Brachytherapy in the management of Soft Tissue Sarcoma

Dr. RAKESH KAPOOR
MD, MAMS, FICRO
Professor & Head Unit II
Department of Radiotherapy and clinical Oncology, Tertiary Cancer Center, PGIMER
Chairman Indian College Of Radiation Oncology.
Founder Director HBCH & RC Punjab. (Unit of T.M.C, Mumbai) DAE,(GOI)
Ex. Head: Department of Biostatistics, P.G.I.M.E.R
Ex. Additional Medical Superintendent, P.G.I.M.E.R

Introduction

- STS arise from a common embryonic ancestry- primitive mesoderm (Mesenchymal origin)- connective tissues in any organ or at any anatomic location of the body
- Soft-tissue sarcomas (STSs) are a heterogeneous and infrequent group of tumors consisting of approximately 1% of neoplasms diagnosed in the adult population and account for over 20% of all paediatric solid malignant cancers
- Incidence- 0.7% of cancers
- ~ 9,400 cases of STS are diagnosed yearly and estimated 3,500 deaths (US)
- Any age can be affected, overall more in older
- Majority of STS occur in the muscle groups of the extremities (Children- Head & Neck and Adults- Limbs)
- Thigh is the m/c sub site of origin

Relative risk for recurrence and survival

• Age >50 years	1.6
• Local recurrence at presentation	2.0
• Microscopically positive margin	1.8
• Size 5.0–10.0 cm	1.9
• Size > 10.0 cm	1.5
• High-grade	4.3
• Deep location	2.5
• Local recurrence	1.5

Radiotherapy - role in optimising local control

- Local control rates for combination of surgery + radiotherapy similar to amputation without affecting patient survival (Potter et al; 1986).
- Yang et al, J Clin Oncol, 1998, looked at high grade extremity lesions: Surgery vs Surgery + EBRT (63Gy in 1.8Gy), - increased local control from 70% to 99%, No difference in OS.
- Brachytherapy can be used as the sole therapy if target volume is localized and accessible.
- Interstitial brachytherapy (BT) found to improve local control rates (LC) in patients with limb-sparing resections of extremity.
- Summary: Post operative radiotherapy is highly effective in preventing local recurrence

- To improve the local control of STSs, several radiotherapy techniques have been developed, one of which is **brachytherapy (BRT) .**

- Nowadays, limb-sparing surgery associated or not with radiotherapy (RT) seems to be the gold standard treatment for STSs, achieving local control rates of approximately 85–90% and curative rates of 50%

- Currently, brachytherapy can be used in three different forms: neoadjuvant, intraoperative and adjuvant or as a separate treatment method for tumors that cannot be removed surgically .

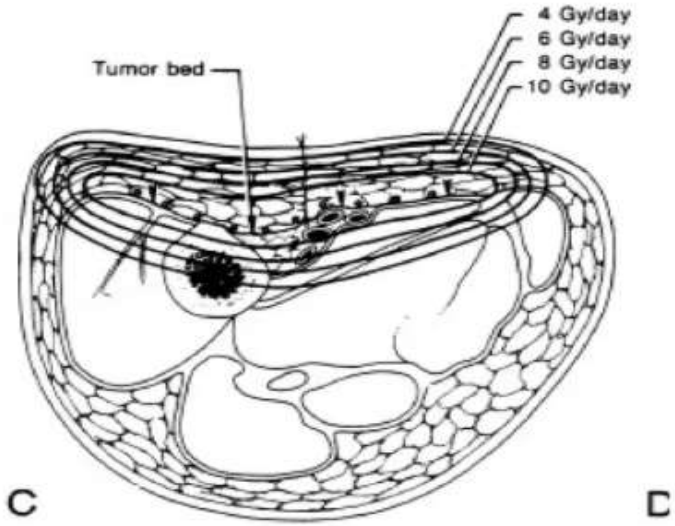
- The advantage of brachytherapy is the fact that it permits applicators to be inserted under visual control. Therefore, the process is very precise and diminishes the number of complications.

American Brachytherapy Society (ABS) consensus statement for sarcoma brachytherapy

- Adjuvant external beam radiation therapy (EBRT) or brachytherapy (BT can enhance local control (LC) in patients undergoing limb-sparing sarcoma resections in the extremity and is supported by Level 1 evidence.
- No controlled studies comparing EBRT with BT.
- Limitations for BT are large target volumes, restrictions in catheter placement because of bone or visceral organs, anatomic sites where good catheter geometry may be difficult to achieve (i.e., around the shoulder), and risk of radiation injury to nerves.
- There is no consensus on whether BT should be combined with EBRT in the setting of positive margins or whether one modality is sufficient C.L Holloway et al / Brachytherapy 12 (2013) 179-190

Indications for Adjuvant RT

- All High Grade STS.
- Low-Int Grade STS with close or positive margins.
- Tumour recurrence
- Tumor size of >5 cm,
- Lesions deep to or invading the superficial fascia, and younger than 50 years



BRACHYTHERAPY –

ABS recommendations for use of brachytherapy in different situations

- When the tumour is completely resected (Gr2 – Gr3): surgery followed by brachytherapy alone;
- When the CTV cannot be adequately implanted, and the surgical margins are positive:
- Surgery followed by brachytherapy and EBRT.
- Other situations, different kinds of brachytherapy may be indicated

Preop RT indicated if:

- If tumour adjacent to or involving critical
- structures.
- Likely difficult resection.
- Tumour initially inoperable at diagnosis

TARGET VOLUME

- Target volume: defined from preoperative imaging and /or intra operative evaluation and is defined in collaboration with the surgeon and the tumour bed implanted according to prescribed rules.
- The TV is based on imaging (MRI) and the pre-operative description,
- CTV is considered to be the ex-GTV plus a 2 - 3 cm margin for BT.
- The radio-opaque markers or clips placed at the time of surgery help the physician contour the CTV.
- 5 - 10 cm margin around the tumour bed is used for external beam therapy. However, margins are now considered to be based more on anatomical muscular compartments than on cm margins.

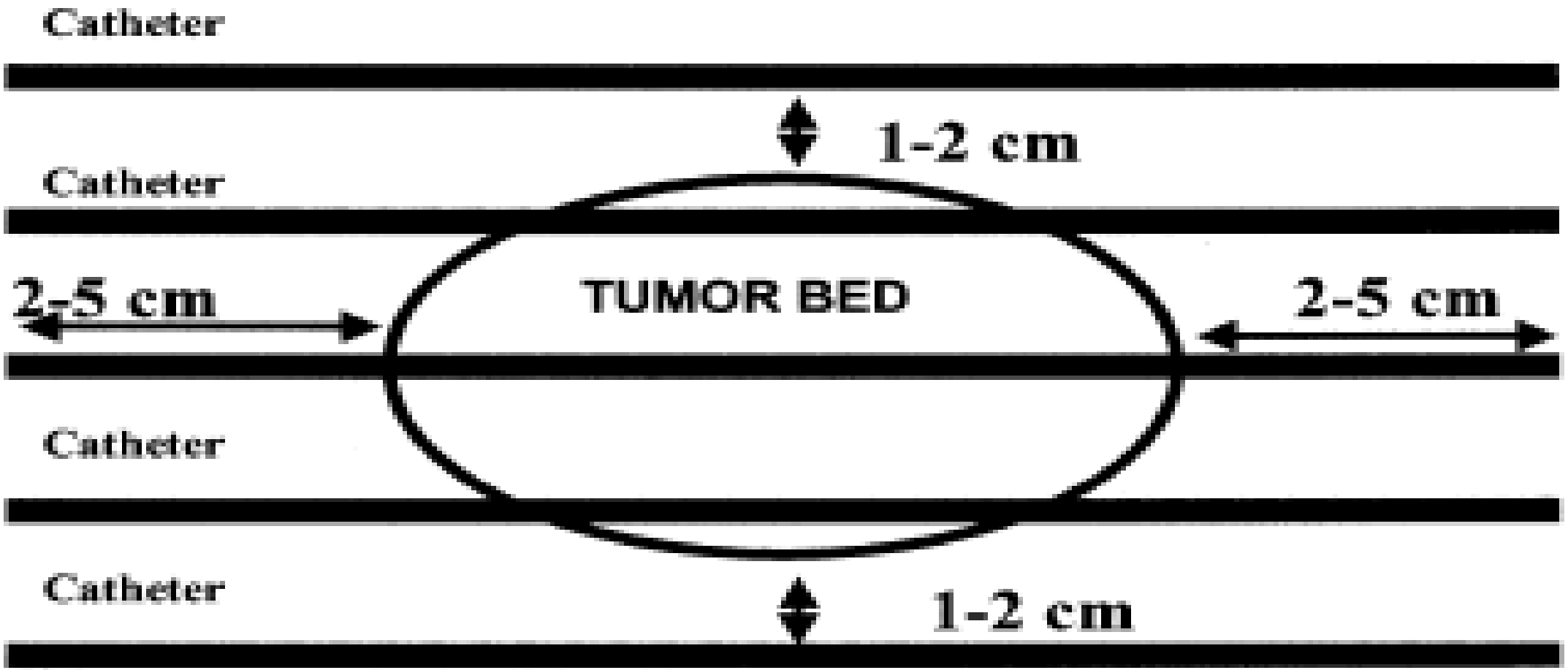
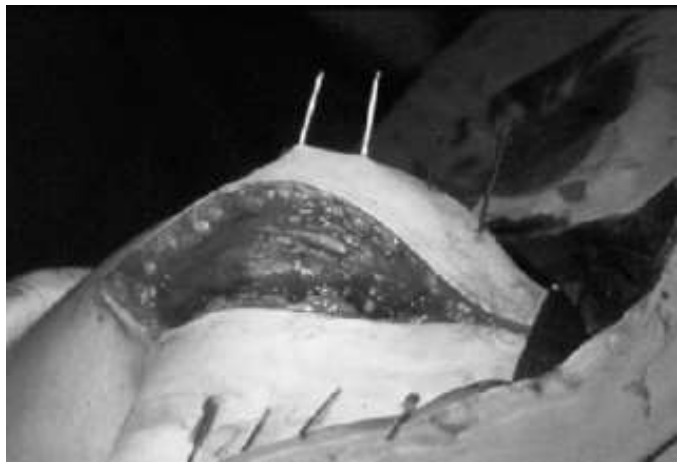
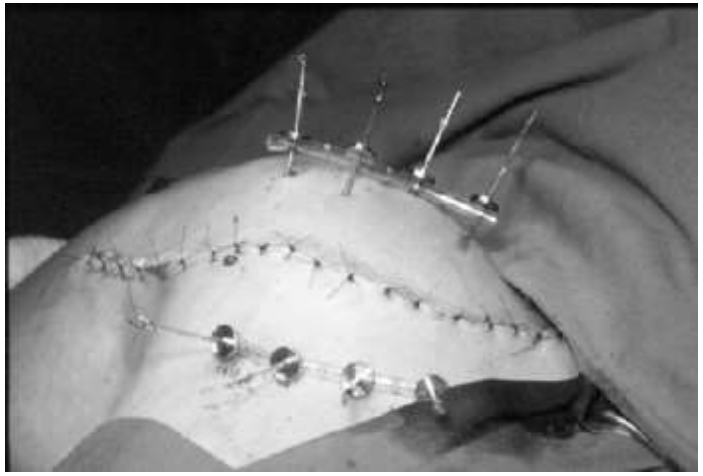


