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Locally advanced cervical cancer & HIV - Radiotherapy challenges in management in Africa

Hannah Simonds, Stellenbosch University

Cervix Cancer Education Symposium, January 2019, South Africa

Challenges to delivering healthcare in Africa

- Low GDP expenditure in health care
- Competing priorities – HIV, malaria, TB, neonatal mortality, NCDs-heart disease, poverty

- User/patient fees –

unaffordable for many

- Lack of infrastructure
- Lack of drug availability
- Lack skilled personnel

Late diagnosis

- Limited access to care – geographic, transport, Financial constraints
- Lack of public health educational resources
- Limited screening programs
- Competing illness -HIV
- Social pressures
- Traditional beliefs
- Neighbourhood myths
- Failure at primary healthcare level
- Failure at tertiary healthcare level

- Staging
- Chemoradiation
- Outcomes

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STAGING

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Staging

Vital importance to establish cART history

- Adherence
- CD4 count
- Viral load **

Frequently anaemia-related issues at presentation (Mangena. et al)

Renal function – tenovofir

Liver function tests - cART

Urgent referral to start cART if newly diagnosed before any oncological intervention

Challenges prior to CRT in Africa

- General condition
- Younger patients – fertility issues/ young children/ social circumstances
- Access to cART – not readily available due to stock-outs/ access to clinics/ user fees
- Stigma
- Availability of radiotherapy resources and waiting lists….

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TREATMENT

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Chemoradiation

- Principles are to treat as per standard protocols
- Evaluate CD4 count and viral load
- Previously hesitant at CD4 counts <200
- Currently management considers PS, compliance, viral load, additional infectious diseases (PTB common in Western cape)
- At what viral load to exclude chemotherapy? <1000; <5000; < 30 000?

External beam radiotherapy resources

- 50% of African countries have no or little access to radiotherapy
- IAEA Acceptable practice

1 machine/ 250 000 population

- Not available in any single country in Africa

Fig. 1. Availability of teletherapy units on the African continent is shown.

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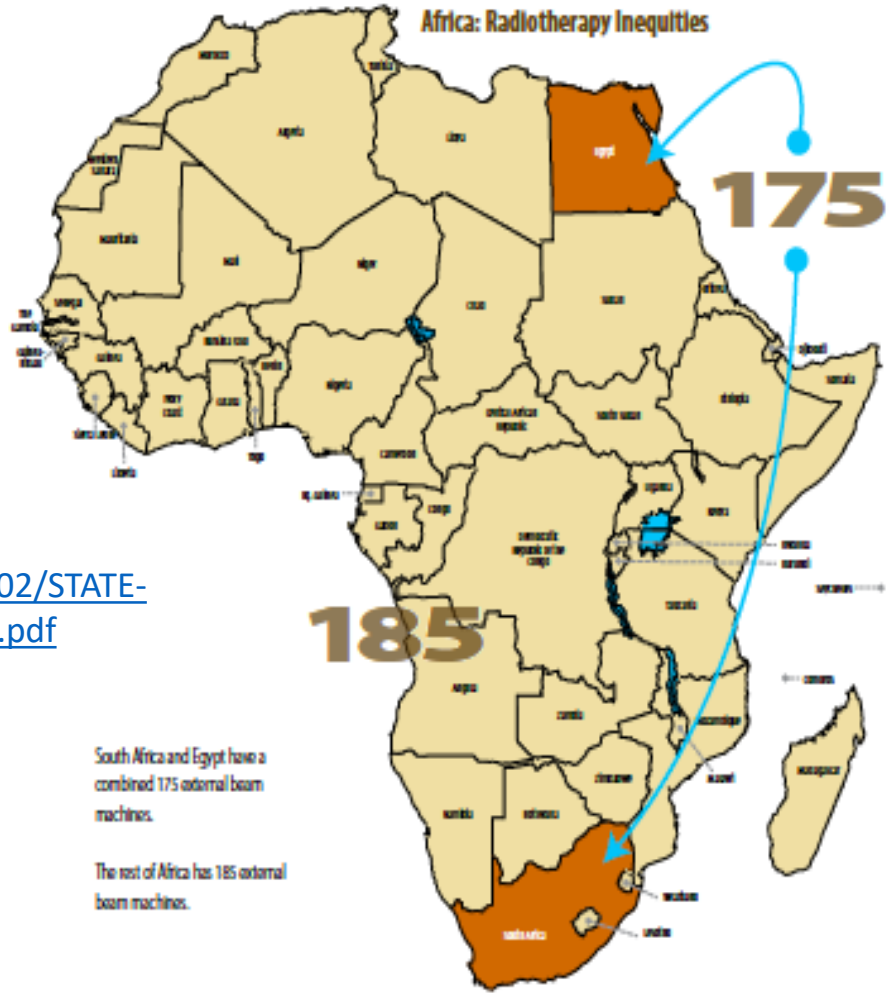

Figure 3: Inequities of Radiotherapy Equipment distribution in Africa

[Boyle et al.-pri.org/wp-content/uploads/2017/02/STATE-OF-ONCOLOGY-IN-AFRICA-2015-WEB-VERSION.pdf]

Toxicity

Variable evidence for toxicity on radiotherapy

Older studies report higher skin toxicities with the use of Co60 and AP/PA fields

Studies using MV EBRT have shown increased haematological toxicity, use of transfusions and treatment interruptions in HIV positive patients

Others have shown no difference in acute toxicity if the patients are well-controlled on cART.

