Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer

Appendixes

Appendix A: Exact Search Strings

- MEDLINE® (January 1, 1990, through September 28, 2009)
- EMBASE® (January 1, 1990, through September 28, 2009)
- Cochrane Controlled Trials Register (no date restriction)

Single-arm studies, which are not a main focus of this review, were selected from studies identified through the January 13, 2009 search result update. Comparative studies were identified through the latest search updates.

In addition to electronic databases, abstracts for the past 5 years of meetings of the American Society of Therapeutic Radiation Oncology (ASTRO) and American Society of Clinical Oncology (ASCO) were searched.

Database Search Strategy:

(head and neck neoplasms [MH] OR ((larynx [TIAB] OR laryngeal [TIAB] OR supraglottic [TIAB] OR glottic [TIAB] OR subglottic [TIAB] OR pharynx [TIAB] OR pharyngeal [TIAB] OR hypopharynx [TIAB] OR hypopharyngeal [TIAB] OR hypo-pharynx [TIAB] OR hypo-pharyngeal [TIAB] OR oropharynx [TIAB] OR oropharyngeal [TIAB] OR oro-pharynx [TIAB] OR oro-pharyngeal [TIAB] OR nasopharynx [TIAB] OR nasopharyngeal [TIAB] OR naso-pharynx [TIAB] OR naso-pharyngeal [TIAB] OR lip [TIAB] OR lips [TIAB] OR oral [TIAB] OR paranasal [TIAB] OR para-nasal [TIAB] OR nasal [TIAB] OR sinus [TIAB] OR salivary [TIAB] OR parotid [TIAB])

AND

(neoplasm [TIAB] OR neoplasms [TIAB] OR tumor [TIAB] OR tumors [TIAB] OR tumour [TIAB] OR tumours [TIAB] OR cancer [TIAB] OR cancers [TIAB] OR adenocarcinoma [TIAB] OR carcinoma [TIAB])

OR

"occult primary" [TIAB] OR "unknown primary" [TIAB]

AND

(radiotherapy, conformal [MH] OR IMRT [TIAB] OR 3dcrt [TIAB] OR "3D-CRT" [TIAB] OR "3-D CRT" [TIAB] OR "3D CRT" [TIAB] OR (intensity [TIAB] AND modulated [TIAB]) OR conformal [TIAB] OR proton [TIAB] OR protons [TIAB] OR protons [MH]))

AND

humans [MH]

Appendix B: Excluded Studies

Full Review Codes

Key Question Codes

NRQ	not relevant question (note if ANM, NDE, NRD, NRO, NRT)
Q#?	unclear if relevant to any key question

Study Design Codes

ADB	administrative database
ANM	animal study
CEA	cost/cost-effectiveness analysis
CCS	case-control study
COH	cohort study
COM	commentary
CR	case report (n≤5)
CS	case series
D?	design unclear/possibly relevant
DAC	diagnostic accuracy study
DPC	dose planning study, comparative
DPN	dose planning study, noncomparative
EDT	editorial
GUI	guideline
INV	in vitro
LTR	letter
MA	meta-analysis
NAB	no abstract
NDE	not relevant design
NPD	no primary data
NRA	narrative review article
PI	phase I trial
PII	phase II trial
PHY	physics study
PHN	phantom study
POS	patient positioning study
PRG	prognostic study
PRO	prospective single-arm study
QEX	quasi-experimental study (nonrandomized comparative)
RAD	radiology/imaging study
RCT	randomized controlled trial
REG	registry
RET	retrospective study
SR	systematic review
STG	disease staging study
XSL	cross-sectional study

Sample Size Code (single-arm only)

FEW	n < 10
N10	10 ≤ n < 25
N25	25 ≤ n < 50
N50	50 ≤ n < 100
N100	n ≥ 100
N?	n unclear

Disease Codes

CNT	central nervous system tumor (including spine)
CRN	cranial nerve tumors
CUT	cutaneous tumors (melanoma, etc.)
DS?	disease unclear
EAR	ear tumors
EST	esophageal or precursors
ETH	ethmoid sinus
EYE	eye tumors
HEM	hematologic tumor (including lymphoma
HNU	head & neck unspecified
HYP	hypopharyngeal
LAR	laryngeal
MAX	maxillary sinus
MIX	mixed head and neck
NRD	not relevant disease
NPH	nasopharyngeal
OCL	oral cavity/lip
OHN	other head and neck tumor
OPH	oropharyngeal
OST	other non-head and neck solid tumor
PAR	paraganglioma
PHR	pharyngeal
PNS	paranasal sinus/nasal cavity
PTH	parathyroid
SAL	salivary gland, including parotid
SB	skull base tumors
SIN	sinus unspecified
THY	thyroid
TR	tracheal tumors
UNP	unknown/occult primary

Intervention Codes

3DC	3D conformal RT
2.5D	2 ½ D RT
2DR	2D conventional RT
ACC	accelerated fractionation
BST	boost dose
BRA	brachytherapy
CHT	chemotherapy only
CRT	chemoradiotherapy
CTP	cytoprotective agent
DFR	definitive RT
HYF	hyperfractionation
IMR	IMRT
IMM	with immobilization
MET	metastatic
NBT	neutron beam therapy
NRT	not relevant treatment
PAL	palliative
PBT	proton beam therapy
PCR	postoperative CRT
PST	postoperative (adjuvant)
PRE	preoperative (neoadjuvant)
REC	recurrent (reirradiation)
RSE	radiosensitizing agent
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
SUR	surgery only
T?	treatment unclear
UCF	unspecified conformal RT
URT	unspecified radiotherapy

[No author]. RTOG 0522: a randomized phase III trial of concurrent accelerated radiation and cisplatin versus concurrent accelerated radiation, cisplatin, and cetuximab [followed by surgery for selected patients] for Stage III and IV head and neck carcinomas. Clin Adv Hematol Oncol 2007;5(2):79-81.
Rec #: 1840
Reprint: EXC NPD

[No author]. AstraZeneca. Formulary 1999;34(10 SUPPL):13-18.
Rec #: 27340
Reprint: EXC NRD

Aarstad AK, Aarstad HJ, Bru E, et al. Psychological coping style versus disease extent, tumour treatment and quality of life in successfully treated head and neck squamous cell carcinoma patients. Clin Otolaryngol 2005;30(6):530-538.
Rec #: 3920
Reprint: EXC URT, MIXED

Abayomi OK. Pathogenesis of cognitive decline following therapeutic irradiation for head and neck tumors. Acta Oncol 2002;41(4):346-351.
Rec #: 8970
Reprint: EXC NRA

Al-Nawas B, Al-Nawas K, Kunkel M, et al. Quantifying radioxerostomia: salivary flow rate, examiner's score, and quality of life questionnaire. Strahlenther Onkol 2006;182(6):336-341.
Rec #: 3330
Reprint: EXC T? URT

Allen AM, Tishler RB. Commentary: IMRT for head and neck cancer: many chapters left to write. Oncologist 2007;12(5):565-568.
Rec #: 1460
Reprint: EXC COM

Amosson CM, Teh BS, Mai WY, et al. Using technology to decrease xerostomia for head and neck cancer patients treated with radiation therapy. Semin Oncol 2002;29(6 Suppl 19):71-79.
Rec #: 8600
Reprint: EXC DPN

Anand AK, Jain J, Negi PS, et al. Can dose reduction to one parotid gland prevent xerostomia?--A feasibility study for locally advanced head and neck cancer patients treated with intensity-modulated radiotherapy. Clin Oncol (R Coll Radiol) 2006;18(6):497-504.
Rec #: 2880
Reprint: EXC N10

Ang KK. Altered fractionation trials in head and neck cancer. Semin Radiat Oncol 1998;8(4):230-236.
Rec #: 36730
Reprint: EXC MA

Ask A, Bjork-Eriksson T, Zackrisson B, et al. The potential of proton beam radiation therapy in head and neck cancer. Acta Oncol 2005;44(8):876-880.
Rec #: 4110
Reprint: EXC NRA

Astreinidou E, Dehnad H, Terhaard CH, et al. Level II lymph nodes and radiation-induced xerostomia. Int J Radiat Oncol Biol Phys 2004;58(1):124-131.
Rec #: 7560
Reprint: EXC N10

