Brachytherapy for Paediatric Malignancies

Indications & Outcomes

Tata Memorial Hospital
(TMH)

Advanced Centre for Treatment, Research
& Education in Cancer (ACTREC)

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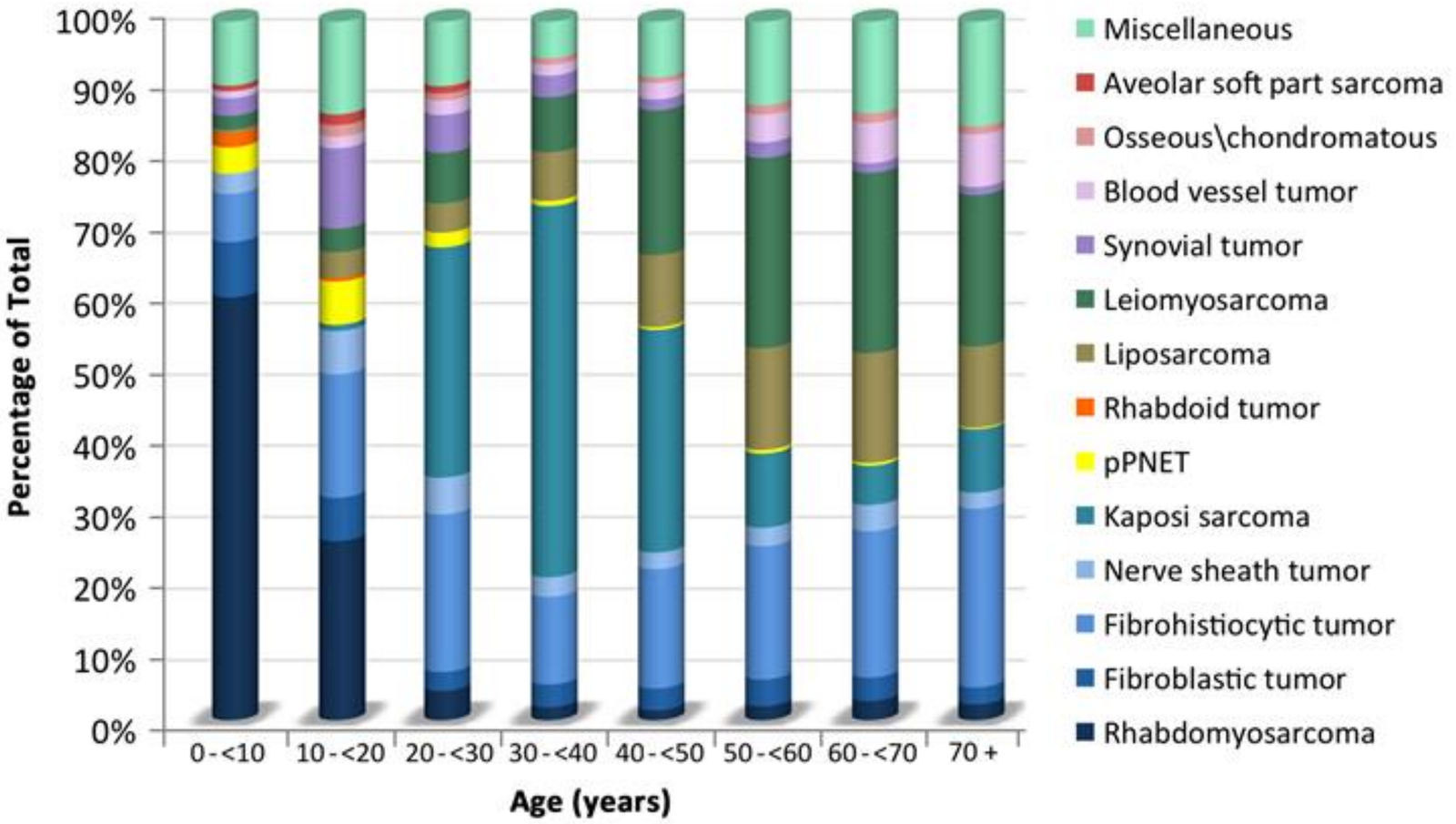
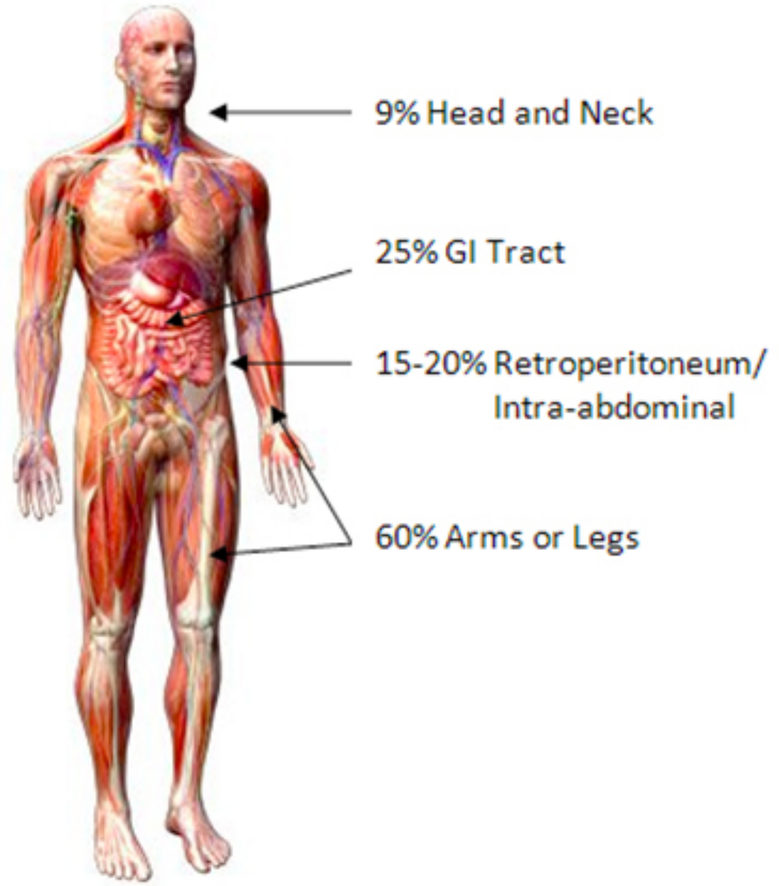
Nothing to Disclose

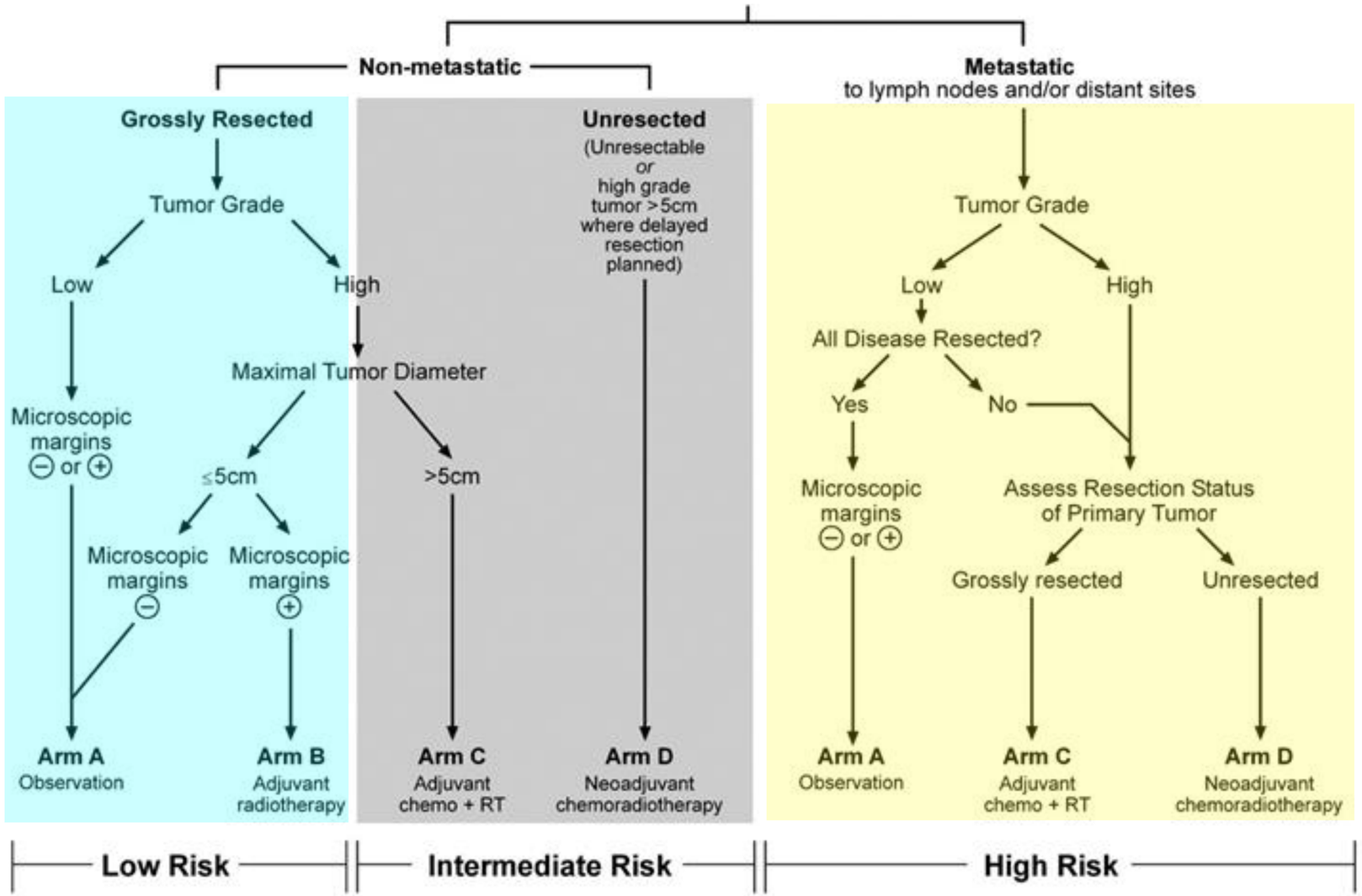
Photographs with Consent

STS Histological Subtypes/ Sites/ Age





Risk Stratification in COG NRSTS Studies



Non-metastatic unresected paediatric non-rhabdomyosarcoma soft tissue sarcomas: Results of a pooled analysis from United States and European groups

Andrea Ferrari[a,*], Rosalba Miceli[b], Annie Rey[c], Odile Oberlin[c], Daniel Orbach[d], Bernadette Brennan[e], Luigi Mariani[b], Modesto Carli[f], Gianni Bisogno[f], Giovanni Cecchetto[g], Gian Luca De Salvo[h], Michela Casanova[a], Max M. Vannoesel[i], Anna Kelsey[j], Michael C. Stevens[k], Meenakshi Devidas[l], Alberto S. Pappo[m], and Sheri L. Spunt[m]

