MAYO CLINIC

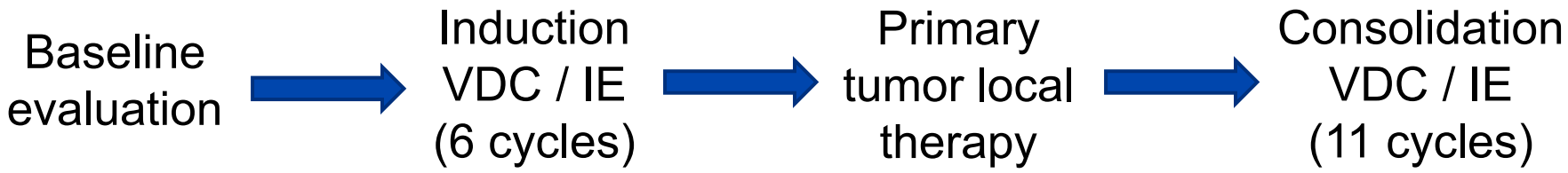
Local Therapy for Ewing Sarcoma:
Current Concepts and Opportunities for Improvement

Safia K. Ahmed, MD
Department of Radiation Oncology
Washington University
August 25, 2017

Outline

- Therapeutic background
- Current local tumor control outcomes
- Identification of patients at higher risk for local failure
- Optimization of local therapy for high risk patients
- Conclusions

Current Treatment Paradigm
Localized Disease



VDC / IE = vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide

Contemporary North American Trials

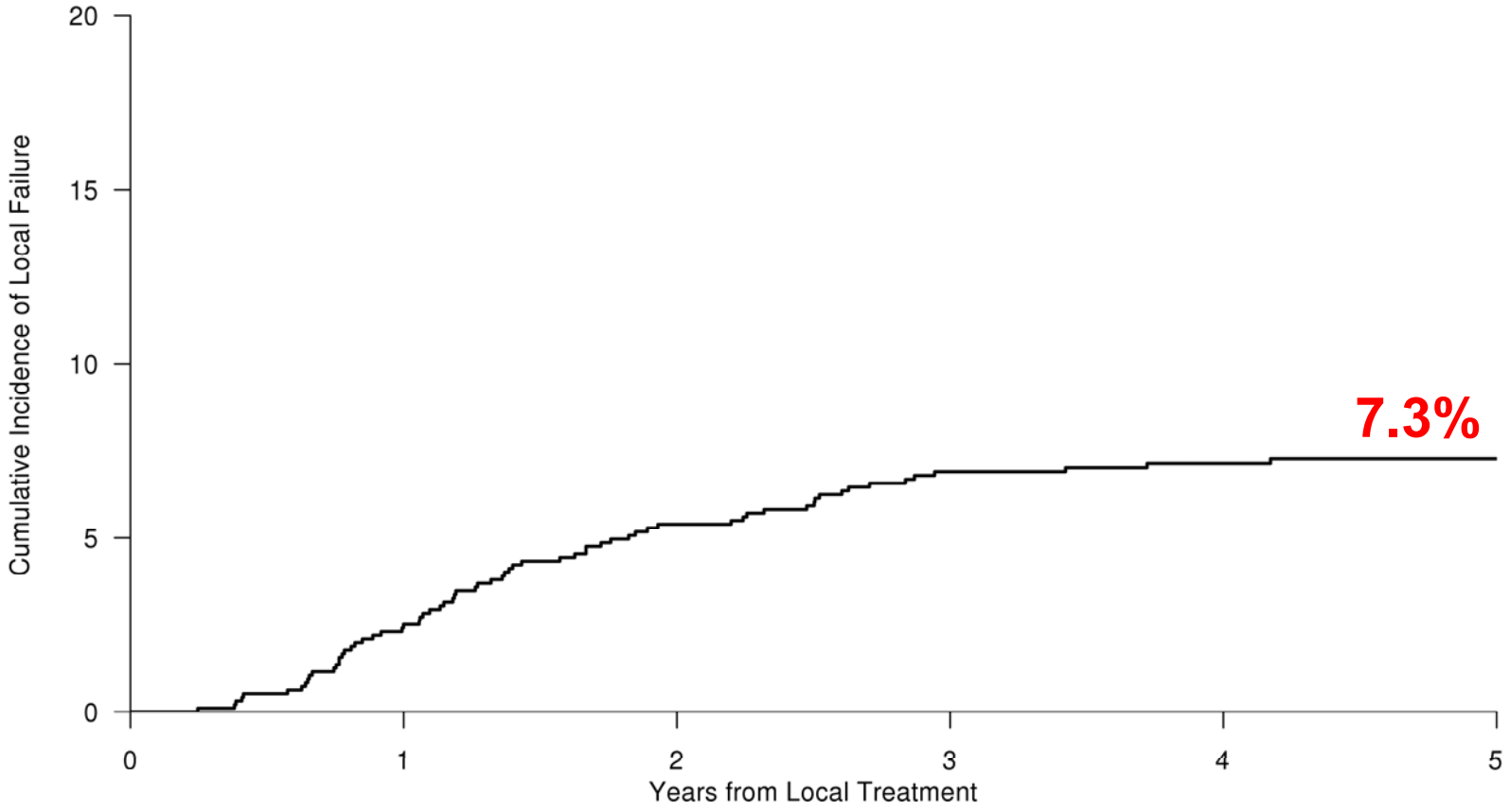
	Chemotherapy	OS	EFS	Local Failure
INT-0091, 1988-1992	VACD, 49 weeks VACD/IE, 49 weeks	61.0% 72.0%	54.0% 69.0%	15% 5%
INT-0154, 1995-1998	VDC/IE, 48 weeks VDC/IE, 30 weeks	80.5% 77.0%	72.1% 70.1%	6.2% 5.4%
AEWS0031, 2001-2005	VDC/IE, q3 weeks VDC/IE, q2 weeks	77.0% 83.0%	65.0% 73.0%	8.0% 7.2%

85% OS and 75% EFS

VACD = vincristine, doxorubicin, cyclophosphamide, actinomycin D
VACD/IE = vincristine, doxorubicin, cyclophosphamide, actinomycin D, ifosfamide, etoposide

Granowetter et. al., *J Clin Oncol*, 2009
Grier et. al., *N Engl J Med*, 2003
Womer et. al., *J Clin Oncol*, 2012

Local Failure
INT-0091, INT-0154, & AEWS0031 Analysis



Ahmed et. al., *Int J Rad Bio Phys*, 2017 (in press)

“Local tumor control is no longer a problem in the modern era.”

-Medical oncologists

Comparative Evaluation of Local Control Strategies in Localized Ewing Sarcoma of Bone

A Report From the Children's Oncology Group

"…similar EFS and OS [between local treatment modalities] reflects the relatively low contribution of local failure to overall disease failure in Ewing Sarcoma."

DuBois et. al., *Cancer,* 2015

Mayo Clinic Ewing Sarcoma Experience

- 500 patient database
- Aims
  - Determine impact of local tumor control
  - Characterize local failure rates across various cohorts
  - Elucidate prognostic variables for local failure
  - Assess importance of local tumor control for metastatic disease
  - Evalute effect of local treatment modality on patient quality of life

What Is The Impact Of Local Therapy?

Impact of Local Therapy

- Systemic therapy alone: <30% survival

Series	5 year post-local relapse survival
Mayo Clinic	22%
St. Jude Children's Research Hospital	21%
CESS 81, CESS 86, & EICESS 92	24%

Local therapy is a crucial component of the multimodal treatment strategy

CESS = Cooperative Ewing's Sarcoma Studies
EICESS = European Intergroup Ewing's Sarcoma Study

Barker et. al., *J Clin Oncol*, 2005
Robinson, Ahmed et. al., *Am J Clin Oncol,* 2014
Stahl et. al., *Pediatr Blood Cancer*, 2011

Are All Patient Cohorts Associated With The Same Local Failure Rate?

Local Therapy Approach

- Definitive surgery
  - Margin negative resection
  - Minimal morbidity

10% local failure rate

- Definitive radiotherapy (RT)
  - Anatomically unfavorable tumors

21% local failure rate

- Surgery + radiation (S+RT)
  - Cases of incomplete resection

3% local failure rate

Ahmed et. al., Manuscript in preparation

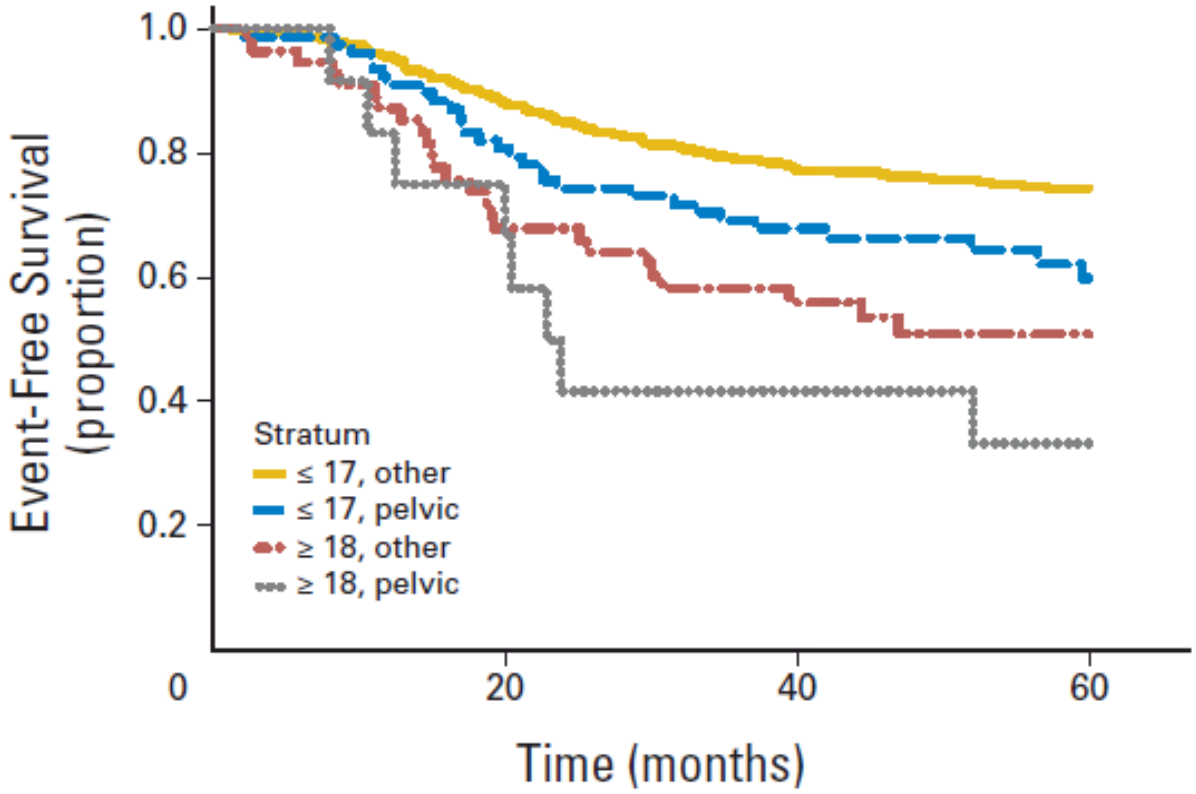
European Outcomes

- CESS 81, CESS 86, & EICESS 92
  - 1981-1999
  - 1,058 patients
  - RT: 26.3%
  - S ± RT: 5.3 - 7.5%
- EURO-EWING99
  - 1998-2009
  - 1,207 patients
  - RT associated with higher local failure rate
  - Await publication

EURO-EWING99 = European Ewing Tumour Working Initiative of National Groups Ewing Tumour Studies 1999

Andreou et. al., CTOS Annual Meeting, 2016
Schuck et. al., *Int J Rad Bio Phys,* 2002

