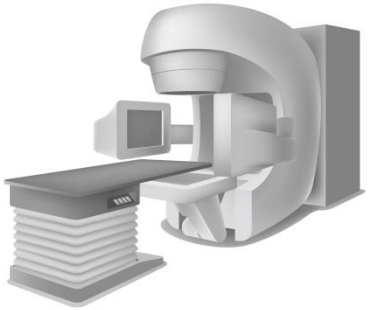
Pelvic palliative radiotherapy for gynecological cancers – present state of knowledge and pending research questions to answer



Esten S. Nakken

MD PhD

Division of Cancer Medicine

Oslo University Hospital

Oslo University Hospital

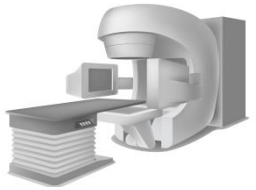
Gynecological cancers and radiotherapy

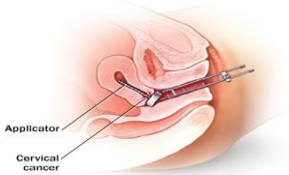
- Include cancers originating from endometrium, ovary, cervix, vulva and vagina

- Radiotherapy used for curative treatment of
  - Locally advanced cervical cancer
  - Locally advanced vulvar/vaginal cancer unfit for surgery
  - Vaginal relapse of endometrial cancer

- Radiotherapy used for palliation to all tumor groups
  - In the pelvic region
  - To all other potential metastatic sites in the body

- Palliative radiotherapy can be given as
  - External beam radiotherapy (EBRT)
  - Brachytherapy





Aim of palliative radiotherapy treatment

- Providing lasting and timely symptom relief
  - Pain
  - Bleeding
  - Vaginal discharge
  - Obstructive symptoms
- Preventing such symptoms from occuring
- Secondary aim: Tumor regression
- Minimizing:
  - side effects
  - visits to the cancer centre
  - resource utilization

⇨ ***Improved quality of life (QoL) until death***

Considerations

- Life prognostication
  - Different tools exist
  - Tend to be over optimistic[1,2]
  - Not all studies support this[3]
- Performance status
- Previous treatment
  - Response to earlier treatment
  - Acute toxicity of earlier treatment
  - Normal tissue tolerance
- Other treatment options
  - Chemotherapy
  - Surgery
- Patient information and preferences
  - Patient understanding of the intent of therapy seems to affect the aggressiveness of end of life care[4,5]

[1]Chow, *Int J Radiat Oncol Biol Phys*, 2005
[2]Fairchild, *Support Care Cancer*, 2014
[3]Onsrud, *Gynecol Oncol*, 2001

[4]Chen, *J Clin Oncol*, 2013
[5]Greer, *J Clin Oncol*, 2012

Palliative compared to curative radiotherapy

- Total dose
  - *Lower dose* to reduce toxicity and shorten treatment time
- Dose per fraction
  - *Hypofractionation* (fewer and larger fractions e.g. 10 Gy x 3 instead of 3 Gy x 10)
  - Increased risk of late toxicity less important beacuse of short expected lifespan
- Treatment volumes
  - Limited to symptom causing tissue (reduced toxicity)
  - Areas at risk of micrometastases should be omitted
- Treatment technique
  - Shortened and simplified planning process

<u>Toxicity in pelvic radiotherapy</u>:

Acute: Nausea, enteritis, proctitis, anorexia, cystitis, vulvovaginitis, dermatitis

Late: Bowel and bladder dysfunction, infertility, sexual dysfunction, microfractures

Radiobiology

- 3 Gy x 10 ≠ 10 Gy x 3
- EQD2 (2 Gy-per-fraction-equivalent-dose)

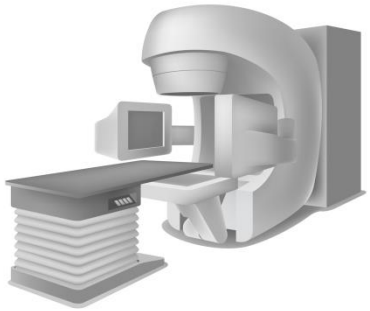
	3 Gy x 10	**10 Gy x 3**
Tumor and acute responding tissue	32,5 Gy	50 Gy
Late responding tissue	36 Gy	78 Gy

Hypofractionation (e.g. 10 Gy):

Pros: Conveniant for patient, cost effective for health care system, effective symptom control

Cons: More late toxicity

Current practice



- 7 Gy x 3, 1-2 weeks interval
- 8 Gy x 1
- 10 Gy x 3, 4 weeks interval
- 4 Gy x 5
- **3 Gy x 10**
- 3 Gy x 13
- 2,5 Gy x 20
- 2 Gy x 25
- 1,8 Gy x 28
- 2 Gy x 30

Does current practice reflect current knowledge?