Participating groups

POG 8654, (1986–1993) – 20 pts

SJCRH, (1981–2004) – 21 pts

INT Milan, (1980–2005) – 43 pts

POG 9553, 1996–2000) – 21 pts

AIEOP-STSC, (1980–2005) – 63 pts[a]

SIOP-MMT, (1980–2005) – 136 pts[b]

Inclusion criteria

Study period: 1980–2005

Patient's age: 0–21 years

Histological diagnosis: synovial sarcoma or adult-type NRSTS

IRS group III

No distant metastases

All tumour sites except for the viscera

No pre-treatment (apart from initial resection)

Treatments details

Initial surgical approach

Delayed surgery

Radiotherapy

Chemotherapy

Response to chemotherapy

n = 304
1980 - 2005
Multimodality Treatment
Majority: Synovial Sa & MPNST

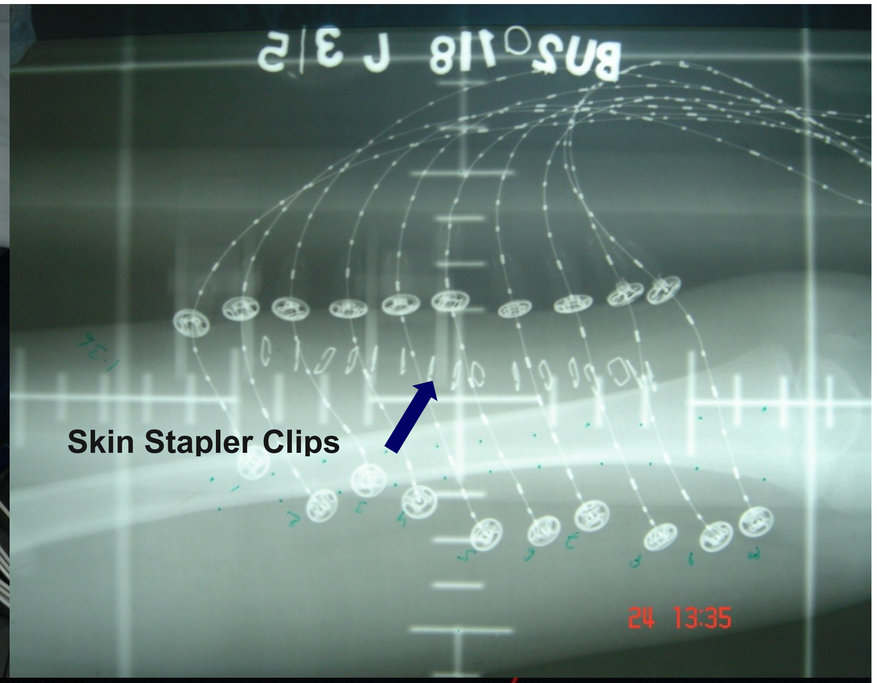
Eu J Cancer 20011

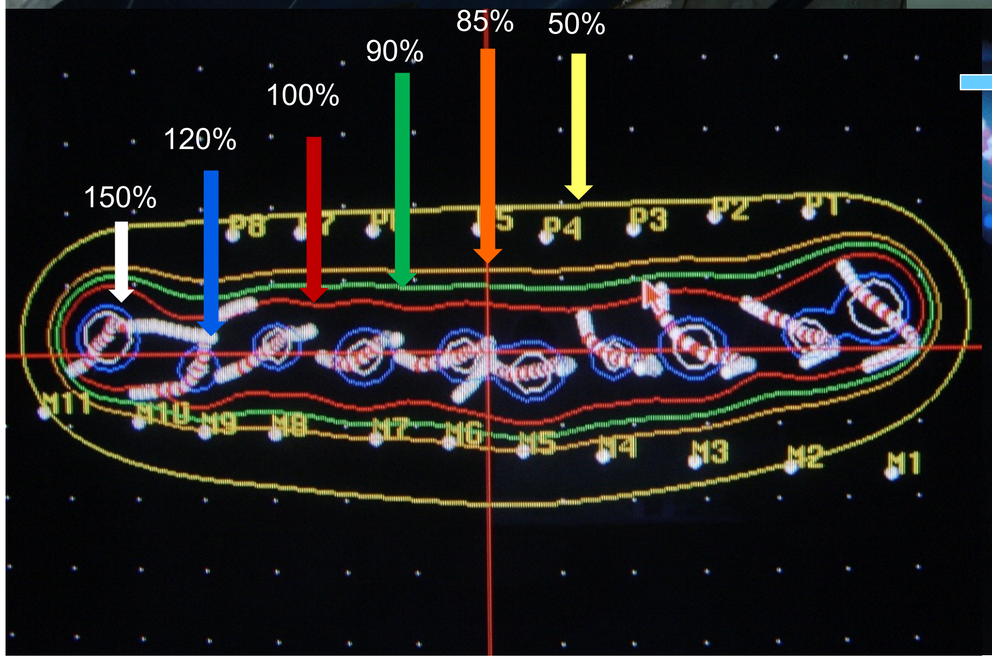
Analysis of the effect of prognostic factors on overall survival using the multivariable Cox model.

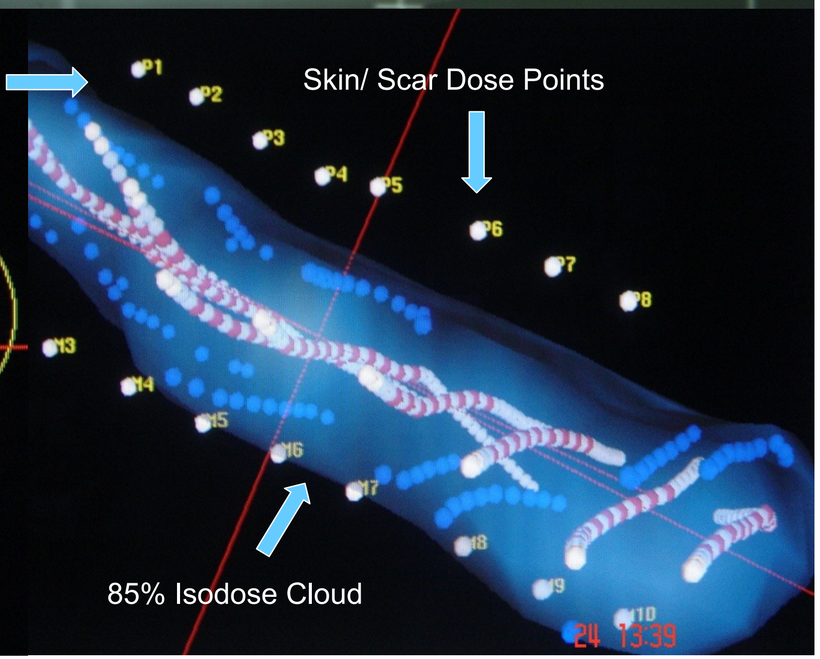
	HR	CI	P[a]
Age, years			
≥10 versus <10	1.7	(1.1,2.6)	0.018
Histologicalsubtype			
MPNST versus other	2.3	(1.5,3.7)	<0.001
Synovial sarcoma versus other	0.7	(0.4,1.2)	
Tumour site			
Head–neck versus extremity	2.0	(1.1,3.7)	0.001
Other versus extremity	2.7	(1.6,4.5)	
Tumour size, cm			
>5 versus ≤5	2.5	(1.3,4.6)	0.006
Delayed surgery			
Not performed versus complete	4.3	(2.4,7.5)	<0.001
Not specified versus complete	3.3	(1.1,9.6)	
Incomplete versus complete	2.2	(1.1,4.3)	
Radiotherapy			
Not performed versus performed	1.8	(1.2,2.8)	0.003
Response to chemotherapy			
Minor versus major	2.1	(1.1,3.7)	<0.001
None versus major	3.2	(1.9,5.1)	

INTERSTITIAL BRACHYTHERAPY

PLANNING & DOSIMETRY







Dose optimization of intra-operative high dose rate interstitial brachytherapy implants for soft tissue sarcoma

Results: Target coverage was suboptimal with coverage index (CI = 0.67) when dose points were defined at the central plane while it was superior when the dose points were defined at the target surface (CI=0.93). The coverage of graphically optimized plans (GrO) was similar to non-GrO with dose points defined on surface or perpendicular to the implant axis. A similar pattern was noticed with conformity index (0.61 vs. 0.82). GrO were more conformal and less homogeneous compared to non-GrO. Sum index was superior for dose points defined on the surface of the target and relatively inferior for plans with dose points at other locations (1.35 vs. 1.27).

Conclusions: Optimization with dose points defined away from the implant plane and on target results in superior target coverage with optimal values of other indices. GrO offer better target coverage for implants with non-uniform geometry and target volume.

Swamidas V. Jamema, Pramod K. Sharma, Dayananda Sharma, Siddhartha Laskar[1], Deepak D. Deshpande, Shyam K. Shrivastava[1]

- **Dose Point Optimization** much superior for single plane implants than geometric optimization
- **Graphical Optimization** can be used as a tool to compensate for the geometrical irregularities of implant and the target. While CI and COIN improve with graphical optimization, other indices such as EI, OI and HI become relatively inferior.
- **Graphical Optimization** improves target coverage at the expense of dose homogeneity; it should be used with caution to avoid creating zones of hyper-dose.

IS BRACHYTHERAPY EFFECTIVE ?