Haematologic toxicities by HIV status

	HIV Status						
	Positive		Negative		Total		
Toxicity	n	%	n	%	n	%	*P*
Leucopenia	10	27.7	47	26.6	57	26.8	0.839
Thrombocytopenia	2	5.5	3	1.7	5	2.35	0.199
Anemia	23	63.8	71	40.1	94	44.1	0.01*
Neutropenia	7	19.4	15	8.5	22	10.3	0.02*

*$P \leq 0.05$ considered significant.

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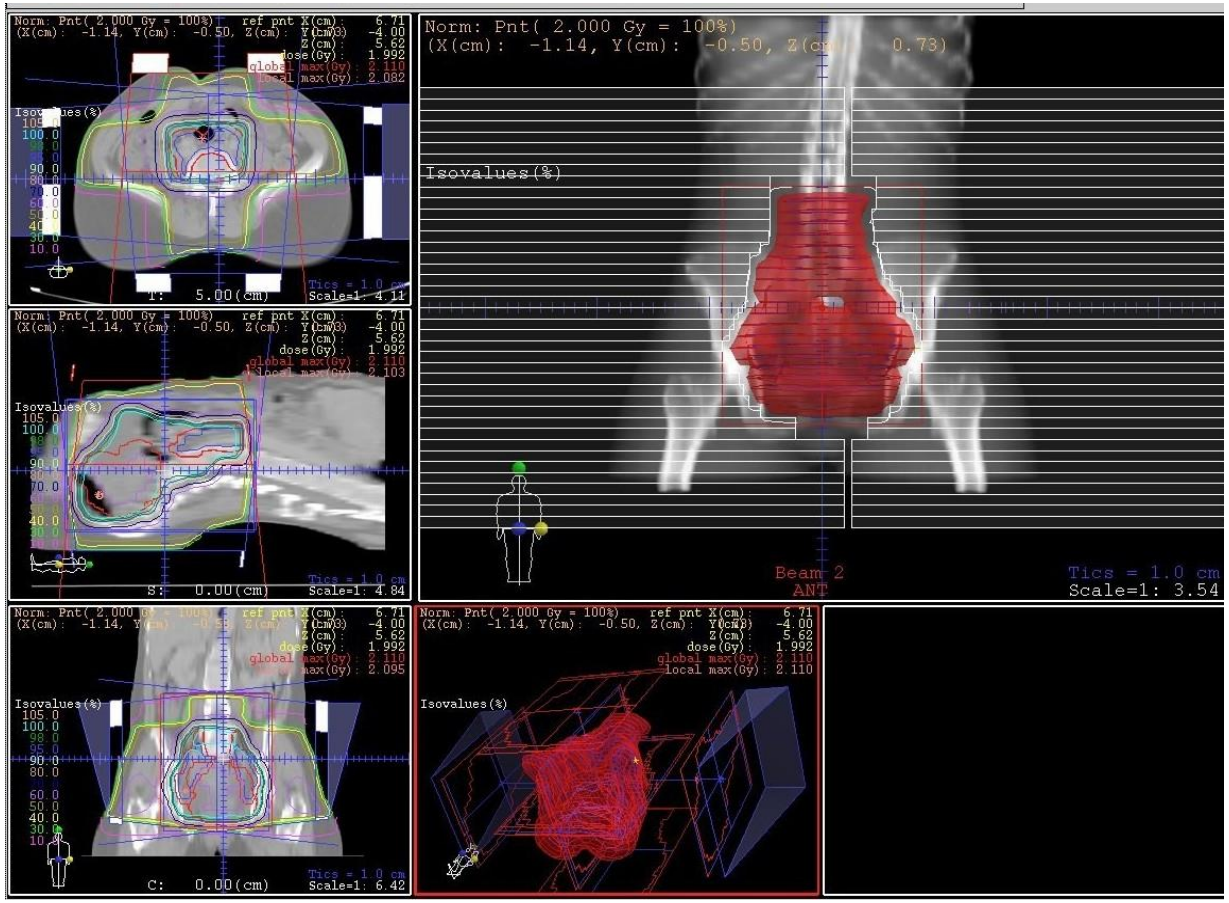
3-D conformal techniques to shield OAR