Common belief: Better and longer palliation is achieved by higher radiation doses and more fractionated schedules, e.g. 45-50 Gy in 20-25 fractions

Current knowledge

Author, Year	Design	Radiation (Gy) x # of fractions	No of pts	Partial or complete improvement %			Toxicity
				Bleeding	Pain	Discharge	
Boulware, 1979	Observational retrospective	10 Gy x 1	86	45	45		9 % acute
		10 Gy x 2, 3-4 weeks interval	58	85	59		17 % late
		10 Gy x 3, 3-4 weeks interval	20	100	63		
Hodson, 1983	Observational retrospective	10 Gy x 3, 4 weeks interval	27	100	100	100	14 % late
Halle, 1986	Observational retrospective	10 Gy x 1-3, 4 weeks interval or at recurrence	42	90	44		7 % acute 12 % severe late
Spanos, 1987 (RTOG 7905)	Prospective						45 % late GI
Adelson, 1987	Observational retrospective	10 Gy x 3, 4 weeks interval	42	71	55		14 % late GI grade 2-4
May, 1990	Observational retrospective	Varying fr schemes	48				
Spanos 1993 (RTOG 8502)	Randomized	3,7 Gy x 2 x 2 (48 hrs) with either 2 weeks (1) or 4 weeks (2) interval	136	97	68		7 % late
Corn, 1994	Observational retrospective	Median fr size 2,5 Gy Median dose 44 Gy	33	85	83		3 % late GI grade 2-4
Onsrud, 2001	Observational retrospective	10 Gy x 1	10	88	0	36	42 % acute GI grade 1-2, 8 % late GI grade 2-4
		10 Gy x 2, 4 weeks interval	34				
		10 Gy x 3, 4 weeks interval	2				
Yan, 2011	Observational retrospective	7 Gy x 3 (0-7-21 days)	51	92	76		12 % late

Old, small sized, retrospective

Current knowledge

Author, Year	Design	Radiation (Gy) x # of fractions	No of pts	Partial or complete improvement %			Toxicity
				Bleeding	Pain	Discharge	
Boulware, 1979	Observational retrospective	10 Gy x 1	86	45	45		9 % acute
		10 Gy x 2, 3-4 weeks interval	58	85	59		17 % late
		10 Gy x 3, 3-4 weeks interval	20	100	63		
Hodson, 1983	Observational retrospective	10 Gy x 3, 4 weeks interval	27	100	100	100	14 % late
Halle, 1986	Observational retrospective	10 Gy x 1-3, 4 weeks interval or at recurrence	42	90	44		7 % acute 12 % severe late
Spanos, 1987 (RTOG 7905)	Prospective	10 Gy x 3, 4 weeks interval w/misonidazole					
Adelson, 1987	Observational retrospective	10 Gy x 3, 4 weeks interval	42	71	55		14 % late GI grade 2-4
May, 1990	Observational retrospective	Varying fr schemes	48				
Spanos 1993 (RTOG 8502)	Randomized	3,7 Gy x 2 x 2 (48 hrs) with either 2 weeks (1) or 4 weeks (2) interval	136	97	68		7 % late
Corn, 1994	Observational retrospective	Median fr size 2,5 Gy Median dose 44 Gy	33	85	83		3 % late GI grade 2-4
Onsrud, 2001	Observational retrospective	10 Gy x 1	10	88	0	36	42 % acute GI grade 1-2, 8 % late GI grade 2-4
		10 Gy x 2, 4 weeks interval	34				
		10 Gy x 3, 4 weeks interval	2				
Yan, 2011	Observational retrospective	7 Gy x 3 (0-7-21 days)	51	92	76		12 % late