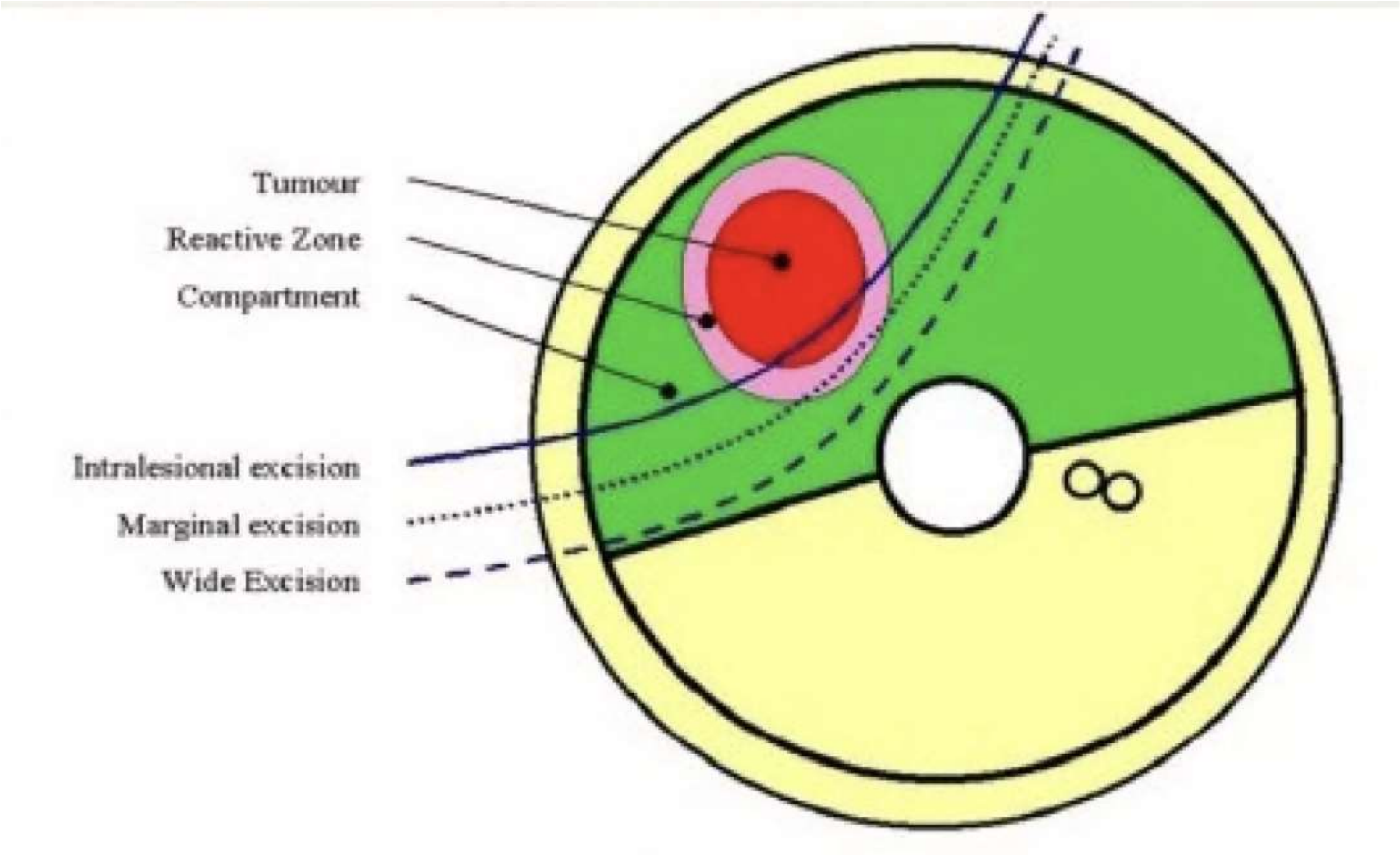
Fig. 1. Catheters are placed 1–2 cm beyond the lateral edge of the clinical target volume (CTV) and 2–5 cm beyond the CTV in the longitudinal direction.

- **Technique:**
  - Usually performed at time of surgery
  - Basic or sealed end temporary implant technique
  - SHRINKING FIELD TECHNIQUE:
    - Initially 5- 7 cm margin around 1^0 tumor with out attempting to cover entire muscle compartment
    - Boost field encompassing primary lesion with 3-4 cm margin
    - A ≥1 cm strip of soft tissue in the circumference of the extremity spared to avoid subsequent edema
    - Avoid circumferential bone radiation, if possible, to reduce fracture risk, and to minimize joint irradiation
    - Routine prophylactic nodal irradiation is not recommended since incidence of nodal involvement is low