Back M, Oliver L, Bromley R, et al. Multicentre quality assurance of intensity-modulated radiotherapy planning: beware the benchmarker. J Med Imaging Radiat Oncol 2008;52(2):197.
Rec #: 28870
Reprint: EXC NRQ

Baker SR, Pankhurst CL, Robinson PG. Testing relationships between clinical and non-clinical variables in xerostomia: a structural equation model of oral health-related quality of life. Qual Life Res 2007;16(2):297-308.
Rec #: 37460
Reprint: EXC NRQ

Bangalore M, Matthews S, Suntharalingam M. Recent advances in radiation therapy for head and neck cancer. ORL J Otorhinolaryngol Relat Spec 2007;69(1):1-12.
Rec #: 2490
Reprint: EXC NRA

Bentzen SM, Trotti A. Evaluation of early and late toxicities in chemoradiation trials. J Clin Oncol 2007;25(26):4096-4103.
Rec #: 37680
Reprint: EXC NRA

Bentzen SM, Wasserman TH. Balancing on a knife's edge: evidence-based medicine and the marketing of health technology. Int J Radiat Oncol Biol Phys 2008;72(1):12-14.
Rec #: 39250
Reprint: EXC COM

Bhatnagar A, Deutsch M. The Role for intensity modulated radiation therapy (IMRT) in pediatric population. Technol Cancer Res Treat 2006;(6):591-595.
Rec #: 2410
Reprint: EXC N10, NRD

Blanco AI, Chao C. Management of radiation-induced head and neck injury. Cancer Treat Res 2006;128:23-41.
Rec #: 4080
Reprint: EXC NRA

Blanco AI, Chao KS, El Naqa I, et al. Dose-volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. Int J Radiat Oncol Biol Phys 2005;62(4):1055-1069.
Rec #: 4970
Reprint: EXC NRT, MIXED

Bourhis J, Guigay J, Temam S, et al. Chemo-radiotherapy in head and neck cancer. Ann Oncol 2006;17(SUPPL. 10):x39-x41.
Rec #: 17030
Reprint: EXC NRA

Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368(9538):843-854.
Rec #: 30800
Reprint: EXC MA

Braaksma M, Levendag P. Tools for optimal tissue sparing in concomitant chemoradiation of advanced head and neck cancer: subcutaneous amifostine and computed tomography-based target delineation. Semin Oncol 2002;29(6 Suppl 19):63-70.
Rec #: 8610
Reprint: EXC NRT, MIXED

Braam PM, Roesink JM, Raaijmakers CP, et al. Quality of life and salivary output in patients with head-and-neck cancer five years after radiotherapy. Radiat Oncol 2007;2:3.
Rec #: 37610
Reprint: EXC 2DR CS

Brada M, Pijls-Johannesma M, De Ruysscher D. Proton therapy in clinical practice: current clinical evidence. J Clin Oncol 2007;25(8):965-970.
Rec #: 1830
Reprint: EXC NRA

Brizel DM. Radiotherapy and concurrent chemotherapy for the treatment of locally advanced head and neck squamous cell carcinoma. Semin Radiat Oncol 1998;8(4):237-246.
Rec #: 37470
Reprint: EXC MA

Budach W, Hehr T, Budach V, et al. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer 2006;6:28.
Rec #: 37480
Reprint: EXC MA

Bussels B, Maes A, Flamen P, et al. Dose-response relationships within the parotid gland after radiotherapy for head and neck cancer. Radiother Oncol 2004;73(3):297-306.
Rec #: 6110
Reprint: EXC N10

Bussels B, Maes A, Hermans R, et al. Recurrences after conformal parotid-sparing radiotherapy for head and neck cancer. Radiother Oncol 2004;72(2):119-127.
Rec #: 6620
Reprint: EXC NRT, MIXED

Butler EB, Teh BS, Grant 3rd WH, et al. Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 1999;45(1):21-32.
Rec #: 11480
Reprint: EXC N10 IMR

Caglar HB, Allen AM. Intensity-modulated radiotherapy for head and neck cancer. Clin Adv Hematol Oncol 2007;5(6):425-431.
Rec #: 15090
Reprint: EXC NRA

Calais G, Le Floch O. [Concomitant radiotherapy and chemotherapy in the treatment of cancers of the upper respiratory and digestive tracts]. Bull Cancer Radiother 1996;83(4):321-329.
Rec #: 37490
Reprint: EXC MA

Cannon DM, Lee NY. Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008;70(3):660-665.
Rec #: 350
Reprint: EXC CS

Castro JR, Linstadt DE, Bahary J-P, et al. Experience in charged particle irradiation of tumors of the skull base: 1977-1992. Int J Radiat Oncol Biol Phys 1994;29(4):647-655.
Rec #: 28540
Reprint: EXC NRD NRT

Cattaneo GM, Ceresoli GL. Optimisation of conformal radiotherapy for lung and nasopharynx cancers: Literature review and clinical experience at HS Raffaele Phys Med 2001;17(SUPPL 2):93-102.
Rec #: 26310
Reprint: EXC NRA

Chambers MS, Garden AS, Kies MS, et al. Radiation-induced xerostomia in patients with head and neck cancer: pathogenesis, impact on quality of life, and management. Head Neck 2004;26(9):796-807.
Rec #: 6470
Reprint: EXC NRA

Chambers MS, Garden AS, Rosenthal D, et al. Intensity-modulated radiotherapy: is xerostomia still prevalent? Curr Oncol Rep 2005;7(2):131-136.
Rec #: 5780
Reprint: EXC NRA

Chambers MS, Rosenthal DI, Weber RS. Radiation-induced xerostomia. Head Neck 2007;29(1):58-63.
Rec #: 2900
Reprint: EXC NRA

Chambers MS, Weber RS, Garden AS. Intensity-modulated radiation therapy and xerostomia. J Calif Dent Assoc 2006;34(9):743-748.
Rec #: 2640
Reprint: EXC NRA

Chan ATC. Head and neck cancer: Treatment of nasopharyngeal cancer. Ann Oncol 2005;16(SUPPL 2):ii265-ii268.
Rec #: 20040
Reprint: EXC NRA

Chang JT, See LC, Liao CT, et al. Locally recurrent nasopharyngeal carcinoma. Radiother Oncol 2000;54(2):135-142.
Rec #: 11090
Reprint: EXC T?

Chao KS. Protection of salivary function by intensity-modulated radiation therapy in patients with head and neck cancer. Semin Radiat Oncol 2002;2(1 Suppl 1):20-25.
Rec #: 9670
Reprint: EXC NRA

Chao KS, Bhide S, Chen H, et al. Reduce in variation and improve efficiency of target volume delineation by a computer-assisted system using a deformable image registration approach. Int J Radiat Oncol Biol Phys 2007;68(5):1512-1521.
Rec #: 1190
Reprint: EXC DPN

Chao KS, Low DA, Perez CA, et al. Intensity-modulated radiation therapy in head and neck cancers: The Mallinckrodt experience. Int J Cancer 2000;90(2):92-103.
Rec #: 11010
Reprint: EXC N10 IMR

Chao KS, Ozyigit G, Tran BN, et al. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2003;55(2):312-321.
Rec #: 8720
Reprint: EXC NRT, MIXED

Chao KS, Wippold FJ, Ozyigit G, et al. Determination and delineation of nodal target volumes for head-and-neck cancer based on patterns of failure in patients receiving definitive and postoperative IMRT. Int J Radiat Oncol Biol Phys 2002;53(5):1174-1184.
Rec #: 9140
Reprint: EXC DPN NRO

Chen WC, Jackson A, Budnick AS, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. Cancer 2006;106(4):820-829.
Rec #: 3870
Reprint: EXC N10 NRO

Chen YJ, Kuo JV, Ramsinghani NS, et al. Intensity-modulated radiotherapy for previously irradiated, recurrent head-and-neck cancer. Med Dosim 2002;27(2):171-176.
Rec #: 9320
Reprint: EXC N10 IMR

Chua DT, Ma J, Sham JS, et al. Long-term survival after cisplatin-based induction chemotherapy and radiotherapy for nasopharyngeal carcinoma: a pooled data analysis of two phase III trials. J Clin Oncol 2005;23(6):1118-1124.
Rec #: 37500
Reprint: EXC 2DR MA