Mostly 10 Gy fractions

Current knowledge

Author, Year	Design	Radiation (Gy) x # of fractions	No of pts	Partial or complete improvement %			Toxicity
				Bleeding	Pain	Discharge	
Boulware, 1979	Observational retrospective	10 Gy x 1	86	45	45		9 % acute
		10 Gy x 2, 3-4 weeks interval	58	85	59		17 % late
		10 Gy x 3, 3-4 weeks interval	20	100	63		
Hodson, 1983	Observational retrospective	10 Gy x 3, 4 weeks interval	27	100	100	100	14 % late
				90	44		7 % acute 12 % severe late
							45 % late GI
				71	55		14 % late GI grade 2-4
May, 1990	retrospective	Varying fr schemes	48				
Spanos 1993 (RTOG 8502)	Randomized	3,7 Gy x 2 x 2 (48 hrs) with either 2 weeks (1) or 4 weeks (2) interval	136	97	68		7 % late
Corn, 1994	Observational retrospective	Median fr size 2,5 Gy Median dose 44 Gy	33	85	83		3 % late GI grade 2-4
Onsrud, 2001	Observational retrospective	10 Gy x 1	10	88	0	36	42 % acute GI grade 1-2, 8 % late GI grade 2-4
		10 Gy x 2, 4 weeks interval	34				
		10 Gy x 3, 4 weeks interval	2				
Yan, 2011	Observational retrospective	7 Gy x 3 (0-7-21 days)	51	92	76		12 % late

Good response rates:
Bleeding 70-100 %
Pain 45-80 %

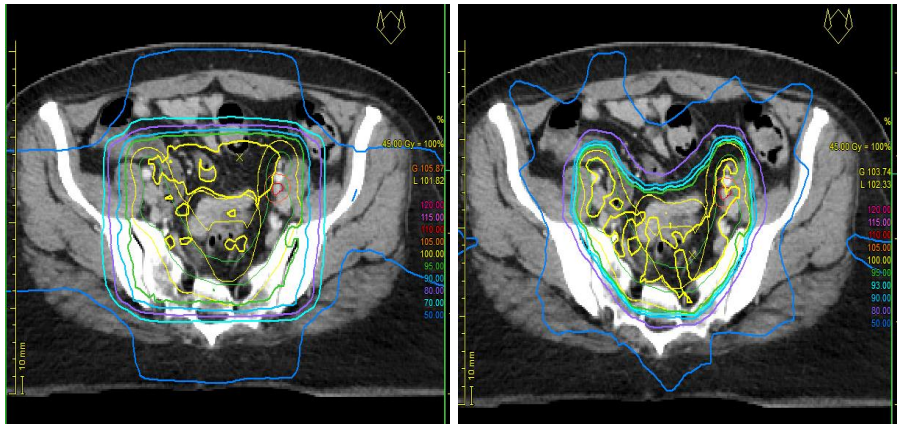
Current knowledge

Author, Year	Design	Radiation (Gy) x # of fractions	No of pts	Partial or complete improvement %			Toxicity
				Bleeding	Pain	Discharge	
Boulware, 1979	Observational retrospective	10 Gy x 1	86	45	45		9 % acute
		10 Gy x 2, 3-4 weeks interval	58	85	59		17 % late
		10 Gy x 3, 3-4 weeks interval	20	100	63		
Hodson, 1983	Observational retrospective	10 Gy x 3, 4 weeks interval	27	100	100	100	14 % late
	Observational	10 Gy x 1-3, 4 weeks					7 % acute
							12 % severe late
(RTOG 7905)	Prospective	w/misonidazole					45 % late GI
Adelson, 1987	Observational retrospective	10 Gy x 3, 4 weeks interval	42	71	55		14 % late GI grade 2-4
May, 1990	Observational retrospective	Varying fr schemes	48				
Spanos 1993 (RTOG 8502)	Randomized	3,7 Gy x 2 x 2 (48 hrs) with either 2 weeks (1) or 4 weeks (2) interval	136	97	68		7 % late
Corn, 1994	Observational retrospective	Median fr size 2,5 Gy Median dose 44 Gy	33	85	83		3 % late GI grade 2-4
Onsrud, 2001	Observational retrospective	10 Gy x 1	10	88	0	36	42 % acute GI grade 1-2, 8 % late GI grade 2-4
		10 Gy x 2, 4 weeks interval	34				
		10 Gy x 3, 4 weeks interval	2				
Yan, 2011	Observational retrospective	7 Gy x 3 (0-7-21 days)	51	92	76		12 % late

