Gynecologic Cancer InterGroup Cervix Cancer Research Network

Cervix Cancer Education Symposium, February 2018



# Locally advanced disease & challenges in management

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## No disclosures









- Heterogenous group: Stage IB2/IIB to IVA disease
- Surgery, chemotherapy, radiation therapy, brachytherapy: treatment based on data vs availability vs tradition
- Challenges in staging and treatment: FIGO stage vs nodal involvement
- Strong improvements in techniques and outcomes
- Toxicity and quality of life impairment in relatively young women



Figure 1. Staging of uterine cervix carcinoma according to FIGO<sup>(3)</sup>.

## **Risk of lymph node metastases**



FIGO	Patients (n)		Lymphnoda	al involven	nent		100							
stage		Positive		Negative			100]						No (N=3364)	
		N	%	N	%	ing	80 -							
Total	5173	1161	22.4	4012	77.6	urvi.							Yes (N=953)	
Ia1	356	14	3.9	342	96.1	N N	60-						Not evaluated (N=745	58)
Ia2	238	23	9.7	215	90.3	tio	10							
Ib1	2687	460	17.1	2227	82.9	lod	40]							
Ib2	685	209	30.5	476	69.5	Pro	20							
IIa	486	140	28.8	346	71.2		20							
IIb	491	185	37.7	306	62.3		0							
IIIa	29	14	48.3	15	51.7		0	1	2		3	4	5	
IIIb	117	71	60.7	46	39.3				Ye	ars	after	r diagr	nosis	
IVa	28	16	57.1	12	42.9									
IVb	24	22	91.7	2	8.3									
Missing	32	7	21.9	25	78.1									

#### Quinn et al. 26th FIGO Annual Report 2006

#### Stage and lymph node involvement





Kidd et al. JCO 2010

#### Stage and lymph node involvement





MRI

PET-CT

#### Stage and lymph node involvement





MRI

**PET-CT** 

#### **Primary surgery vs radiotherapy**



#### 343 women, stage IB-IIA cervical cancer

	Surgery (n=17	/0)	Radiotherapy (n=167)			
	≪4 cm	>4 cm	≪4 cm	>4 cm 54		
Number of patients	115	55	113			
Mean (SD) age in years	51.8 (11.3)	46.1 (10.1)	55.2 (10.9)	50.0 (9.8)		
FIGO stage						
lb	107 (93%)	47 (85%)	99 (88%)	45 (83%)		
lla	8 (7%)	8 (15%)	14 (12%)	9 (17%)		
Positive lymphangiography	12 (10%)	12 (22%)	9 (8%)	13 (24%)		
Histological type						
Squamous	94 (82%)	44 (80%)	97 (86%)	45 (83%)		
Adenocarcinoma	18 (16%)	8 (15%)	13 (11%)	7 (13%)		
Small cells	3 (2%)	3 (5%)	3 (3%)	2 (4%)		
Postoperative						
radiotherapy	54%	84%				
Morbidity G2-3	30%	25%	12%	11%		



Time since treatment (months)

#### **Primary radiotherapy with chemotherapy**



Trial ID	even	ts pts.	even	ts pts.	0-E	Variance	Hazard Ratio (Fixed)
Trials of Chemoradiation v	radiot	herapy					
(a) Platinum-based CTRT							
Onishi44 (CDDP or CDBCA)	16	26	15	23	1.52	7.59	F-+
Pearcey <sup>43</sup> (CDDP)	53	130	60	129	-5.00	28.20	F+
GOG01236 (CDDP)	49	185	69	189	-12.90	29.38	► <b></b>
Chen <sup>23</sup> (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00	F
Chen <sup>23</sup> (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25	<b>⊢</b> ₊
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15	· · · · · · · · · · · · · · · · · · ·
GOG016526 (a) (CDDP)	8	26	12	24	-3.03	4.92	···
Cikaric47 (CDDP)	37	100	48	100	-8.02	21.12	
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91	
Gariapagaoglu <sup>48</sup> (CDDP)	9	22	8	22	0.70	4.23	<b>⊢</b> ₊ <b>_</b>
Lal <sup>50</sup> (CDDP)	14	94	12	86	0.62	6.49	⊢ <b>⊢</b> – – – – – – – – – – – – – – – – – – –
Sub-total	292	841	340	829	-29.89	157.23	-
(b) Non-platinum-based CT	RT						HR = 0.83, <i>F</i>
Thomas <sup>24</sup> (a) (FU)	24	57	32	58	-5.16	13.83	·····
Thomas <sup>24</sup> (b) (FU)	26	58	25	60	0.71	12.74	
Lorvidhaya <sup>25</sup> (a) (MMC FU)	40	233	59	242	-12.52	24.57	<b>⊢</b> +−−− <b>■</b> −−−−+−+
Lorvidhaya <sup>25</sup> (b) (MMC FU)	54	230	49	221	0.31	25.67	·····
Roberts <sup>49</sup> (MMC)	25	124	39	124	-8.39	15.92	··
GOG016526 (b) (FU)	11	27	12	24	-0.82	5.55	H
Sub-total	180	729	216	729	-25.87	98.28	HR = 0.77, F
Total	472	1,570	544	1,534	-54.56	251.54	HR = 0.81, F
Trials of CTRT + adjuvant ch	nemot	herapy	v radi	otherar	v		
SWOG87978,46 (CDDP FU)	28	135	54	133	-15.61	20.36	<b>⊢−−</b>