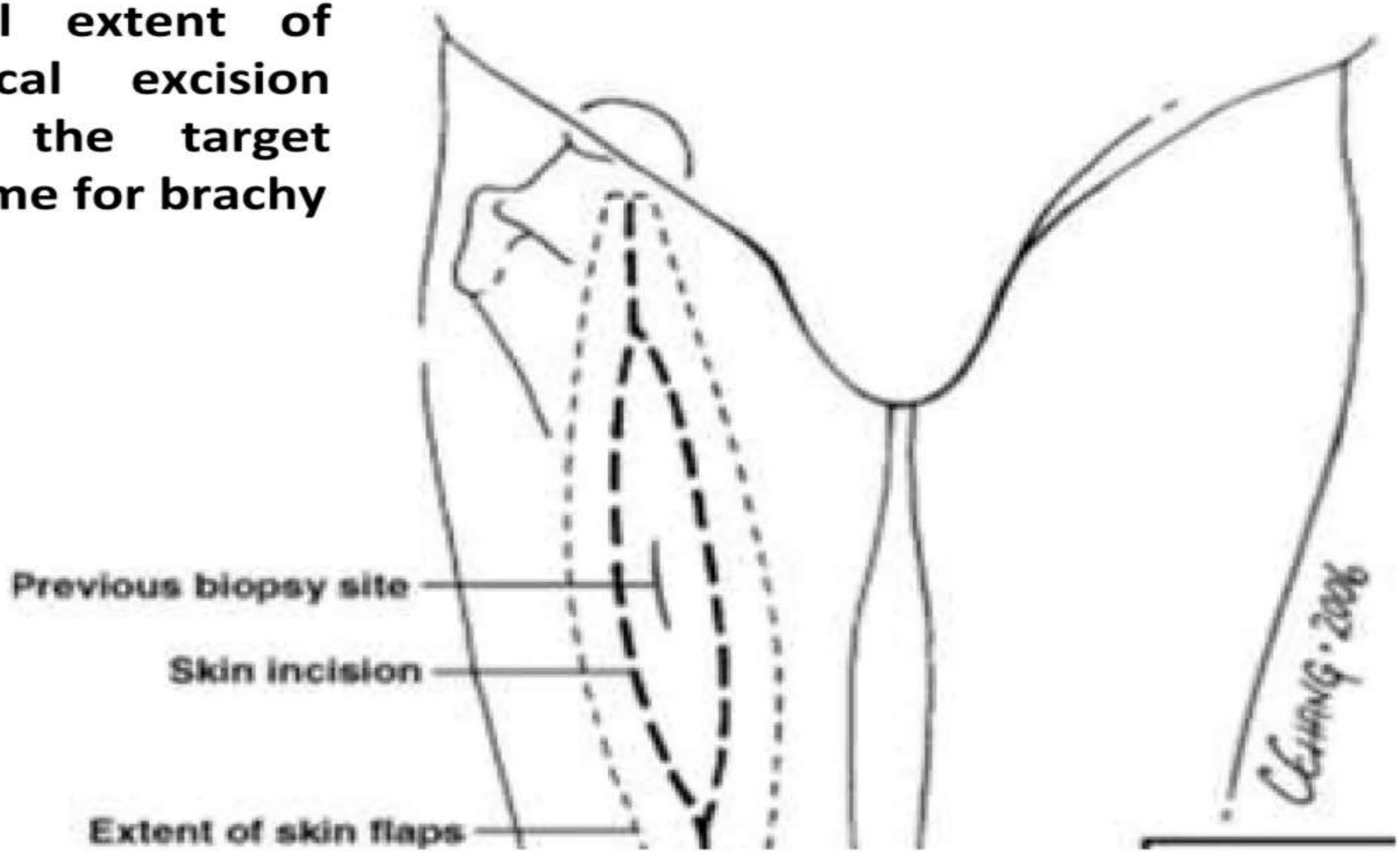




Enneking's System of Margins

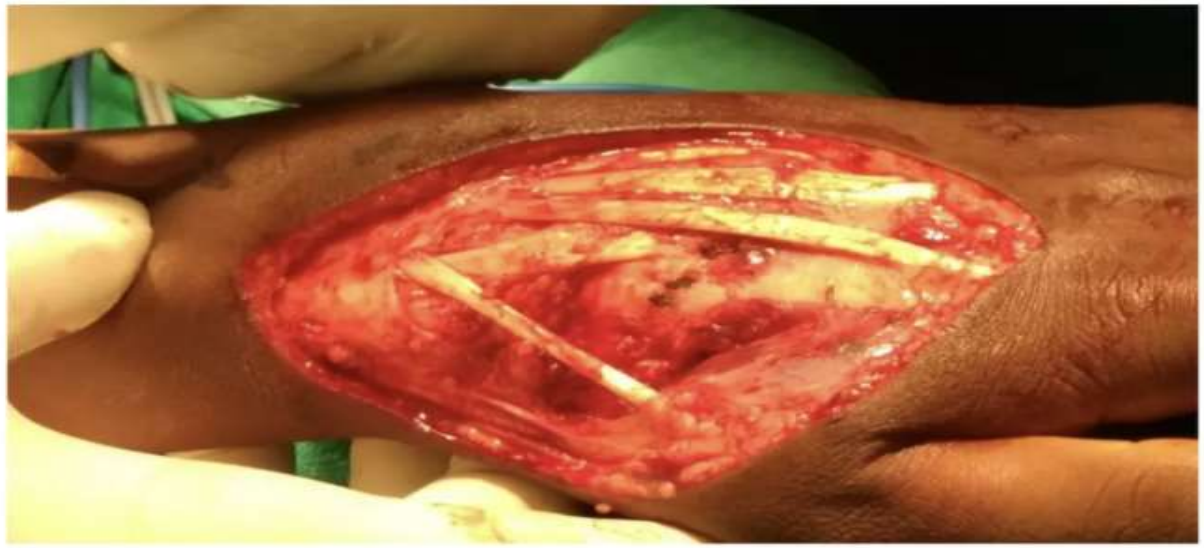


Usual extent of surgical excision and the target volume for brachy



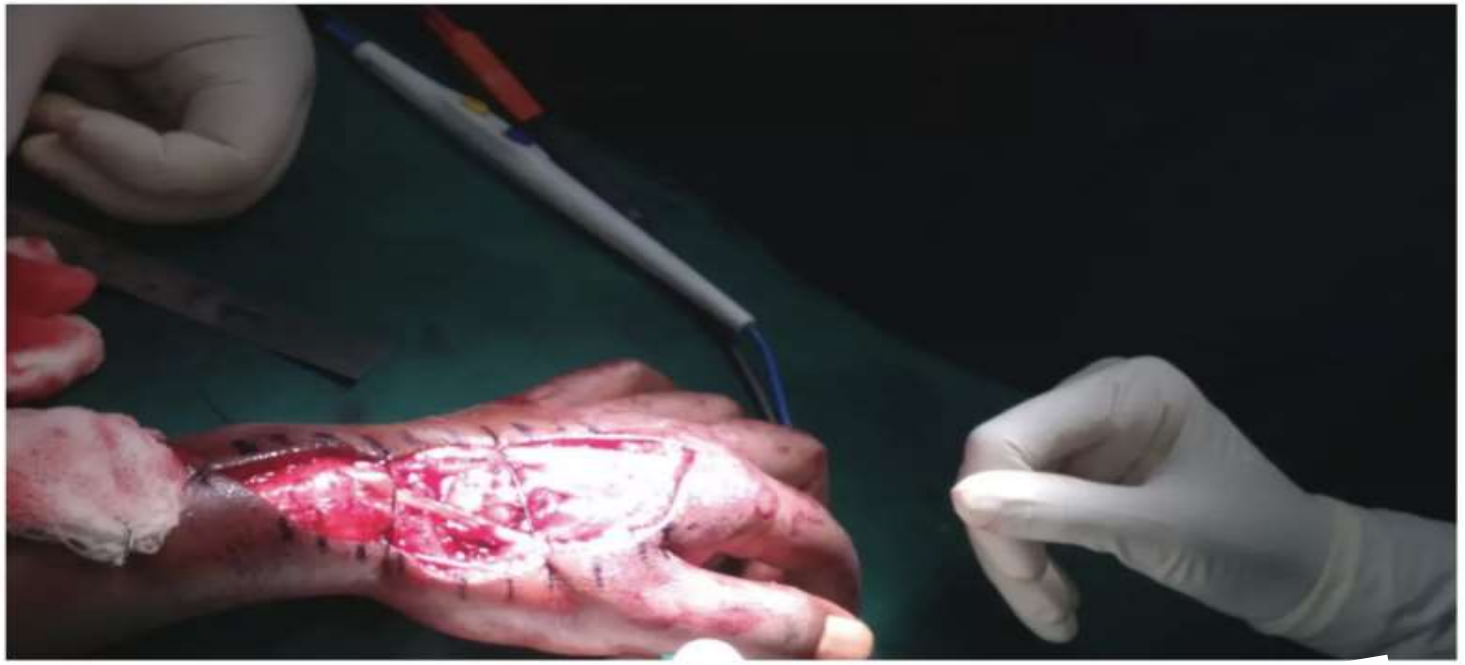
What I would like from my surgeon

- Place metallic clips at boundaries of resection
- Skin exit point of drain to be near the incision
- Bury the neurovascular bundle if exposed and mark the site with a clip
- Please give me clear radial margins; RT boost does not improve results, better to re-excise for clear margins



Exposed Neuro-vascular bundle can be "buried" under a muscular pedicle

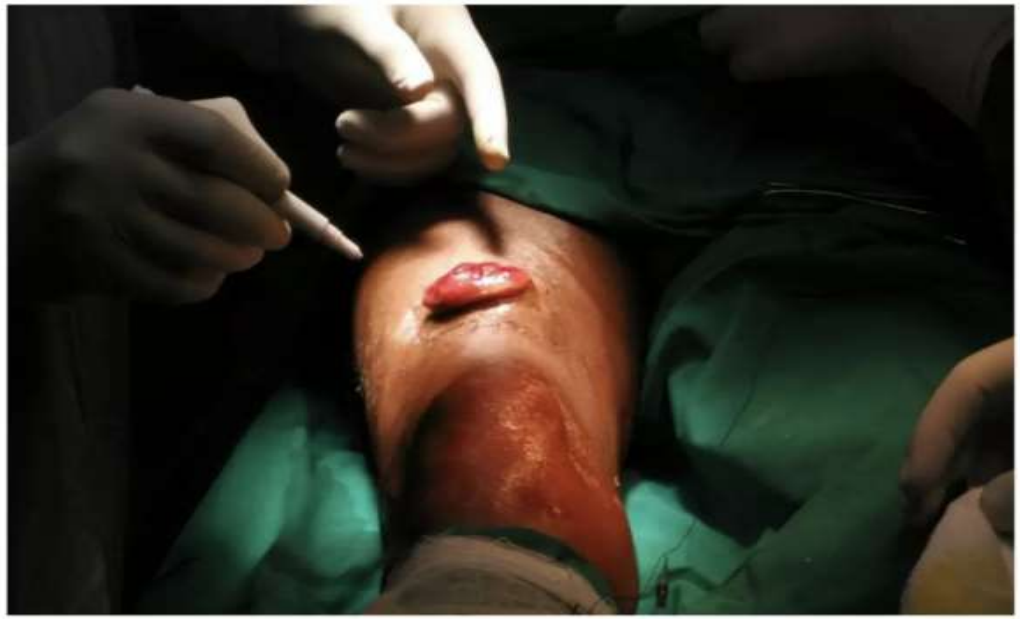
The bed or the target volume is re-aligned anatomically by stay sutures

