IVa (bladder / rectal mucosa), IVb distal

Modality of adjuvant Radiotherapy For Endometrial Cancer

1. Brachytherapy= Curietherapy: Intravaginal disposal

2. Teleradiotherapy= External radiotherapy: External beam

Radiotherapy reduces the risk of locoregional recurrence from endometrial cancer

Study	RT	NO	Yes
Dobbie et al.(1953)	Brahy	11%	2.5%
Graham et al.(1971)	Brahy	12%	0%
Morris et al.(1969)	Brachy	6%	2%
Aalders et al.(1980)	B+Exter	7%	2%
Creutzberg al.(2000)	Exter	14%	4%

Adverse effects of external radiotherapy

- Urinary problems: incontinence, cystitis, bladder instability.
- Digestive problems: bowel movement, cramps, diarrhoea.
- Cure from relapse: 5% if previous radiation *Vs* 20-30% if not (Ackerman1996, Sears1997, Salazar 1977).
- Survival after relapse: 43%if no previous radiotherapy *Vs* 65% if not (Creutzberg 2003).

Identical survival

Radiotherapy	No	Yes
Carl et al (1995)(myoinvasion >1/3)	77%	77%
Carl et al (1995)(myoinvasion <1/3)	88%	88%

Little survival advantage (1-4%)

Radiotherapy	NO	Yes	Benefit
Ayhan et al (2002)	92%	96%	4%
Straugh et al (2002)	98%	100%	2%
Straugh et al (2003)	90%	92%	2%
Rittenberg et al (2002)	94%	95%	1%

Little survival disadvantage (2-6%)

Radiotherapy	NO	Yes	Fatality
Fanning et al (1987)	98%	96%	4%
Aalders et al (1980)	91%	89%	2%
Creutzberg et al (2002)	85%	81%	4%
Creutzberg et al (2003)	77%	71%	6%

Shortcomings-1

	Stage	TypeRT	Grade
• Carl et al (1995)(High rish)	I(<33%)	Extern	NOS
• Carl et al (2002)(Low risk)	I(>33%)	Extern	NOS
• Ayhan et al (2002)	Ic,G3	E/Brachy	Ic, Nos
• Straugh et al (2002)	Ic	E/Brachy	NOS
• Straugh et al (2003)	Ib	E/Brachy	NOS
• Rittenberg et al (2002)	Ic	E+B vs B	NOS

Shortcomings-2

	Stage	RT	Grade
Fanning et al (1987)	G2(I<33%)	E/Brachy	2
Aalders et al (1980)	I	E+B vs B	NOS
Creutzberg et al (2002,2003)	IcG1/2,IbG2/3	E	------

Objective

What is the real impact of different adjuvant modalities of Adjuvant Radiotherapy on the survival of different sub stages of stage I endometrial cancer?

Type of study

- Population based study
- Retrospective cohort study (Geneva tumour registry) : all incident cases followed up until death.
- All cases reviewed and re-staged

Patients : inclusion

- Period of diagnosis 1980 - 1996
- Area: Swiss Canton of Geneva
- Identification: Geneva Tumour Registry
- Variables: sociodemographic factors, diagnosis, stage, ATCD, treatment within 6 months, survival

Patients: exclusion

- Total of patients: 731
- Other tumours: 74 (5 years before - 6 months after)
- Absence of surgical staging: 87
- Sarcomas: 41
- Stage II,III-IV : 122
- Missing information on staging / histology/Radiotherapy:15
- Stage Ia: 95
- Final inclusion: 297

297 patients finally included

Radiotherapy	No	Brachy	E+/-B
IbG1/2	61	75	26
IbG3+Ic	31	19	85

R-1: 5-year specific survival

Radiotherapy	All	IbG1/2	IbG3,Ic
No radiotherapy	94.0	96.6	88.3
Brachytherapy	94.5	97.2	84.2
External+/-Brachy	88.2	88.5	84.2

- Log rank test: No statistical difference found

R2: Risk of death for all patients

Hazard ratios's to die from cancer

(adjusted on : age, Grade , myomatrial invasion)

Radiotherapy	Survival(%)	Adjusted HR (95% CI)	
NO	94.0	1	
Curie	94.5	1.5	(0.4 - 5.4)
E+/- Curie	88.2	4.1*	(1.2 - 13.6)

* = P< 0.05

R3:Risk of specific death for IbG1/2

Hazard ratios's to die from cancer
(For stage IbG1/2 adjusted on age)

Radiotherapy	Survival(%)	Adjusted HR	(95% CI)
NO	96.6	1	
Curie	97.2	1.7	(0.2 - 13.3)
E+/- Curie	88.5	11.0 *	(1.4 - 85.0)

* = P< 0.05

R4: Risk of specific death for IbG3+IC

Hazard ratios's to die from cancer

(For stage IbG3 + IC adjusted on age)

Radiotherapy	Survival(%)	Adjusted HR (95% CI)	
NO	88.4	1	
Curie	84.2	1.9	(0.4 - 9.4)
E+/- Curie	84.2	2.6	(0.7 - 10.1)

Conclusions

- Study with few shortcomings
- For stage IbG1/2, survival altered by External Radiotherapy.
- For stageIbG3+Ic, same survival for any modality of Radiotherapy
- External radiotherapy is not reasonable for stage I endometrial cancer.
- Still unknown: By which mechanism radiotherapy might induce metastases?

Aknowledgements

- Dept of Obstetrics-Gynecology HUG
- Dept of Radiation Oncology HUG
- Geneva Tumour Registry - IMSP - University of Geneva
- Geneva League Against Cancer
- Cameroon - Swiss Cooperation