Fairly high GI toxicity (poorly documented)

Other characteristics of the studies

- Old radiation **techniques** (whole pelvis)



- **Time to optimal symptom control** not documented, duration poorly documented
- No use of **PROM**s (Patient Reported Outcome Measures)
- Causes of failure to return to monthly treatment not well documented, **poor follow-up**
- **Toxicity** not consistently documented

Possible conclusions from the studies (?)

- Documentation of effect on **bleeding** > pain > vaginal discharge
- **10 Gy** up to 3 fractions maybe not optimal due to high attrition rates and GI toxicity
- **Late bowel/urinary toxicity** is seen after 6-12 months[1,2,3]
- **Duration of effect**
  - 2 Gy x 25 reported median duration of effect 7,2 months[4]
  - 10 Gy fr reported median progression free interval of 6 months[1]
  - Median duration 4 months with diff fractionation regimens[5]
- **GI obstruction** is more effectively treated with radiotherapy in the large bowel than small bowel[4]

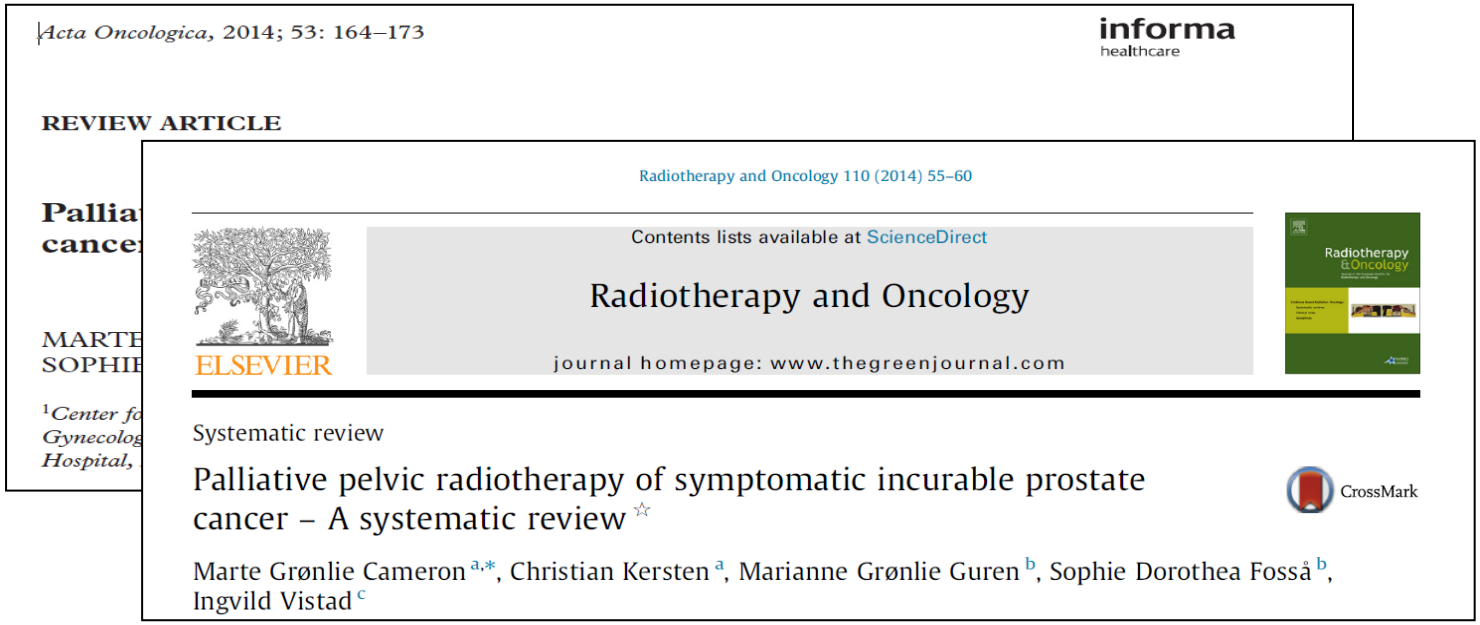
[1]Onsrud, *Gynecol Oncol*, 2001
[2]Adelson, *Int J Radiat Oncol Biol Phys*, 1987
[3]Halle, *Int J Radiat Oncol Biol Phys*, 1986
[4]May, *Gynecol Oncol*, 1990
[5]Corn, *Cancer*, 1994