MSKCC Trial (Pisters et al, JCO 1996)

Extremity / Superficial Trunk STS (n=164)
- LSS Alone (n=86)
- LSS + Interstitial Brachytherapy (n=78)

Brachytherapy: 42-45Gy in 4-6 days

Median FU: 76mths

Local Control
- LSS Alone: 69%
- LSS + Interstitial Brachytherapy: 82%

p=0.04

+ve impact in 119 pts. with high grade sts only
no improvement in 45 pts. with low grade sts

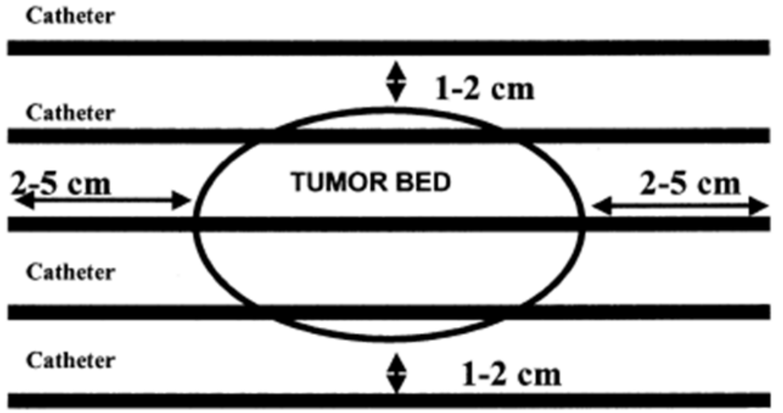
Level I Evidence

Tata Memorial Hospital Guidelines

TARGET VOLUME

Radical brachytherapy : GTV + 2-3 cm margin

Brachytherapy as boost: GTV + 2 cm margin



DOSIMETRY

LDR Manual afterloading technique: Paris system

HDR remote afterloading:

Dose point (0.5cm) +/- Graphical Optimization
Reference Isodose: 85%

SIMULATION & START:

3nd -5th day after surgery (Influenced by dose to Skin/ Scar/ Flap)

DOSE

NRSTS Brachy Only (LDR): 45-50Gy @ 45-50cGy/hr, ***(HDR): 36Gy/9# @ 4Gy/# x 2 #/ day***

NRSTS Brachy as Boost (LDR): 15-20Gy @ 45-50cGy/hr, ***(HDR): 15Gy/5# @3Gy/# x 2#/ day***

RCT ***R0 or R1 (HDR): 28Gy/ 7# @ 4Gy/ # x 2 #/ day***

RCT ***R2 (HDR): 32Gy/ 8# @ 4Gy/ # x 2#/ day***

Interstitial Brachytherapy for Childhood Soft Tissue Sarcoma

Siddhartha Laskar, MD,[1]* Gaurav Bahl, MD,[1] Mary Ann Muckaden, MD,[1] Ajay Puri, MS,[2] Manish G. Agarwal, MS,[2] Nikhilesh Patil, MD,[1] Shyam K. Shrivastava, MD,[1] and Ketayun A. Dinshaw, FRCR[1]

Background. To evaluate the efficacy of interstitial brachytherapy (BRT) in children undergoing combined modality treatment for soft tissue sarcomas (STS). ***Procedure.*** From September 1984 to December 2003, 50 children (median age 13 years, range 1 to 18) with STS who received BRT as part of loco-regional treatment were included. There were 30 males and 20 females, the majority (68%) had primary lesions, synovial sarcoma (32%) was the most common histological type, and 26% had high-grade lesions. Treatment included wide local excision and BRT with or without external beam radiotherapy (EBRT). Thirty children (60%) received BRT alone. ***Results.*** After a median follow-up of 51 months, the local control (LC), disease-free survival, and overall survival were 82%, 68%, and 71%, respectively. LC was superior in patients with tumor size ≤ 5 cm versus >5 cm (96% vs. 67%, $P=0.04$), symptom duration <2 months versus >2 months (100% vs. 73%, $P=0.05$), and Grade I versus Grade II versus Grade III tumors (100% vs. 93% vs. 57%, $P=0.03$). Children receiving a combination of BRT and EBRT had comparable LC to those receiving BRT alone (78% vs. 84%, $P=0.89$). There was no significant difference in LC for patients receiving LDR versus HDR BRT (77% vs. 92%, $P=0.32$, for BRT alone; and 67% vs. 100%, $P=0.17$, for BRT+EBRT). ***Conclusion.*** Interstitial BRT with or without EBRT appears to result in satisfactory outcome in children with STS. Radical BRT alone, when used judiciously in select groups of children, results in excellent local control and functional outcome with reduced treatment-related morbidity. Pediatr Blood Cancer

Key words: interstitial brachytherapy; pediatric; radiotherapy; soft tissue sarcoma

Median FU: 51mths 2007

LC: 82%

DFS: 68%

OS: 71%

Laskar et al, Pediatric Blood & Cancer 2007

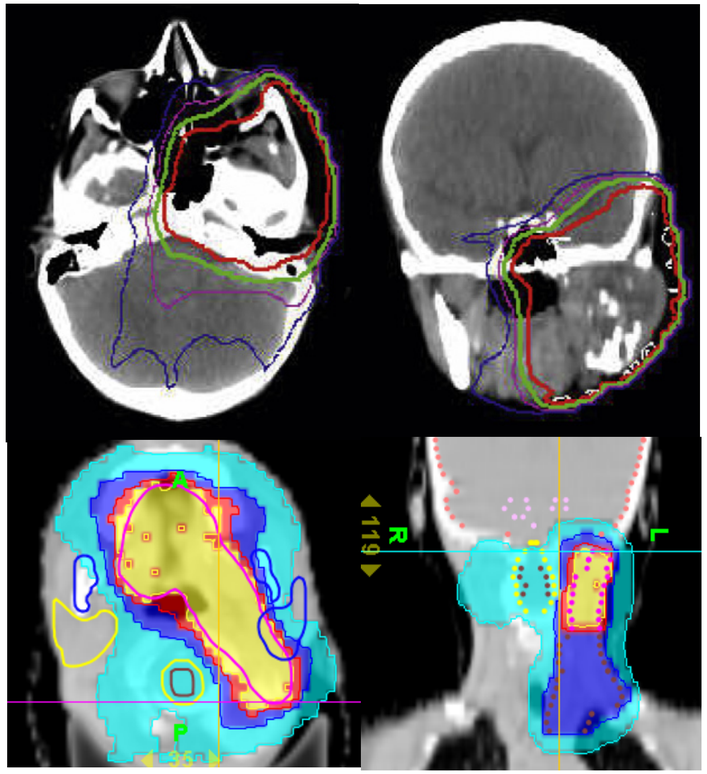
Prognostic factor	5-year local control (LC)	5-year disease free survival (DFS)	5-year overall survival (OS)
Sex			
Male	80%	62%	60%
Female	83% ($P=0.99$)	76% ($P=0.66$)	92% ($P=0.28$)
Age			
≤10 years	81%	81%	100%
>10 years	82% ($P=0.65$)	63% ($P=0.67$)	63% ($P=0.15$)
Symptom duration			
<2 months	100%	100%	100%
>2 months	73% ($P=0.05$)	51% ($P=0.01$)	55% ($P=0.04$)
Tumor depth			
Superficial	92%	92%	100%
Deep	78% ($P=0.41$)	56% ($P=0.11$)	65% ($P=0.08$)
Size of tumor			
≤5 cm	96%	89%	93%
>5 cm	67% ($P=0.04$)	44% ($P=0.01$)	52% ($P=0.06$)
Primary site			
Extremities	82%	66%	69%
Axial/trunk	86% ($P=0.99$)	86% ($P=0.65$)	100% ($P=0.38$)
Type of lesion			
Primary	89%	71%	71%
Recurrent	67% ($P=0.09$)	56% ($P=0.22$)	68% ($P=0.57$)
Tumour grade			
Gr I	100%	100%	100%
Gr II	93%	75%	81%
Gr III	57% ($P=0.03$)	29% ($P=0.03$)	36% ($P=0.12$)
Surgical margins			
Negative	82%	68%	68%
Positive/close	80% ($P=0.74$)	67% ($P=0.88$)	100% ($P=0.45$)
Treatment			
BRT alone	84%	84%	95%
BRT + EBRT	78% ($P=0.89$)	45% ($P=0.11$)	55% ($P=0.10$)
Radiotherapy type (BRT + EBRT)			
LDR	67%	28%	31%
HDR	100% ($P=0.17$)	100% ($P=0.05$)	100% ($P=0.17$)
Radiotherapy type (BRT alone)			
LDR	77%	77%	90%
HDR	92% ($P=0.32$)	92% ($P=0.33$)	100% ($P=0.34$)

Laskar et al, Pediatric Blood & Cancer 2007

Head & Neck RMS

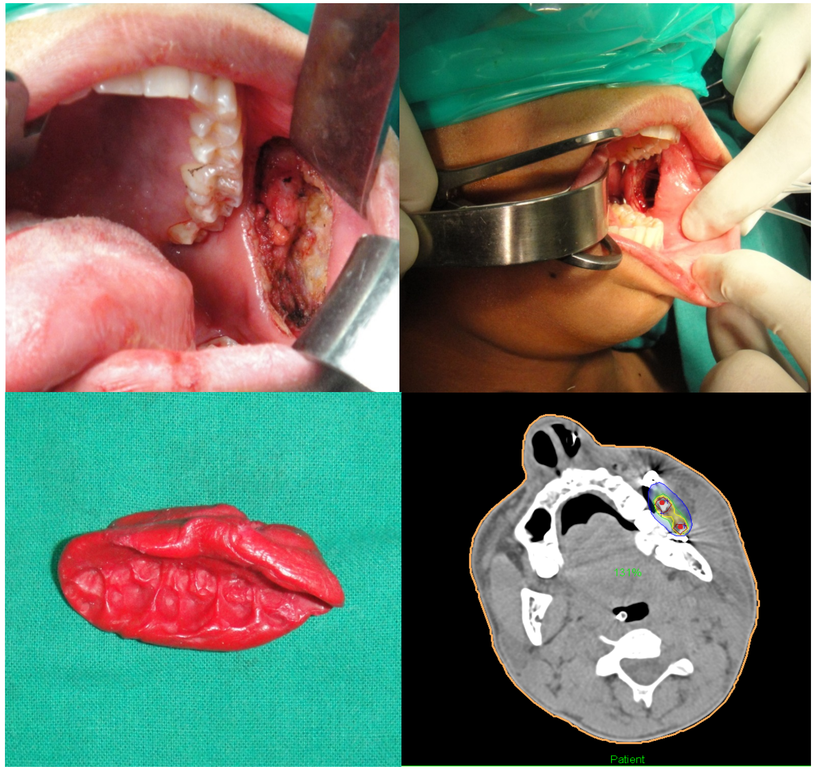
Parameningeal

Middle ear, Paranasal sinuses, Nasopharynx,
Nasal cavity, Infratemporal fossa, &
Parapharyngeal area