Chua DT, Sham JS, Au GK. Induction chemotherapy with cisplatin and gemcitabine followed by reirradiation for locally recurrent nasopharyngeal carcinoma. Am J Clin Oncol 2005;28(5):464-471.
Rec #: 4460
Reprint: EXC N10 NRT, MIXED

Chua DT, Sham JS, Leung LH, et al. Re-irradiation of nasopharyngeal carcinoma with intensity-modulated radiotherapy. Radiother Oncol 2005;77(3):290-294.
Rec #: 4190
Reprint: EXC NRT, MIXED

Chua DTT, Tian Y, Wei WI. Late oral complications following radiotherapy for head and neck cancers. Expert Rev Anticancer Ther 2007; 7(9):1215-1224.
Rec #: 14540

Claus F, Duthoy W, Boterberg T, et al. Intensity modulated radiation therapy for oropharyngeal and oral cavity tumors: clinical use and experience. Oral Oncol 2002;38(6):597-604.
Rec #: 9050
Reprint: EXC N10 IMR

Cohen SM, Garrett CG, Dupont WD, et al. Voice-related quality of life in T1 glottic cancer: irradiation versus endoscopic excision. Ann Otol Rhinol Laryngol 2006;115(8):581-586.
Rec #: 37510
Reprint: EXC NDE NRT

Combs SE, Behnisch W, Kulozik AE, et al. Intensity Modulated Radiotherapy (IMRT) and Fractionated Stereotactic Radiotherapy (FSRT) for children with head-and-neck-rhabdomyosarcoma. BMC Cancer 2007;7:177.
Rec #: 880
Reprint: EXC NRD

Corry J, Hornby C, Fisher R, et al. 'Boomerang' technique: an improved method for conformal treatment of locally advanced nasopharyngeal cancer. Australas Radiol 2004;48(2):170-180.
Rec #: 6730
Reprint: EXC N10 IMR

Corvo R. Evidence-based radiation oncology in head and neck squamous cell carcinoma. Radiother Oncol 2007;85(1):156-70.
Rec #: 1510
Reprint: EXC SR

Cox JD, Fu KK, Pajak TF, et al. Radiation Therapy Oncology Group (RTOG) trials for head and neck cancer. Rays 2000;25(3):321-323.
Rec #: 35850
Reprint: EXC NRA

Das IJ, Cheng CW, Chopra KL, et al. Intensity-modulated radiation therapy dose prescription, recording, and delivery: patterns of variability among institutions and treatment planning systems. J Natl Cancer Inst 2008;100(5):300-307.
Rec #: 70
Reprint: EXC DPN

Davies AN, Broadley K, Beighton D. Salivary gland hypofunction in patients with advanced cancer. Oral Oncol. 2002;38(7):680-685.
Rec #: 25250
Reprint: EXC T?

Davies AN, Broadley K, Beighton D. Xerostomia in patients with advanced cancer. J Pain Symptom Manage 2001;22(4):820-825.
Rec #: 26240
Reprint: EXC T? NRD

Dawson LA, Anzai Y, Marsh L, et al. Patterns of local-regional recurrence following parotid-sparing conformal and segmental intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2000;46(5):1117-1126.
Rec #: 11050
Reprint: EXC T?, MIXED

Dawson LA, Myers LL, Bradford CR, et al. Conformal re-irradiation of recurrent and new primary head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;50(2):377-385.
Rec #: 10320
Reprint: EXC NRT, MIXED

de Arruda FF, Puri DR, Zhung J, et al. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: the Memorial Sloan-Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys 2006;64(2):363-373.
Rec #: 5150
Reprint: EXC NRT, MIXED

de Castro Jr G, Federico MH. Evaluation, prevention and management of radiotherapy-induced xerostomia in head and neck cancer patients. Curr Opin Oncol 2006;18(3):266-270.
Rec #: 3620
Reprint: EXC NRA

DeLaney TF. Clinical proton radiation therapy research at the Francis H. Burr Proton Therapy Center Technol Cancer Res Treat 2007;6(4 Suppl):61-66.
Rec #: 1020
Reprint: EXC NRA

Ding Y, Wu DH, Chen LH. [Value of 18F-fluorodeoxyglucose positron emission tomography in three-dimensional conformal radiotherapy for locally persistent or recurrent nasopharyngeal carcinoma]. Di Yi Jun Yi Da Xue Xue Bao 2005;25(12):1568-1570.
Rec #: 4000
Reprint: EXC FLA CS

Dinshaw KA, Agarwal JP, Ghosh-Laskar S, et al. Radical radiotherapy in head and neck squamous cell carcinoma: an analysis of prognostic and therapeutic factors. Clin Oncol (R Coll Radiol) 2006;18(5):383-389.
Rec #: 3110
Reprint: EXC NRT, MIXED

Dirix P, Nuyts S, Van den Bogaert W. Radiation-induced xerostomia in patients with head and neck cancer: a literature review. Cancer 2006;107(11):2525-2534.
Rec #: 2510
Reprint: EXC NRA

Douglas JG, Einck J, Austin-Seymour M, et al. Neutron radiotherapy for recurrent pleomorphic adenomas of major salivary glands. Head Neck 2001;23(12):1037-1042.
Rec #: 9860
Reprint: EXC NRT

Dulguerov P, Jacobsen MS, Allal AS, et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. Cancer 2001;92(12):3012-3029.
Rec #: 37520
Reprint: EXC 2DR CS

Eisbruch A. Reducing xerostomia by IMRT: what may, and may not, be achieved. J Clin Oncol 2007;25(31):4863-4864.
Rec #: 540
Reprint: EXC COM

Eisbruch A. Intensity-modulated radiation therapy in the treatment of head and neck cancer. Nat Clin Pract Oncol 2005;2(1):34-39.
Rec #: 4300
Reprint: EXC NRA

Eisbruch A, Kim HM, Terrell JE, et al. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;50(3):695-704.
Rec #: 10300
Reprint: EXC T?, MIXED

Eisbruch A, Levendag PC, Feng FY, et al. Can IMRT or brachytherapy reduce dysphagia associated with chemoradiotherapy of head and neck cancer? The Michigan and Rotterdam experiences. Int J Radiat Oncol Biol Phys 2007;69(2 Suppl):S40-S42.
Rec #: 630
Reprint: EXC NRT

Eisbruch A, Marsh LH, Dawson LA, et al. Recurrences near base of skull after IMRT for head-and-neck cancer: implications for target delineation in high neck and for parotid gland sparing. Int J Radiat Oncol Biol Phys 2004; 59(1):28-42.
Rec #: 7100
Reprint: EXC NRT, MIXED

Eisbruch A, Schwartz M, Rasch C, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys 2004;60(5):1425-1439.
Rec #: 6070
Reprint: EXC NRO DPN

Eisbruch A, Ship JA, Dawson LA, et al. Salivary gland sparing and improved target irradiation by conformal and intensity modulated irradiation of head and neck cancer. World J Surg 2003;27(7):832-837.
Rec #: 7920
Reprint: EXC N10 IMR 3DC

Eisbruch A, Ship JA, Martel MK, et al. Parotid gland sparing in patients undergoing bilateral head and neck irradiation: techniques and early results. Int J Radiat Oncol Biol Phys 1996;36(2):469-480.
Rec #: 12230
Reprint: EXC N10 3DC

Eisbruch A, Ten Haken RK, Kim HM, et al. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45(3):577-587.
Rec #: 11400
Reprint: EXC T?, MIXED

Eisbruch A, Terrell JE, Logemann JA, et al. Letters to the Editor (multiple letters). Head Neck 2003;25(12):1082-1083.
Rec #: 24760
Reprint: EXC LTR

Ernst-Stecken A, Grabenbauer G, Iro H, et al. Phase II trial of hyperfractionated accelerated split-course radiochemotherapy with 5-FU and Cis-DDP in advanced head and neck cancer: results and toxicity. Strahlenther Onkol 2004;80(12):805-810.
Rec #: 6030
Reprint: EXC NRT 2DR CS

Feng J, Coppes RP. Can we rescue salivary gland function after irradiation? TheScientificWorld Journal 2008;8(-):959-962.
Rec #: 38890
Reprint: EXC COM