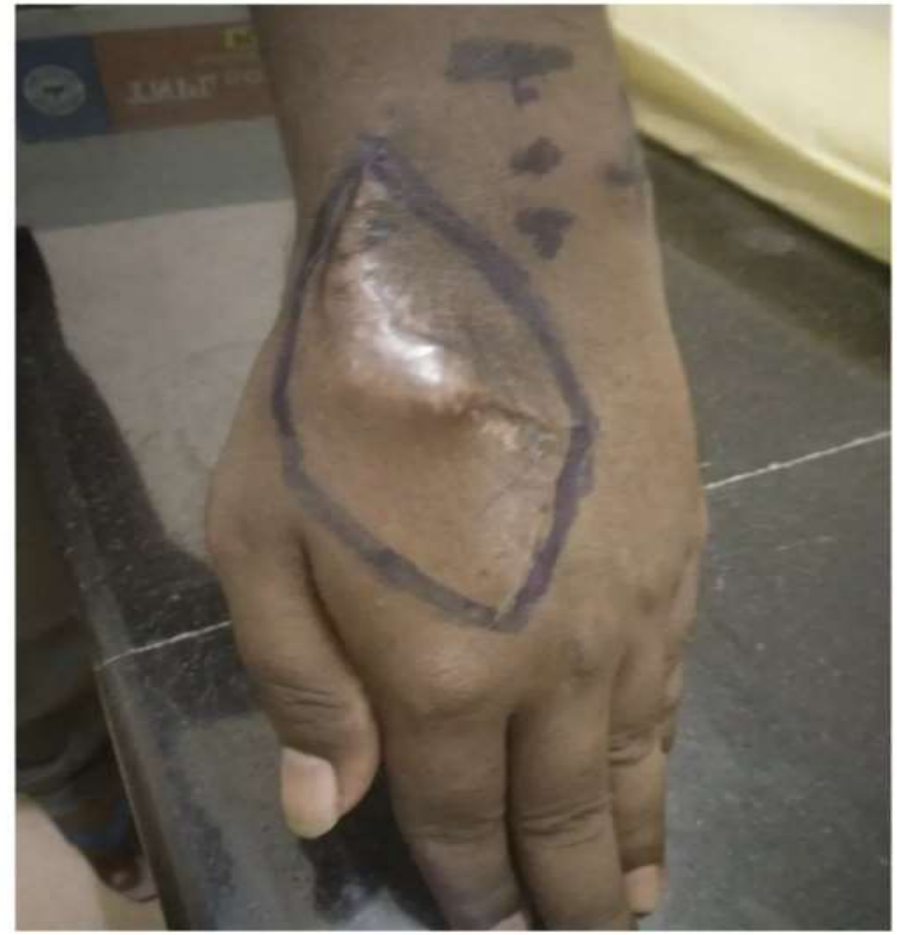


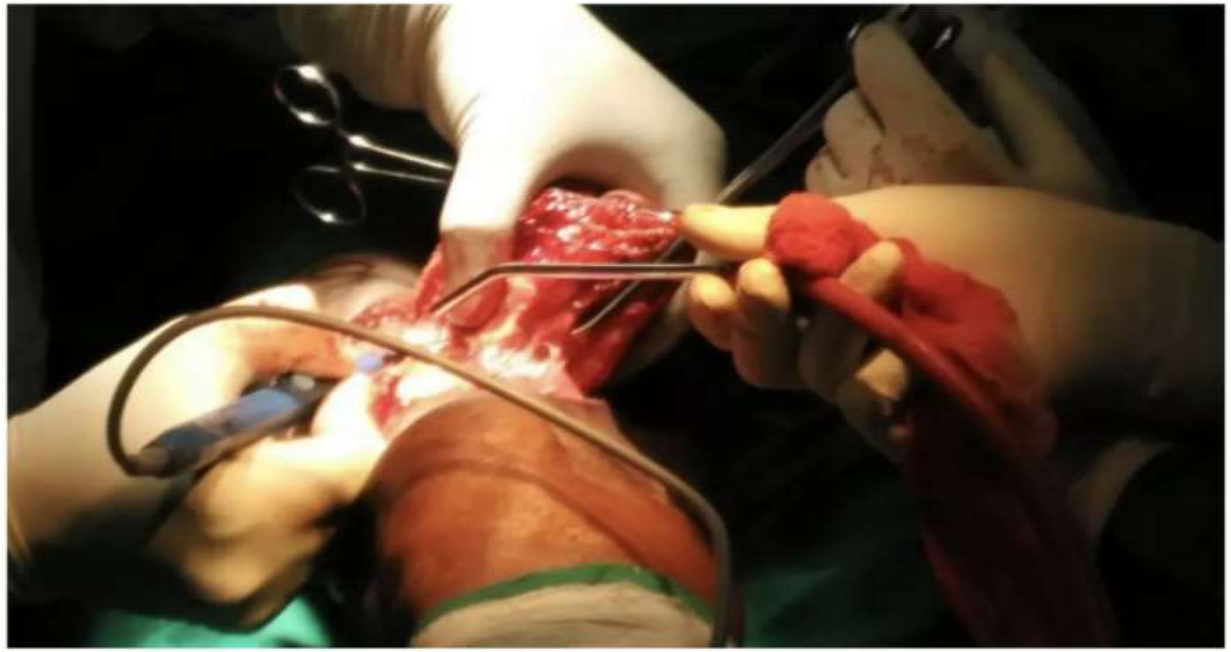
- The plastic tubes should be implanted parallel and equidistant, transverse (IGR method) or parallel (MSKCC method) to the surgical incision.
- A single plane is sufficient in most cases of resection in RO and microscopical residual disease R1
- In macroscopic residual disease R2, a double plane is necessary.

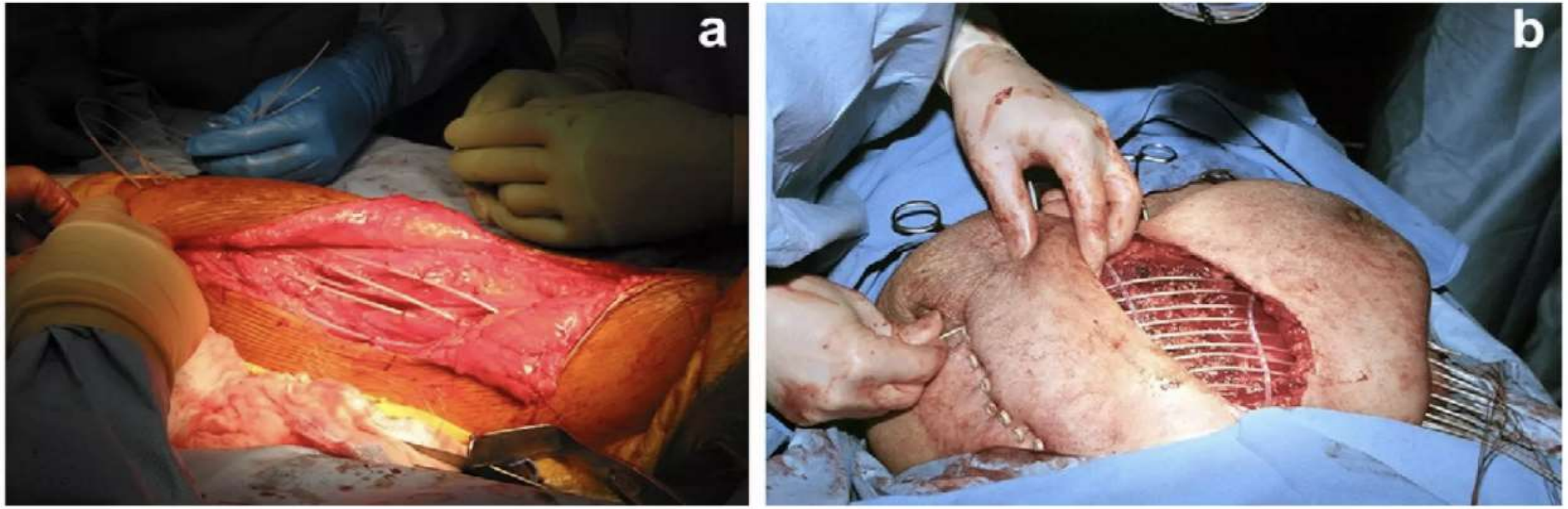
- Guide needles are implanted through the skin at least 2 cm away from the surgical incision; these are then replaced by plastic tubes.

Procedure

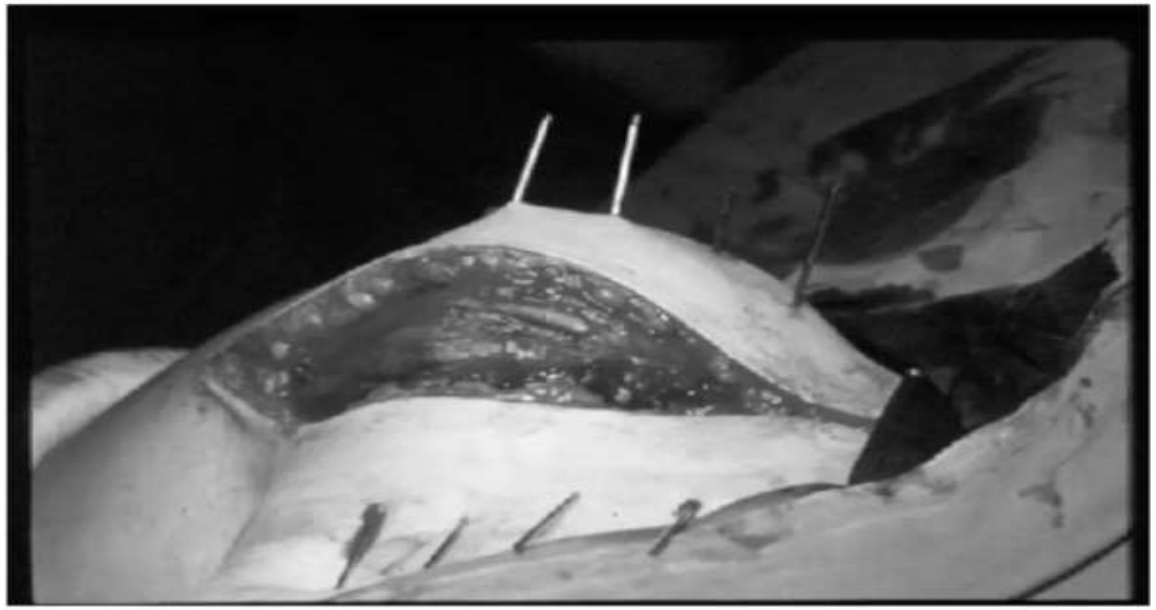






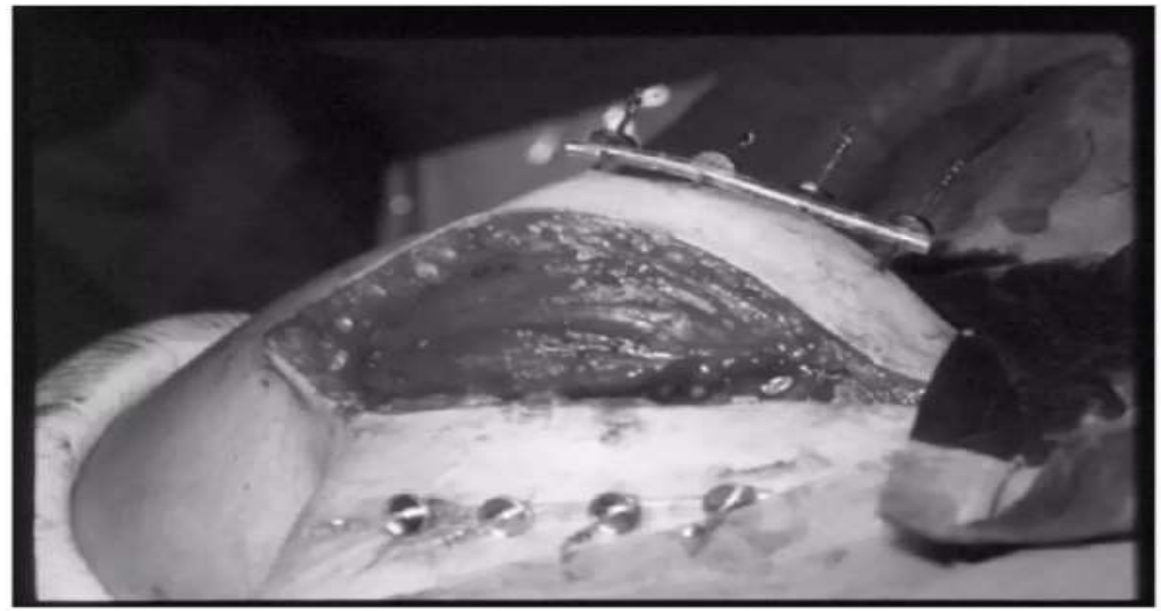


Intraoperative placement of brachytherapy catheters demonstrating both (a) parallel and (b) perpendicular orientation of the catheters in relation to the wound.