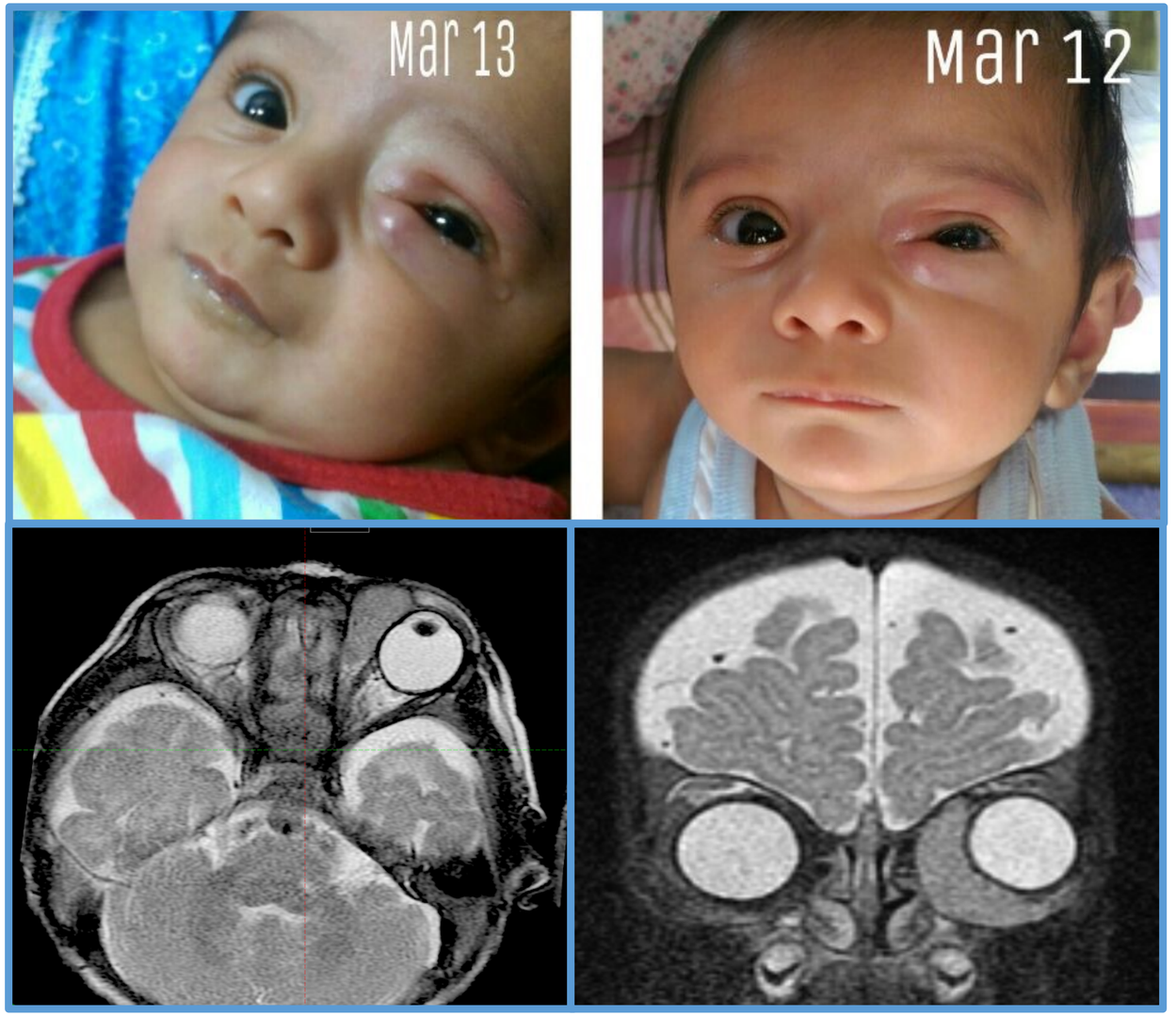


Non - Parameningeal

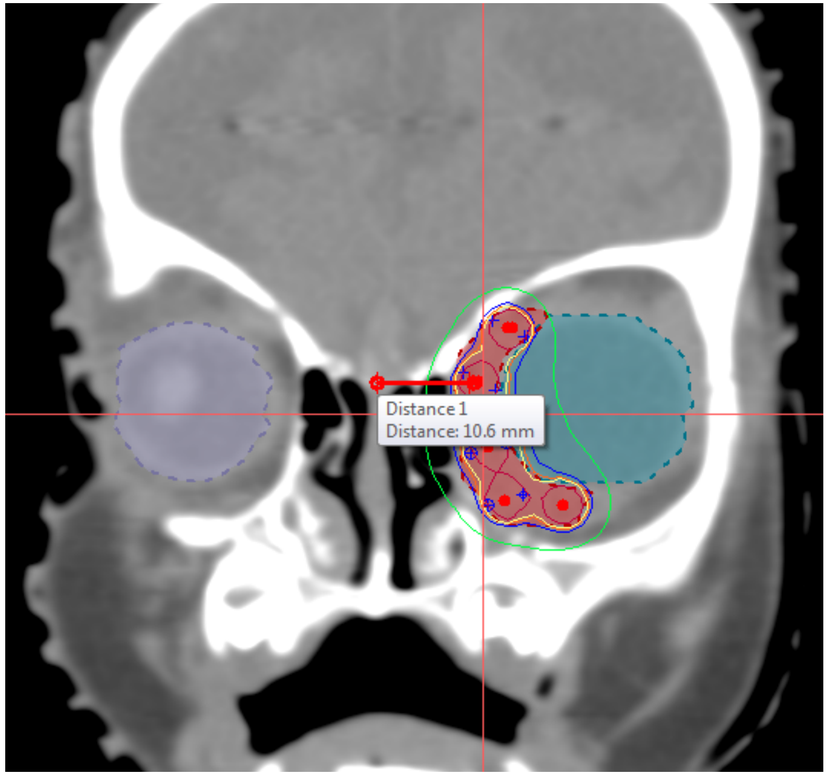
Orbit, Buccal Mucosa, Oral Cavity
Oropharynx, Hypopharynx, & Larynx

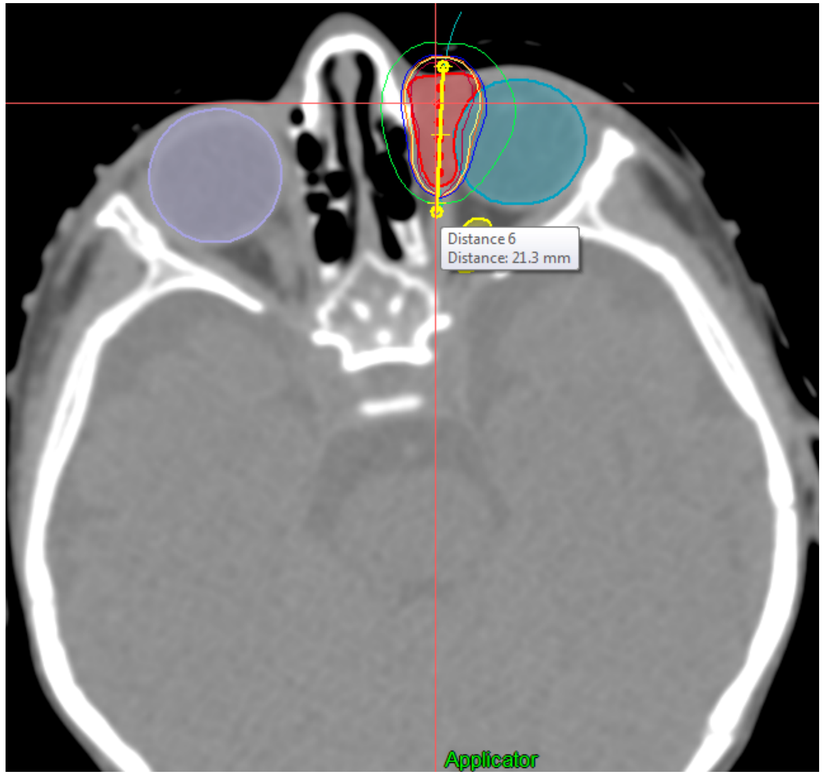


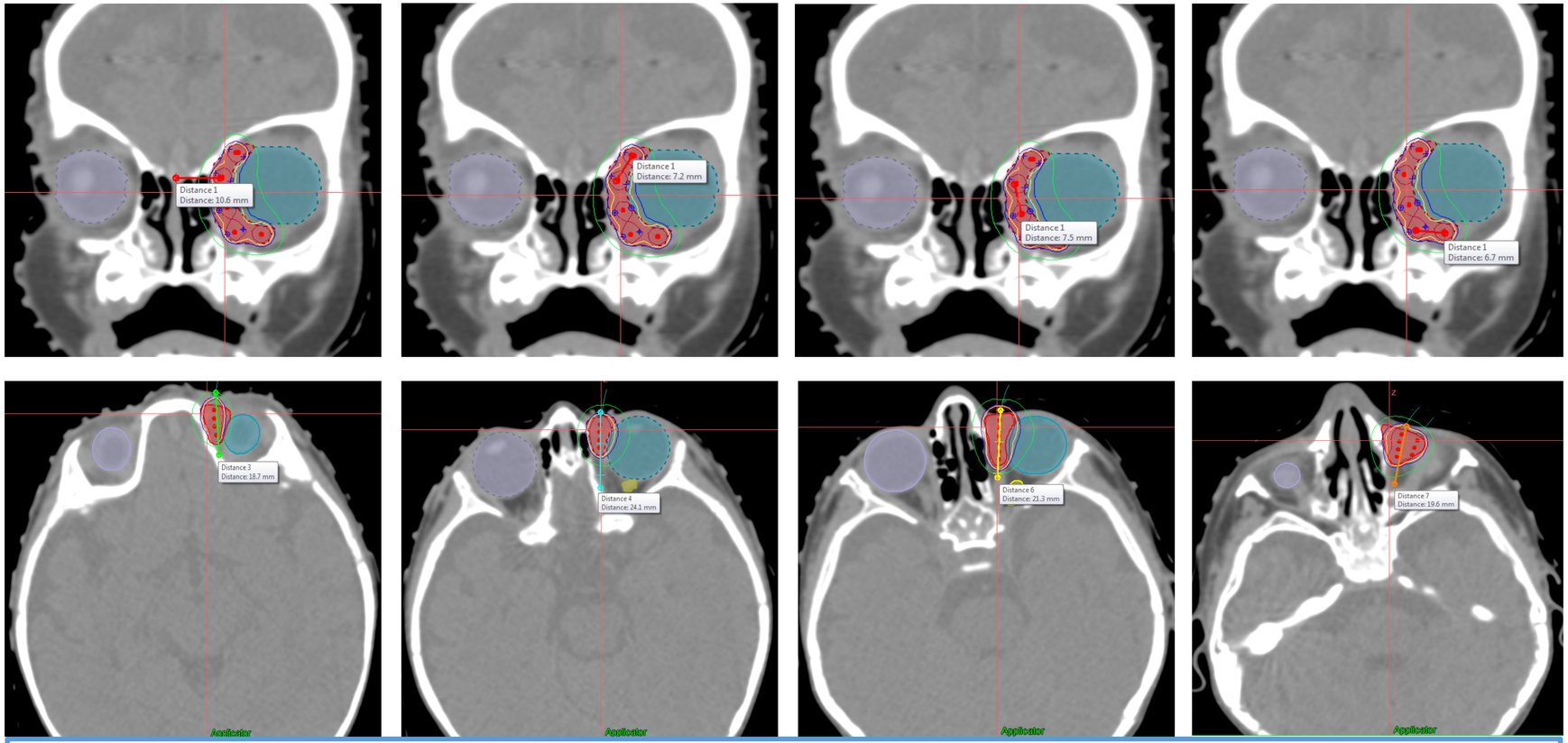
ARMS Lt Orbit (4mths M)