Feng M, Eisbruch A. Future issues in highly conformal radiotherapy for head and neck cancer. J Clin Oncol 2007;25(8):1009-1013.
Rec #: 1820
Reprint: EXC NRA

Feng M, Jabbari S, Lin A, et al . Predictive factors of local-regional recurrences following parotid sparing intensity modulated or 3D conformal radiotherapy for head and neck cancer. Radiother Oncol 2005;77(1):32-38.
Rec #: 4680
Reprint: EXC NRT, MIXED

Fischer M, Pottgen C, Wechsler S, et al. [Accelerated hyperfractionated radiotherapy with concurrent chemotherapy in locally advanced nasopharyngeal carcinomas]. HNO 2007;55(12):950-955.
Rec #: 1810
Reprint: EXC FLA, CS

Fitzek MM, Thornton AF, Varvares M, et al. Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy. Cancer 2002; 94(10):2623-2634.
Rec #: 9040
Reprint: EXC NRT, MIXED

Foote RL. Radiotherapy Alone for Early-Stage Squamous Cell Carcinoma of the Larynx and Hypopharynx. Int J Radiat Oncol Biol Phys 2007;69(2 SUPPL):S31-S36.
Rec #: 14900
Reprint: EXC GUI NRA

Fu KK. Combined radiotherapy and chemotherapy for nasopharyngeal carcinoma. Semin Radiat Oncol 1998;8(4):247-253.
Rec #: 37530
Reprint: EXC MA

Fua TF, Corry J, Milner AD, et al. Intensity-modulated radiotherapy for nasopharyngeal carcinoma: clinical correlation of dose to the pharyngo-esophageal axis and dysphagia. Int J Radiat Oncol Biol Phys 2007;67(4):976-981.
Rec #: 2070
Reprint: EXC N10

Garden AS, Lewin JS, Chambers MS. How to reduce radiation-related toxicity in patients with cancer of the head and neck. Curr Oncol Rep 2006;8(2):140-145.
Rec #: 3740
Reprint: EXC NRA

Goitein M, Cox JD. Should randomized clinical trials be required for proton radiotherapy? J Clin Oncol 2008;26(2):175-176.
Rec #: 250
Reprint: EXC COM

Graff P, Lapeyre M, Desandes E, et al. Impact of intensity-modulated radiotherapy on health-related quality of life for head and neck cancer patients: matched-pair comparison with conventional radiotherapy. Int J Radiat Oncol Biol Phys 2007;67(5):1309-1317.
Rec #: 1960
Reprint: EXC NRT, MIXED

Gregoire V, De Neve W, Eisbruch A, et al. Intensity-modulated radiation therapy for head and neck carcinoma. Oncologist 2007;12(5):555-564.
Rec #: 1470
Reprint: EXC NRA

Guerrero Urbano MT, Nutting CM. Clinical use of intensity-modulated radiotherapy: part I. Br J Radiol 2004;77(914):88-96.
Rec #: 7300
Reprint: EXC NRA

Guerrero Urbano MT, Nutting CM. Clinical use of intensity-modulated radiotherapy: part II. Br J Radiol 2004;77(915):177-182.
Rec #: 37620
Reprint: EXC NRA

Harari PM. Promising new advances in head and neck radiotherapy. Ann Oncol 2005;16 Suppl 6:vi13-vi19.
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Reprint: EXC NRA

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Reprint: EXC NRA

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Reprint: EXC NRA

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Reprint: EXC NRT, MIXED

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Reprint: EXC NRT, MIXED

Appendix C: Summary Tables and Figures

Appendix Table C1. Numbers of comparative studies and participants by single setting and site

	All	One Setting	One Site	NPC	OPH	PNS	UNP	LAR	MIX
IMRT vs. 3DCRT									
Comparisons	14	2	7	2	4	1	0	0	7
Total n	1752	127	766	288	410	68	0	0	986
3DCRT vs. 2DRT									
Comparisons	12	3	8	3	1	2	1	1	4
Total n	1497	398	940	373	130	231	87	122	526
IMRT vs. 2DRT									
Comparisons	22	4	12	6	4	1	1	0	10
Total n	2441	573	1502	662	717	82	41	0	939
All comparisons									
Total comparisons	48	9	27	11	9	4	2	1	21
Total studies	38	9	21	9	7	2	2	1	17
Grand total n	5061	1098	2787	1174	1109	254	128	122	2274

Appendix Table C2. Numbers of comparisons, studies and participants by outcome

		QOL/Adverse Events							Tumor Control			Patient Survival	
		QOL	XST	SF	DYS	MUC	SKN	ORH or BON	LC	LRC	DFS	DSS	OS
IMRT vs. 3DCRT													
Comparisons	14	3	9	1	3	7	6	2	2	4	4	1	8
Total n	1752	429	879	41	729	735	540	152	112	569	274	195	800
3DCRT vs. 2DRT													
Comparisons	12	1	6	1	1	6	4	2	5	1	4	1	7
Total n	1497	94	1013	33	137	939	716	231	579	345	360	127	931
IMRT vs. 2DRT													
Comparisons	22	4	13	3	5	8	7	2	3	2	5	0	7
Total n	2441	317	1873	481	674	943	868	512	316	466	704	0	867
All comparisons													
Total comparisons	48	8	28	5	9	21	17	6	10	7	13	2	22
Total studies	38	6	22	5	7	15	11	4	6	7	9	2	16
Grand total n	5061	694	3322	555	1391	2193	1700	768	732	1380	1152	322	2264

Appendix Table C3. Summary of study quality characteristics: comparative studies

Selection Prospective/ Retrospective	Inclusion/ Exclusion Criteria Clear	Representative Selection	Initial Groups Comparable	Balanced by Design (Random/ Matched)	Baseline Characteristics Clearly Comparable
Pro 15	Yes 31	Yes 25	Yes 10	Yes 5	Yes 17
Retro 23	No 7	Unclear 8	Unclear 21	No 33	Unclear 17
		No 5	No 7		No 4

Treatments Given During Same Time Period	Unbiased Treatment Allocation	Other Treatments Equal	Maintenance of Comparable Groups
Yes 13	Clearly Random 2	NA 3	NA 25
Unclear 11	Unclear 18	Yes 12	Yes 3
Yes and No 1	Unclear/Era 1	Unclear 16	Unclear 9
No 13	Era 12	No 7	No 1
	Availability/Preference 2		
	Waiting List 1		
	Risk to Sensitive Areas 2		

Outcomes Valid, Reliable, Equal	Outcome Assessors Blind	Treatments Clearly Described	Multivariable Analysis (MVA) Conducted?	Well-done MVA or Intention-to-Treat Analysis (ITT)	USPSTF
Yes 38	Yes 1	Yes 32	NA 2	2 ITT	Good 1
Unclear 0	Unclear 13	No 6	Yes 20	1 unclear if ITT 13 unclear if well-done MVA	Fair 1
No 0	No 24		No 16	1 not ITT 21 not well-done MVA	Poor 36

Appendix Table C4. Summary of results for tumor control outcomes

Comparison	Tumor Site	Setting	Study	n	Outcome	UV p	MV p	Pro/ Retro	USPSTF
IMRT:3DCRT	OPH	1^{o} RT + CCTx	Rustoven, 2008	87	LRC DFS	4yr ↑ NS 4yr ↑ NS	0.075 NS	Retro	Poor
	NPH	MIX: 1^{o} RT ± CCTx	Fang, 2008	203	LRC	3yr, ≈ NS	NS	Pro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	44	LC	2yr ↑ NS	NS	Retro	Poor
	OPH	MIX: 1^{o} RT ± CCTx	Hodge, 2005	195	LRC	4yr ↑ p NR		Retro	Poor
	OPH	MIX: 1^{o}/postop RT ± preRT CTx	Nutting, 2009 (RCT)	84	LRC	1yr ≈ NS		Pro	Good
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	68	LC DFS	5yr, ≈ NS NS		Retro	Poor
	MIX	MIX: 1^{o}/postop/repeat RT ± pre/post RT CTx/CCTx	Marchal, 2004	87	DFS	1yr, ≈ NS		Pro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	42	DFS	NS	RT not in MVA	Retro	Poor
3DCRT:2DRT	NPH	1^{o} RT + split CTx	Wu, 2005 (RCT)	96	LC	1yr, ↑ 0.003		Pro	Poor
	LAR	1^{o} RT	Zouhair, 2004	122	LC	5yr, ≈ NS	NS	Retro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	130	LC	2yr ≈ NS	NS	Retro	Poor
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	104	LC DFS	5yr, ≈ NS NS		Retro	Poor
	NC/PNS	1^{o}/preop/postop RT	Dirix, 2007	127	LC DFS	NS NS		Retro	Poor
	UNK	1^{o}/postop RT± preRT CTx/CCTx	Beldi, 2007	87	DFS	5yr, ↑ <0.01	NS	Retro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	32	DFS	NS	RT not in MVA	Retro	Poor
	MIX	MIX: 1^{o}/postop RT± CCTx	Rades, 2008	345	LRC	3yr, ≈ NS		Retro	Poor