- Careful volume delineation to ensure no geographic miss and reduce dose to OAR



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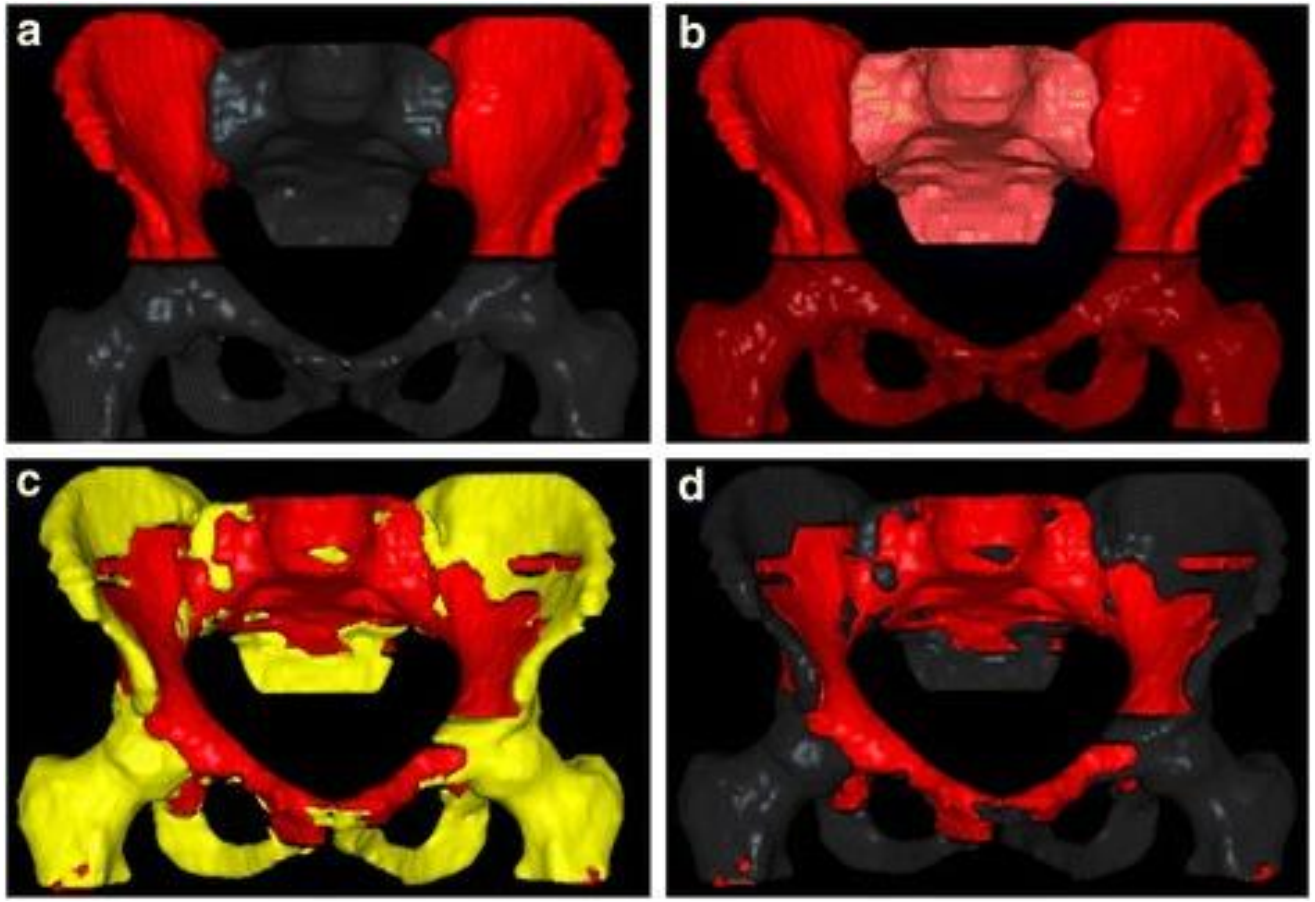
Bone marrow as an OAR

- Incorporate the use of PET-CT in volume delineation.

- Advanced RT techniques e.g. VMAT to reduce toxicities if available – but many centres are reliant of Co60, low energy LINACS, no conformal planning options



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OUTCOMES

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Completion of treatment

- Dryden-Peterson et al.
  - No difference in ability to complete RT treatment between HIV pos and negative patients in Botswana.
  - Only 48% in each group completed >79EQD2 Gy.
  - In most cases this was due to lack of brachytherapy.
  - No difference in toxicities
- Grover et al.
  - Cohort 2013-2015
  - No difference in completion of chemotherapy/ RT or toxicity
  - 76% HIV+ and 68% HIV neg completed EBRT and HDR
- Simonds et al.
  - Older cohort (2007-2012)
  - 74% HIV+ vs 84% HIV negative patients completed RT - more likely to complete HDR