Current knowledge

Author, Year		Design	Radiation (Gy) x # of fractions	No of pts	Partial or complete improvement %			Toxicity	
					Bleeding	Pain	Discharge		
Boulware, 1979		Observational retrospective	10 Gy x 1	86	45	45		9 % acute	
			10 Gy x 2, 3-4 weeks interval	58	85	59		17 % late	
			10 Gy x 3, 3-4 weeks interval	20	100	63			
Hodson, 1983		Observational retrospective	10 Gy x 3, 4 weeks interval	27	100	100	100	14 % late	
Halle, 1986		Observational retrospective	10 Gy x 1-3, 4 weeks interval or at recurrence	42	90	44		7 % acute late	12 % severe
Spanos, 1987	(RTOG 7905)	Prospective	10 Gy x 3, 4 weeks interval w/misonidazole					45 % late GI	
Adelson, 1987		Observational retrospective	10 Gy x 3, 4 weeks interval	42	71	55		14 % late GI grade 2-4	
May, 1990		Observational retrospective	Varying fr schemes	48					
Spanos 1993	(RTOG 8502)	Randomized	3,7 Gy x 2 x 2 (48 hrs) with either 2 weeks (1) or 4 weeks (2) interval	136	97	68		7 % late	
Corn, 1994		Observational retrospective	Median fr size 2,5 Gy Median dose 44 Gy	33	85	83		3 % late GI grade 2-4	
Onsrud, 2001								acute GI grade 1-2, 8 % GI grade 2-4	
			10 Gy x 3, 4 weeks interval	2					
Yan, 2011		Observational retrospective	7 Gy x 3 (0-7-21 days)	51	92	76		12 % late	

Corn et al: EQD2 > 37 Gy increased probability of complete palliative response (e.g. 2.5 Gy x 14). Ovarian cancer.

Evidence of radiotherapy as effective palliation in other pelvic soft tissue tumors



Acta Oncologica, 2014; 53: 164–173

informa
healthcare

REVIEW ARTICLE

Palliat
cancer

MARTE
SOPHIE

[1]Center fo
Gynecolog
Hospital,

Radiotherapy and Oncology 110 (2014) 55–60

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Systematic review

Palliative pelvic radiotherapy of symptomatic incurable prostate cancer – A systematic review ☆