Appendix Table C4. Summary of results for tumor control outcomes (continued)

Comparison	Tumor Site	Setting	Study	n	Outcome	UV p	MV p	Pro/ Retro	USPSTF
IMRT:2DRT	NPH	1^{o} RT + split CTx	Laskar, 2008	36	LRC DFS	2yr ↑ NS 2yr ↑ NS	RT not in MVA	Pro	Poor
	OPH	1^{o} RT + CCTx	Lee, 2006	112	LC LRC DFS	5yr, ↑ NS 5yr, ↑ NS 5yr, ↑ NS		Retro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	122	LC	2yr, ↑ NS		Retro	Poor
	OPH	MIX: 1^{o}/pre/postop RT ± CCTx	Chao, 2001	430	LRC DFS	2yr, def, ↑ NS; postop, ↑ NS 2yr, def, ↑ 0.002; postop, ↑ 0.008		Retro	Poor
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	82	LC DFS	5yr, ≈ NS NS		Retro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	44	DFS	NS	RT not in MVA	Retro	Poor

Appendix Table C5. Summary of results for patient survival outcomes

Study	Tumor Site	Setting	Study	n	Outcome	UV p	MV p	Pro/ Retro	USPSTF
IMRT:3DCRT	OPH	1^{o} RT + CCTx	Rustoven, 2008	87	OS	4yr ↑ NS	NS	Retro	Poor
	NPH	MIX: 1^{o} RT ± CCTx	Fang, 2008	203	OS	3yr, ≈ NS	NS	Pro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	44	OS	2yr ~↑ NS	NS	Retro	Poor
	OPH	MIX: 1^{o} RT ± CCTx	Hodge, 2005	195	DSS OS	4yr ↑ p NR 4yr ↑ 0.02	 NS	Retro	Poor
	OPH	MIX: 1^{o}/postop RT ± preRT CTx	Nutting, 2009 (RCT)	84	OS	1yr, ≈ NS		Pro	Good
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	68	OS	5yr, ↓ NS		Retro	Poor
	MIX	MIX: 1^{o}/postop/repeat RT ± pre/post RT CTx/CCTx	Marchal, 2004	87	OS	1yr, ≈ NS		Pro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	42	OS	NS	RT not in MVA	Retro	Poor
3DCRT:2DRT	NPH	MIX: 1^{o} RT ± CTx (t?)	Wu, 2005 (RCT)	96	OS	1yr, ≈ NS		Pro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	130	OS	2yr ~↑ NS	NS	Retro	Poor
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	104	OS	5yr, ~↑ NS		Retro	Poor
	NC/PNS	1^{o}/preop/postop RT	Dirix, 2007	127	OS DSS	NS NS		Retro	Poor
	UNK	1^{o}/postop RT± preRT CTx/CCTx	Beldi, 2007	87	OS	5yr, ↑ <0.01	NS	Retro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	32	OS	NS	RT not in MVA	Retro	Poor
	MIX	MIX: 1^{o}/postop RT± CCTx	Rades, 2008	345	OS	3yr, ≈ NS		Retro	Poor

Appendix Table C5. Summary of results for patient survival outcomes (continued)

Study	Tumor Site	Setting	Study	n	Outcome	UV p	MV p	Pro/ Retro	USPSTF
IMRT:2DRT	NPH	1^{o} RT + split CTx	Laskar, 2008	36	OS	2yr ↑ NS	RT not in MVA	Pro	Poor
	OPH	1^{o} RT + CCTx	Lee, 2006	112	OS	5yr, ↑ NS		Retro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	122	OS	2yr, ↑ NS		Retro	Poor
	OPH	MIX: 1^{o}/pre/postop RT ± CCTx	Chao, 2001	430	OS	2yr, def, ↑ 0.001; postop, ↑ 0.003		Retro	Poor
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	82	OS	5yr, ≈ NS		Retro	Poor
	UNK	1^{o}/postop RT ± CTx (t?)	Madani, 2008	41	OS	1yr, ↑ NS		Retro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	44	OS	NS	RT not in MVA	Retro	Poor