Implantation of the metallic needles

Replacement of the needles by parallel plastic tubes

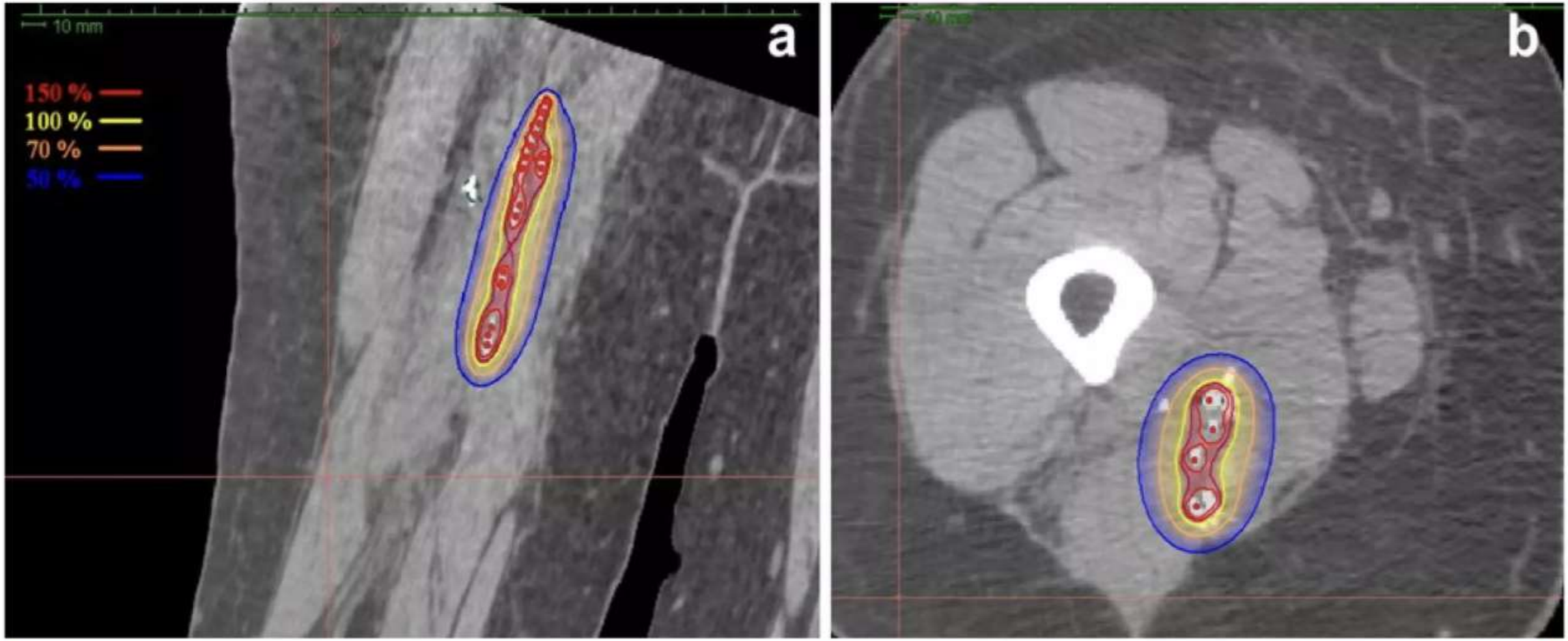


- The positioning of the plastic tubes is adapted to the dimensions of the CTV. Parallel and equidistant plastic tubes are spaced 10 to 20 mm, according to the depth of the tissue to be treated.

- To achieve good parallelism and equidistance between the plastic tubes, they can be partially fixed by surgical sutures either inside the tumour bed or at skin level (at the entrance and exit points).

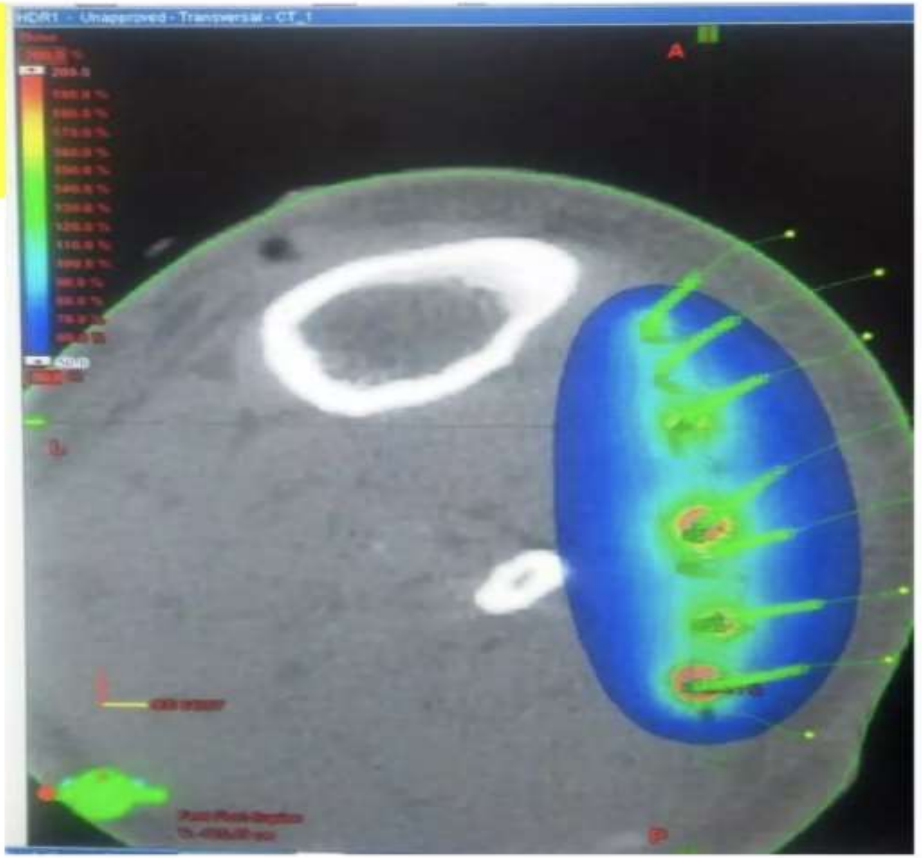
- CT simulation is the current standard for BT dosimetry of sarcomas. It allows for 3D dosimetry of the implant.

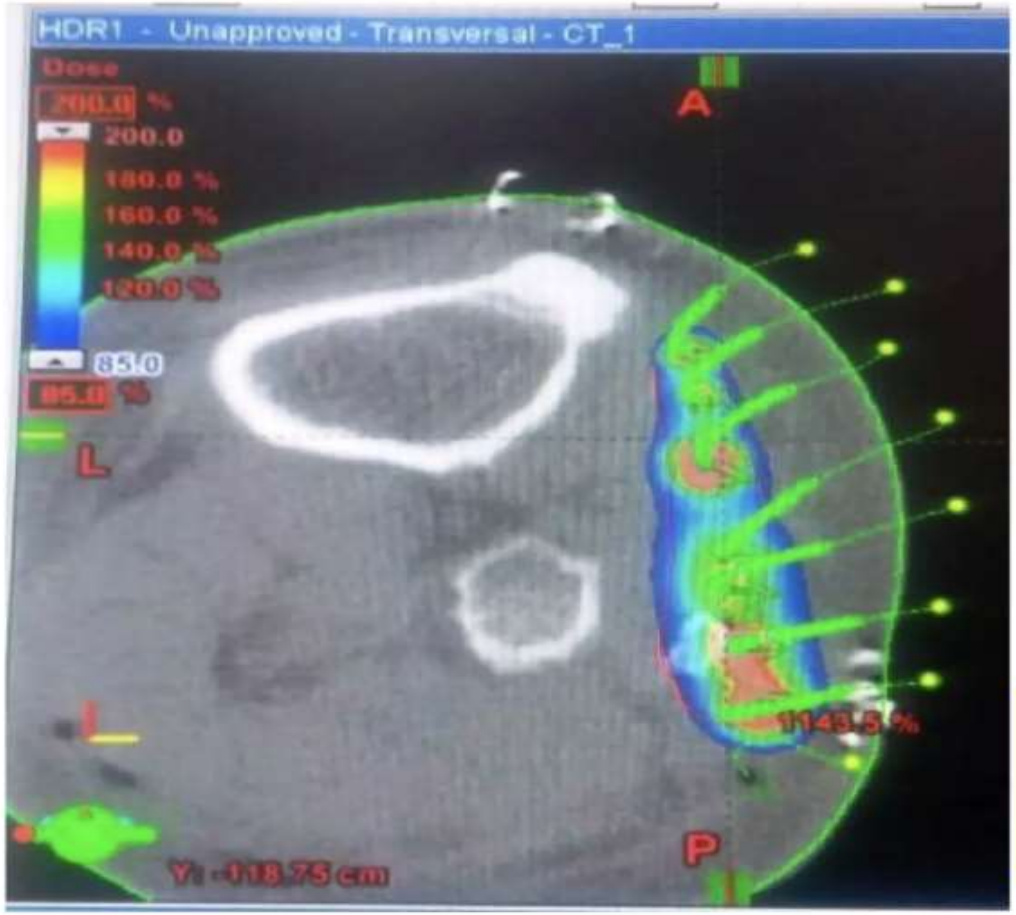
- Presentation of axial isodose curves, dose volume histogram (DVH) data, and virtual images facilitates understanding of the target doses and permits placement of dose constraints.



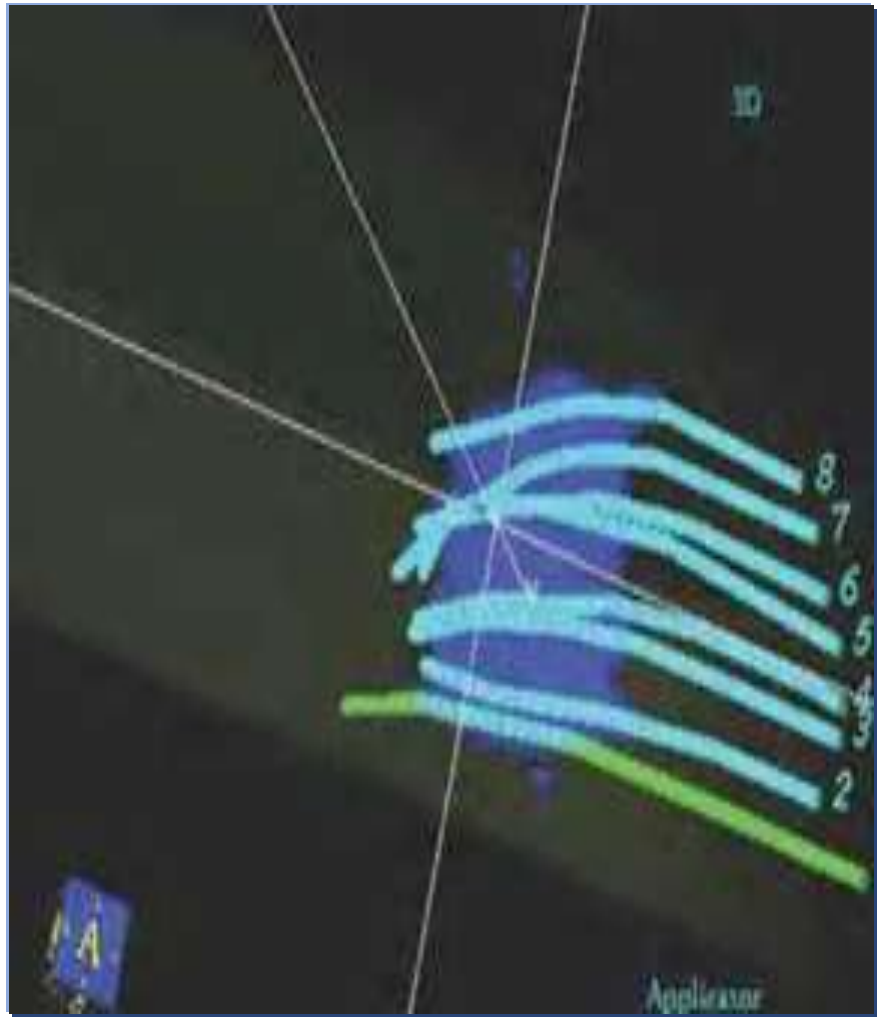
3D CT-based dosimetry of an implant in (a) coronal and (b) axial planes. The 150-50% isodoses are demonstrated. (b) Surgical clips help to delineate the clinical target volume

