Evidence Table – Literature Summary:

SFRT for Sarcoma

This collated literature table presents, for your reference, a summary of major pertinent studies that were considered in developing these recommendations. This summary table is structured based on type and objective, patient selection, SFRT and conventional radiation therapy parameters, and treatment outcome criteria.

Abbreviations:	
gr	= grade
LC	= local control
LR	= local recurrence
DSS	= disease-specific survival
PFS	= progression-free survival
OS	= overall survival
Tox	= toxicity
yr	= year
pt, pts	= patient, patients
*	= per author's communication

Abbreviations:	
RR	= response rate
PR	= partial response
CR	= complete response
NR	= no response
cCR	= clinical complete response
pCR	= pathologic complete response
cERT	= Conventional radiation
fr	= fraction
n/a	= not applicable
–	= no data

Multiple-site Studies including Sarcoma Patients						
Author, Year	**Pt No. Sites**	**Objectives**	**Methods**	**Results**	**Dose/ Spatial Fx**	**Conclusion**
Mohiuddin M et *al.* (Radiat Oncol Invst 1996; 4:41-7) Treated: ~1990-1995	61 (72 sites)	Multiple, Palliative only: GI (18) **Sarcoma (12)** GU (9) Gyn (9) Melan (5) ENT(SCCa) (4) Lung (1) Breast (2) Thyroid (4)	Study type: Clinical trial Study Population: Palliative only tx refractory Primarily lg soft tissue masses. 44/72 pts abdomen/pelvis 24% (17 sites) had prior RT (12.6-79 Gy) Outcome Measures: Palliation (pain, bleeding, mass effects): RR, CR, PR, NR Tox (EORTC grading) Technique: Block Follow-up: 0.5-28 mo (d/t adv stg) 10 pts alive ≥ 1 yr	RR: 91% LC: Durable response in most pts w longer survival. GRID ≥15 Gy: 100% vs 79% RR cERT ≥40 Gy: 100% vs 92% RR DSS: – OS: 27/71 pts: 3-28 mo. 10/71 pts: survived >1 yr Toxicity: No grade 2 or higher tox No bwl tox despite 44 pts w abd/pelvis tx (1 bwl obstr d/t tumor @ lap)	GRID sequencing: GRID only: 44% GRID generally 1st (40/72, pts with life expectancy of >1 mo.): GRID + cERT GRID method: Block (50% open) 6, 24MV Single field GRID dose: 10-15/1 (for GRID+ cERT) 15-25/1 for GRID only) to Dmax cERT dose: (in 44/72) wide range; 78 Gy Dose to periphery: – OAR dose: – Concurr tx: No	GRID therapy results in high (>90%) symptomatic tumor response rate, with minimal toxicity. Dose response relationship: High cumulative GRID and cERT doses are needed for satisfactory CR rates: GRID dose ≥15 Gy: higher RR, CR, cERT DRR ≥40 Gy: higher RR, CR. Response by tumor type: Best RR in sarcoma (94%) and SCCa (92%); least RR in adenocarcinoma (69%). Parallelism of GRID therapy with brachytherapy, enabling delivery of high doses to small volumes with modest doses over a larger volumes of tissue.

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Mohiuddin M et *al.* (IJROBP 1999;45:721-7) Treated: 1/1995-3/1998	71 (87 sites) Overall sites: Lung: 18 H&N: 17 **Sarcoma: 10** GI: 4 GU: 5 Gyn: 8 Skin: 11 Melan: 3 Breast: 3 Thyr: 2 UNK:4 Liver: 2	Multiple, Palliative 89% Curative: +/- surgery 11%	Study type: Retrosp Study Population: Palliative: 89% (63/71) Adv, definitive: ENT, 11% (8/71) Tu >8 cm Prior RT: 9% (8/87 sites) Outcome Measures: RR Pts who died during / p 1 mo. of tx (7) ineval for RR, but included in tox analysis. Path response (part of 8 pts) Technique: Block Follow-up: 7 (3-42) mo.	RR: 76% Palliative pts: 78% cCR 62% (5/8 defintive pts) pCR 50% (4/8 defintive pts) GRID dose >15 Gy: RR 94 vs 62% (p-.002) cERT DRR >40 Gy: 0 Gy: 86%, 0% (RR, CR) <40 Gy: 91%, 13% (RR, CR) ≥ 0 Gy: 94%, 24% (RR, CR) LC: – DSS: – OS: – Toxicity: 1 gr 3 (mucositis) 1 gr 5 (carotid blowout) during tx (rapid tumor lysis)	GRID sequencing: Only: 20% (14/71) GRID > eERT 66%(47/91) GRID method: Block (50% open) 6, 18 MV GRID dose: 10-20 Gy/1 median: 15 Gy/1 to 10-12 Gy (for prior RT), at Dmax cERT dose: Definitive pts (8): 50-70 Gy Palliative pts: – Dose to periphery: – OAR dose: – Concurr tx: No	High response, low toxicity. Dose response relationship: Validating the results from Mohiuddin et *al.* (Radiat Oncol Invst 1996): GRID dose >15 Gy: higher RR, cERT DRR >40 Gy: Higher RR, CR. Response by tumor site: SCCa had better CR (29%). Sarcoma (11%) had worse RR: larger tumors (>20 cm) and early death.