Patient Age
AEWS0031

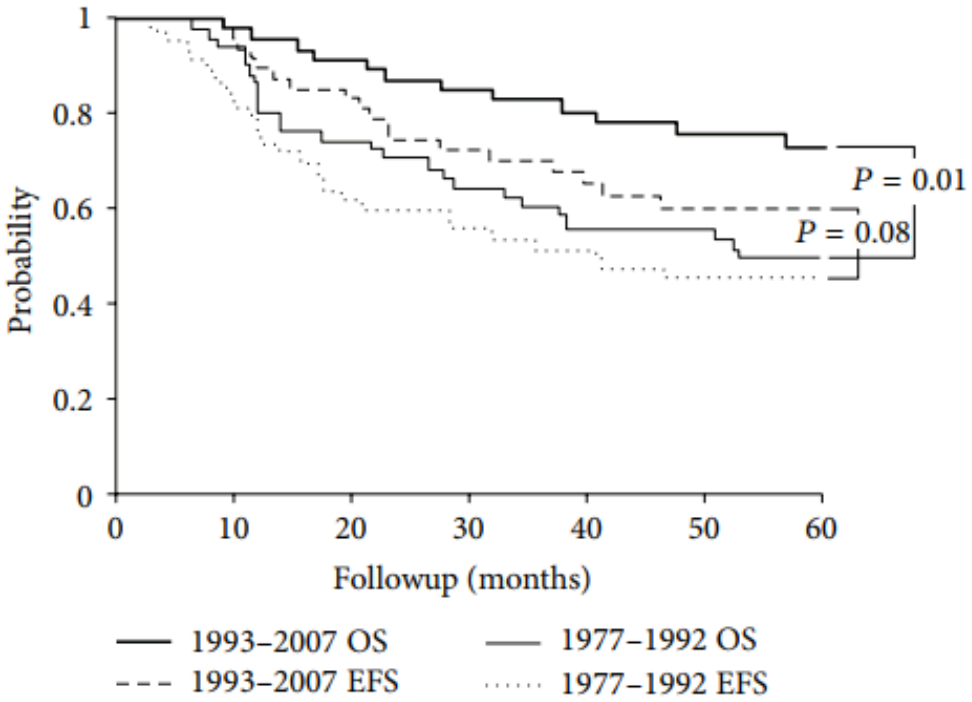


Womer et. al., *J Clin Oncol*, 2012

Research Article

Adult Ewing Sarcoma: Survival and Local Control Outcomes in 102 Patients with Localized Disease

Safia K. Ahmed,[1] Steven I. Robinson,[2] Scott H. Okuno,[2] Peter S. Rose,[3] and Nadia N. Issa Laack[4]



	Local Failure Rate
Surgery	18%
RT	33%
S+RT	0%

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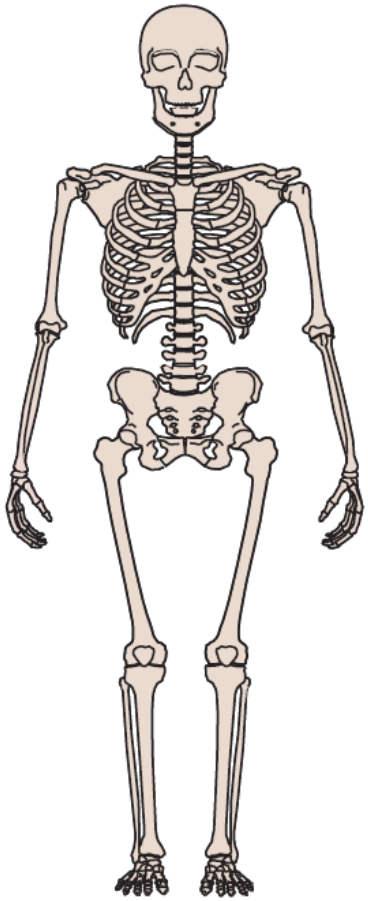
Ahmed et. al., *Sarcoma*, 2013
Baldini et. al., *Annals of Surgery*, 1999
Casey et. al., *Radiotherapy and Oncology*, 2014
Pretz et. al., *Oncologist*, 2017

Primary Tumor Site

Humerus	6%
Ulna	1%
Radius	1%
Hand	1%
Femur	20%
Fibula	8%
Tibia	10%
Foot	3%



Skull	2.0%
Clavicle	1.5%
Scapula	4.0%
Sternum	0.5%
Ribs	10.0%
Spine	6.0%
Pelvis	26.0%

Skeletal	85%
Extraskeletal	15%

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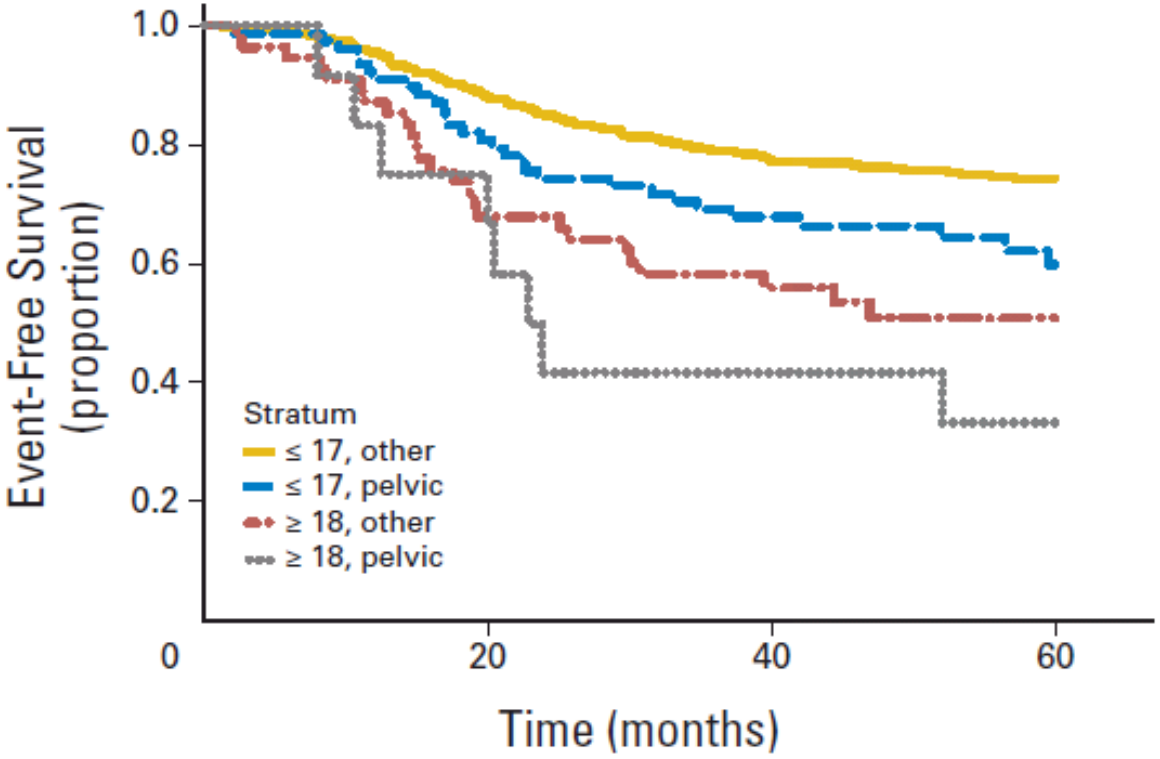
Ahmed et. al., *Pediatric Radiation Oncology,* 2017 (in press)
Marina et. al., *Sarcoma,* 2015

Pelvis Tumors
AEWS0031



EURO-EWING99: 30% local failure rate

Dirksen et. al., SIOP Annual Meeting, 2016
Womer et. al., *J Clin Oncol,* 2012

RESEARCH ARTICLE

Pediatric Blood & Cancer

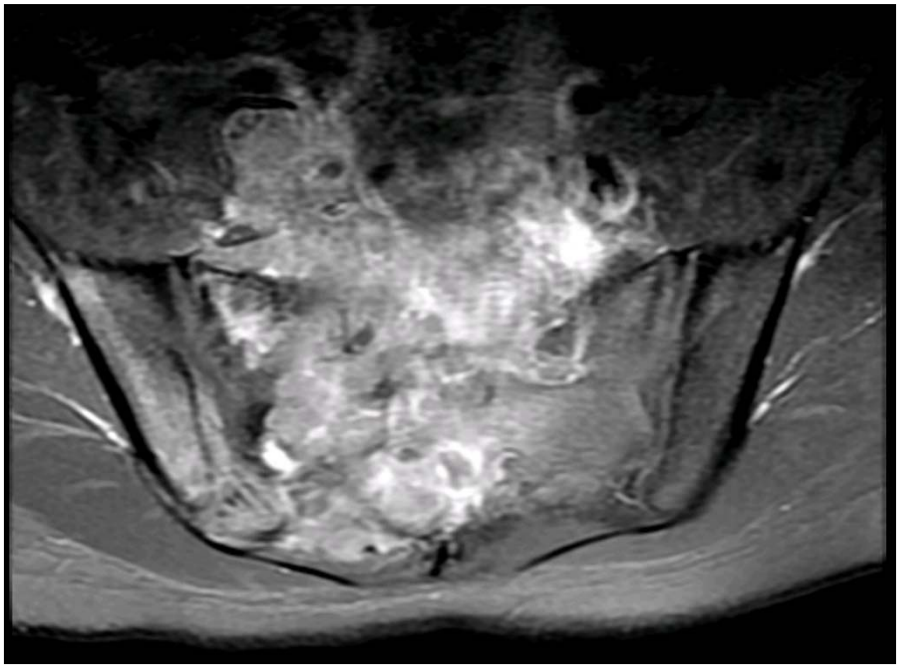
Pelvis Ewing sarcoma: Local control and survival in the modern era

Safia K. Ahmed[1] | Steven I. Robinson[2] | Carola A. S. Arndt[3] | Ivy A. Petersen[1] | Michael G. Haddock[1] | Peter S. Rose[3,4] | Nadia N. Issa Laack[1]

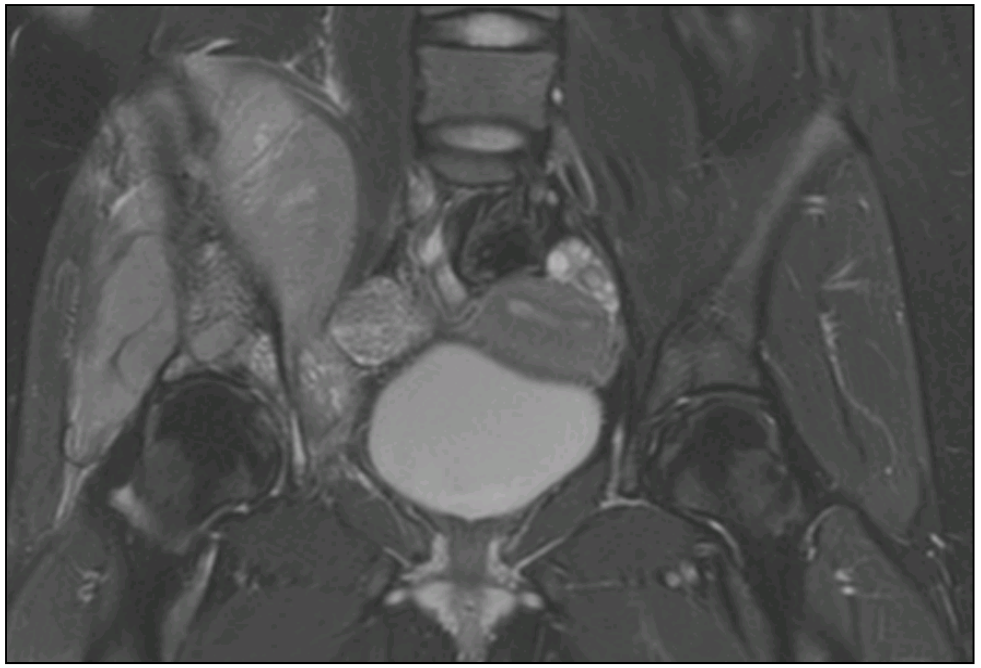
	Local Failure Rate
All patients	19%
Definitive surgery	13%
Definitive radiation (RT)	26%
Surgery + radiation (S+RT)	0%

Ahmed et. al., *Pediatr Blood Cancer,* 2016

Pelvis Tumors Treated with RT



Tumor involves L5-S3, right iliac wing, spinal canal, nerves, and soft tissue
12.3 x 8.1 x 6.3 cm



Tumor involves right ilium, acetabulum, superior pubic ramus, vasculature, and soft tissue
15.0 x 13.2 x 9.3 cm

What Clinical Variables Are Prognostic For Local Failure?

