Appendix to:

Consensus Guideline Recommendations for the Design of Clinical Trials in Spatially Fractionated Radiation Therapy for Head and Neck Cancer

Evidence Table - Literature Summary:

SFRT for Head & Neck Cancer

This collated literature table presents a summary of major pertinent studies that were considered in developing the recommendations. This summary table is structured based on study type, study objective, patient selection, SFRT and conventional radiation therapy parameters, SFRT technology 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
pts	= 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

Studies of Multiple Tumor Sites Including Head and Neck Cancer 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) GI: 18 Sarcoma: 12 GU: 9 Gyn: 9 Melanoma: 5 **H&N** (SCCa): **4** Lung: 1 Breast: 2 Thyroid: 4	Multiple sites Palliative only	Study type: Clinical trial Study Population: Palliative only tx refractory Primarily large 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 bowel tox despite 44 pts w abdom/pelvis tx (1 bowel obstruction due to tumor at laparotomy)	GRID sequencing: GRID only: 44% GRID generally first (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.

Author, Year	Pt No. Sites	Objectives	Methods	Results	Dose/ Spatial Fx	Conclusion
Mohiuddin M et *al.* (IJROBP 1999;45:721-7) Treated: 1/1995-3/1998	71 (87 sites) Overall sites: Lung: 18 **H&N: 17** Sarc: 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: Retrospective Study Population: Palliative: 89% (63/71) Advanced, definitive: ENT, 11% (8/71) Tumor >8 cm Prior RT: 9% (8/87 sites) Outcome Measures: RR Pts who died during/within 1 mo. of tx (7) inevaluable for RR, but included in toxicity analysis. Path response (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, then cERT 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.

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Neuner G et *al.* (2012;82(5):1642-9) Treated: 2003-2008	79 Lung: 18 **H&N: 14** Sarcoma:14 Liver: 6 Skin: 5 Breast: 4 Colon/ Anus: 5 Kidney: 3 Thyroid: 3 Esoph: 2 Lymph: 2 Prostate:1 Ovary: 1 Unknown:1	Multiple, Palliative 77% Most lung, H&N Curative: 23% Most lung,H&N Pre-op RT 4 pts	Study type: Retrospective review Study Population: Bulky, median 7.6 cm (4-10 cm) Most lung, H&N, Sarc Most common tx site: neck Outcome Measures: Symptom response: CR= complete resolution PR= any improvement NR= no improvement or progression Imaging response (n=40): RECIST Technique: Retrospective comparison of Block vs. MLC Follow-up: 2 (0-51.6) mo. 28% (22 pts) lost to f/u	RR: Block vs MLC Pain: 75% 74% Mass eff: 67% 73% Bleeding: 50%, 80% Other symptoms: high response. Imaging RR (CR+PR): Block vs MLC 27% 32% LC: – DSS: – OS: 29% (23/79) (study not intended to report survival) Median survival: 2.2 mo. (Block) 4.1 mo. (MLC), p=NS Toxicity: 2 early gr4 (skin) 3 late gr3-4 (skin) *Early:* 2 pts Grade 4 dermatitis *Late:* 3 pts: late gr3-4: chronic skin ulceration p cERT dose of 40 Gy, 45 Gy, 60 Gy (2/3 pts with skin involvement)	GRID sequencing: Only: 20%(palliative pts) First: 72%, with 1-2 day gap to cERT In early cERT: 8% GRID method: - Block - MLC: average open/ closed ratio 0.31. GRID dose: 10-20 Gy (median 15 Gy)/ 1 fr Block: at Dmax MLC: GTV, no expansion cERT dose: ≥35-40 Gy, No dose reduction for GRID, (e.g. 70.2 Gy for H&N), but nl tissue dose reduction Dose to periphery: – OAR dose: Blocking of neural structures, kidney, GI tract, heart; minimizing exit dose Concurr tx: H&N ca/curative: GRID 15 Gy, 1-2 d break, then definitive cERT 70.2 Gy + chemotx (type not reported)	High symptom response rate; no difference in response between Block vs MLC based GRID. No difference in imaging response for Block vs MLC based GRID therapy. Low toxicity rates. Ease and efficacy of MLC-based GRID may enable more widespread adoption of SFRT.

Head and Neck Cancer Specific Studies						
Author, Year	**Pt No. Sites**	**Objectives**	**Methods**	**Results**	**Dose/ Spatial Fx**	**Conclusion**
Huhn J et *al.* (TechnCaResTx 2006;5:607-12) Treated: 7/1995-12/2002	27 Oral cav: 5 Oroph: 14 Nasoph: 1 Hypoph: 1 Unknown:5 Oral cav +hypoph: 1	H&N ca Advanced neck disease 2 groups: Definitve RT (14) Pre-op RT (13)	Study type: Clinical Trial Study Population: H&N SCCa, Bulky N2-3 neck disease *RT* (14 pts): med tumor size 7 (6-10) cm *Pre-op RT* (13 pts); med 8 (6-13) cm Outcome Measures: LC, DSS, Tox Technique: GRID Follow-up: *RT:* 10 (3-44) mo *Pre-op RT:* 38 (5-116) mo.	RR: Pre-op RT: pCR 85% LC: (regional/neck): RT: 93% (13/14) Pre-op RT: 92% (12/13) LC/regional rate (overall): RT: 86% Pre-op RT: 92% (12/13) DSS: (3-yr) RT: 50% Pre-op RT: 85% OS: RT: 21% (3/14) Pre-op RT: 62% (8/13) @ 116 mo. Toxicity: *Definitive RT*: Early: gr 2-3 skin (#'s NR) Late: no gr 3 *Pre-op RT*: 3 wound healing complications	GRID sequencing: GRID first GRID method: Block GRID dose: 15/1; 1 pt with 20 Gy/1 at Dmax To neck disease only GRID field off cord cERT dose: *RT/definitive pts* (8): median 70 (68-79) Gy *RT/ non-definitive* (6): median 59 (54-60) Gy *Preop RT*: median 59.4 (54-72) Gy Hyperfx or accel fx/ concomitant boost: 7/27 Dose to periphery: – OAR dose: Cord excluded from GRID tx Concurr tx: during cERT: 7/27 (type not reported)	Very high complete pathologic response rate (185%) for locally advanced neck involvement in H&N cancer. First study to assess pathologic response to GRID and its impact on subsequent local control. High regional control in the neck with pre-op and definitive radiation. High survival in preoperative group. Surgical approach was feasible and required no alteration. Manageable toxicity, including would healing complications. Appraisal: Chemo type not reported