Sarcoma-specific Studies						
Author, Year	**Pt No. Sites**	**Objectives**	**Methods**	**Results**	**Dose/ Spatial Fx**	**Conclusion**
Mohiuddin, M et *al.* (IJRIBP 2009; 75:S526) (abstr) Treated: ~before 2009	33 44 tumor sites: Abdomen: 20 H&N: 3 Chest: 7 Extremities: 15	Soft tissue sarcoma Definitive/ palliative RT Recurrent, un-resectable	Study type: Retrospective Study Population: Bulky: median 13 (6-32 cm) Outcome Measures: cRR, pRR, LC, OS Technique: GRID Follow-up: – Survival: median: 9 (2- 44) mo.	RR: CR: 26% PR: 50% cERT>50 Gy: RR 95% , CR 45%) cERT<50 Gy: RR 59%, CT 10% LC: – DSS: – OS: 9/33 alive >1 year Toxicity: Early gr 3 (skin): 2/33 No late reactions	GRID sequencing: GRID first (4: GRID alone) GRID method: Block GRID dose: 12-20 (median 15 Gy) / 1 fr @ Dmax (6MV) cERT dose: 22-70 Gy (median 50 Gy) Dose to periphery: – OAR dose: – Concurr tx: No	High response and local control in unresectable and recurrent soft tissue sarcoma, and encouraging survival outcomes (9/33 patients alive >1 year). Response higher (95% vs 59%) with cERT dose of >50 Gy.

Author, Year	Pt No. Sites	Objectives	Methods	Results	Dose/ Spatial Fx	Conclusion
Mohiuddin, M et *al.* (J Clin Oncol 2014;32: 10575) (abstr) Treated: ~before 2014	14 Soft tissue sarcoma Sites: Extremities	Curative: Neo-adjuvant, pre-op RT/concurrent chemo-therapy	Study type: Clinical trial Study Population: Locally advanced soft tissue sarcoma, >8 cm, median 11.5 cm (8-26 cm) Outcome Measures: Tumor necrosis (>90%) Resectability, Limb salvage LC DSS, OS Technique: GRID Follow-up: median 14 (3-43) mo.	RR: >90 % tu necrosis: 65% >80% tu necrosis: 2/14 pCR: 2/14 Limb salvage surgery: 93% (13/14) LC: 100% DSS: 86%: 12/14 alive/ NED OS: 86%: 12/14 alive/NED Toxicity: 1 grade skin reaction resulting to tx interruption/dis-continuation 2 delayed wound healing	GRID sequencing: GRID first GRID method: Block GRID dose: 18 Gy/1 cERT dose: 50 Gy Dose to periphery: – OAR dose: – Concurr tx: Iphosfamide/Mesna q 3 wks	Induction SFRT / GRID therapy and conventional ERT with chemotherapy enhances necrosis and response to neoadjuvant chemo-radiation, and potentially improves local control, limb salvage and survival in locally advanced extremity sarcoma.

Author, Year	Pt No. Sites	Objectives	Methods	Results	Dose/ Spatial Fx	Conclusion
Snider, JW et *al.* Rad Res 2020; 194: 707-14 Treated: 2005-2019	26 Soft tissue sarcoma: 21 Extra-osseous osteo-sarcoma: 4 Chondro-sarcoma: 1	Curative: Neo-adjuvant, pre-op RT Prior tx: Resection (followed by pro-gression):3 Chemo-therapy (followed by pro-gression):4	Study type: Retrosp Study Population: Locally advanced sarcoma, all except 2 pts > 10 cm, median 14.2 cm (8.8-40 cm) Grade 2-3: 88% Grade 1: 3/26 Outcome Measures: pCR, LC, PFS, OS, Tox Technique: GRID Follow-up: median 25 (7-109*) mo.	RR: pCR (>80% necrosis): 32% Hi gr soft tissue sarcoma: 35% (6/17) pCR Hi gr extremity sarcoma: 50% (4/8) pCR pCR poor in low grade tumors Negative resection margins: __% (20/26), close margins common R0/R1 resection in all pts. pathologic stage: ypT2a (3 pts) ypT2b (23 pts) LC (2-yr): 85% PFS (2-yr): 65% OS (2-yr): 86% Toxicity: 35% major wound complications	GRID sequencing: GRID first 2-3 day break between GRID and cERT GRID method: Block and MLC Image- guidance GRID dose: 15 Gy /1 cERT dose: 45-50.4 Gy at 1.8-2.25 Gy/fr (protons in 2 pts), no boost Dose to periphery: – OAR dose: – Avoiding critical organs Concurr tx: No (prior chemotherapy followed by progression: 4 pts)	SFRT with GRID therapy, followed by conventional ERT is a safe and effective neoadjuvant regimen for high-risk soft tissue sarcomas. The pathologic response rate of 35% exceeds that of conventionally fractionated RT alone (19.4% in RTOG 0630) and RT/chemotherapy (27.5% in RTOG 9514) despite the larger tumor size in the current series. Toxicity is acceptable and less than in the NCIC trial.