Control

Kantardzic <sup>45</sup> (CDDP BLM)	15	40	25	40	-7.74	9.74
Sub-total	43	175	79	173	-23.35	30.10

CTRT



## Primary chemoradiation and brachytherapy



- External beam radiotherapy combined with weekly Cisplatin 40 mg/m<sup>2</sup>, 5-6 cycles
- CT-based planning, 45-46 Gy in 1.8-2 Gy fractions
- 3-dimensional conformal treatment planning versus intensity modulated and volumetric arc techniques
- Simultaneous integrated boost to nodal disease (55-60 Gy)
- Image guided adaptive brachytherapy

#### **Better imaging, better techniques**







#### **3D CRT and IMRT**





NRG – RTOG Time-C trial presented at ASTRO 2016

- Randomised trial of IMRT vs 4-field pelvic radiotherapy
- IMRT reduces acute GI and GU toxicity at 5 wks
- IMRT improved QOL with regard to physical functioning

#### **Pro-CTCAE Results**



#### **EPIC Bowel Score**



#### Challenges





Tumor regression during treatment

#### Challenges





Organ motion depending on bladder and rectum filling

- Plan-of-the-day treatment schedules based on bladder filling - current
- Adaptive treatment by replanning (daily vs weekly) future

#### **Treatment results**







#### **Results: local control and survival**



#### **RetroEMBRACE** analysis, N=731

- EBRT plus cisplatin
- IMRT plus simultaneous boost 55-60 Gy
- Image guided brachytherapy



#### Locoregional recurrence **Overall Survival** Local control at 3-5 year 10 10 98%-98% (2 ev IB1-2 IGBT-group 0,8 0,8 Cummulative recurrence Cummulative Survival IIB 93%-91% 0,6 0.6 IIIB 79%-75% CBT-group 0.4 CBT-group 0,2 0.2 **Overall and cancer-spec** IGBT-group 0.07 0.0 log-rank: 0.000 log-rank: 0.000 74%-65% and 79-73% at no. at risk 12 24 36 48 60 (months) 60 (months) no, at risk 0 12 24 36 Conventional BT 27 17 37 19 29 22 21 19 Conventional BT 21 13 Image-guided BT 58 78 58 25 47 28 16 Image-guided BT

Fig. 1. Overall survival and pelvic recurrence rates by treatment group (CBT vs. IGBT).

Sturdza et al. Radiotherapy Oncology 2016; Rijkmans et al, Gynecol Oncol 2014

## Primary chemoradiation vs neoadjuvant chemo?





Benedetti-Panici JCO 2002; Kenter, IGCS 2016; Gupta et al, ESMO 2017





- Nodal involvement: surgery or radiotherapy boost?
- Para-aortic involvement: surgical sampling or PET-CT based? Risk based on pelvic nodal involvement?
- Control of distant disease ongoing trials
- Expensive and complicated techniques PET-CT, MRI, IMRT, VMAT, RapidArc: are they really needed?
- MRI-based versus ultrasound based brachytherapy

#### **PET-CT detection of lymph node metastases**



No. of					Ly	ymph No	ode Ty	/pe					
Total		Lymph Nodes		Pelvic		Para- Aortic		Sup clavio	ora- cular				
Stage	Patients	No.	%	No.	%	No.	%	No.	%				
IA1	1	1	100	0		0		0					
IA2	11	10	91	1	9	Size	Size of Tumor and Co			ol Achieved with 6000	nads Alone and		
IB1	146	118	81	28	19	Size of Tunior and Co		with	Cheme-Dadiation	Taus Aione and			
IB2	81	40	49	41	51				with				
IIA	14	7	50	7	50						Control of		
IIB	161	74	46	87	54			Dose F	Required	Control of	Tumor Achieved		
IIIA	4	2	50	2	50	Size of	f	to A	chieve	Tumor Achieved	with Cisplatin		
IIIB	111	36	32	75	68	Tumor	- [	90%	Control	with 6000 rads	and 6000 rads		
IVA	11	5	45	6	55								
IVB	20	3	15	17	85	2  cm		6000	RADS (	90%	94%		
All	560	189	34	264	47	2–4 cn	1	7000	) RADS	75%	85%		
-						4–6 cm	1	8000	) RADS	65%	80%		
						6 ст		10,000	RADS (	55%	74%		