Tumor Size

- COG Trials
  - < / ≥ 8 cm in maximum dimension
  - INT-0154: No correlation with outcomes
  - IINT-0091 & INT-0154: Tumors ≥ 8 cm associated with inferior EFS
- EURO-EWING99
  - Tumors ≥ 200 ml associated with higher local failure rate

Andreou et. al., CTOS Annual Meeting, 2016
Dirksen et. al., SIOP Annual Meeting, 2016
Marina et. al., *Sarcoma*, 2015

Tumor Size
Mayo Clinic Experience

- No correlation with local failure rate by < / ≥ 8 cm in maximum dimension

- Radiographic response to chemotherapy
  - Partial or complete response: 13%
  - Less than partial response: 36%

Ahmed et. al., *Sarcoma*, 2013
Ahmed et. al., *Pediatr Blood Cancer,* 2016

Prognostic Factors
Pelvis Anatomic Subsites

- Mayo Clinic
  - 36% local recurrence rate for tumors with sacral involvement

- Scandinavian Sarcoma Group
  - Inferior EFS for tumors involving innominate bones

Ahmed et. al., *Pediatr Blood Cancer,* 2016
Hesla et. al., *J Bone Joint Surg Am,* 2016

Prognostic Factors
Histologic Response to Neoadjuvant Chemotherapy

Series	Histologic Response	EFS	Local Failure Rate
CESS 86	≤10% viable tumor cells >10% viable tumor cells	64% 38%	
AEWS0031	<90% necrosis ≥90% necrosis No viable tumor cells	~65% ~70% ~80%	
Mayo Clinic	≤5% viable tumor cells >5% viable tumor cells	76% 59%	
MD Anderson	≤95% necrosis >95% necrosis	36% 74%	44% 9%

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Chihak, Ahmed et. al., Manuscript in preparation
Pan et. al., *Int J Rad Onc Bio Phys*, 2015
Paulussen et. al., *J Clin Oncol*, 2001
Womer et. al., CTOS Annual Meeting, 2016

Local Tumor Control
Mayo Clinic Experience

- Cohorts associated with higher local failure rate
  - Patients treated with RT
  - Patients with pelvis tumors
- Prognostic variables
  - Response to neoadjuvant chemotherapy
  - Anatomic subsites

Ahmed et. al., Manuscript in preparation

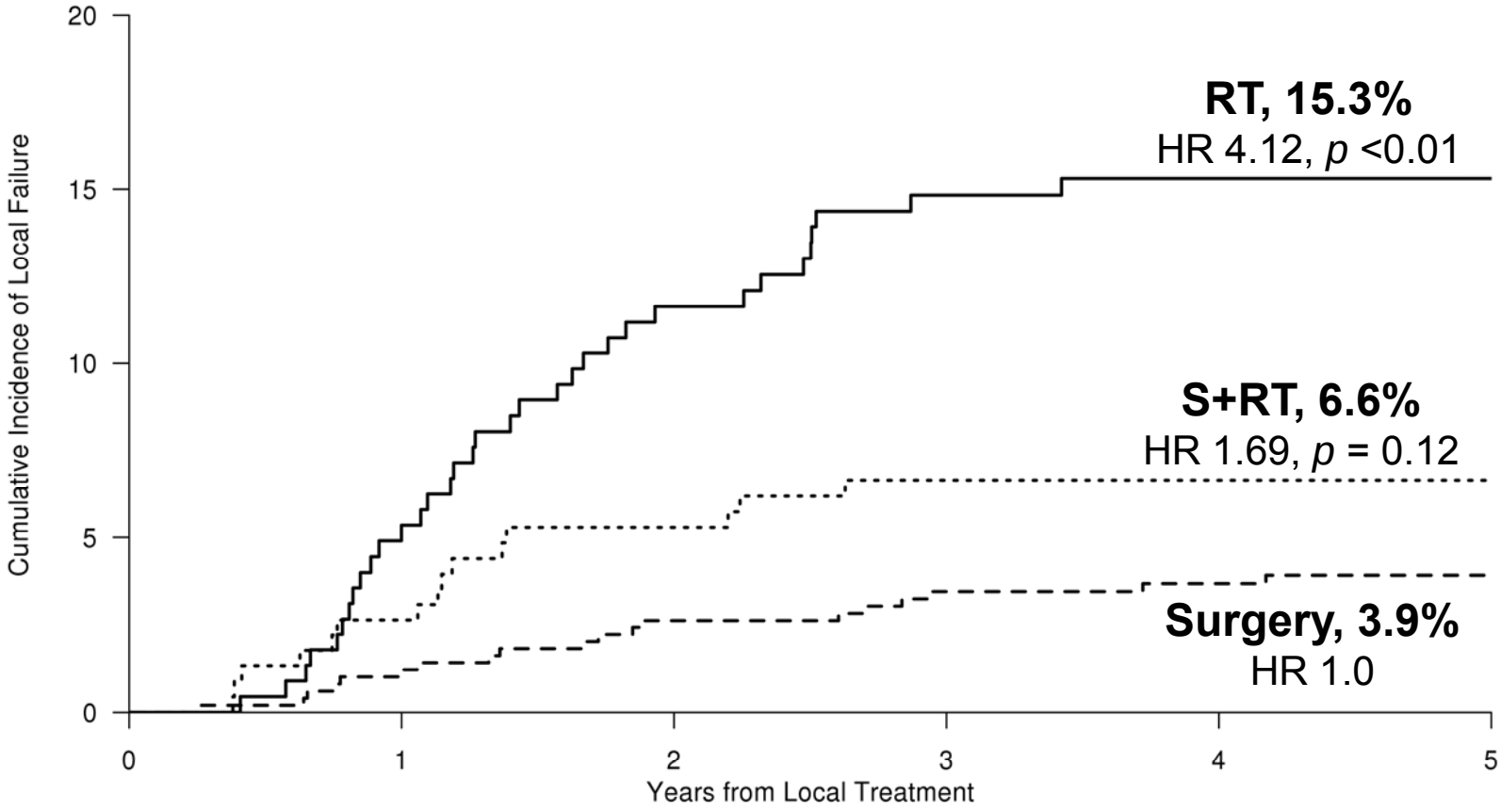
Can We Validate Our Findings?

COG Local Failure Analysis

- Purpose: To identify clinical and treatment variables associated with higher risk of local failure in Ewing sarcoma patients treated on recent COG protocols

- 956 patients treated with IE based chemotherapy on INT-0091, INT-0154, and AEWS0031 trials

Optimal Local Therapy
COG Local Failure Analysis



Ahmed et. al., *Int J Rad Bio Phys,* 2017 (in press)

Primary Tumor Site
COG Local Failure Analysis

	Local Failure	Hazard Ratio	*p*	
Extremity	5.4%	1.0	--	74%, surgery
Pelvis	13.2%	2.47	<0.01	49%, RT
Axial non-spine	5.3%	0.95	0.90	53%, surgery
Spine	3.6%	0.60	0.49	63%, RT
Extraskeletal	9.1%	1.82	0.08	43%, S+RT

Axial non-spine = ribs, scapula, clavicle, sternum

Ahmed et. al., *Int J Rad Bio Phys,* 2017 (in press)

Primary Tumor Site
COG Local Failure Analysis

PELVIS TUMORS			
	Local Failure	**Hazard Ratio**	***p***
Surgery	3.9%	1.0	--
RT	22.4%	6.31	0.01
S+RT	5.1%	1.31	0.78
EXTREMITY TUMORS			
	Local Failure	**Hazard Ratio**	***p***
Surgery	3.7%	1.0	--
RT	14.8%	3.99	<0.01
S+RT	5.4%	1.42	0.59

Echoed by EURO-EWING99 analysis

Ahmed et. al., *Int J Rad Bio Phys*, 2017 (in press)
Andreou et. al., CTOS Annual Meeting, 2016

Extremity Tumors Treated with RT

Tumor extends 30.0 cm along the right femur,
with a 23.0 x 22.0 x 12.6 cm soft tissue mass

Ahmed et. al., *Int J Rad Bio Phys*, 2017 (in press)

Tumor Size
COG Local Failure Analysis

- Available in only 40% of cohort

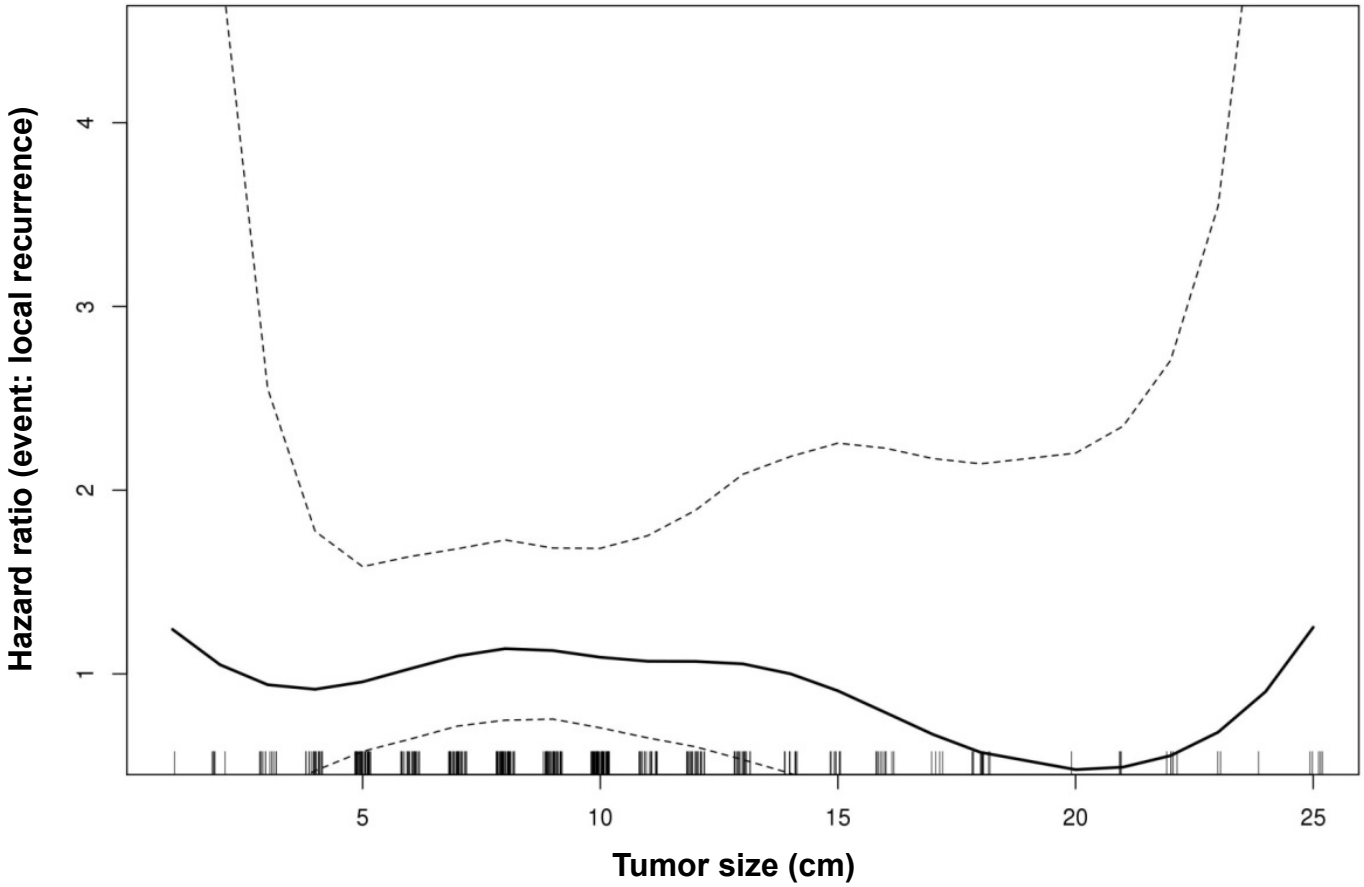
	Surgery	RT	S+RT	*p*
<8 cm	73 (54%)	42 (31%)	21 (15%)	0.21
≥8 cm	134 (54.2%)	60 (24.2%)	53 (21.4%)	