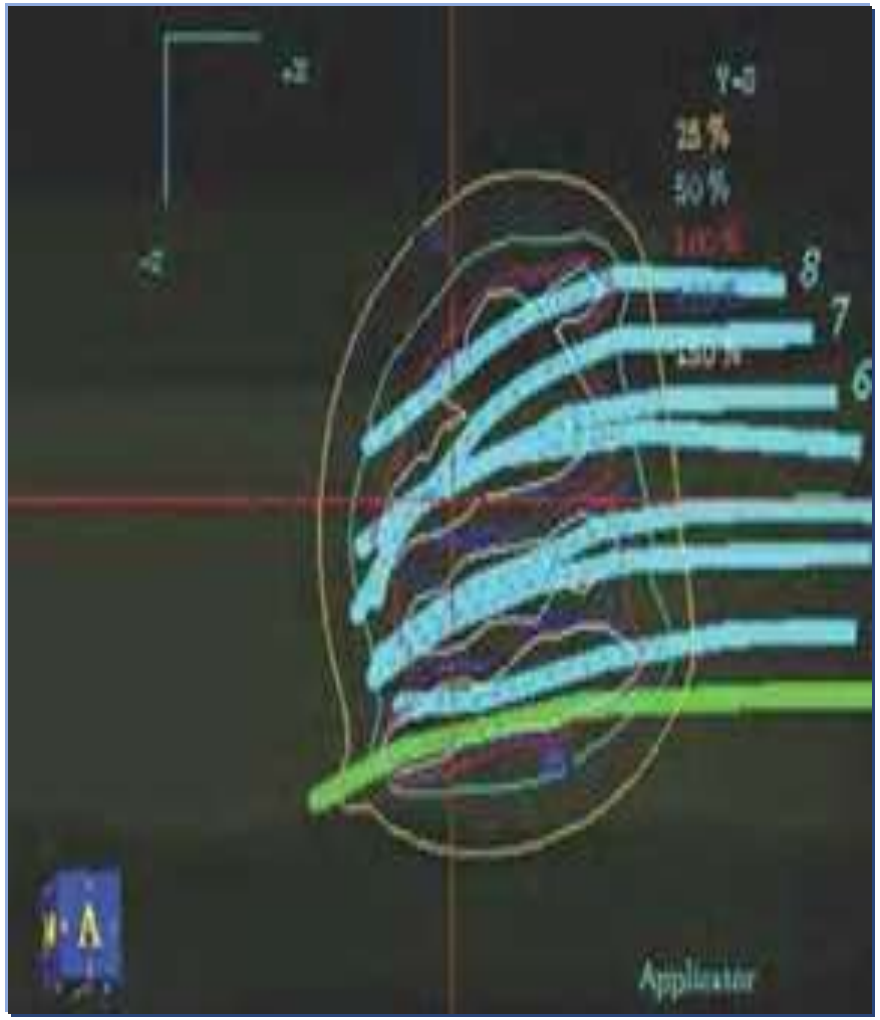
Dose covering 50% isodose line





Dose covering 90% isodose / prescribed dose


8
7
6
5
2
Applicator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Applicator

Dose of XRT

- 60 Gy for negative margin (Ro resection)
- 66 Gy for microscopic residual disease (R1 resection)
- 75Gy -gross residual disease (R2 resection)

- Brachytherapy or IORT may be used in combination with either preop or postop EBRT.Doses of 12 to 25 Gy may be given by IORT.
- LDR Brachy : 42Gy – 46Gy
- HDR Brachy : 18 Gy- 32Gy
- The Dose is selected depending on the dose rate and weather alone or in combination with Ext RT.

- The quality of the implant can be measured in terms of
- D90 (dose to 90% of the CTV),
- V100 (percent of the CTV that receives the 100% isodose),
- V150 (percent of the CTV that receives the 150% isodose).
- Attempt should be made to limit the dose to the surgical incision to less than 100% isodose unless it is considered at high risk for tumor involvement.
- The dose to the skin ideally should be no more than two-thirds of the prescribed dose.
- In addition, source loading should be no close than 0.5 cm from the skin surface to minimize skin toxicity.

Long-Term Results of a Prospective Randomized Trial of Adjuvant Brachytherapy in Soft Tissue Sarcoma

- Pisters et al, JCO 1996 Mar
  - 164 patients
  - Randomized to post-operative **brachytherapy** (BRT) or not
  - Freedom from local recurrence @ 5y
    - High grade 89% with BRT, 66% without (p=0.0025)
    - Low grade no impact (p=0.6)
  - No significant impact on **distant metastasis** or **disease specific survival**

- **Results:**

Table 27.1 Results of perioperative LDR brachytherapy: comparison between first-line (F) and salvage (S) brachytherapy

Author	Pts N.	Treatment	Brachy	Survival %	Local control %	Complications %
Delannes (10) *	85	A 31 B 54	F 62 S 38	AS: F 75 S 62	F96 S 68	15
Gerbaulet (15) *	50	A 48 B 2	F 15 S 35	OS 68	F 96 S 64	25
Habrand (17) *	48	A 44 B 4	F 22 S 26	OS, F 62 S 57	68 81 **	20

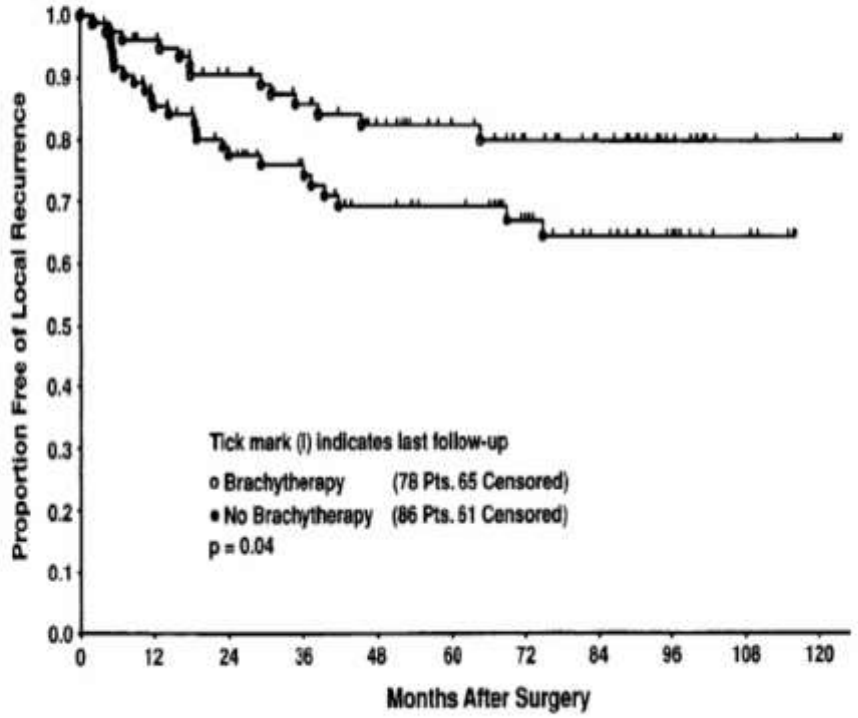
Legends:
A: Surgery + brachytherapy *B: Surgery + Brachytherapy + EBRT*

- Pisters et al, n=164
  - Sx vs Sx + BT
  - At 60 mths, Actuarial LR 31% vs 18%

- With a median follow-up time of 76 months, the 5-year actuarial local control rates were 82% and 69% in the BRT and no BRT groups (P = .04), respectively.
- Patients with high-grade lesions had local control rates of 89% (BRT) and 66% (no BRT) (P = .0025).
- BRT had no impact on local control in patients with low-grade lesions (P = .49).
- The 5-year freedom-from-distant-recurrence rates were 83% and 76% in the BRT and no BRT groups (P = .60), respectively

Brachytherapy:

MSKCC, Ph III. Harrison. JCO 1996.



42-46Gy LDR, from 6th POD. (Benefit for High Grade only).