Dryden-Peterson et al

Table 2. Treatment Delivered and Complications

Treatment or Toxicity	Group, No. (%) HIV Infection	No HIV Infection	Overall	*P*
Treatment intent				.32
Curative	187 (81.0)	84 (87.5)	271 (82.9)	
Palliative	36 (15.6)	11 (11.5)	47 (14.4)	
Not recorded	8 (3.5)	1 (1.0)	9 (2.8)	
Therapy received for participants treated with curative intent*				
Radiotherapy completion				.21
Received recommended dose (> 79 Gy [EQD2])	85 (48.0)	40 (48.0)	125 (48.5)	
Received minimally adequate dose (71.2-79 Gy [EQD2])	42 (23.7)	12 (14.8)	54 (20.9)	
Received inadequate dose (≤ 71.2 Gy [EQD2])	50 (28.3)	29 (35.8)	79 (30.6)	
Median radiation received (IQR), Gy [EQD2]				
Total	78.4 (68.3-79.8)	78.4 (62.9-79.8)	77.4 (67.3-79.8)	.83
External beam	50.0 (45.8-50.0)	50.0 (50.0-50.0)	50.0 (46.0-50.0)	.038
Brachytherapy	29.8 (17.9-29.8)	29.8 (14.2-29.8)	29.8 (16.7-29.8)	.79
Delayed treatment (> 8 weeks)†	14 (11.0)	9 (17.3)	23 (12.8)	.32
Median treatment duration (IQR)†	6.6 (5.9-7.6)	6.6 (6.0-7.6)	6.6 (6.0-7.6)	.77
Received any brachytherapy	144 (81.4)	66 (81.5)	210 (81.4)	1.0
Completed brachytherapy (> 29 Gy EQD2)	110 (62.1)	48 (59.3)	158 (61.2)	.68
Received of concurrent cisplatin‡	114 (84.4)	46 (73.0)	160 (80.8)	.080
Received recommended treatment (> 79 Gy and at least one dose of cisplatin)‡	66 (48.9)	29 (46.0)	95 (48.0)	.76
Received minimally adequate treatment (> 71.2 Gy and at least one dose of cisplatin)‡	94 (69.6)	37 (58.7)	131 (66.2)	.15
Treatment response				.39
Complete or nearly complete	112 (63.3)	52 (64.2)	164 (63.6)	
Residual tumor	22 (12.4)	7 (8.6)	29 (11.2)	
Unknown	43 (24.3)	22 (27.2)	65 (25.2)	

Dryden-Peterson et al. J Clin Oncol 34:3749-3757

Grover et al

Treatment characteristics			
No. of chemo cycles received	4 (3-5)	4 (2-4)	.45
No. of chemotherapy cycles completed			.40
1	10 (10.4)	4 (8.5)	
2	8 (8.3)	9 (19.2)	
3	22 (22.9)	9 (19.2)	
4	29 (30.2)	15 (31.9)	
5	27 (28.1)	10 (21.3)	
≥4	56 (58.3)	25 (53.2)	.56
Received EBRT dose ≥45 Gy	95 (99.0)	45 (95.7)	.21
Received brachytherapy dose ≥20 Gy	73 (76.0)	32 (68.1)	.31
EQD2 (Gy)			
Median (IQR)	79.8 (74-79.8)	79.8 (68.8-79.8)	.90
Mean (standard deviation)	75.6 (8)	74.7 (10)	
Treatment duration (d)	45 (41-52)	48 (42-54)	.34
Tumor response			.39
Complete	44 (45.8)	20 (42.6)	
Partial	12 (12.5)	3 (6.4)	
Not available	40 (41.7)	23 (51.1)	

Grover et al, Int J Radiation Oncol Biol Phys,
Vol. 101, No. 1, pp. 201e210, 2018

Simonds et al

Table 2
Treatment characteristics by HIV status.

Variable	HIV-negative n = 421	HIV-positive n = 71	Total n = 492	p-Value
Standard fractionation	369 (87.6%)	64 (90.1%)	433 (88.0%)	0.55
Hypofractionation	52 (12.4%)	7 (9.9%)	59 (12.0%)	
Median EQD2 Gy (interquartile range)	77.7 Gy (75.0–80.8)	76.3 Gy (69.3–81.5)	77.7 Gy (75.0–80.9)	0.94
≥69.25 Gy EQD_2 total dose	356 (84.6%)	54 (74.1%)	410 (83.3%)	0.08
≥20 Gy HDR[a]	333 (90.3%)	51 (79.7%)	384 (88.5%)	0.02*
Chemo 4 or more cycles[b]	252 (76.1%)	31 (58.5%)	283 (73.7%)	0.007*
1–3 cycles	79 (23.9%)	22 (41.5%)	101 (26.4%)	
Transfusion given[c]	173 (42.3%)	45 (66.2%)	218 (45.7%)	<0.001*