Pre Planning





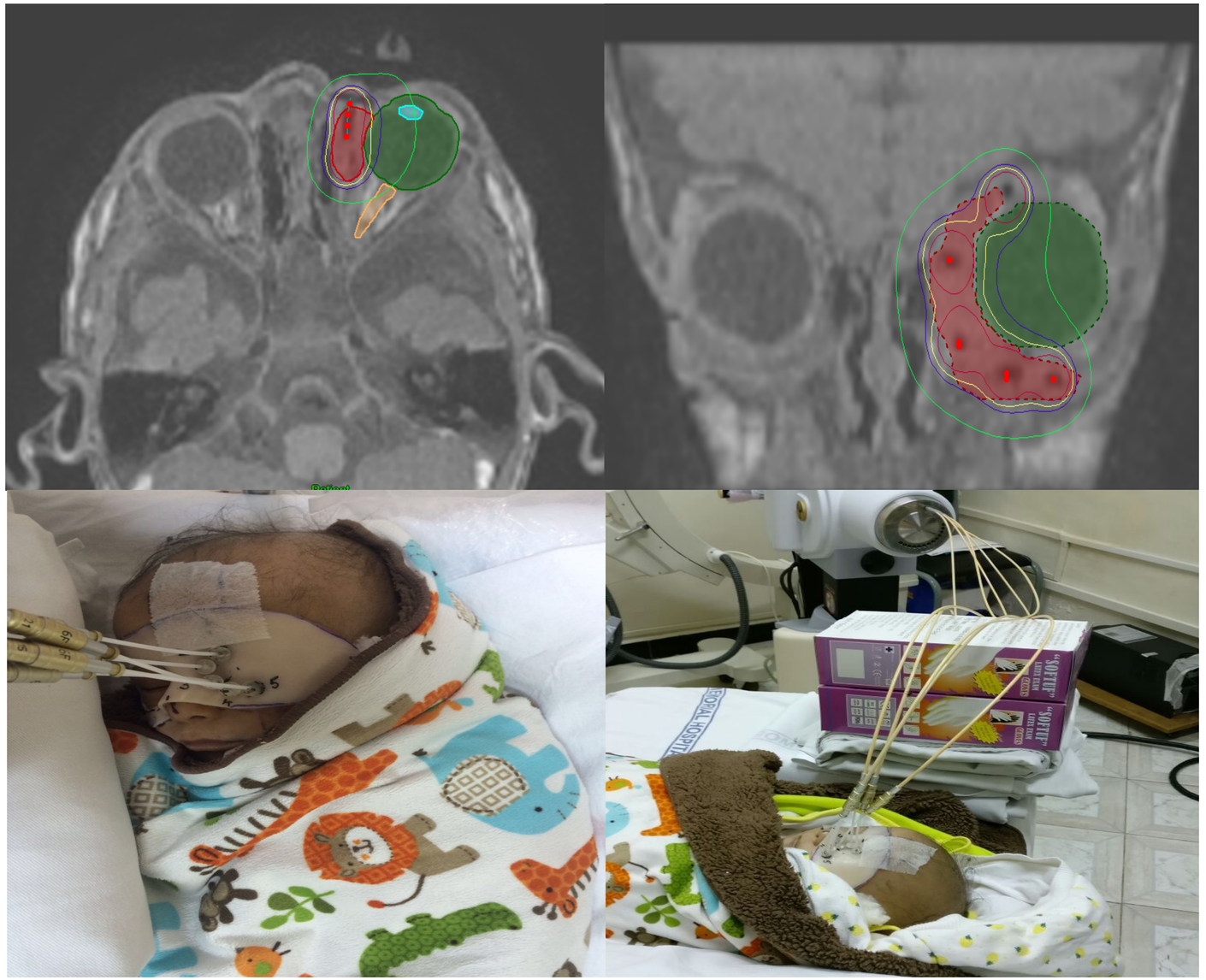


PRE-Planning→ Planning CT scan was done to determine

1. Ideal needle position
2. Safe depth for each needle
3. First needle position → Nasion as a reference point

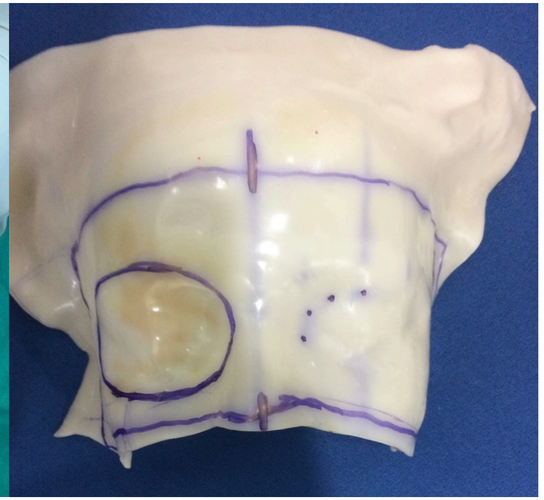
Procedure

MRI Fusion & Treatment

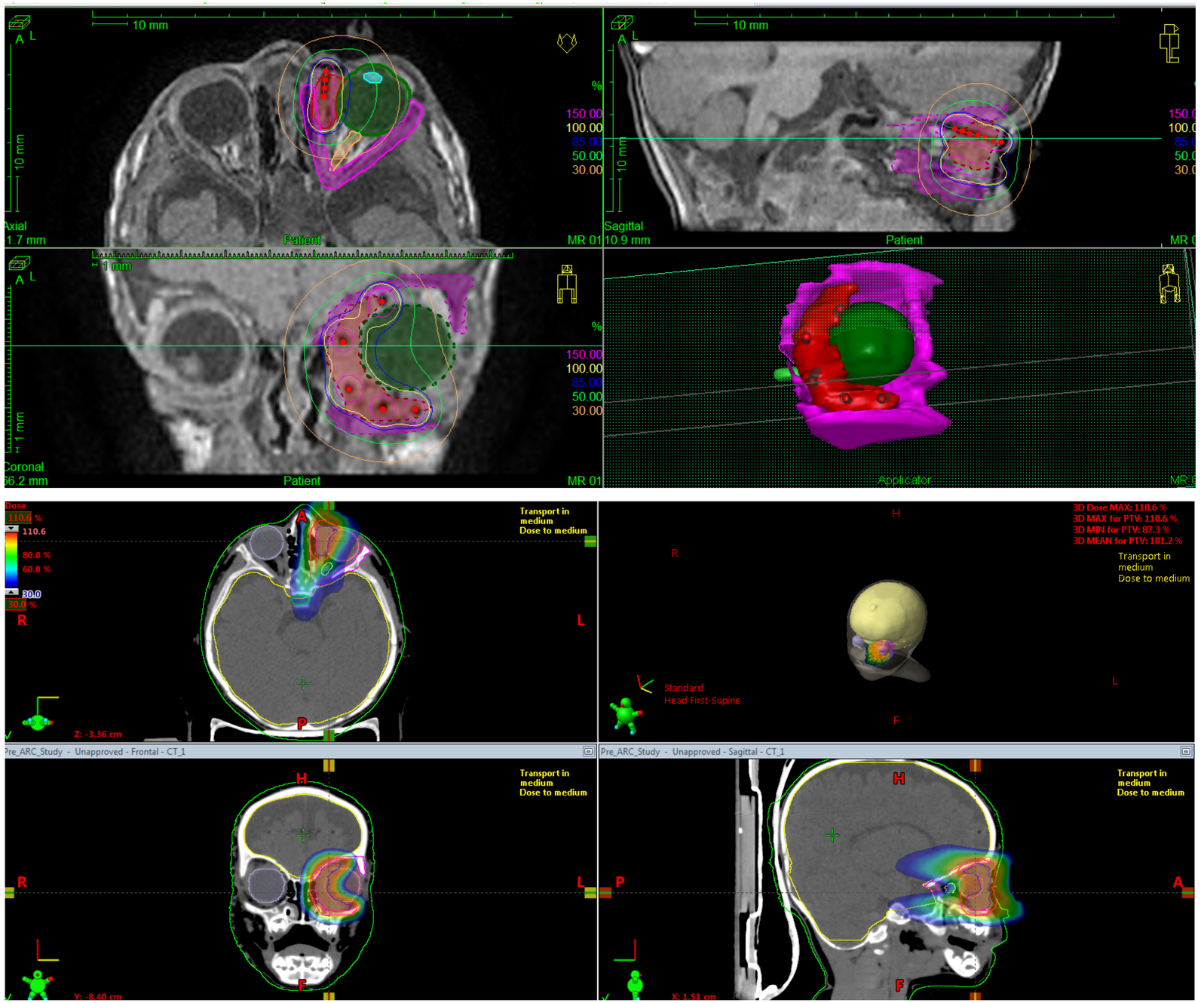


32Gy/ 8# @ 4Gy/ # BD






Dosimetric Comparison of Brachytherapy & IMRT



Dosimetric Comparison of EBRT & BRT

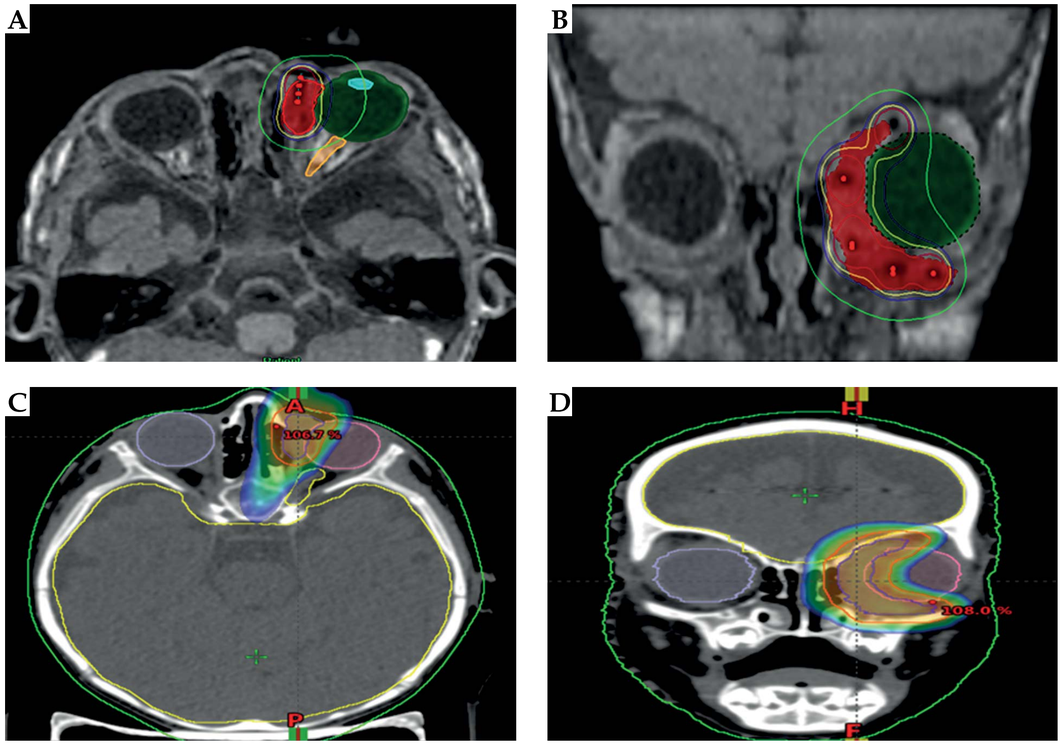


Fig. 5. A and B) High-dose-rate brachytherapy plan on magnetic resonance imaging sequences (isodose lines: yellow – 100% and green – 50%). **C and D)** Rapid arc external beam radiotherapy (EBRT) plan (isodose wash: orange – 95%, dark blue – 50%). Note higher doses to pituitary and bony orbit with EBRT