 
 Table 1. Frequency and Level of Lymph Node Metastasis Observed on FDG-PET by FIGO Stage of Cervical Cancer

#### Kidd et al. J Clin Oncol 2010, Kupets et al. Gyn Onc 2002

## Nodal debulking?



- Definitive radiotherapy combined with weekly Cisplatin
- Extended field IMRT + simultaneous integrated boost
- 40 patients positive pelvic nodes, elective PAO RT, elective dose 45 Gy
- 21 patients positive pelvic and PAO nodes, PAO SIB boost up to 55 Gy (54-59.4)



Vargo et al. IJROBP 2014, Sturdza et al Radiother Oncol 2016

## Nodal debulking?



- Para-aortic lymphadenectomy to tailor radiation field versus
- Risk stratification for elective radiotherapy of para-aortic nodes
- Prediction models (Tumor size on T2 MRI; PET-CT node status)

Risk Group LN	Definition	EBRT lymph node regions
Low Risk (LR LN)	Tumour size ≤4cm AND stage IA/IB1/IIA1 AND N0 AND squamous cell carcinoma AND no uterine invasion	<b>"Small Pelvis"</b> internal iliac external iliac obturator presacral
Intermediate Risk (IR LN)	Not low risk No high risk features	<ul> <li>"Large Pelvis"</li> <li>Nodes included in "Small Pelvis" and common iliac region (including the aortic bifurcation).</li> <li>In addition: <ul> <li>inguinal in case of distal vaginal involvement.</li> <li>Mesorectal space in case of mesorectal nodes and advanced local disease</li> </ul> </li> </ul>
High Risk (HR LN)	<ul> <li>Based on nodal pathology</li> <li>≥ 1 pathologic node at common iliac or above</li> <li>OR ≥ 3 pathologic nodes</li> </ul>	"Large Pelvis + Para-aortic" Nodes included in "Large Pelvis" and para-aortic region with the upper border of CTV minimum at the level of renal veins (usually incl. L2), and at least 3 cm cranial of the highest pathological node in case of para-aortic nodes].



#### **Target definition using rectal ultrasound**





Good correlation between MRI and ultrasound



Schmid et al, Strahlenther Onkol 2013, Nesvacil et al, Brachytherapy 2016

#### **Target definition: MRI vs rectal ultrasound plus CT**







## Can we omit brachytherapy?





SEER analysis of 7359 cases with stage IB2-IVA cervical cancer Survival by brachytherapy use for matched cohorts between 2000 and 2009

- Cause-specific survival (64 vs 51%) and overall survival (58 vs 46%)
- Brachytherapy was independently associated with CSS and OS

Han et al, IJROBP 2013

#### **Chemoradiation as effective for stage IIIB?**



# Phase 3 randomised trial of cisplatin chemoradiation vs radiation therapy alone in FIGO stage IIIB squamous cell carcinoma of the cervix

- EBRT 50 Gy plus brachytherapy (HDR 3x Gy or LDR 25-30 Gy point A)
- Weekly cisplatin for at least 5 cycles
- >90% treatment compliance
- median follow-up: 88 months
- 5-year PFS 52 vs 44%; 5-yr OS 54 vs 46% (p=0.03), 8% absolute survival gain



Mahanshetty et al, ESGO 2017

## Trials of adjuvant chemotherapy





Accrual completed (n=900)

Ongoing (n > 265 / 630)

Interlace: PI Mary McCormack (NCRI UK)

#### Long term toxicities and QOL



- Relationship of smoking, habitus, comorbidities to risk of side effects
  - Eifel et al: heavy smoking: 3-fold higher risk of bowel toxicity and 2-fold higher risk of any complications
- Impact on physical, social, role and sexual functioning
- Rehabilitation programme







Eifel et al, Jco 2002, Kirchheiner et al, IJROBP 2016; Bakker et al, Supp Care Cancer 2016

### Conclusions



- Primary chemoradiation with brachytherapy is standard of care
- Many treatment and patient related challenges
- Avoid triple-modality treatment to reduce toxicities
- Newer image-based techniques have significantly improved outcomes: lymph node boosts, image-guided brachytherapy
- Excellent pelvic control; reducing risk of distant relapse essential for further improving OS
- 3D-CRT effective and safe treatment
- Ultrasound-based brachytherapy may be equivalent
- Survivorship care essential for QOL