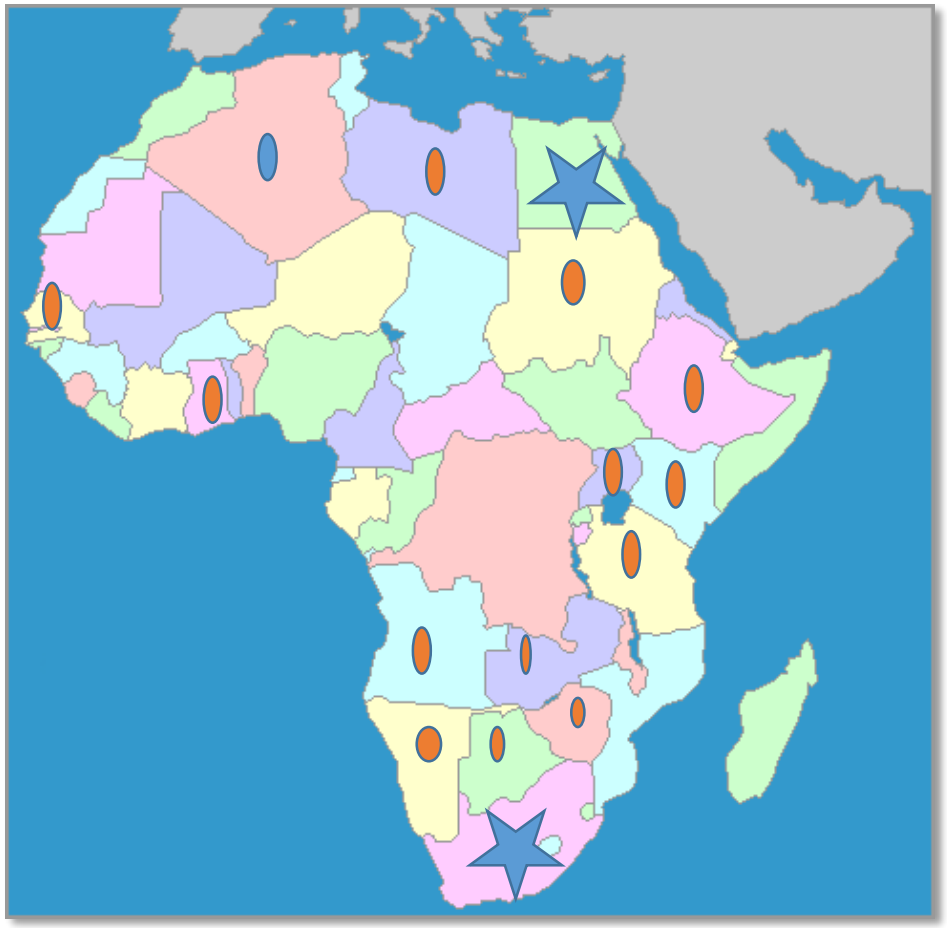
H.M. Simonds et al. / Gynecologic Oncology 151 (2018) 215–220

Evidence for early response

Table 5. Factors Associated With Partial Response Versus Complete Response at Six Weeks

Variable	OR	95% CI	*P*
HIV status			
Negative	1.00	Referent	
Positive	1.71	0.85-3.36	.135
FIGO stage			
IB1-IIIA	1.00	Referent	
IIIB	2.41	1.45-4.00[a]	.001[a]
Age group, y			
<40	1.00	Referent	
40-49	0.87	0.44-1.69	.67
50-59	0.68	0.35-1.33	.26
≥60	0.51	0.22-1.17	.11
Completion of EBRT, Gy			
≥45	1.00	Referent	
<45	1.18	0.36-3.89	.78
Completion of HDR, Gy			
≥18	1.00	Referent	
<18	3.13	1.28-7.61	.012[a]
Completion of chemotherapy			
≥4 Cycles	1.00	Referent	
<4 Cycles	0.62	0.36-1.06	.08

Brachytherapy access in Africa



https://dirac.iaea.org/

DIRAC data

Region	Country	RT Centres	LDR Manual	LDR Remote	HDR Ir-192	HDR Co-60	Total
North Africa	5	113	1	8	13	12	34
Middle Africa	15	26	0	3	7	9	19
Southern Africa	4	50	2	0	14	8	22
Africa	24		3	11	34	29	**77 sources in Africa**

https://dirac.iaea.org/

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MORTALITY OUTCOMES

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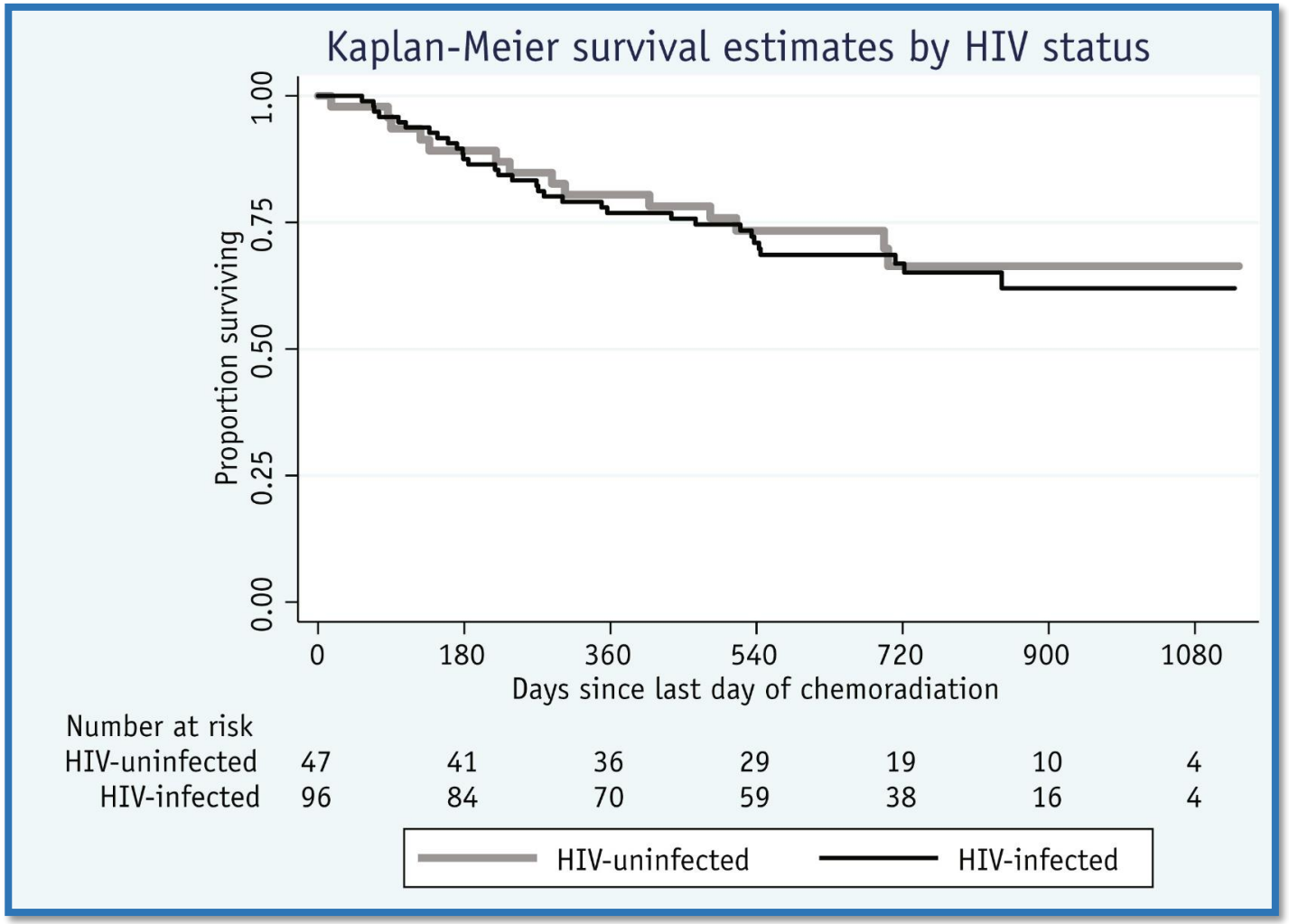
Associations of HIV and early mortality