- No difference in local failure incidence: ~8%

	Surgery	RT	S+RT
<8 cm	7.2%	12.2%	4.8%
≥8 cm	3.1%	20.0%	5.9%

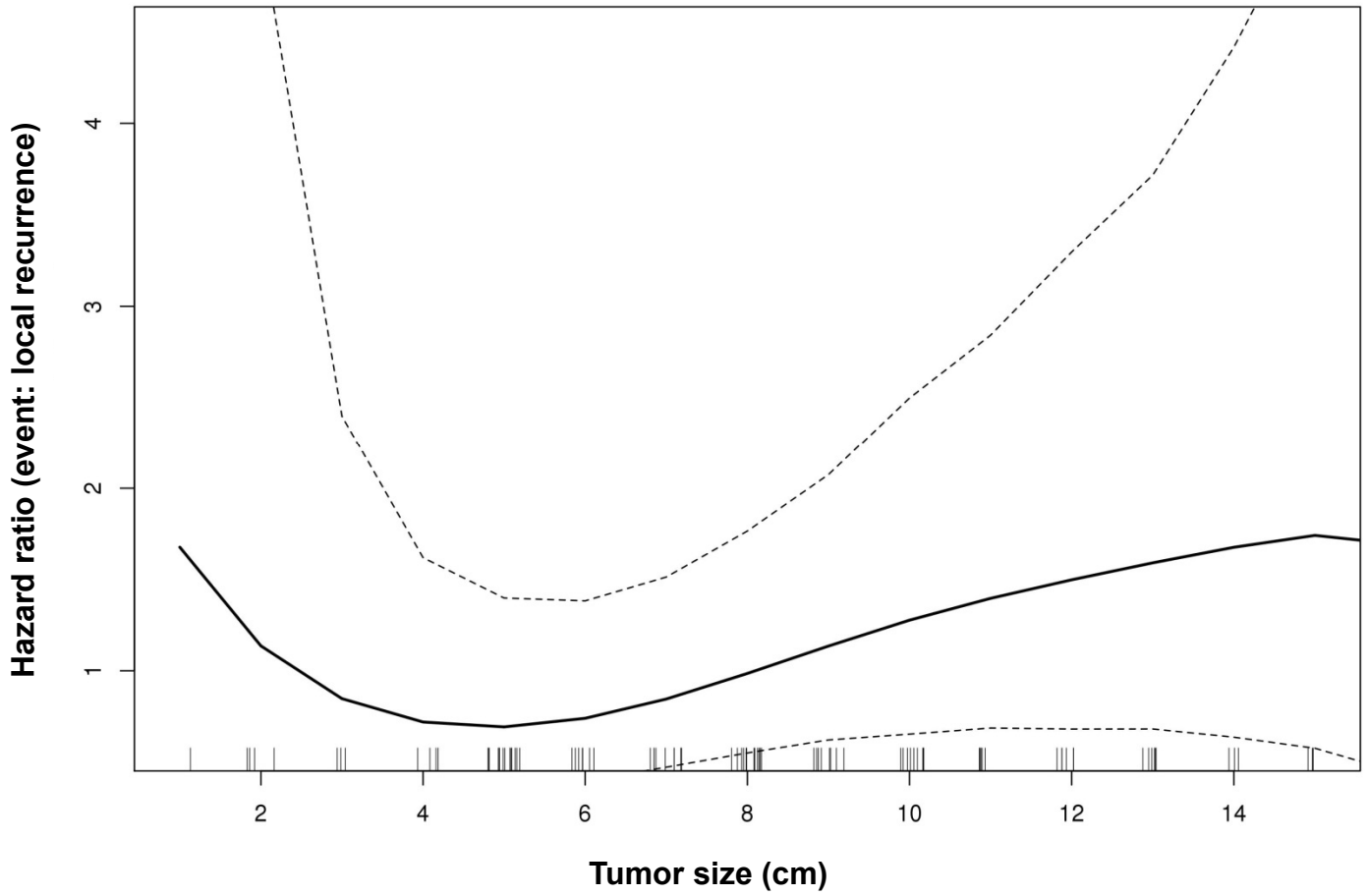
Ahmed et. al., *Int J Rad Bio Phys*, 2017 (in press)

Tumor Size: All Patients
COG Local Failure Analysis



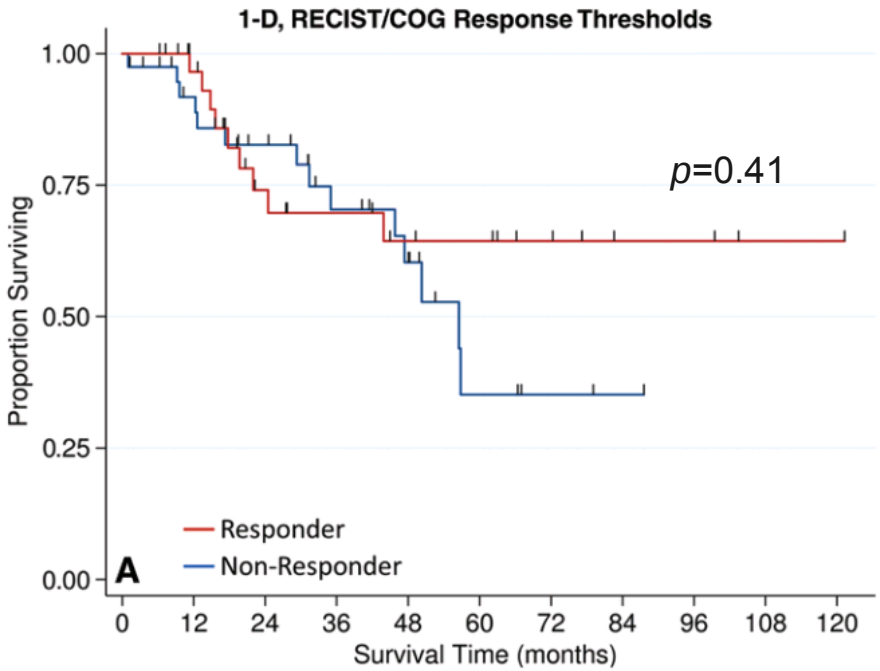
Ahmed et. al., *Int J Rad Bio Phys*, 2017 (in press)

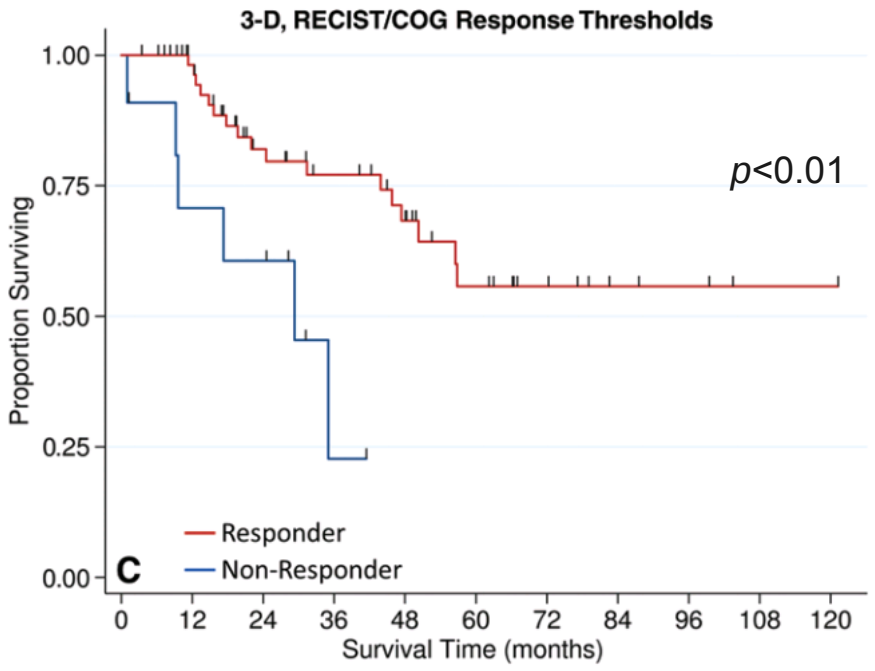
Tumor Size: RT Patients
COG Local Failure Analysis



Ahmed et. al., *Int J Rad Bio Phys*, 2017 (in press)

Tumor Size
1D Measurements Inadequate?

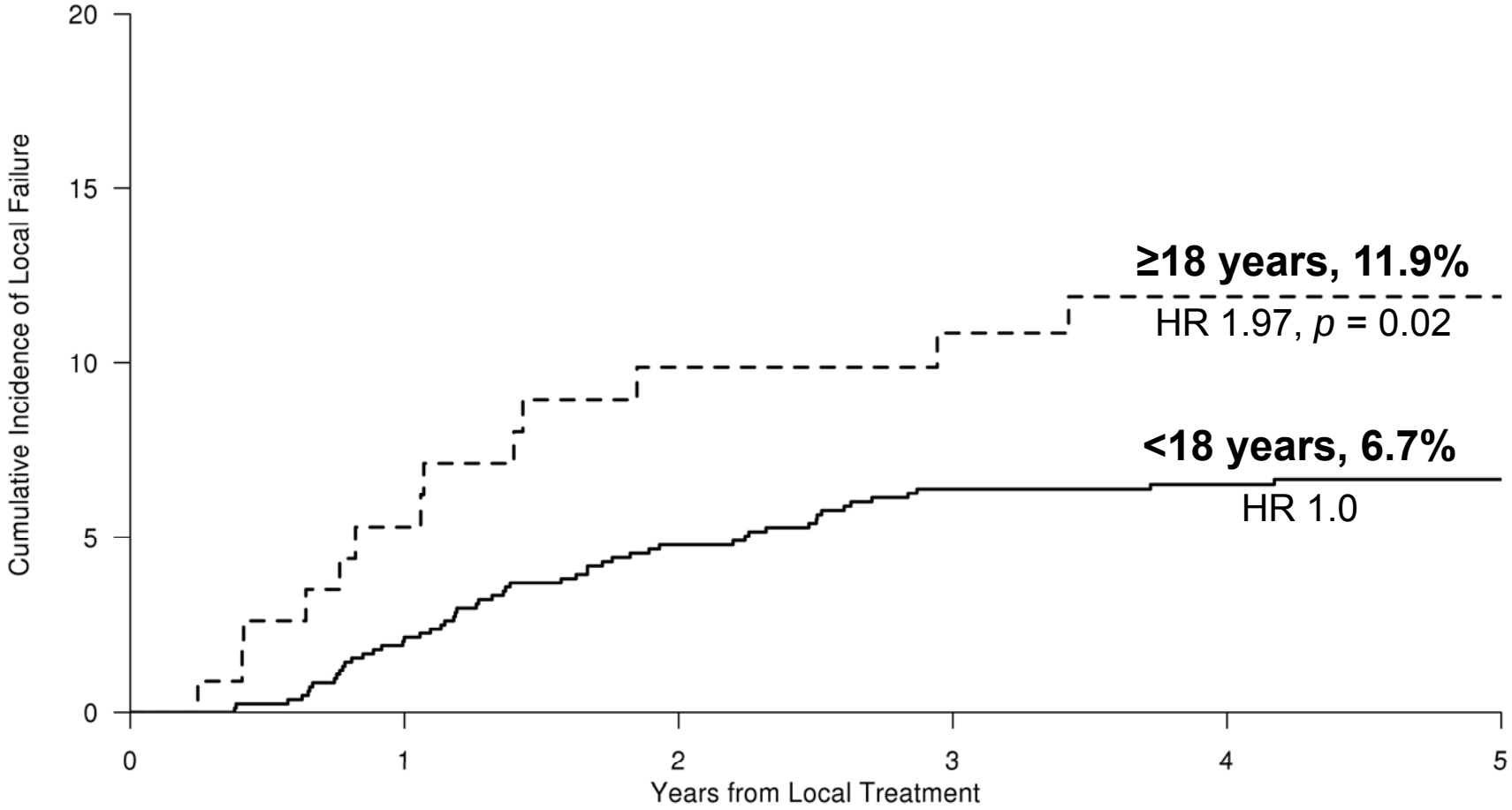




AEWS1031: Evaluate volumetric tumor size as prognostic factor for EFS

Aghighi et. al., *Radiology*, 2016
Childrensoncologygroup.org

Patient Age
COG Local Failure Analysis



Ahmed et. al., *Int J Rad Bio Phys,* 2017 (in press)

Local Failure Summary
High Risk Patients

- RT: ~3x higher risk
  - Pelvis tumors: ~6x higher risk
  - Extremity tumors: ~4x higher risk
- Adult patients: ~2x higher risk
- No association with tumor size in maximum dimension

Ahmed et. al., *Int J Rad Bio Phys*, 2017 (in press)

How Can We Optimize Local Tumor Control For Patients At High Risk For Local Failure?