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Penagaricano J et *al.* (IJROBP 2010;76:1369-75) Treated: 2005-2007*	14 Tonsil: 4 Retromol trigone: 1 Base of tongue: 3 Larynx: 2 Nasoph: 1 Maxillary sinus: 2 Paotid: 1	SCCa H&N Definitive RT, concurrent chemo-therapy	Study type: Clinical trial Study Population: Bulky H&N ca, >6 cm Outcome Measures: LC, DSS, OS, Tox (RTOG criteria) Technique: GRID Follow-up: 19 (2-38) mo. 10/14 pts f/u >1 yr	RR: pCR in 8/10 pts (per resection path or biopsy of GRID volume) LC: crude 79% (11/14) in-field control; no local recurrence in GRID volume DSS: crude 79% (11/14) OS: 10/14 (1 patient from death of disease) Toxicity: Acute: gr 3 (skin) 7/14 gr 3 (mucosal): 4/14 Late: gr 3 (fibrosis): 1/14 PEG dependent (trismus): 2/14 Gr 5 carotid blowout p neck dissection (at 10 mo.): 1/14 Xerostomia: –	GRID sequencing: First, cERT next day GRID method: MLC, ~50%open GRID dose: 20 Gy/1 fr to Grid-GTV (=bulky, ≥6 cm disease, primary or nodes with no expansion) cERT dose: SIB-IMRT/ simultaneous integrated boost (SIB): 66 Gy/ 30 fr. PTV: 66 Gy Intermed-risk PTV: 60 Gy Low-risk PTV: 54 Gy Dose to periphery: – OAR dose: Exclusion of spinal cord, brain stem Concurr tx: Full-dose chemotx, most Carboplatin/Docetaxel; 1 pt with 5FU Chemotherapy started on the day of GRID fr*	Uniformly treated cohort, all with concurrent chemotx. Chemotherapy also given chemo also during GRID fraction. High response rate, pathologic complete response and local control with no local recurrence within the treated GRID volume. Higher acute skin toxicity. One gr 5 carotid complication (that might be also related to surgical technique). Mucosal toxicity similar to chemotherapy/IMRT series.

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Choi JI et *al.* (Cureus 2019; ;11(5):e4637. doi: 10.7759/cureus.4637) Treated: 2007-2015	21 (primary sites not reported)	H&N ca 9 definitive 12 palliative intent 9 definite pts: Definitive RT, concurrent chemo-therapy	Study type: Retrospective Study Population: Bulky H&N ca, >5 cm; 5-25 cm, median 9.5 cm *Definitive*: All SCCa *Palliative*: Most SCCa Outcome Measures: RR, symptom response, Tox (RTOG criteria) Technique: GRID Follow-up: 7 (4-16) mo. (definitive pts)	RR: *Definitive**: CR 4/9 PR 1/9 Symptom response 8/9 * 1 pt completed only 1 cERT fraction *Palliative*: CR 0/12 PR 5/12 Symptom response 6/12 If received <75% of dose, only 25% symptom response. LC: – DSS: – OS: *Definitive:* 7/9 alive at median 7 mo. Toxicity: Skin gr >3: 5/21 (total) gr 5: 4 /21 Bleeding: 3/21 (2 required hospitalization) No gr ≥3mucous membrane tox	GRID sequencing: First, cERT start 1-3 d after GRID GRID method: MLC (before 2008) Block (2009-15) GRID dose: 15 Gy/1 20 Gy/1 - 5 pts (2010-11) cERT dose: *Definitive*: IMRT 69.96 - 72.08 Gy at 2.12 Gy/ fr *Palliative*: 25 Gy/ 10 fr - 78 Gy/39 fr Dose to periphery: – OAR dose: Maximal avoidance of mandible, spinal cord, brainstem, brain, brachioplexus). Traversing smallest possible skin to GTV separation. Concurr tx: In all definitive pts. Start after the GRID fr. Cisplatin (9), Cispl+Taxol or Etoposide (5), Cetuximab (2)	SFRT feasible in definitive and Palliative setting for large H&N tumors. Excellent clinical response with SFRT, cERT and chemotherapy. Treatment toxicity acceptable. Need for careful patient selection to identify pts who tolerate a full course cERT following SFRT.