Associations of HIV infection with overall mortality and cancer-specific mortality, overall and in patient subgroups

Ferreria et al. AIDS. 2017 February 20; 31(4): 523–53

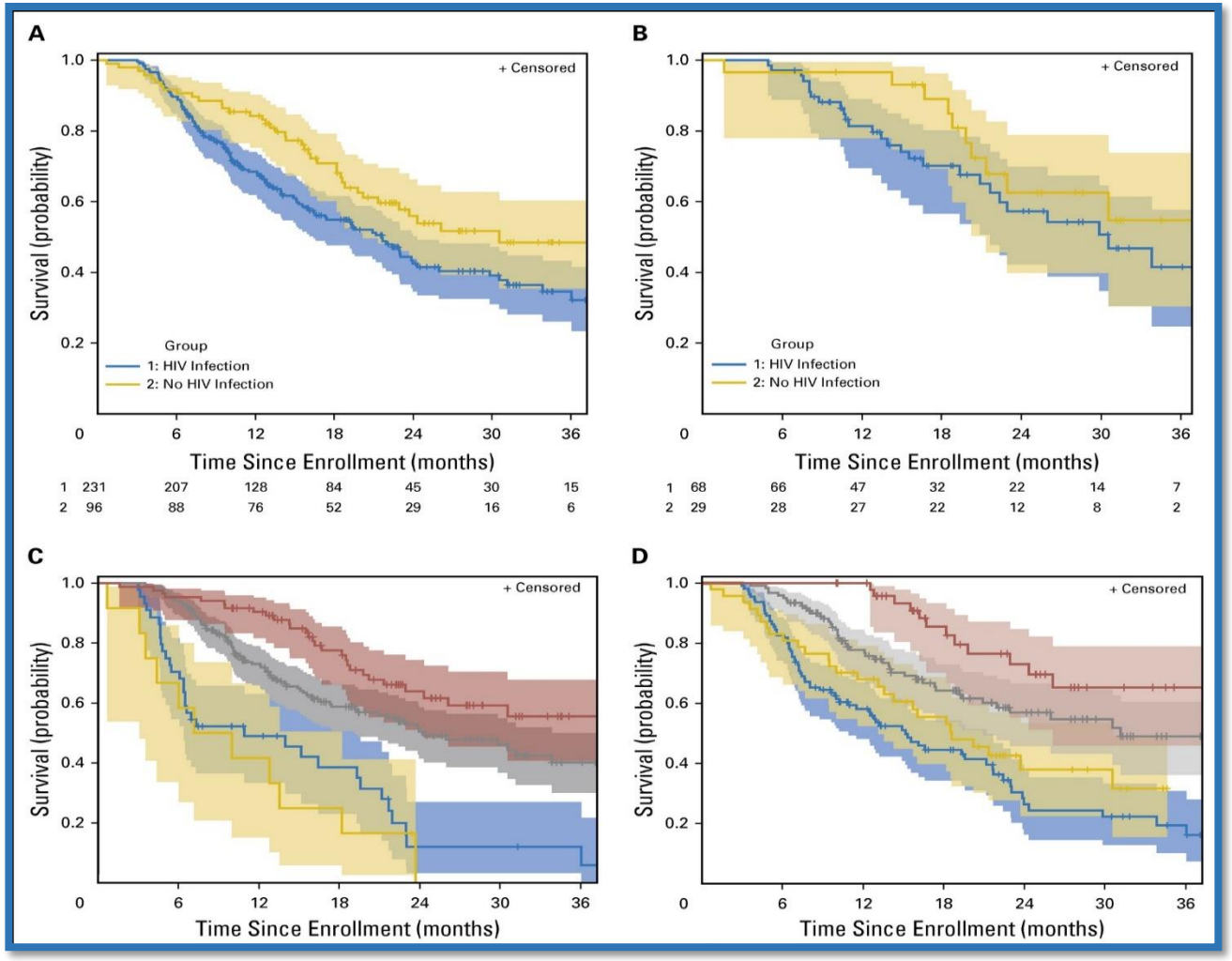
Patient group	Overall mortality HR (95%CI)	Cancer-specific mortality HR (95%CI)
All patients, unadjusted	1.38 (1.02–1.87)	1.31 (0.94–1.82)
All patients, adjusted for clinical stage	1.29 (0.95–1.75)	1.18 (0.85–1.65)
Models stratified by cancer treatment		
Patients treated with surgery, unadjusted	8.70 (1.59–47.5)	--
Patients treated with radiation, adjusted for clinical stage and brachytherapy	1.22 (0.82–1.82)	0.96 (0.62–1.48)
Models stratified by follow-up time, adjusted for clinical stage *		
Early follow-up	0.97 (0.65–1.45)	0.99 (0.69–1.42)
Late follow-up	2.02 (1.27–3.22)	4.35 (1.86–10.2)