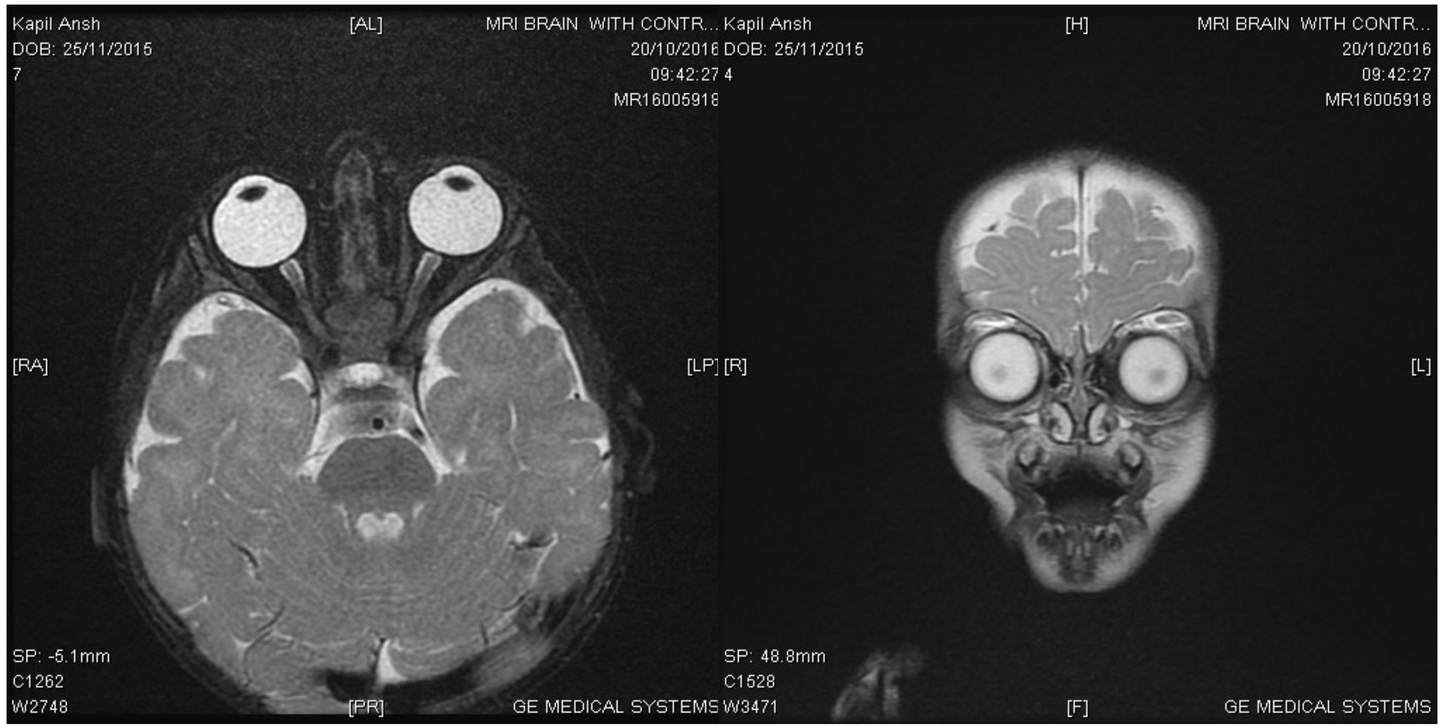
Dosimetric parameters of external beam radiotherapy and brachytherapy plans

Structures	EBRT rapid arc (%)	Brachytherapy (%)
CTV (mean dose)	101	158
CTV D_{90}	100	92
CTV V_{100}	95	90
CTV V_{150}	–	30
CTV V_{200}	–	16
DHI	–	66
Eye left (mean dose)	61	61
Lens left (mean dose)	66	51
Optic nerve left (max dose)	72	54
Bony orbit left (mean dose)	68	39
Pituitary gland (mean dose)	42	6

EBRT – external beam radiotherapy, BT – brachytherapy, CTV – clinical target volume, D_{90} – minimum dose received by 90% of the target volume, V_{100} – volume receiving by 100% of the prescription dose, V_{150} – volume receiving by 150% of the prescription dose, V_{200} – volume receiving by 200% of the prescription dose, DHI (dose homogeneity index) – $(V_{100}–V_{150})/V_{100}$

Dose Delivered: 32Gy/8# (4Gy b.i.d)

MRI 3 Months Post Brachytherapy



Clinical Outcome 3 Mths. Post Brachy

Interstitial brachytherapy for orbital soft tissue sarcoma: an innovative technique

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J Contemp Brachytherapy 2017; 9, 5: 466–471

Conservative surgery plus brachytherapy treatment for boys with prostate and/or bladder neck rhabdomyosarcoma: a single team experience

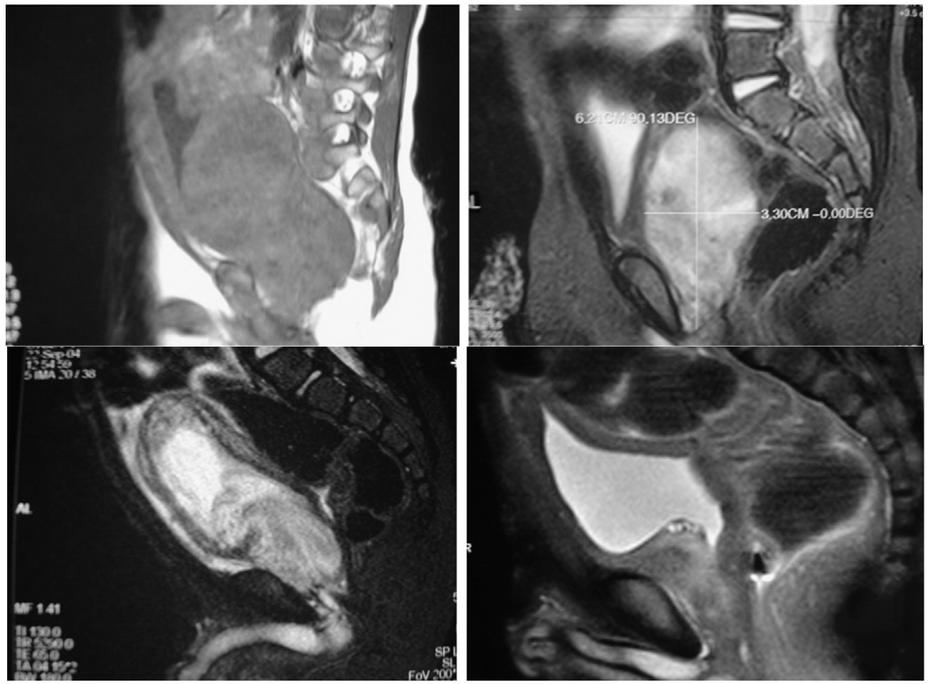
Hélène Martelli[a,*], Christine Haie-Meder[b], Sophie Branchereau[a], Stéphanie Franchi-Abella[c], Maria-Rosa Ghigna[d], Isabelle Dumas[e], Nathalie Bouvet[f], Odile Oberlin[g]

From 1991 to 2007, 26 boys with BP RMS

Treated according to SIOP (MMT 89, 95, and 98) & European protocol RMS 2005 protocols

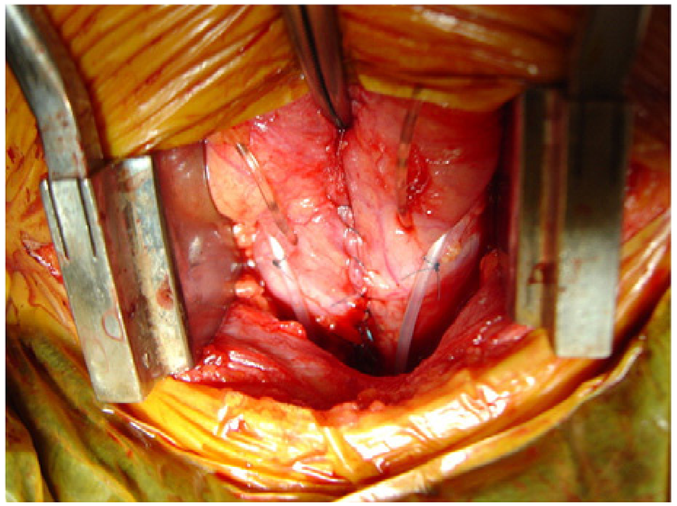
Evaluated for conservative combined treatment (ultrasound and MRI pre & post CTh)

No disease extension above level of Trigone



Journal of Ped Surg 2009

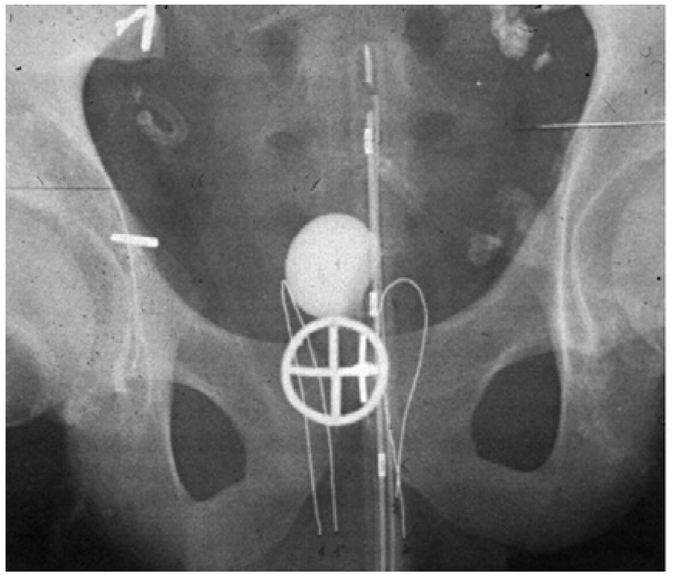
BRACHYTHERAPY TECHNIQUE



- Function preserving surgery
- Plastic tubes inserted via perineal approach
- 2 loops encompassing prostate & bladder neck
- Orthogonal X Rays for Dosimetry on day 5-7
- Manual afterloading Iridium wires used
- Dose: 60Gy @ 10Gy/ day
- Ext RT added for pts with nodal involvement

  EBRT Dose: 45Gy/ 25# @ 1.8Gy/ #

  Brachy Dose: 20Gy LDR
- CTh continued as per protocol



RESULTS

- Follow-up: Oncology team, Surgeon, Brachytherapist
- Tools: ultrasound, MRI, and cystoscopy for bladder tumors.
- Functional results assessed by clinical examination until 6 years of age.
- After 6 years, children with abnormal symptoms (diurnal incontinence, dribbling, etc) underwent urodynamic studies
- Parents and/or children were questioned about erection and for the older boys about sexual function.