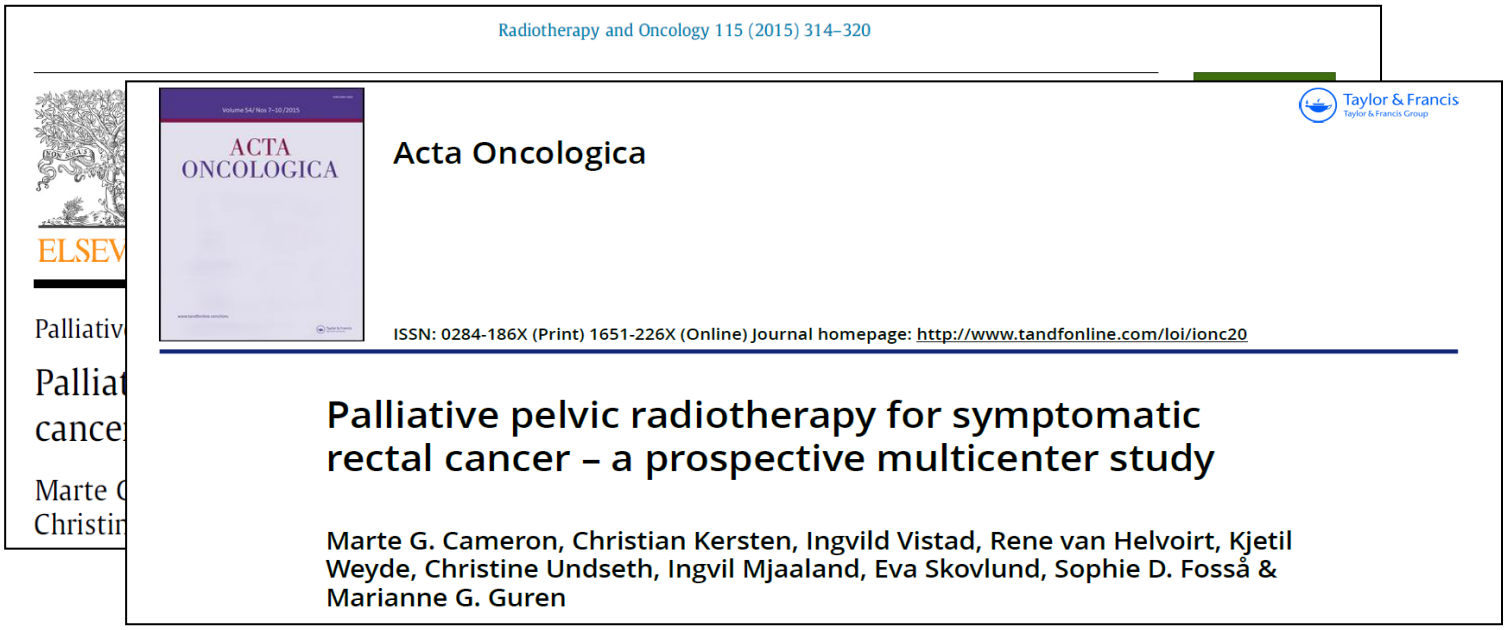
CrossMark

Marte Grønlie Cameron [a,*], Christian Kersten [a], Marianne Grønlie Guren [b], Sophie Dorothea Fosså [b], Ingvild Vistad [c]

<u>Common conclusion</u>:

- Shortcomings of studies
- Indication that palliative radiotherapy is effective
- No evidence of dose-response or one preferred fractionation scheme
- Need further research

Evidence of radiotherapy as effective palliation in other pelvic soft tissue tumors



Radiotherapy and Oncology 115 (2015) 314–320

ELSEV

Palliativ

Palliat

cance

Marte C

Christin

ACTA ONCOLOGICA

Acta Oncologica

Taylor & Francis

Taylor & Francis Group

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: http://www.tandfonline.com/loi/ionc20

Palliative pelvic radiotherapy for symptomatic rectal cancer – a prospective multicenter study

Marte G. Cameron, Christian Kersten, Ingvild Vistad, Rene van Helvoirt, Kjetil Weyde, Christine Undseth, Ingvil Mjaaland, Eva Skovlund, Sophie D. Fosså & Marianne G. Guren

<u>Common conclusion</u>:

- Palliative pelvic radiotherapy is effective in the range of 27-39 Gy
- No significant toxicity
- Stable or improved QoL
- Limited survival in rectal cancer patients suggests simpler fractionation schedules

Pending questions

- Find prognostic models that are clinically useful to guide treatment decisions

- Appropriate radiation fractionation regimens
  - No RCT exists comparing fractionation schemes

- «Optimal» rate of palliative RT use near the end of life
  - Over-use or under-use? Quality indicator?
  - Use of RT last 14-30-60 days of life?
  - < 10 % of remaining days receiving radiotherapy?[1]
  - Increased use of multidisciplinary teams

Jones, *CA Cancer J Clin*, 2014

Different treatment schedules for different gynecological cancers?

- Ovary
  - Might come to RT with a longer life expectancy. Benefit of prolonged fractionation schemes?

- Vulva
  - locally advanced disease without distant metastases benefit of higher total dose (despite advanced age at presentation) due to severe symptoms and difficult reirradiation?

Conclusions

- Little evidence exists
- RT is an effective loco-regional palliative modality in patients with gynecological malignancies
  - **Pain 45-80 % response**
  - **Bleeding 70-100 % response**
- Assessment of
  - site and extent of disease
  - patients' symptoms
  - anticipated lifespan
  - risk of toxicity
  - patients' preferences

⇨ Guide treatment decision

- Poor evidence for different fractionation schemes
- Hypofractionation probably as effective as protracted schemes, but GI toxicity a problem
- Further research is warrented