Overall Survival 2 years



Grover et al, Int J Radiation Oncol Biol Phys, Vol. 101, No. 1, pp. 201e210, 2018

Overall survival at 3 years



A = Overall cohort

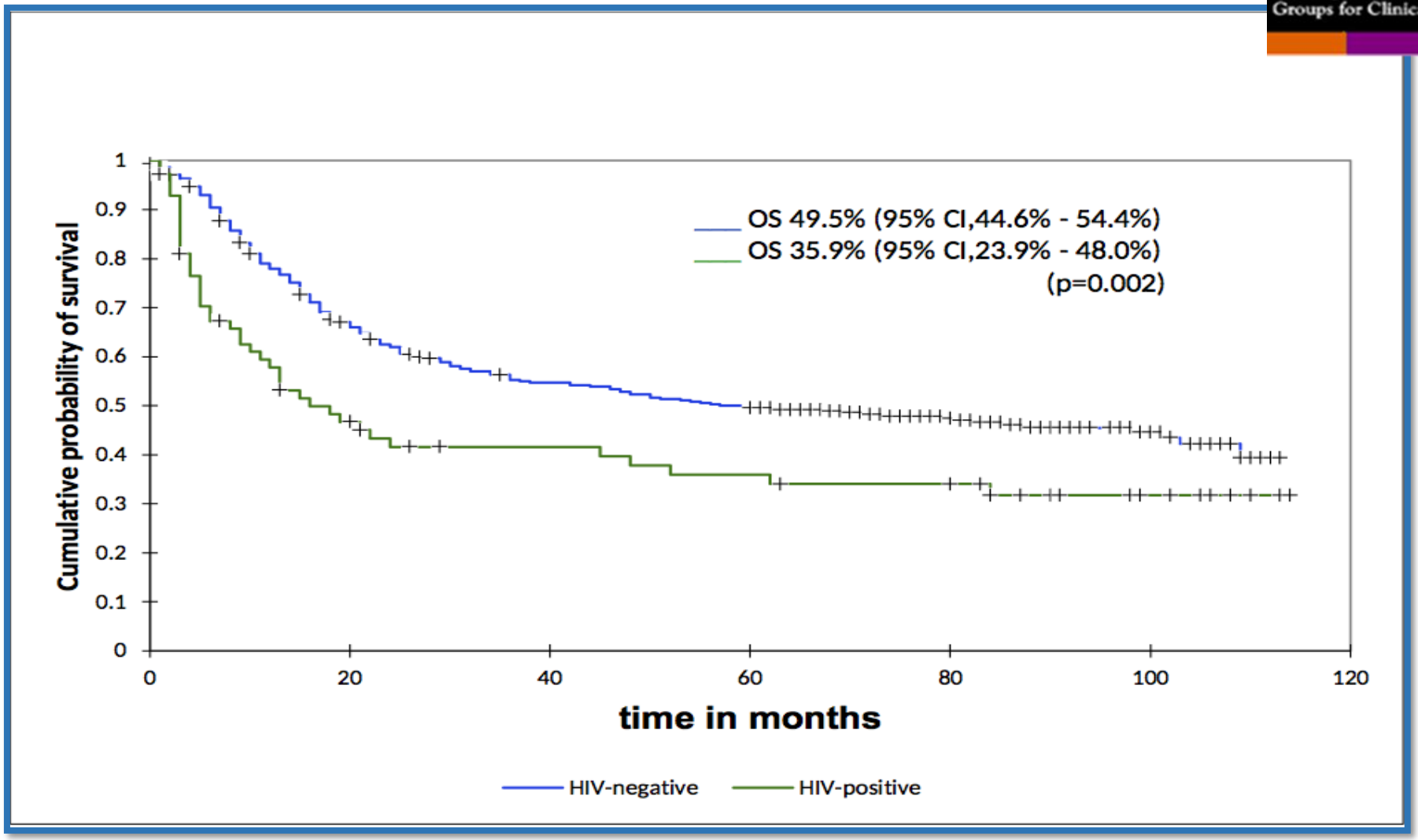
B= Completed curative intent treatment

C= Radical vs palliative

D = By stage

Dryden-Peterson et al. J Clin Oncol 34:3749-3757

Overall survival at 5 years



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Survival at 5 years –Stage and RT dose