Figure C1. Acute xerostomia, IMRT vs. 3DRCT

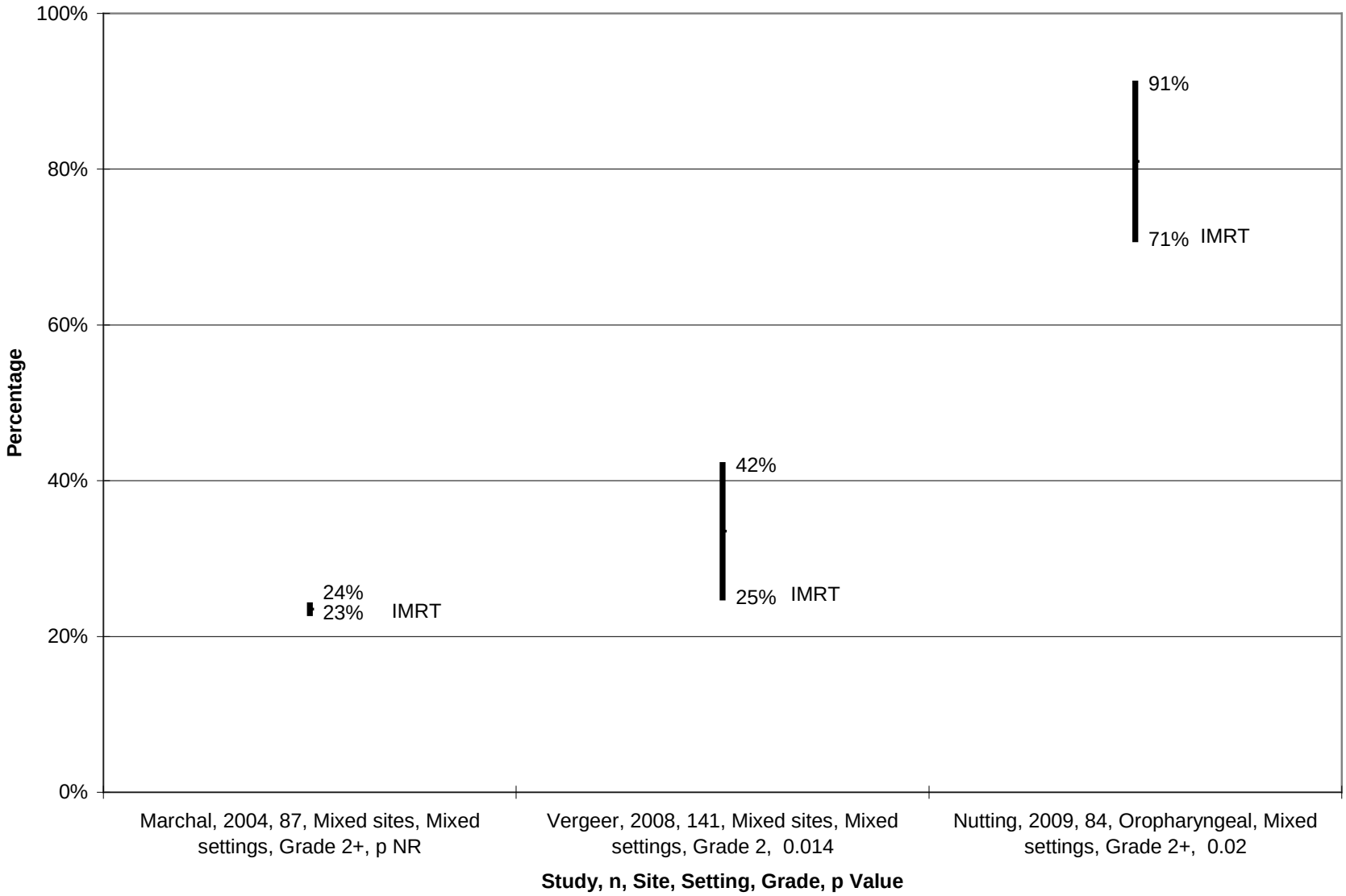


Figure C2. Late xerostomia, IMRT vs. 3DCRT

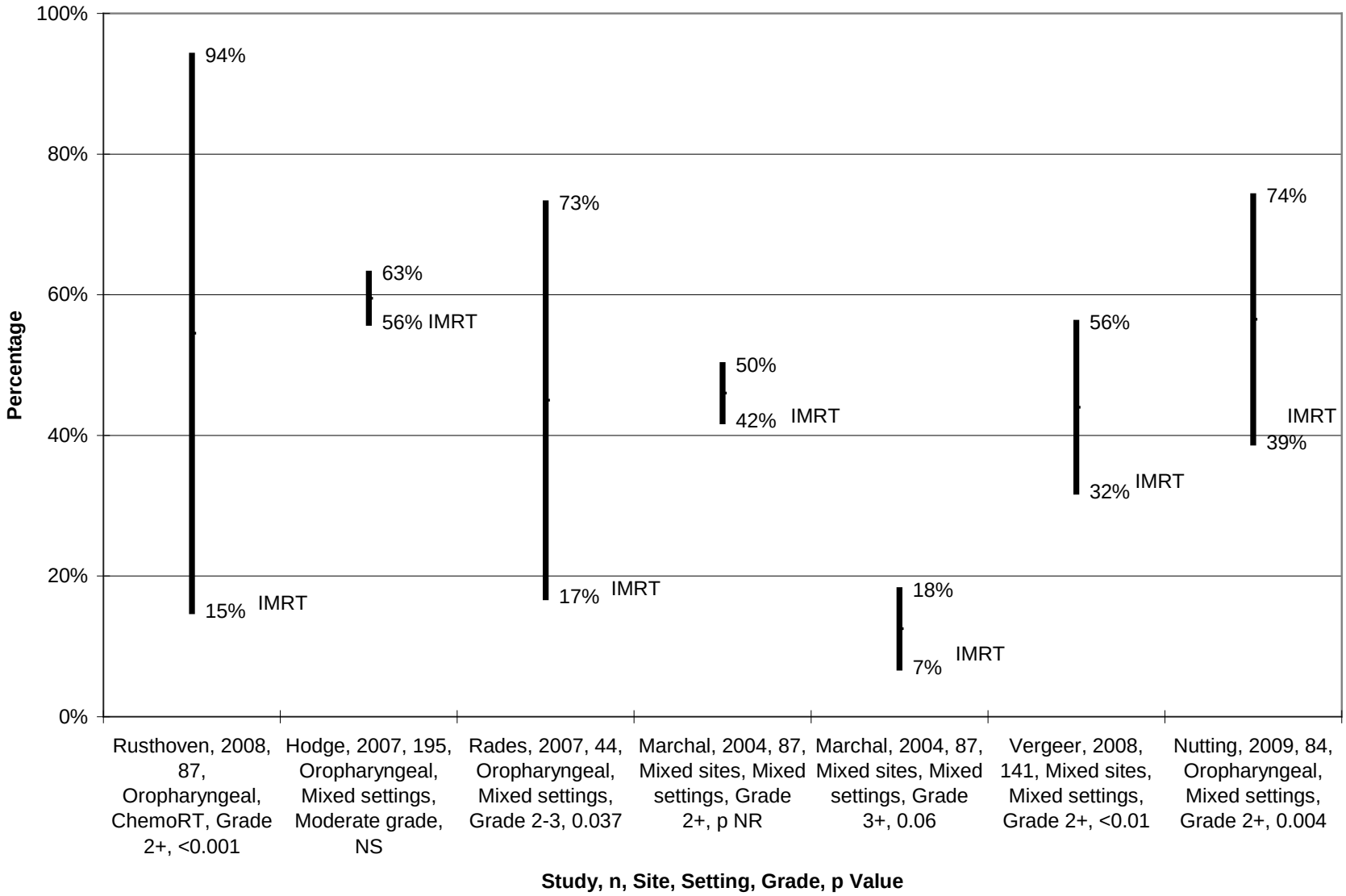


Figure C3. Acute mucositis, IMRT vs. 3DCRT