Disease Control (Median FU - 4 years):

OS: 24/26 (92%)

Local Failure: 1/26 (4%)

Bladder Dysfunction: 1/22 (4.5%). 4 Pts very young for functional assessment

Boys > 6Yrs: 9/11 (82%) were normally continent

Urinary dribbling could be treated with bladder education

Complications:

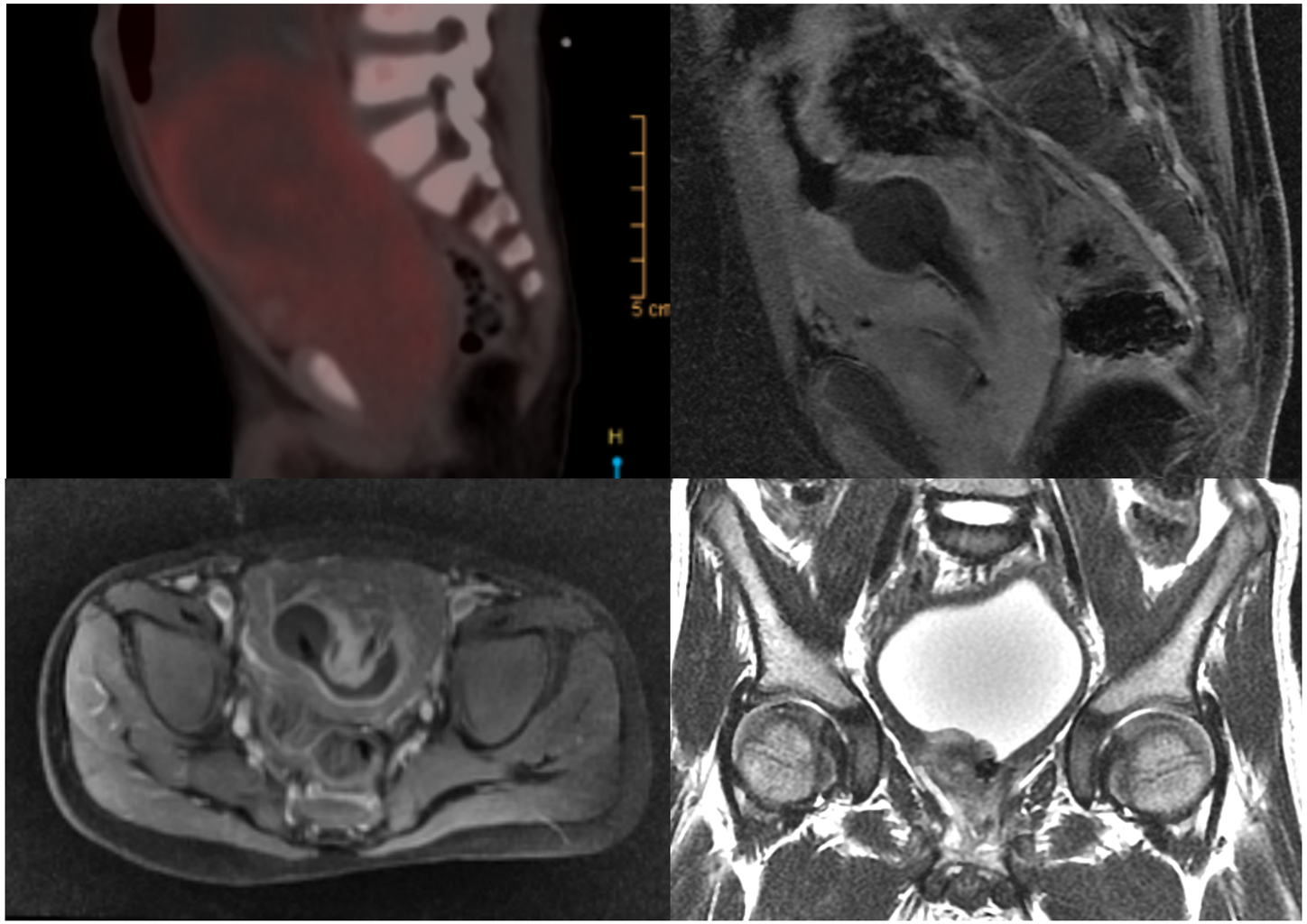
Mild Rectal bleeding post brachytherapy

Urethral stenosis (1 pt)

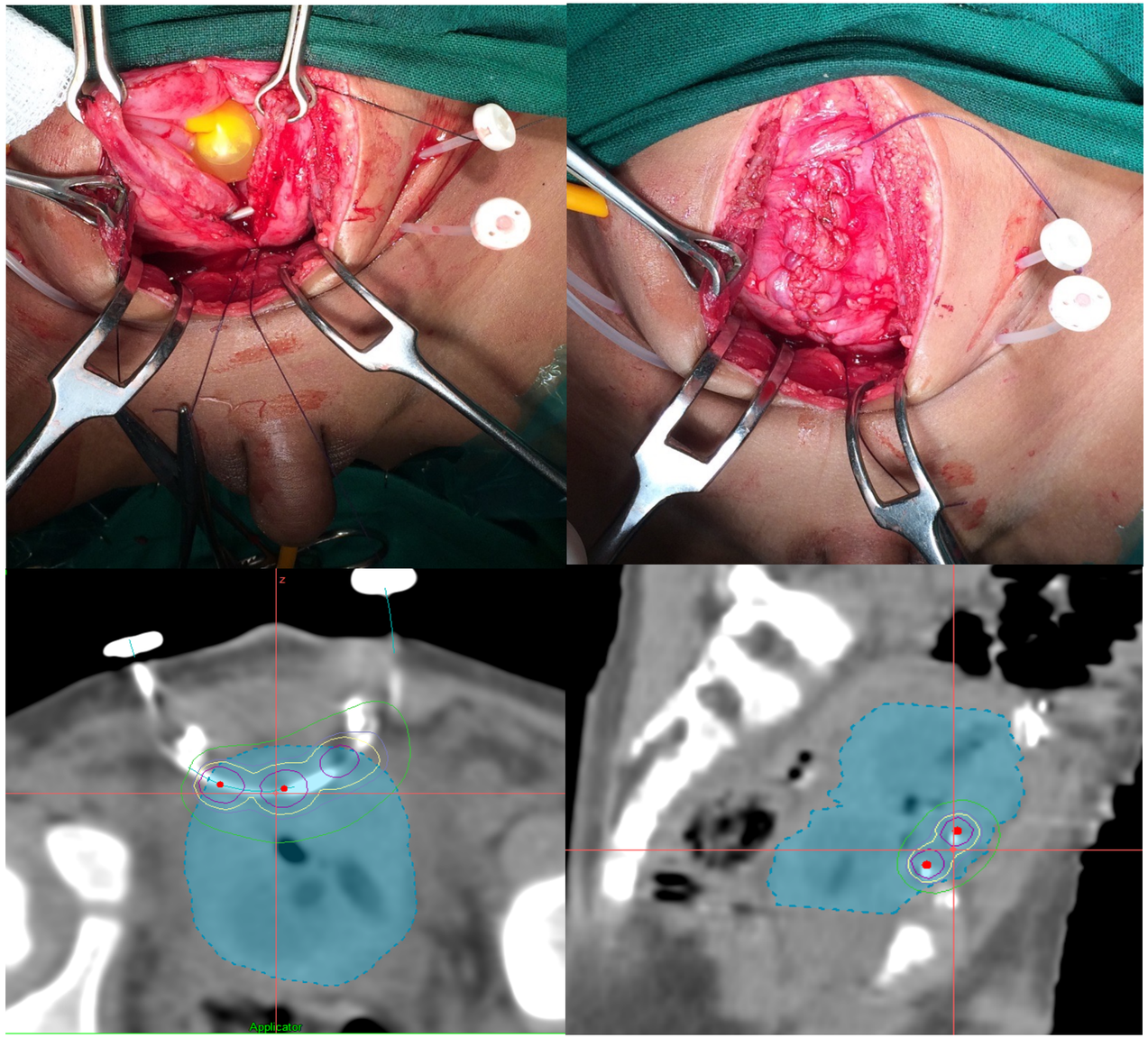
Erectile Function (2 Boys 17 & 18Yrs): Normal

Conclusion: Even if very long-term sequelae of brachytherapy cannot be evaluated, this conservative combined treatment may allow normal continence in nearly all patients, even after temporary diurnal incontinence and should be discussed as an alternative to external radiotherapy or radical surgery.

ERMS Urinary Bladder (3 1/2 Yrs M)



Tata Memorial Hospital (TMH) Technique for ERMS Urinary Bladder



Dose: 28Gy/ 7# @ 4Gy/ # HDR (One # per day)

Pediatr Blood Cancer 2011;57:76–83

Local Control and Outcome in Children With Localized Vaginal Rhabdomyosarcoma: A Report From the Soft Tissue Sarcoma Committee of the Children's Oncology Group

David O. Walterhouse, MD,[1]* Jane L. Meza, PhD,[2] John C. Breneman, MD,[3] Sarah S. Donaldson, MD,[4] Andrea Hayes-Jordan, MD,[5] Alberto S. Pappo, MD,[6] Carola Arndt, MD,[7] R. Beverly Raney, MD,[5] William H. Meyer, MD,[8] and Douglas S. Hawkins, MD[9]

Background. The local control approach for girls with non-resected vaginal rhabdomyosarcoma (RMS) enrolled onto Intergroup RMS Study Group (IRSG)/Children's Oncology Group (COG) studies has differed from that used at other primary sites by delaying or eliminating radiotherapy (RT) based on response achieved with chemotherapy and delayed primary resection. ***Procedures.*** We reviewed locoregional treatment and outcome for patients with localized RMS of the vagina on the two most recent COG low-risk RMS studies. ***Results.*** Forty-one patients with localized vaginal RMS were enrolled: 25 onto D9602 and 16 onto Subset 2 of ARST0331. Only four of the 39 with non-resected tumors received RT. The 5-year cumulative incidence of local recurrence was 26% on D9602, and the 2-year cumulative incidence of local recurrence was 43% on ARST0331. Increased local failure rates appeared to correlate with chemotherapy regimens that incorporated lower cumulative doses of cyclophosphamide. Estimated 5-year and 2-year failure free survival rates were 70% (95% CI: 46%, 84%) on D9602 and 42% (95% CI: 11%, 70%) on ARST0331, respectively. ***Conclusions.*** To prevent local recurrence, we recommend a local control approach for patients with non-resected RMS of the vagina that is similar to that used for other primary sites and includes RT. We recognize that potential long-term effects of RT are sometimes unacceptable, especially for children less than 24 months of age. However, when making the decision to eliminate RT, the risk of local recurrence must be considered especially when using a chemotherapy regimen with a total cumulative cyclophosphamide dose of $\leq$4.8 g/m^2. Pediatr Blood Cancer 2011;57:76–83.