Histologic Response

Series	Histologic Response	EFS	Local Failure Rate
CESS 86	≤10% viable tumor cells >10% viable tumor cells	64% 38%	
AEWS0031	<90% necrosis ≥90% necrosis No viable tumor cells	~65% ~70% ~80%	
Mayo Clinic	≤5% viable tumor cells >5% viable tumor cells	76% 59%	
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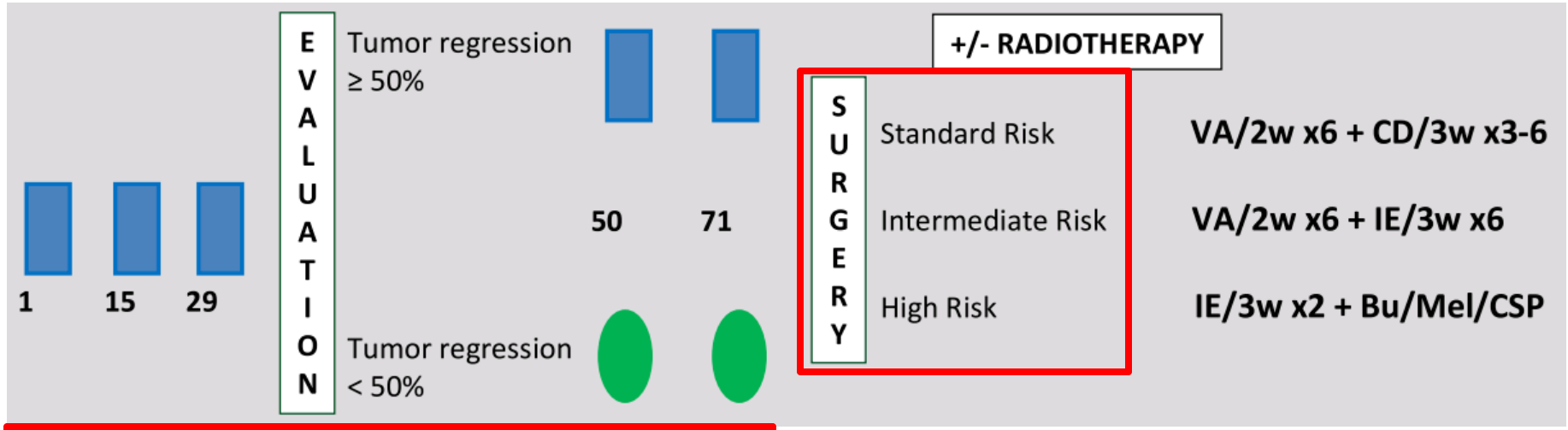
Chihak, Ahmed et. al., Manuscript in preparation
Pan et. al., *Int J Rad Onc Bio Phys*, 2015
Paulussen et. al., *J Clin Oncol*, 2001
Womer et. al., CTOS Annual Meeting, 2016

Histologic Response
French EW93



Risk group	% residual viable after induction
Standard risk	< 5%
Intermediate risk	5-29%
High risk	≥30%

Clinical response and Initial tumor volume (ITV)

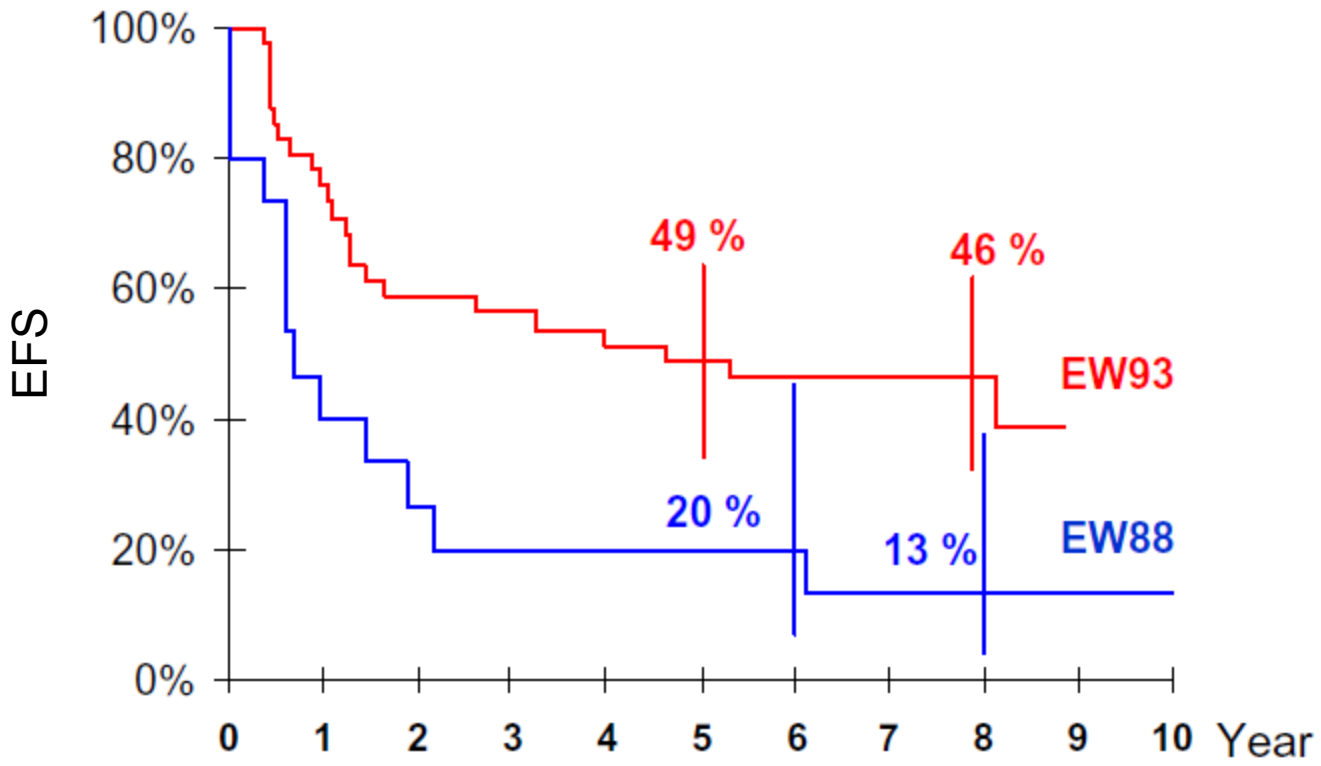
Responders and low ITV < 100 ml

Responders and high ITV > 100 ml

Non responders (reduction of initial volume less than 50%)

Gaspar et. al., *Eur J Cancer*, 2012

Histologic Response
French EW93

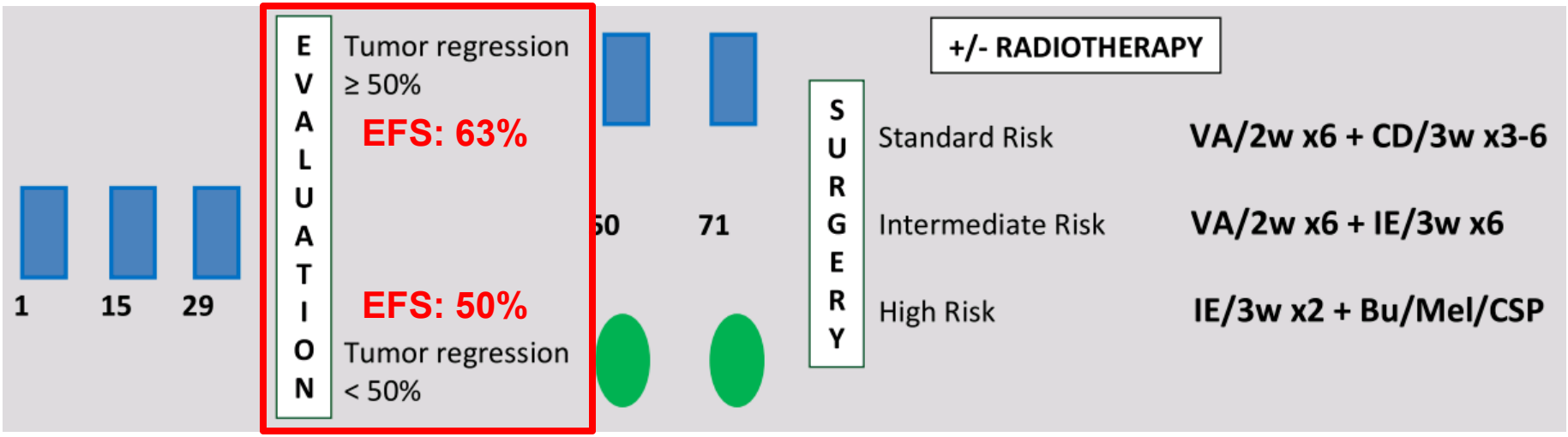


Gaspar et. al., *Eur J Cancer*, 2012

Histologic Response

- Potential to determine patients at higher risk of recurrence
- AEWS1031: Evaluate histologic response as prognostic factor for EFS
- Can only be assessed in surgical cases

Radiologic Response

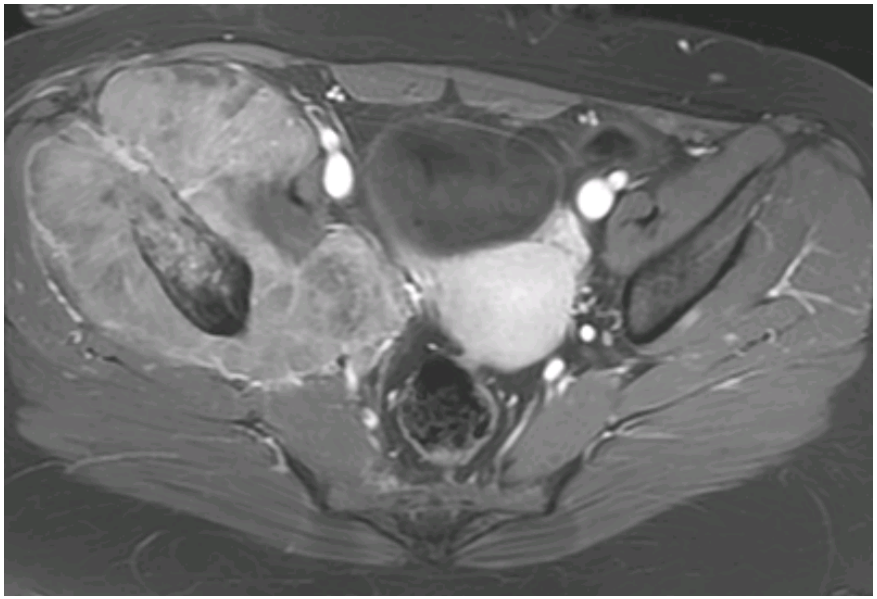


EURO-EWING99 :Tumor regression >90% associated with lower local failure rate

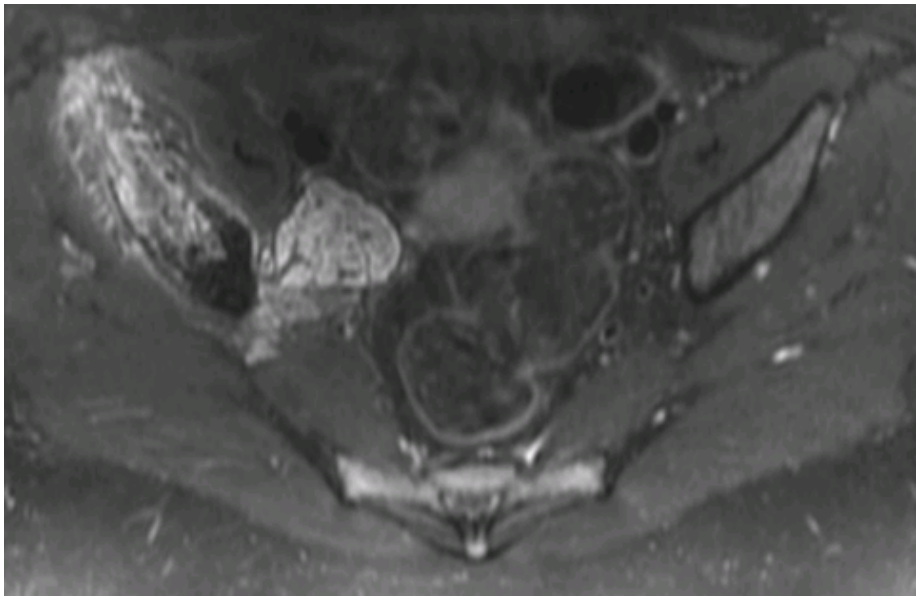
Andreou et. al., CTOS Annual Meeting, 2016
Gaspar et. al., *Eur J Cancer*, 2012

Radiologic Response

- Assessment of soft tissue response sufficient?
- How best to interpret osseous changes?