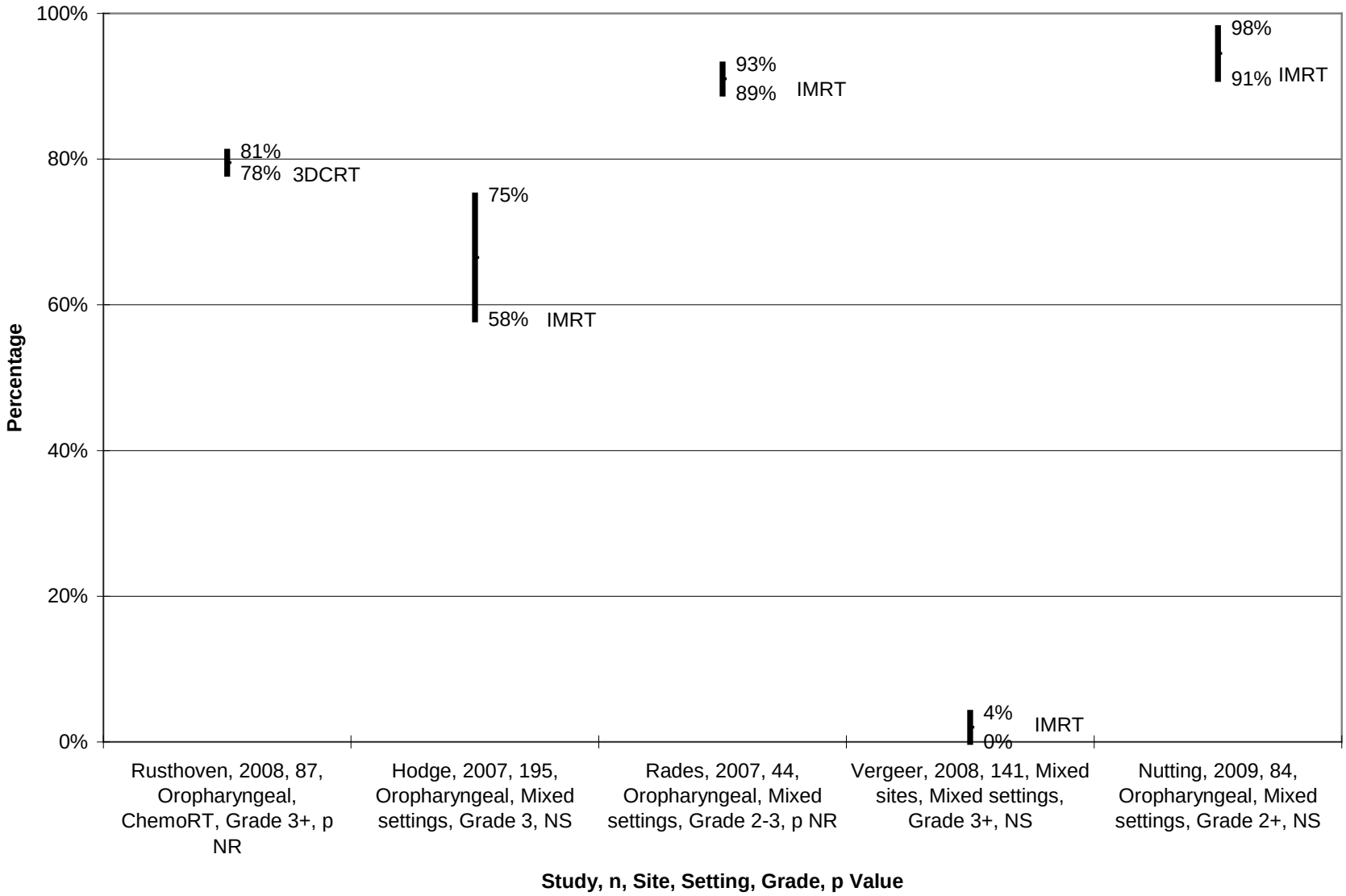


Figure C4. Late mucositis, IMRT vs. 3DCRT

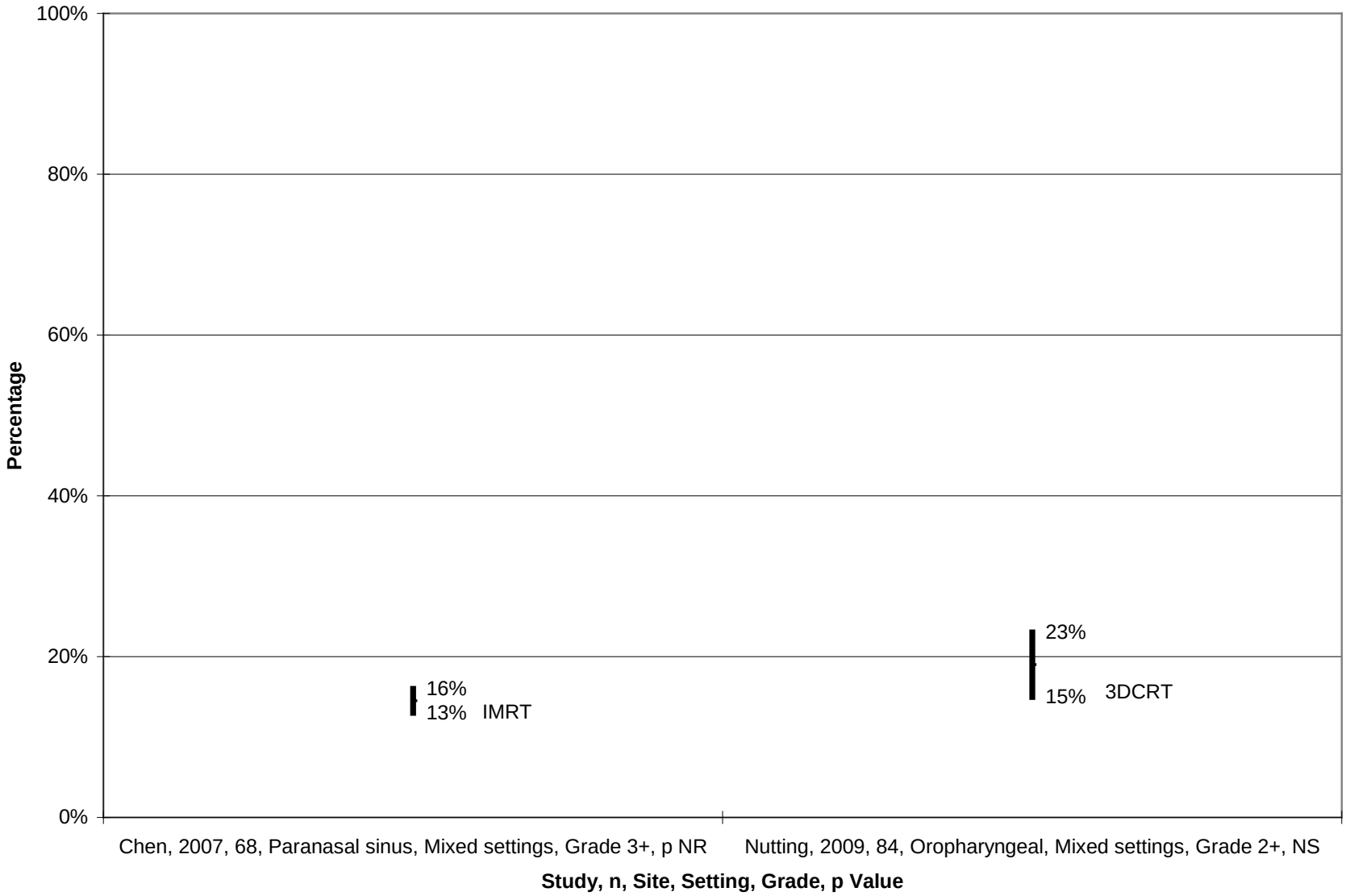


Figure C5. Acute dysphagia, IMRT vs. 3DCRT

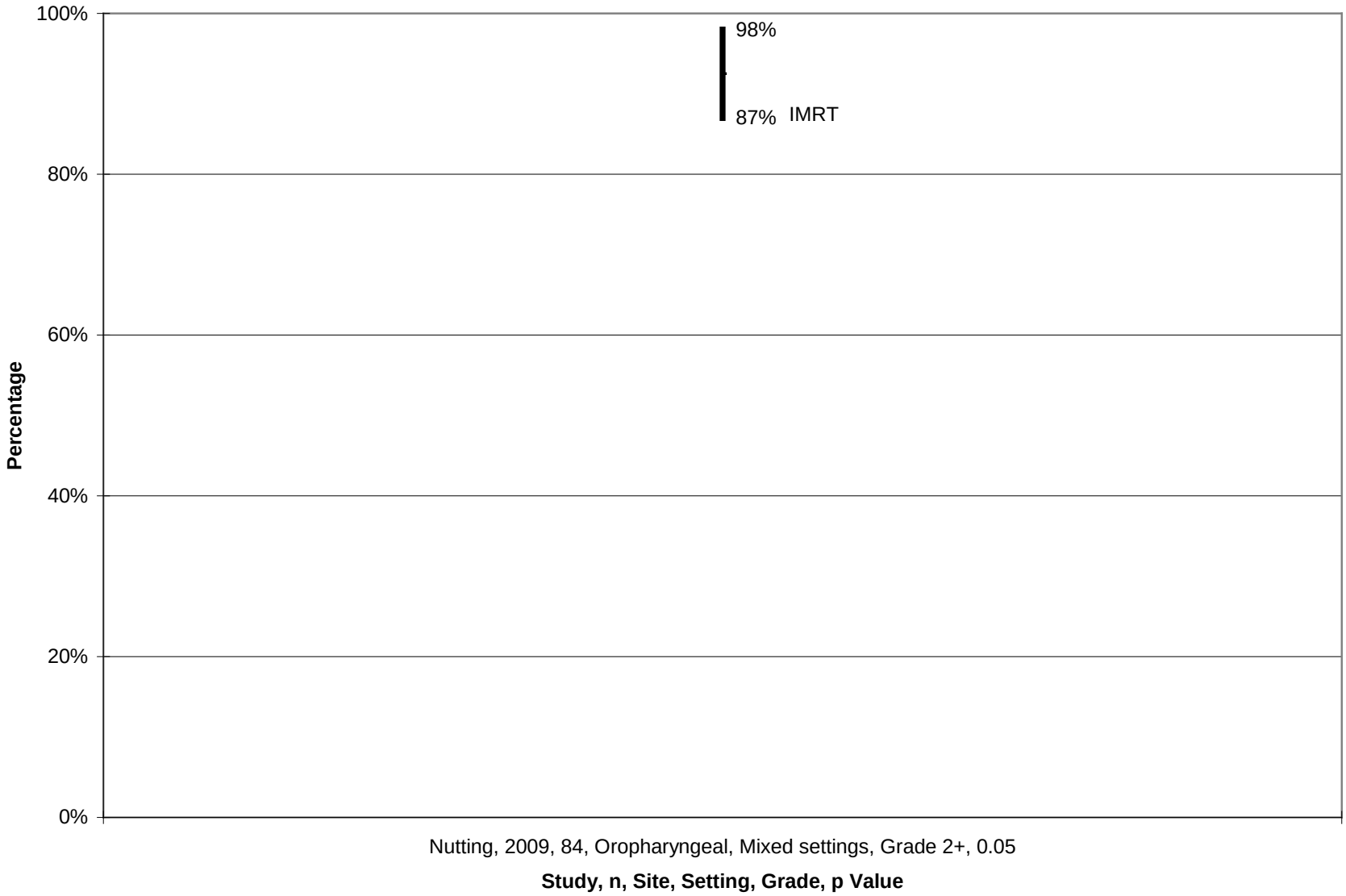