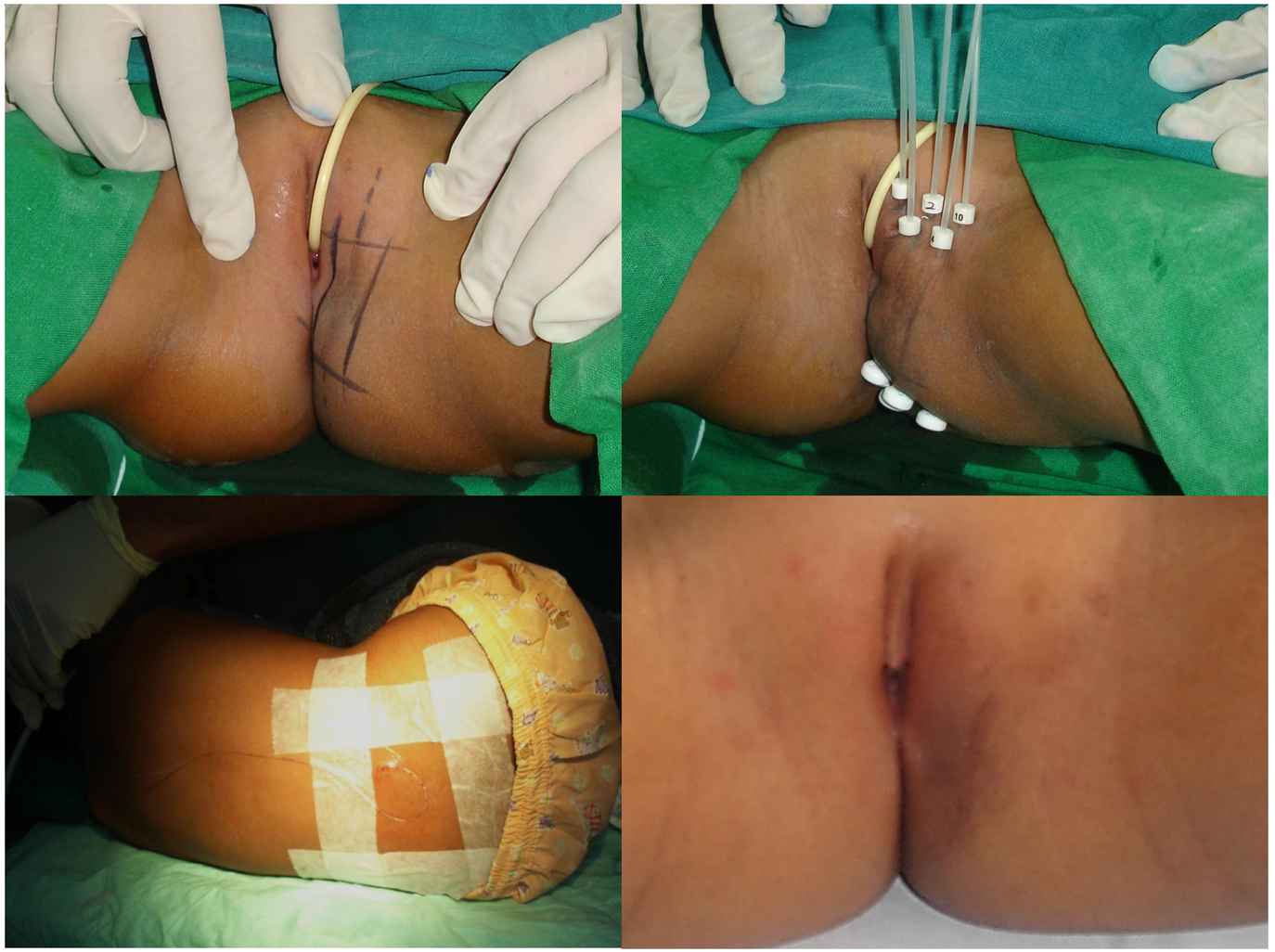
Key words: female; genitourinary; radiotherapy; rhabdomyosarcoma; vagina

D9602 (n=25), Loc Recc (5Yr): 26%

ARST0331 (n=16), Loc Recc (2Yr): 43%

Increased risk of Recc if RT avoided & Cyclo dose < 4.8g/m²

ERMS Vulva (Post Op Gr III)



VULVAL AND VAGINAL RHABDOMYOSARCOMA IN CHILDREN: UPDATE AND REAPPRAISAL OF INSTITUT GUSTAVE ROUSSY BRACHYTHERAPY EXPERIENCE

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- 39 Girls from 1971 - 2005
- Before 1990 (20): Target volume included pre treatment disease
- After 1990 (19): Target volume included residual disease only
- Dose: 50 - 60Gy @ 10Gy/ day
- Median Age: 16.3 mths
- **Median Follow up: 8.4Yrs**
- **OS: 91% at 5 Yrs**
- **Local Relapse: 6/36 (17%)**
- Complications:
  - Vaginal or Urethral Stenosis: Pts treated before 1990 - 75%
    Pts treated after 1990 - 20%

IJROBP 2008

20-Year Experience With Intraoperative High-Dose-Rate Brachytherapy for Pediatric Sarcoma: Outcomes, Toxicity, and Practice Recommendations

Michael R. Folkert, MD, PhD,* William Y. Tong, MD,* Michael P. LaQuaglia, MD,† Leonard H. Wexler, MD,‡ Alexander J. Chou, MD,‡ Heather Magnan, MD,‡ Michael J. Zelefsky, MD,* and Suzanne L. Wolden, MD*

Characteristic	No. of patients (N = 81)	%
Location		
Pelvis	26	25.5
Retroperitoneal	16	15.7
Thoracic	19	18.6
Extremity	8	7.8
Abdominal	5	4.9
Head and Neck	5	4.9
Other/Mixed	2	2.0
Median channels used (range)	6 (2-12)	
Median treated area (cm^2) (range, cm^2)	30 (4-345)	
Shields used	68	66.7
Median IORT overall dose (range [Gy])	12 (4-17.5)	
Median IORT dose for previously irradiated patients (range [Gy])	12 (8-17.5)	

- Paediatric Sarcomas
- 1993 - 2013
- 75 Children treated at MSKCC with HDR IORT
- Surgery + IORT (45%) +/- EBRT (55%)
- HDR IORT Dose: Median 12Gy (Range 4-17.5Gy)
- Median FU: 7.8Yrs
- LC: 63%
- EFS: 33%
- OS: 43%
- Acute Toxicity (> Gr III): 2.5%
- Late Toxicity (>Gr III): 5.4%
- Toxicity reduced with reduction in HDR IORT Applicator size
- HDR IORT Dose <12Gy result in reduced complications

IJROBP 2013

Interstitial brachytherapy for pediatric soft tissue sarcoma: Evolving practice over three decades and long-term outcomes

Siddhartha Laskar[1] | Avinash Pilar[1] | Nehal Khanna[1] | Ajay Puri[2] | Ashish Gulia[2] | Sajid Qureshi[3] | Girish Chinnaswamy[4] | Tushar Vora[4] | Mukta Ramadwar[5]

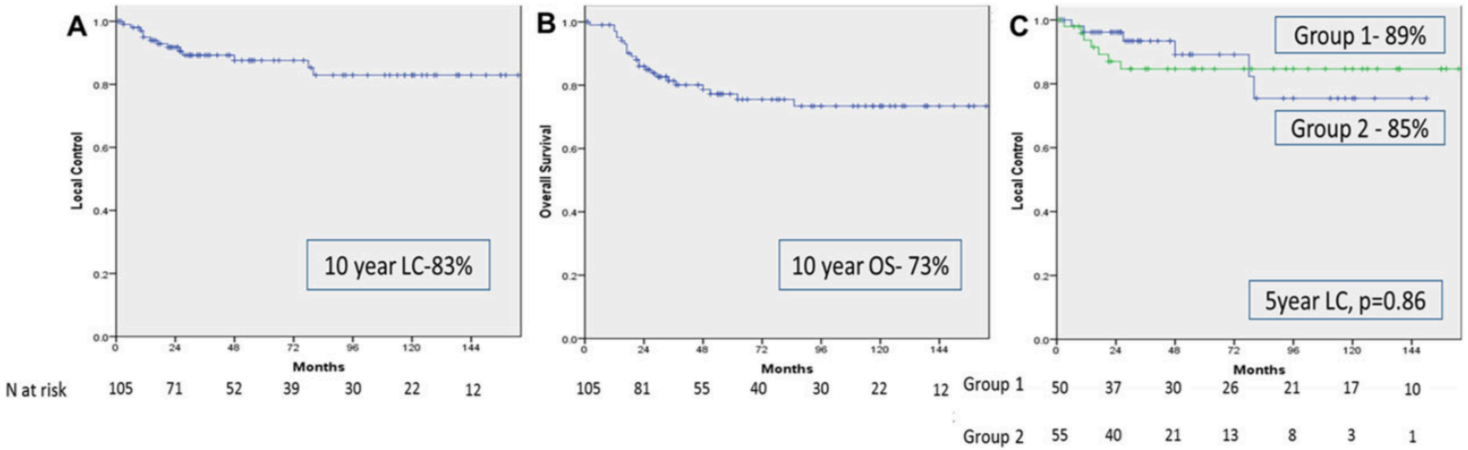

TABLE 4 Acute and late complications

Variables	Total (1984–2014) n = 105	Group1 (1984–2003) n = 50	Group 2 (2004–2014) n = 55	*P*
Acute wound complications	6 (6%)	3 (6%)	3 (5%)	0.904
Subcutaneous fibrosis	26 (25%)	17 (34%)	9 (16%)	0.037
Chronic lymphedema	6 (6%)	3 (6%)	3 (5%)	0.904
Neuropathy	1 (1%)	0	1 (2%)	0.338
Limb deformity	3 (3%)	1 (2%)	2 (4%)	0.615
Stiffness/fibrosis of joint	2 (2%)	0	2 (4%)	0.173
Overall patients with complications	31 (30%)	17 (34)	14 (25%)	0.165

Peds Blood & Cancer 2018

SUMMARY

Results:

- Optimal disease control
- Reduced toxicity

Advantages over Ext. Radiotherapy:

- Shorter overall treatment time (4-6 days vs. 5-6 wks)
- Post-op RT can be started sooner
- Smaller irradiated volume
- Reduced toxicity, Better functional outcome
- Less Expensive

Disadvantages:

- Restricted target coverage
- Difficult for lesions close to neurovascular bundle
- Learning Curve & Expertise

Thank You