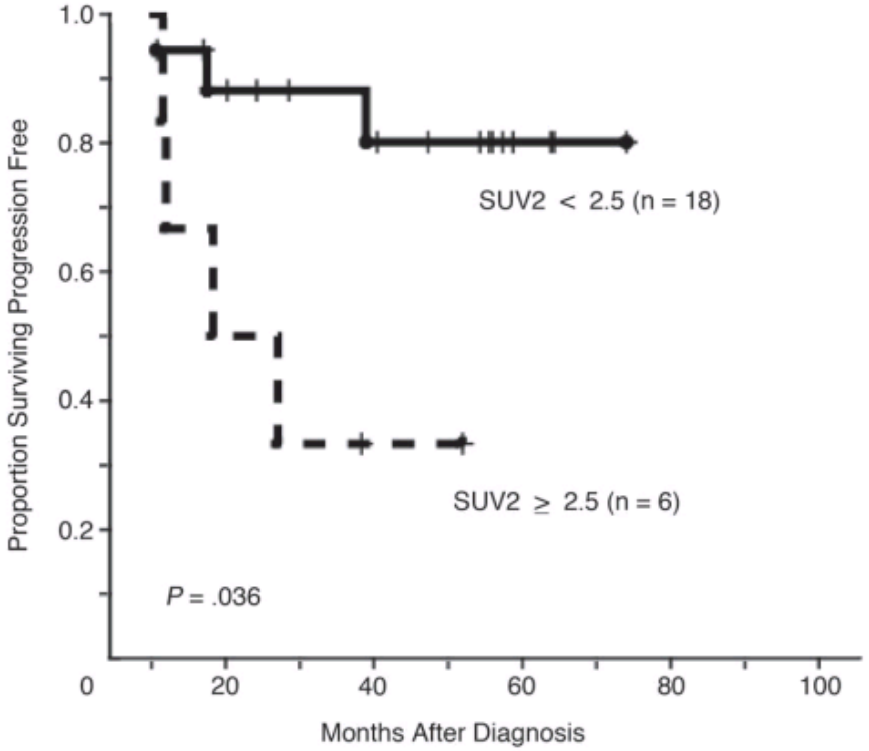
At diagnosis



S/p neoadjuvant chemotherapy

Garcia-Castellano et. al., *Sarcoma*, 2011

Radiologic Response
PET/CT



Role for determining high risk RT cases?

Childrensoncologygroup.org
Hawkins et. al., *J Clin Oncol,* 2005
Koshkin et. al., *J Clin Oncol,* 2016

Other Radiologic Assessments
Tumor Hypoxia

- German analysis: Increasing tumor hypoxia associated with increased risk of metastses

- Correlation of tumor hypoxia with local tumor control?

- Hypoxia PET Tracers: ^{18}F-FDG, ^{18}F-FMISO, ^{18}F-FAZA, and ^{64}Cu-ATSM

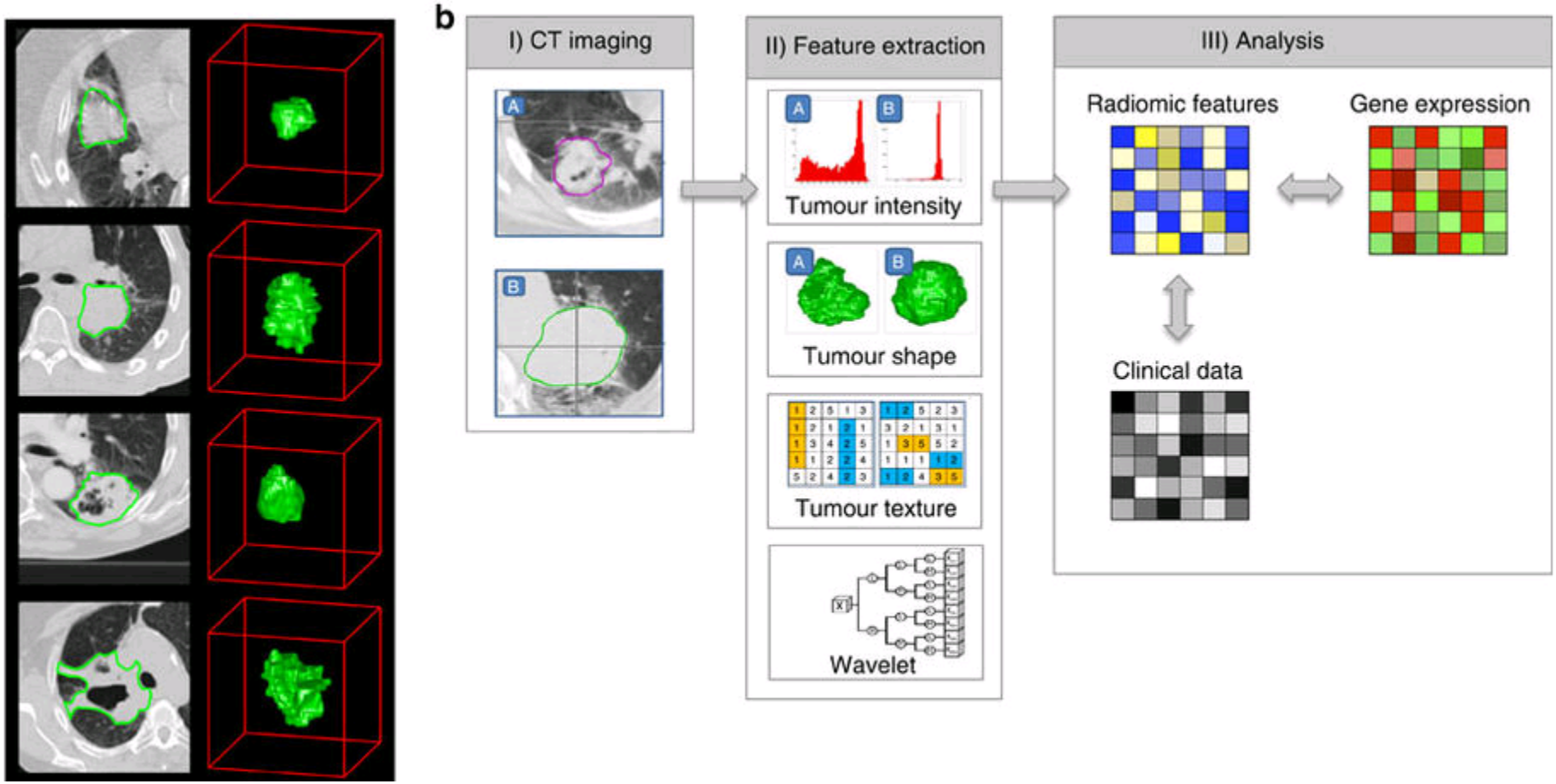
Dunst et. al., *Strahlenther Onkol*, 2006

Other Radiologic Assessments
Advanced MRI Imaging

- Perfusion MRI
- Advanced MR Elastography
- Current Mayo Clinic Protocol: Establish correlation between perfusion MRI, ^{18}F-FDG PET activity, MRI contrast enhancement, MRE and pathologic response for sarcomas

Pafundi et. al., 2015

Other Radiologic Assessments
Radiomics



Aerts et. al., *Nature Communications*, 2014

High Risk Patients
Optimization of Local Tumor Control

- Additional prognostic variables
  - Histologic response for surgical cases
  - Imaging characteristics and response for unresectable cases
- Intensification of local therapy

Intensification of Local Therapy
S+RT

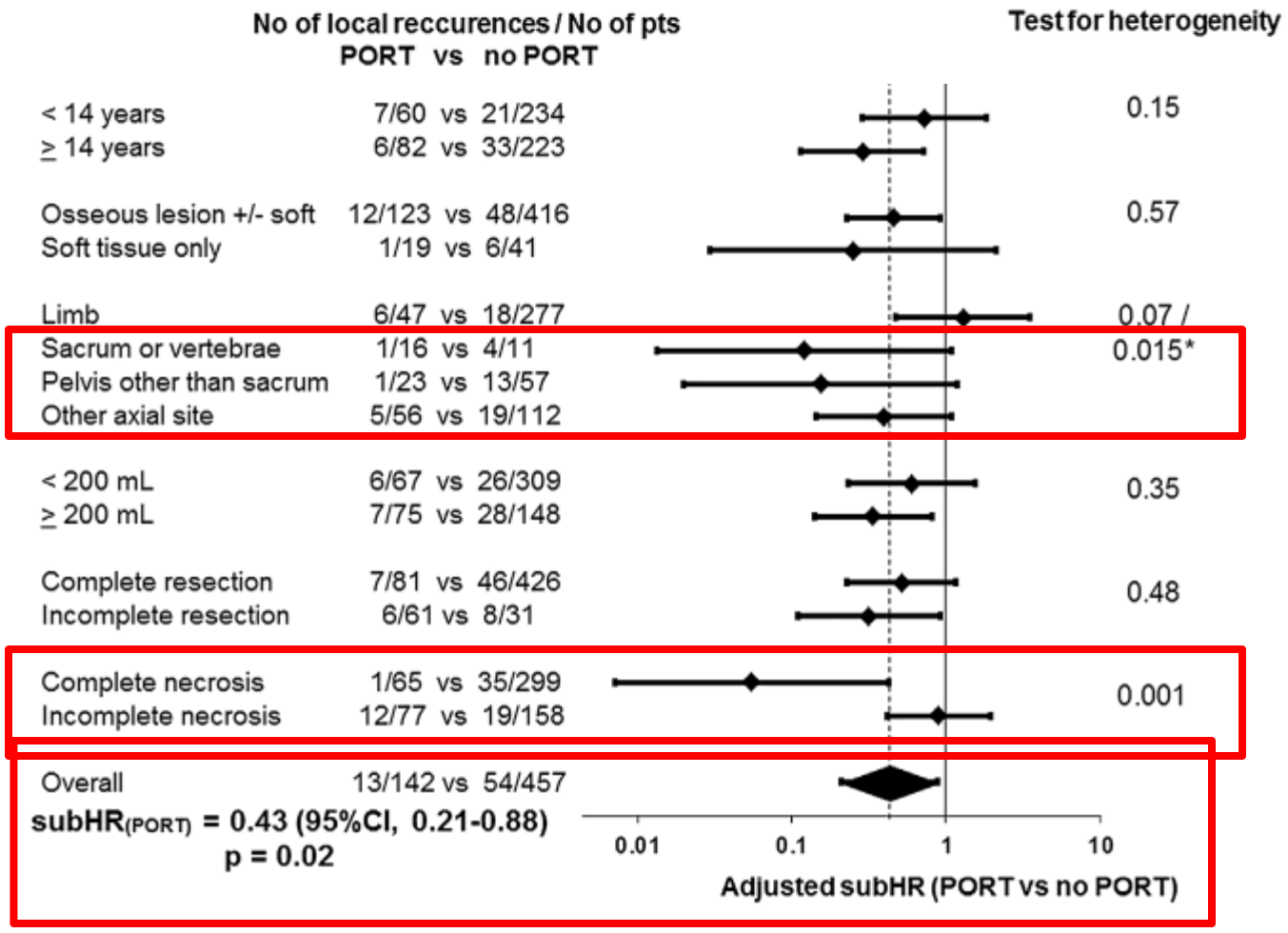
- Local failure incidence similar to surgery and superior to RT despite higher risk cases

	Local Failure Incidence	Hazard Ratio	*p*
Surgery	3.9%	1.0	--
RT	15.3%	4.12	<0.01
S+RT	6.6%	1.69	0.12

- Standard of care for majority of high risk soft tissue sarcomas

Ahmed et. al., *Int J Rad Bio Phys*, 2017 (in press)
O'Sullivan et. al., *Lancet*, 2002

S+RT
EURO-EWING99



Dirksen et. al., SIOP Annual Meeting, 2016
Foulan et. al., *Eur J Cancer*, 2016

Functional Outcomes & Quality of Life

- European Survivorship Study
  - Survivors returned to normal life with minor limitations
  - 56% received S+RT

- Mayo Clinic Survivorship Analysis
  - Local therapy modality does not significantly affect musculoskeletal outcomes or quality of life

Ranft et. al., *J Clin Oncol,* 2017
Stish, Ahmed et. al., *Pediatr Blood Cancer,* 2015

Preoperative RT?