RESULTS ADJUVANT LDR BRACHYTHERAPY IN SOFT TISSUE SARCOMAS OF EXTREMITIES

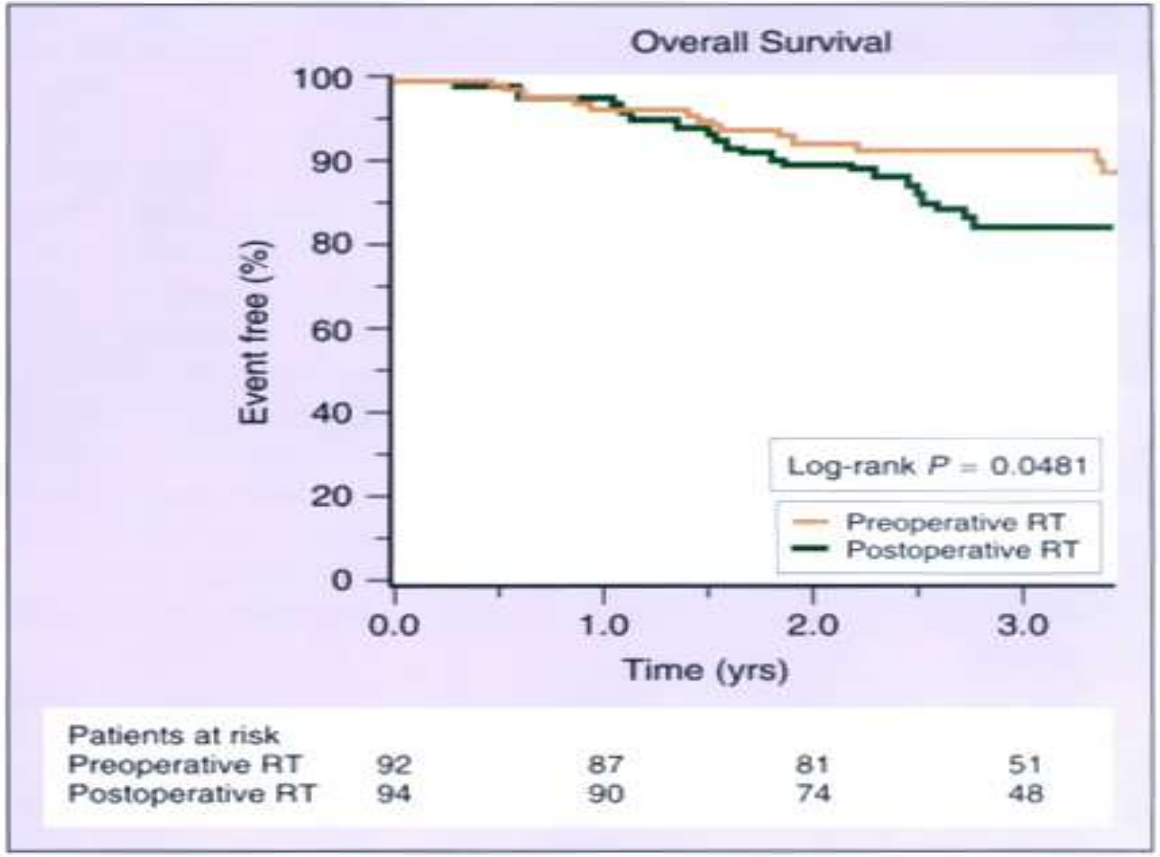
Author	Brachy used	Sample size	Local control %	Complications %
Chaudhary	LDR	118	96	10
Cionini	LDR	33	91	6
Gemer	LDR	25	80	36
O' Connor	LDR	68	91	22
Schray	LDR	63	96	10
Thomas	LDR	57	89	28
Rosenblatt	LDR	11	100	15

RESULTS ADJUVANT HDR BRACHYTHERAPY IN SOFT TISSUE SARCOMAS OF EXTREMITIES

Author	Brachy used	Sample size	Local control%	Complications %
Alekhteyar	LDR-HDR	18	90	38
Chuba	HDR	32	82	48
Crownover	HDR	10	100	0
Donath	HDR	19	70	16
Koizumi	HDR	16	50	6
Pellizzon	HDR	25	84	24
Yoshida	HDR	13	72	8

Pre-op or post-op radiation?

- Some avoid pre-op use because of increased wound complications (although this is debatable)
    - RCT looking at wound complication rate pre-op vs post-op radiation showed 35% vs 17%
        - Risk confined to lower extremity
    - Conclusions: pre-op may be better for upper extremity and head & neck because of equal wound complication risk and benefit of lower radiation doses to more vital tissues



Local recurrence with post-op brachytherapy

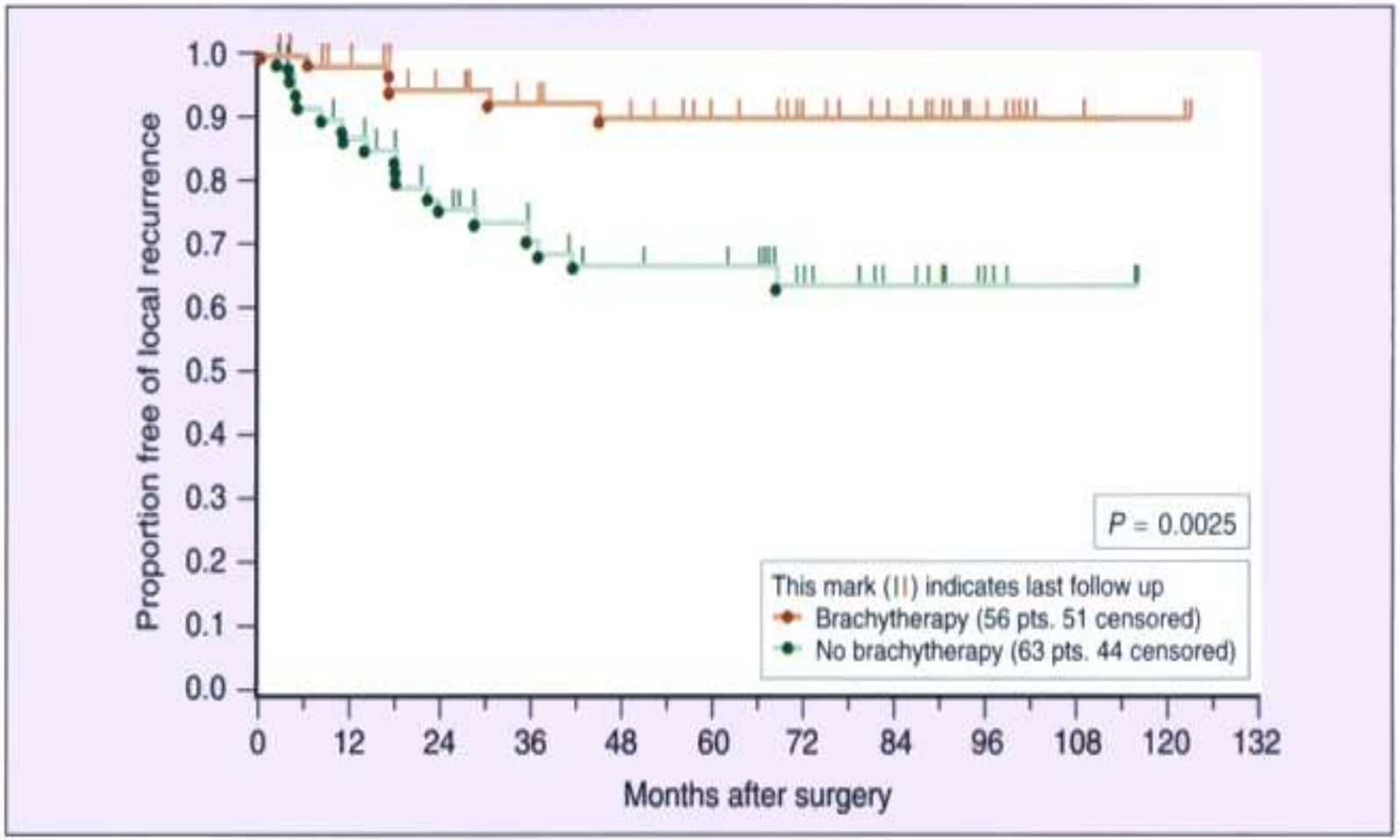


Table 1. Detailed study characteristics of included publications with level of evidence (LoE).

ID	Study	Year	Region	Country	Sample Size	Follow-Up	Treatment	Study Type	LoE
1	Mills et al. [29]	1981	Africa	South Africa	17	28 months	HD-BRT	Retrospective study	3
2	Brennan et al. [30]	1987	North America	USA	117	16 months	BRT vs. No BRT	Prospective randomized trial	2
3	Arbeit et al. [31]	1987	North America	USA	105	11.9 months	BRT vs. No BRT	Prospective randomized trial	2
4	Ormsby et al. [32]	1989	North America	USA	52	3 months	BRT vs. No BRT	Retrospective study	3
5	Zelefsky et al. [33]	1990	North America	USA	45	4 years	BRT	Retrospective study	3
6	Nori et al. [34]	1991	North America	USA	40	36 months	BRT	Retrospective study	3
7	Brennan et al. [35]	1991	North America	USA	126	40.8 months	BRT vs. No BRT	Prospective randomized trial	2
8	Habrand et al. [36]	1991	Europe	France	48	82 months	BRT	Retrospective study	3
9	Harrison et al. [37]	1993	North America	USA	126	66.5 months	BRT vs. No BRT	Prospective randomized trial	2
10	Pisters et al. [38]	1994	North America	USA	45	67 months	BRT vs. No BRT	Prospective randomized trial	2
11	Janjan et al. [39]	1994	North America	USA	35	n.a.	BRT vs. EBRT	Comparative study	3
12	Catton et al. [40]	1996	North America	Canada	25	24 months	BRT or EBRT or BRT + EBRT vs. Surgery alone	Retrospective study	3
13	Alekhteyar et al. [41]	1996	North America	USA	105	22 months	BRT vs. BRT + EBRT	Retrospective study	3
14	Pisters et al. [14]	1996	North America	USA	164	76 months	BRT vs. No BRT	Prospective randomized trial	2
15	Panchal et al. [42]	1996	Europe	United Kingdom	4	27.5 months	Surgery + BRT	Retrospective study	3
16	Chaudhary et al. [43]	1998	Asia	India	151	24 months	BRT vs. BRT + EBRT	Comparative study	3
17	Alektiar et al. [44]	2000	North America	USA	164	100 months	BRT vs. No BRT	Prospective randomized trial	2
18	Alektiar et al. [45]	2002	North America	USA	202	61 months	BRT	Retrospective study	3
19	Mccarter et al. [46]	2002	North America	USA	n.a.	n.a.	n.a.	Review	5
20	Ballo et al. [3]	2003	North America	USA	n.a.	n.a.	n.a.	Review	5
21	Rachbauer et al. [47]	2003	Europe	Austria	39	26 months	HD-BRT + EBRT	Prospective study	2
22	Strander et al. [48]	2003	Europe	Sweden	n.a.	n.a.	n.a.	Review	5
23	Murray et al. [49]	2004	North America	USA	n.a.	n.a.	n.a.	Review	5
24	Maples et al. [50]	2004	North America	USA	n.a.	n.a.	n.a.	Review	5
25	Kretzler et al. [51]	2004	Europe	Germany	28	4.3 years	BRT ± EBRT	Retrospective study	3
26	Fontanesi et al. [52]	2004	North America	USA	31	60.5 months	Surgery ± BRT ± EBRT	Retrospective study	3