Variable	HIV-negative	HIV-positive	Overall	p-value
Stages				
1Bi-IIIA				
5-years	**63.0%**	**46.3%**	61.5%	0.09
(95% CI)	(54.7-71.3%)	(18.5-74.1%)	(53.5-69.5%)	
IIIB				
5-years	**42.9%**	**32.9%**	41.3%	**0.02***
(95% CI)	(36.9-48.9%)	(19.6-46.2%)	(35.8-46.7%)	
≥69.25 GY EQD_2				
5-years	**52.1%**	**34.7%**	50.0%	**<0.01***
(95% CI)	(46.8-57.5%)	(20.8-48.6%)	(45.0-55.0%)	

Factors influencing all-cause mortality

Table 3
Predictors of all-cause mortality.

Variable	Hazard ratio	95% CI	p-Value
HIV status			
Negative	Referent		
Positive	1.45	1.01–2.08	0.04*
Stage			
IB1-IIIA	Referent		
IIIB	1.50	1.10–2.05	0.01*
Hydronephrosis			
Absent	Referent		
Present	1.70	1.12–2.59	0.01*
Total EQD_2 dose			
>69.25 Gy	Referent		
<69.25	1.01	0.65–1.57	0.96
Chemotherapy			
≥4 cycles	Referent		
1–3	1.18	0.84–1.65	0.34
0	1.86	1.26–2.76	0.02*

* $p < 0.05$

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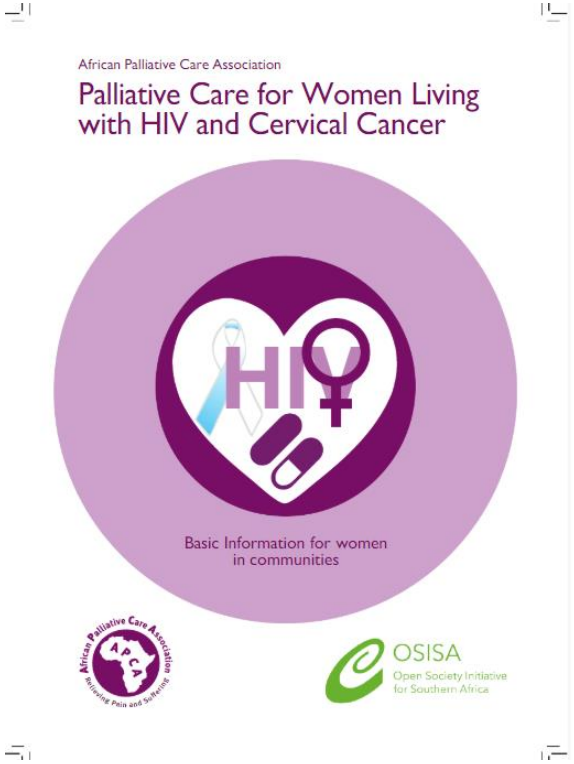
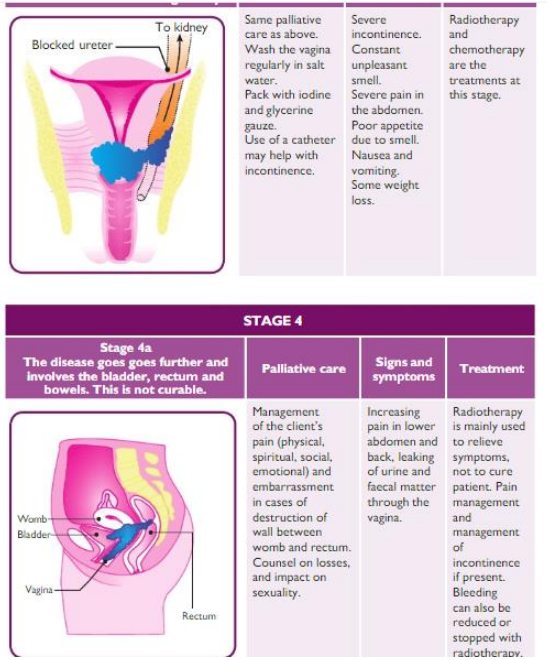
Palliative care

- For those who have locally advanced disease and poor PS/ renal dysfunction/ low CD4 counts
- Consider 40Gy in 15#; 10Gy x 3
- Palliative chemotherapy for those with PS0/1/2 and adequate immunocompetence –as for HIV-negative patient





Concluding thoughts

Collaborate with ID colleagues to maximize cART and encourage adherence

The roll-out of cART may reduce high risk HPV but as yet has no impact on ICC

Effective screening programs vital to diagnose early stage

Evidence suggests that treatment is related to increased toxicity in some centres. Improve RT techniques.

Overall survival is lower despite radical intent – HIV-infection may be related to more aggressive disease/ treatment may cause decreased immunocompetence post therapy.

Whenever possible treat as per HIV-negative patients