- Advantageous compared to postoperative RT for soft tissue sarcomas
- Lower dose and more limited treatment volumes
- AEWS1031: 36.0 Gy

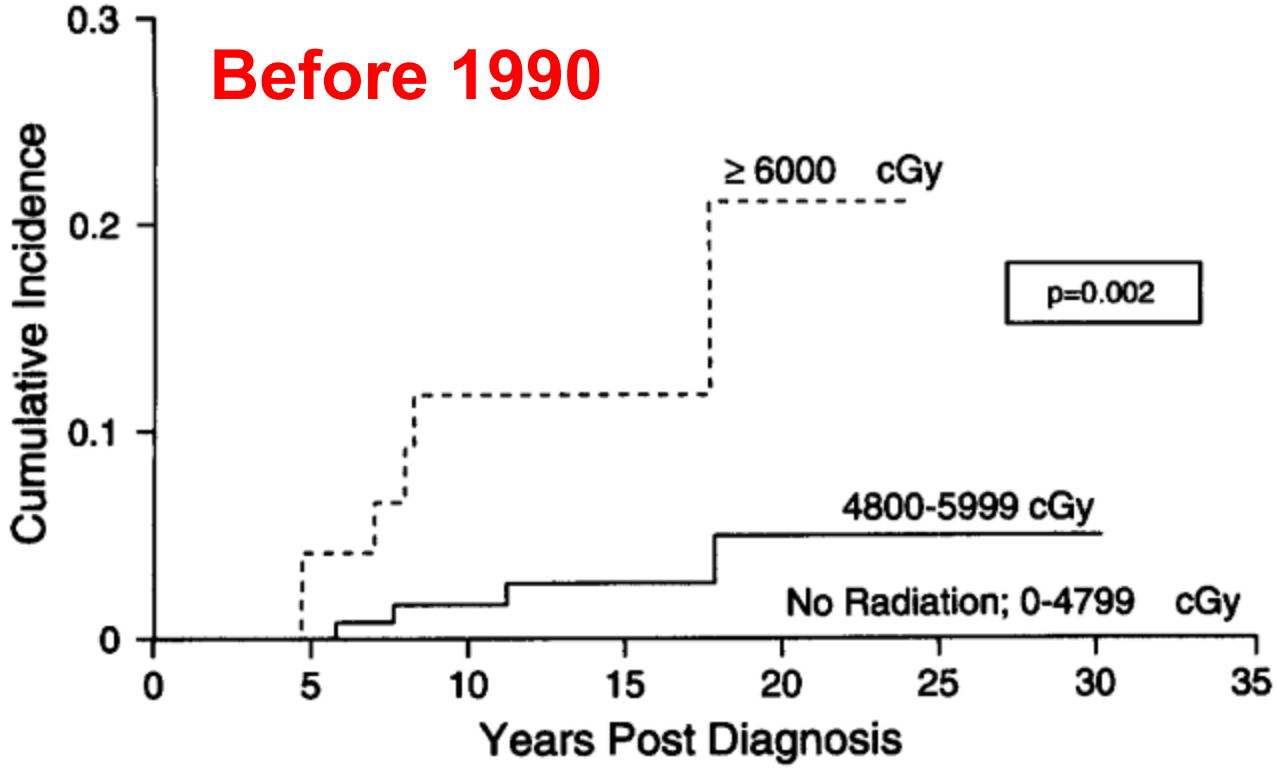
Intensification of Local Therapy
RT Dose Escalation

Series	RT Dose	Local Failure
IESS I	<40 Gy ≥60 Gy	0% 6%
Baylor / Methodist Hospital	≤8 cm, <49 Gy ≥49 Gy ≥8 cm, <54 Gy ≥54 Gy	100% 6.7% 100% 14.3%
Mayo Clinic	<56 Gy ≥56 Gy	36% 0%
St. Jude, Phase II trial	≥8 cm, 64.8 Gy	0%

IESS = Intergroup Ewing's Sarcoma Study

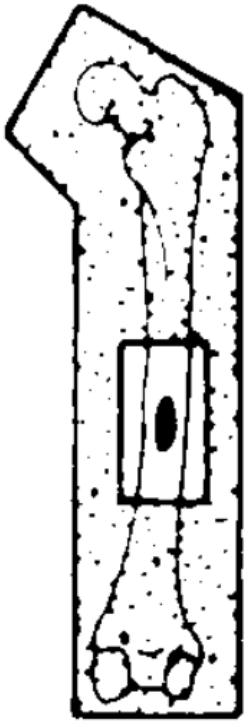
Ahmed et. al., *Sarcoma*, 2013
Paulino et. al, *Pediatr Blood Cancer*, 2007
Razek et. al., *Cancer*, 1980
Talleur et. al., *Int J Rad Bio Phys*, 2016

RT Dose Escalation
Secondary Sarcoma Risk

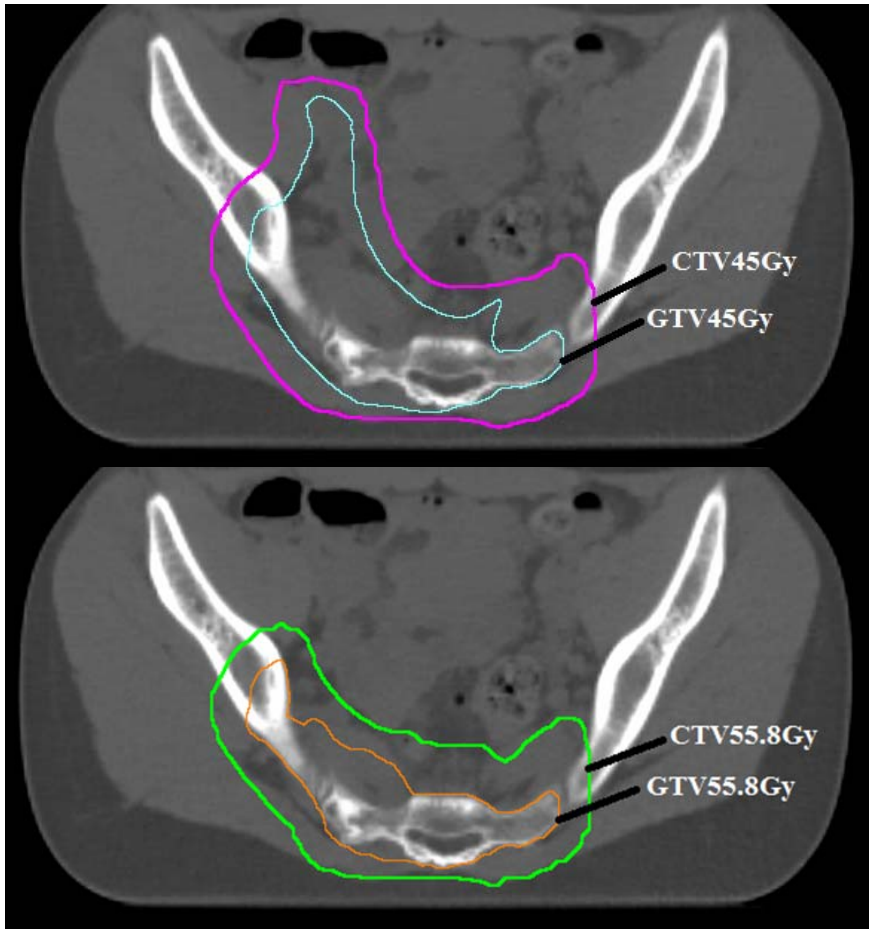


Kuttesch et. al., *J Clin Oncol*, 1996

Secondary Sarcoma Risk
RT Treatment Volume

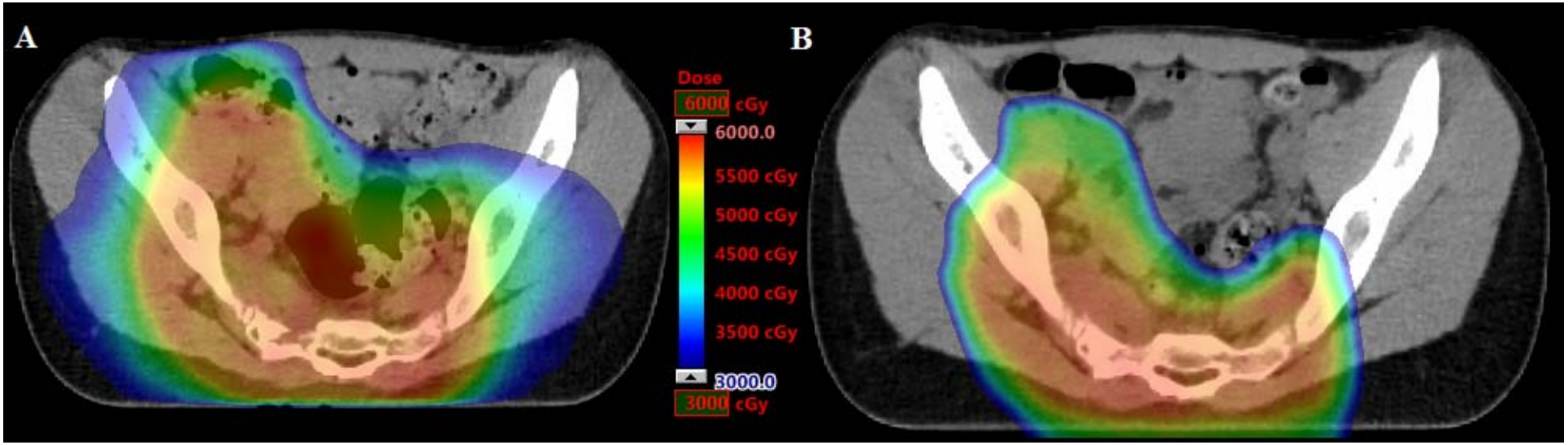


Early cooperative group trials



Ahmed et. al., Pediatric Radiation Oncology, 2017 (in press)
Razek et. al., *Cancer*, 1980