ID	Study	Year	Region	Country	Sample Size	Follow-Up	Treatment	Study Type	LoE
27	Baumert et al. [53]	2004	Europe	Switzerland	1	n.a.	BRT	Case report	4
28	Moureau-Zabotto et al. [54]	2004	Europe	France	83	13 years	Surgery ± BRT ± EBRT	Retrospective study	3
29	Fontanesi et al. [55]	2004	North America	USA	13	76 months	Surgery ± BRT ± EBRT	Retrospective study	3
30	Schuetze et al. [56]	2005	North America	USA	n.a	n.a.	n.a.	Review	5
31	DeLaney et al. [57]	2005	North America	USA	n.a	n.a.	n.a.	Review	5
32	Martínez-Monge et al. [25]	2005	Europe	Spain	25	23.2 months	HD-BRT + EBRT	Retrospective study	3
33	Lazzaro et al. [58]	2005	Europe	Italy	42	34 months	BRT ± EBRT	Retrospective study	3
34	Aronowitz et al. [59]	2006	North America	USA	12	34 months	HD-BRT	Retrospective study	3
35	Mierzwa et al. [60]	2007	North America	USA	43	39 months	BRT ± EBRT	Retrospective study	3
36	Torres et al. [61]	2007	North America	USA	62	6 years	BRT vs. No BRT	Retrospective study	3
37	Laskar et al. [20]	2007	Asia	India	155	45 months	BRT ± EBRT	Retrospective study	3
38	Pohar et al. [62]	2007	North America	USA	37	47 vs. 17 months	LD-BRT + EBRT vs. HD-BRT + EBRT	Retrospective study	3
39	Beltrami et al. [5]	2008	Europe	Italy	112	75 months	BRT + EBRT	Retrospective study	3
40	Muhic et al. [63]	2008	Europe	Denmark	39	3.4 years	PDR-BRT + EBRT	Retrospective study	3
41	Kaushal et al. [64]	2008	North America	USA	n.a.	n.a.	n.a.	Review	5
42	Rimner et al. [65]	2009	North America	USA	255	71 months	BRT or EBRT or BRT + EBRT	Retrospective study	3
43	Rudert et al. [66]	2009	Europe	Germany	n.a.	n.a.	n.a.	Review	5
44	Petera et al. [67]	2010	Europe	Czech Republic	45	3.2 years	BRT ± EBRT	Retrospective study	3
45	Shukla et al. [68]	2011	Asia	India	300	n.a.	BRT ± EBRT	Retrospective study	3
46	Bradley et al. [69]	2011	North America	USA	11	20.8 months	HD-BRT	Retrospective study	3
47	Alektiar et al. [70]	2011	North America	USA	134	46 months	LD-BRT or IMRT	Retrospective study	3
48	Atean et al. [71]	2012	Europe	France	87	69 months	EBRT vs. EBRT + BRT	Retrospective study	3
49	Guzik et al. [13]	2012	Europe	Poland	1	n.a.	BRT	Case report	4
50	Emory et al. [72]	2012	North America	USA	190	40 months	EBRT or BRT or BRT + EBRT	Retrospective study	3
51	Delaney et al. [73]	2012	North America	USA	n.a.	n.a.	n.a.	Review	5
52	Ghadimi et al. [74]	2014	Europe	Germany	n.a.	n.a.	n.a.	Review	5
53	Pellizzon et al. [6]	2014	South America	Brazil	n.a.	n.a.	n.a.	Review	5
54	Ren et al. [15]	2014	Asia	China	110	43.7 months	BRT	Retrospective study	3
55	Miller et al. [75]	2015	North America	USA	n.a.	n.a.	n.a.	Review	5
56	Röper et al. [76]	2015	Europe	Germany	n.a	n.a	n.a	Prospective study	3
57	Larrier et al. [77]	2016	North America	USA	n.a.	n.a	n.a	Review	5

ID	Study	Year	Region	Country	Sample Size	Follow-Up	Treatment	Study Type	LoE
58	Naghavi et al. [78]	2016	North America	USA	40	27 months	BRT	Retrospective study	3
59	Mukherji et al. [79]	2017	Asia	India	3	34 months	BRT	Case report	4
60	Naghavi et al. [4]	2017	North America	USA	n.a.	n.a.	n.a.	Review	5
61	Cortesi et al. [80]	2017	Europe	Italy	107	100 months	BRT + EBRT	Retrospective study	3
62	Correa et al. [1]	2018	Europe	Spain	n.a.	n.a.	n.a.	Review	5
63	Klein et al. [81]	2018	North America	USA	171	71.8 months	HD-BRT or EBRT or HD-BRT + EBRT	Retrospective study	3
64	Healey et al. [82]	2018	North America	USA	n.a.	n.a.	n.a.	Expert opinion	7
65	Manir et al. [24]	2018	Asia	India	27	20 months	BRT ± EBRT	Retrospective study	3
66	Gimeno et al. [83]	2019	Europe	Spain	106	7.1 years	HD-BRT + EBRT	Prospective controlled study	2
67	Spoto et al. [84]	2020	Europe	Italy	90	4.2 years	BRT vs. EBRT vs. BRT + EBRT	Retrospective study	3
68	Roeder et al. [85]	2020	Europe	Austria	n.a.	n.a.	n.a.	Review	5
69	Sarria et al. [8]	2020	Europe	Germany	31	4.9 years	BRT	Retrospective study	3
70	Vavassori et al. [86]	2021	Europe	Italy	1	40 months	HD-BRT	Case report	4

BRT, brachytherapy; HD, high dose; LD, low dose; PDR, pulsed dose rate; EBRT, external beam radiotherapy; IMRT, intensity-modulated radiotherapy; n.a., not available.

- A total of 175 studies were identified, of which 70 were eligible for analysis based on the inclusion and exclusion criteria.
- They were analysed according to (a) local complications, (b) the recurrence rate and its correlation with margins of resection, and (c) the use of BRT in regard to tumor grading.
- In 39 studies, the level of evidence (LoE) was 3, while in 17 published studies, the LoE was 5.
- In nine manuscripts, LoE was two; in four papers, it was four; and in one study, LoE was one.

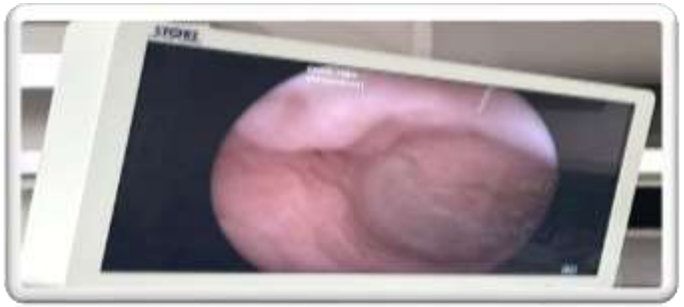
- Despite the positive data supporting IORT, brachytherapy is not a standard method used for the complementary treatment of soft-tissue sarcomas.
- The biggest problem seems to be its limited accessibility and technical limitations resulting from the fact that brachytherapy facilities are rarely located near surgical or oncologic orthopaedic departments offering the possibility of a shared surgical path.
- The recent introduction of portable linear accelerators, delivering low-energy (50 kV) photons, could be an option for solving this limitation.

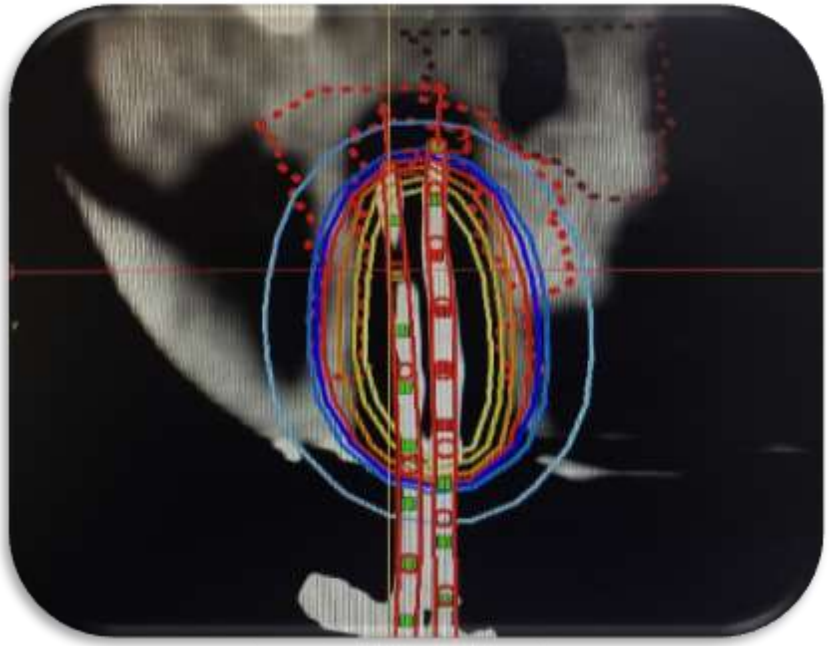
Case- ca vaginal rhabdomyosarcoma

- 6 months old infant present with mass protruding out of the vagina
- Patient presented to Pediatric-oncology
- MRI- revealed 2.5*2.3*8cm mass arising from right sided vagina mucosa
- Biopsy- Embryonal RMS
- Received 10 weeks of Vincristine, Actinomycin-D, Cyclophosphamide
- CEMRI Pelvis- 1*0.8cm residual mass in the vaginal lumen
- Followed by genitoscopy + cystoscopy + excision (R1) of residual mass
- I/V/O R1 resection
- Patient was planned for IVBT
- Two major challenges were-

- Unavailability of paediatric sized applicator
- Lack of monitoring system for anaesthesia in brachytherapy suit

- Cylindrical wax mould with four catheters
- Planning CT taken with applicator inserted
- Delineation of target volume and organ at risk
- Treatment plan – Bebig CO-60 HDR machine
- Dose- 30Gy/12#, once daily fraction (2.5Gy/#)
- Treatment delivered





Conclusions

- Adjuvant brachytherapy improves local control after complete resection of soft tissue sarcomas especially in high-grade tumours. IMRT in recent years can replicate results.
- But brachy does not significantly reduce distant metastasis or improve disease-specific survival.
- Surface mould brachytherapy useful alternative to interstitial brachytherapy. Important where target volume is extensive / underlying critical structures present or catheter placement difficult.

Areas like nose, scalp, peri-orbital regions, shoulder or knees

areas where surface mould brachytherapy can be successfully applied

THANK YOU