RT Dose Escalation
Contemporary Planning Techniques

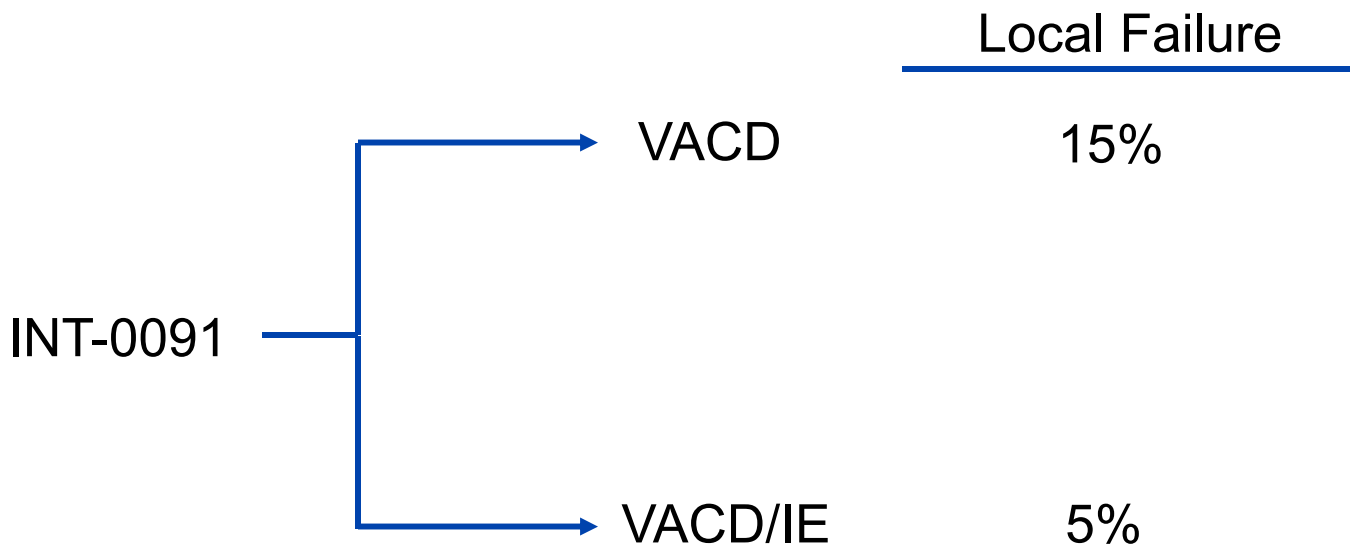


IMRT IMPT

Doses ~70.0 GyRBE for osteosarcoma, chordoma, and chondrosarcoma

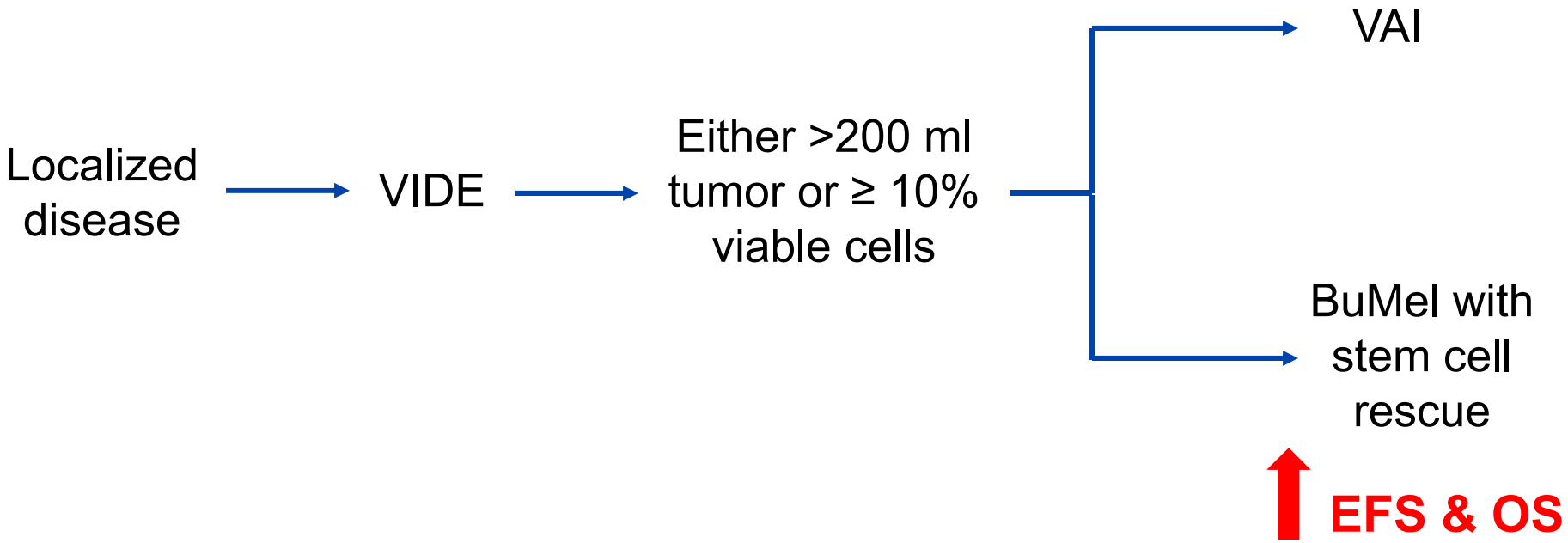
Ahmed et. al., Pediatric Radiation Oncology, 2017 (in press)
Ciernik et. al., *Int J Rad Bio Phys*, 2011
DeLaney et. al., *Int J Rad Bio Phys*, 2009
Indelicato et. al., *Int J Rad Bio Phys*, 2016

Intensification of Local Therapy
Systemic Agents



Grier et. al., *N Engl J Med*, 2003

EURO-EWING99 R2



VIDE = vincristine, doxorubicin, ifosfamide, etoposide
VAI= vincristine, actinomycin D, ifosfamide
BuMel = busulfan, melphalan

Intensification of Local Therapy
Systemic Agents

- AEWS1031: VDC/IE/VTC
- SARC 028: Pembrolizumab
  - No significant response in bone tumors
- DNA repair pathway inhibitors
  - Ewing sarcoma cells express high levels of DNA replication stress

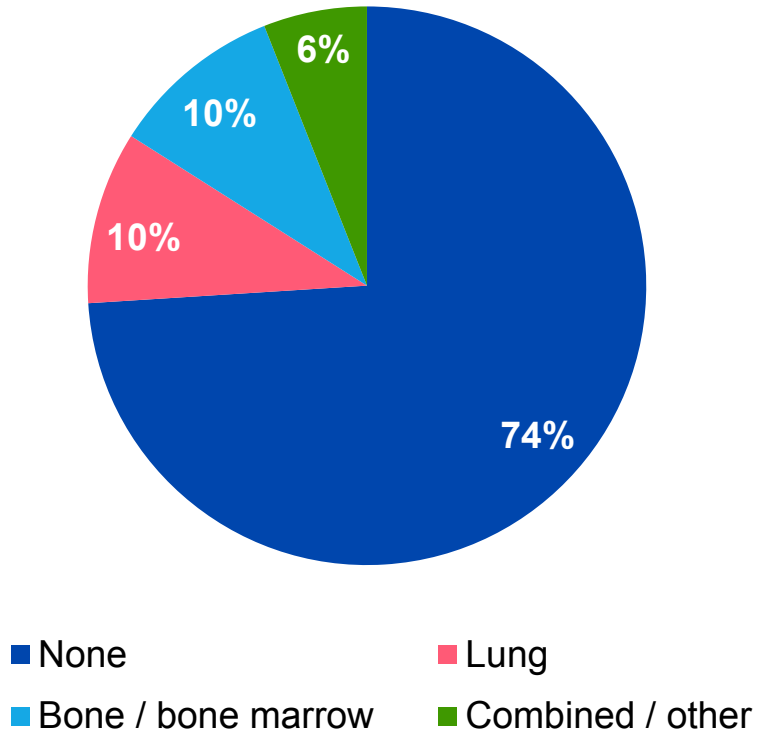
Childrensoncologygroup.org
Mackintosh et. al., *Oncogene*, 2013
Nieto-Soler et. al., *Oncotarget*, 2016
Tawbi et. al., ASCO Annual Meeting, 2016

What Are The Future Directions For Local Therapy In Ewing Sarcoma?

Future Directions

- Comprehensive analysis of pelvis tumors treated on INT-0091, INT-0154, and AEWS0031 trials
- Further characterization of tumors at diagnosis and in response to neoadjuvant chemotherapy with newer imaging techniques
- High risk pilot study

Metastatic Disease



	INT-0091 5 year OS
Localized disease	72%
Metastatic disease	34%

Ahmed et. al., *Pediatric Radiation Oncology*, 2017 (in press)
Grier et. al., *N Engl J Med*, 2003

Metastatic Disease
Local Tumor(s) Control

Series	Treatment	EFS
Methodist	Absence of local therapy to primary site	Median OS: 9 mo
EURO-EWING99	Absence of local therapy to metastases Local therapy to metastases	17% 39%
Mayo Clinic	Absence of local therapy to all metastases Local therapy to all metastases	0% 11%

- AEWS1221: SBRT for bone metastases

Ahmed et. al., *Am J Clin Oncol*, 2014
Childrensoncologygroup.org
Hauesler et. al., *Cancer*, 2009
Paulino et. al., *Am J Clin Oncol*, 2013

Conclusions

- Local therapy crucial component of multimodal therapy for Ewing Sarcoma
- Choice of local therapy modality made on a case by case basis
- Current 5 year local failure rates: 3-25%

Conclusions

- Highest risk cohorts for local failure:
  - Patients treated with definitive radiotherapy
    - Especially pelvis and extremity tumors
  - Adult patients
  - Question tumor size

Conclusions

- Additional prognostic factors
  - Alternative to tumor size in maximum dimension
  - New imaging techniques
  - Response to neoadjuvant chemotherapy

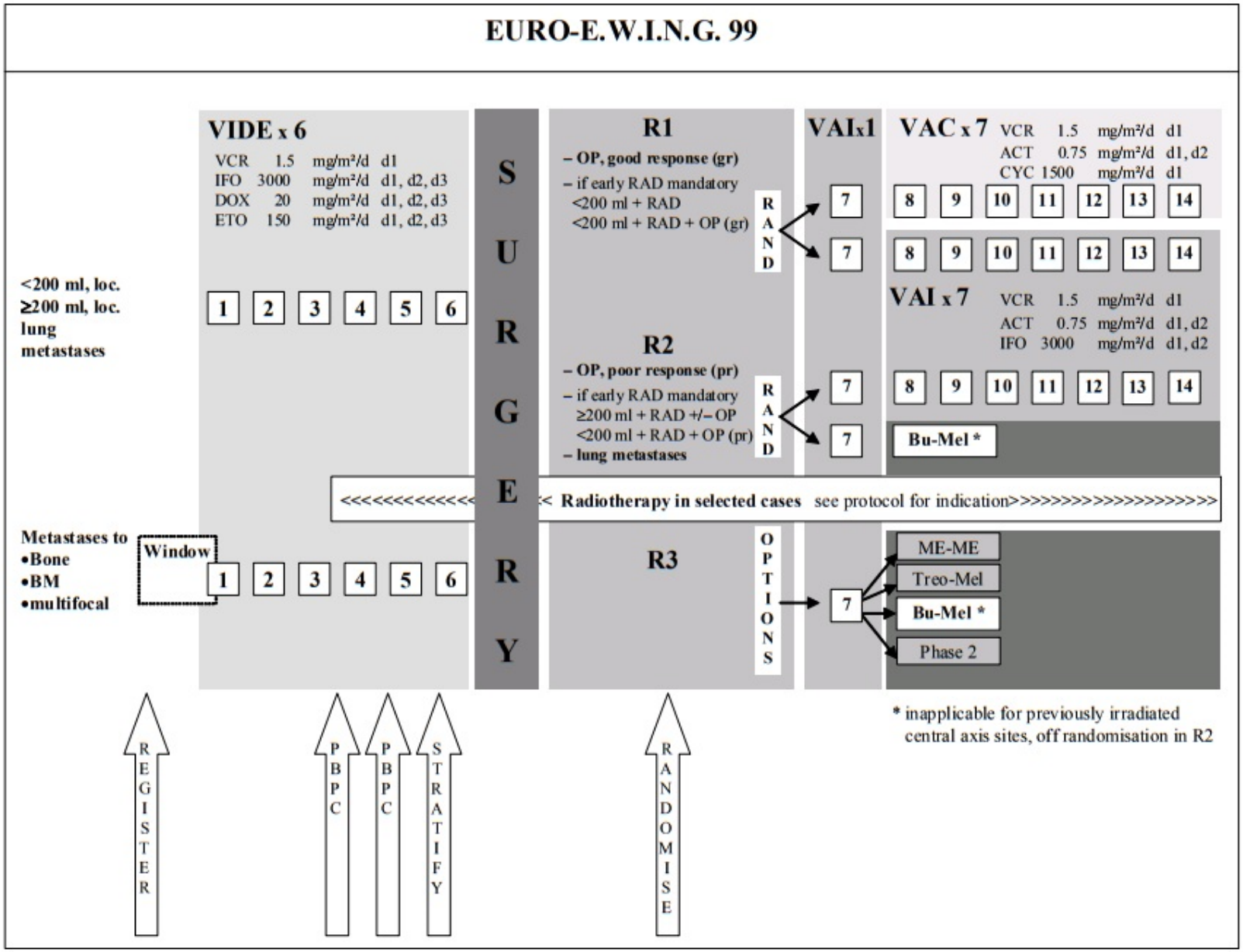
Conclusions

- Local therapy intensification for high risk patients
  - S+RT
  - RT dose escalation
  - New systemic agents
  - Local therapy of all metastases

Acknowledgements

- Co-investigators
- Children’s Oncology Group
- Dr. Nadia Laack

Questions & Discussion


EURO-E.W.I.N.G. 99
VIDE x 6
VCR 1.5 mg/m²/d d1
IFO 3000 mg/m²/d d1, d2, d3
DOX 20 mg/m²/d d1, d2, d3
ETO 150 mg/m²/d d1, d2, d3
<200 ml, loc.
≥200 ml, loc.
lung
metastases
1 2 3 4 5 6
Metastases to
•Bone
•BM
•multifocal
Window
1 2 3 4 5 6
S U R G E R Y
R1
– OP, good response (gr)
– if early RAD mandatory
<200 ml + RAD
<200 ml + RAD + OP (gr)
RAND
R2
– OP, poor response (pr)
– if early RAD mandatory
≥200 ml + RAD +/– OP
<200 ml + RAD + OP (pr)
– lung metastases
RAND
R3
OPTIONS
VAIx1
7
7
7
7
7
VAC x 7 VCR 1.5 mg/m²/d d1
ACT 0.75 mg/m²/d d1, d2
CYC 1500 mg/m²/d d1
8 9 10 11 12 13 14
8 9 10 11 12 13 14
VAI x 7 VCR 1.5 mg/m²/d d1
ACT 0.75 mg/m²/d d1, d2
IFO 3000 mg/m²/d d1, d2
8 9 10 11 12 13 14
Bu-Mel *
<<<<<<<<<<<< Radiotherapy in selected cases see protocol for indication>>>>>>>>>>>>>>>>>>>
ME-ME
Treo-Mel
Bu-Mel *
Phase 2
* inapplicable for previously irradiated central axis sites, off randomisation in R2
REGISTER
PBPC
PBPC
STRATIFY
RANDOMISE