Figure C6. Late dysphagia, IMRT vs. 3DCRT

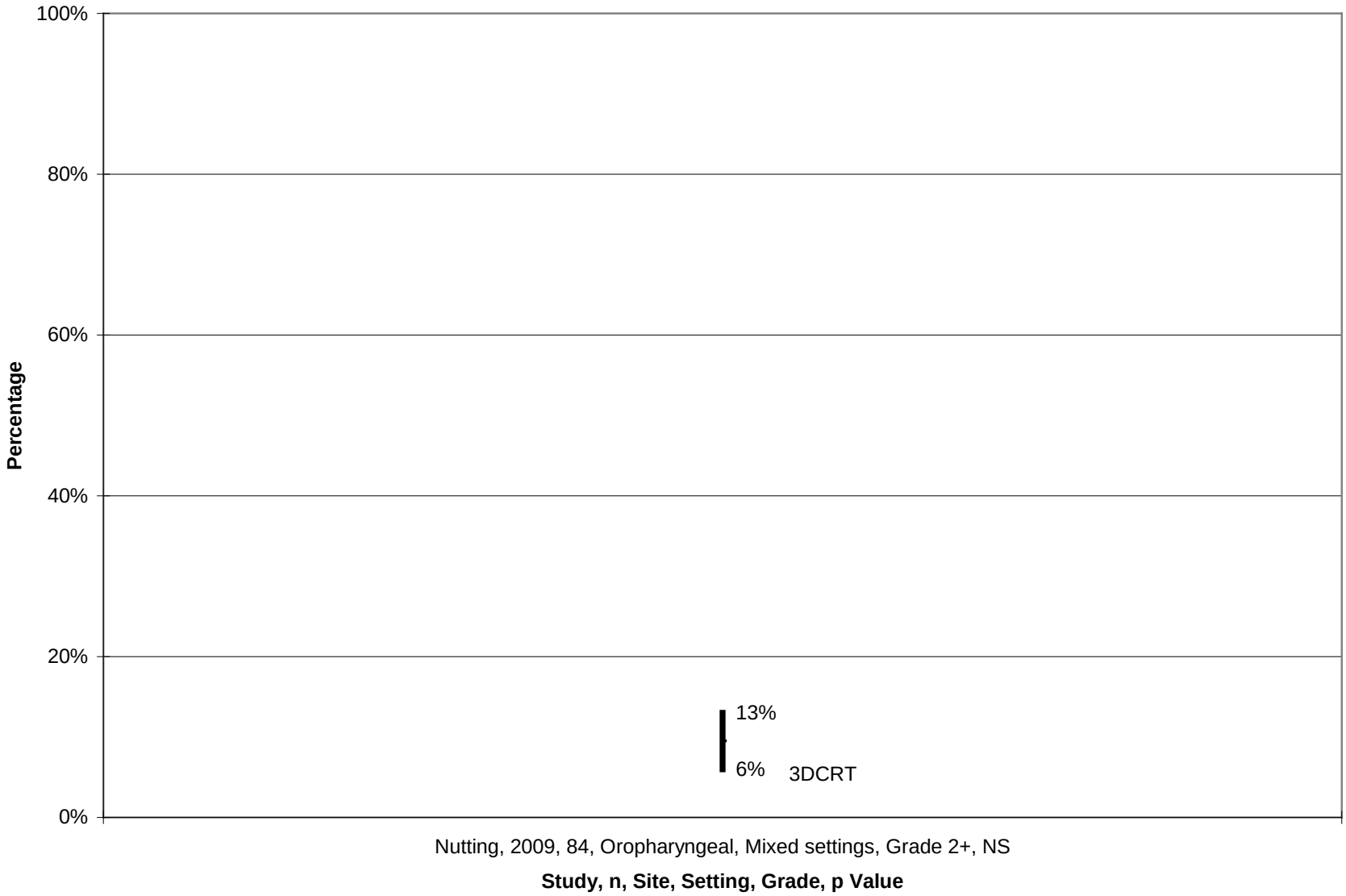


Figure C7. Acute skin toxicity, IMRT vs. 3DCRT

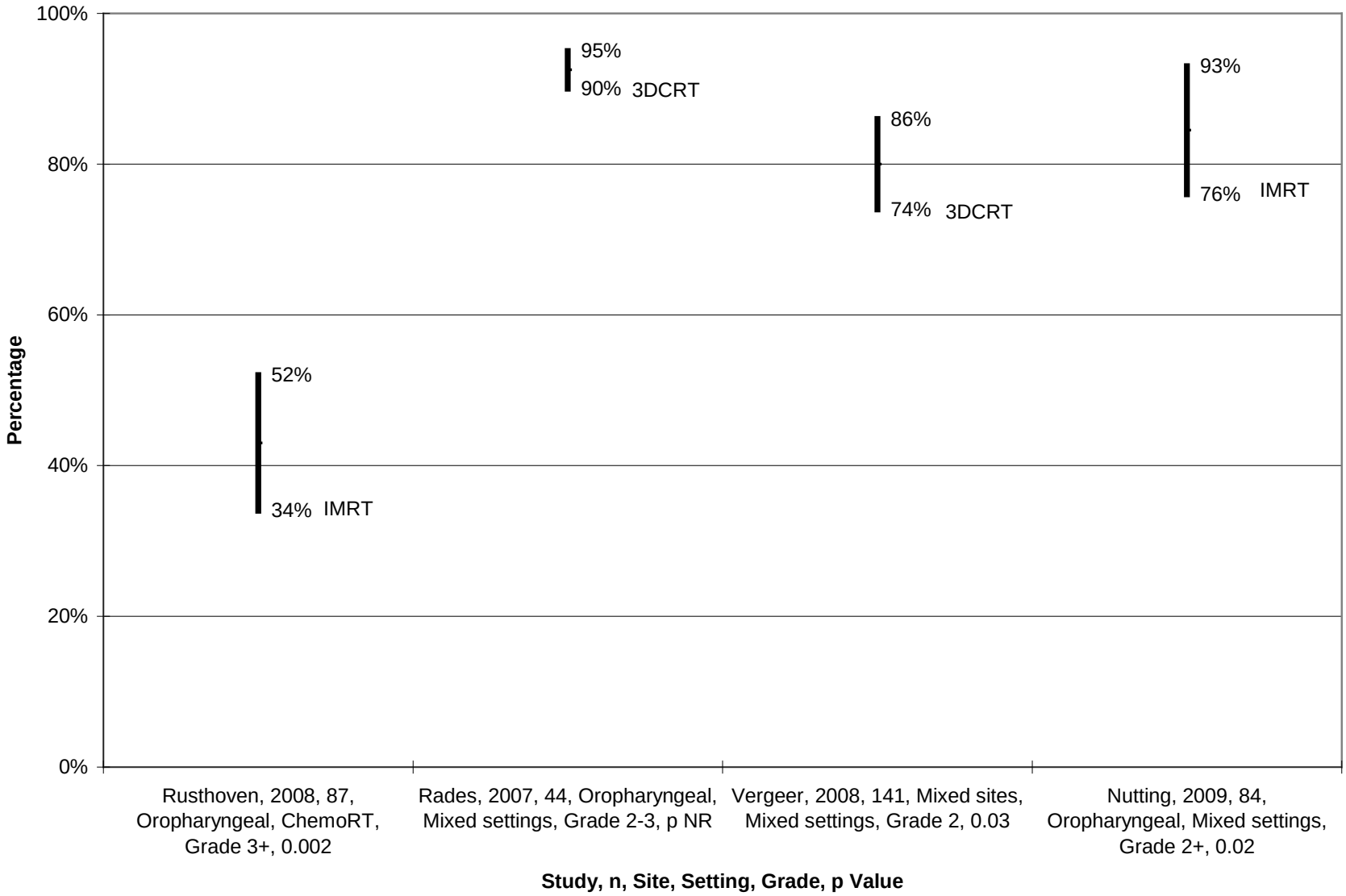


Figure C8. Late skin toxicity, IMRT vs. 3DCRT

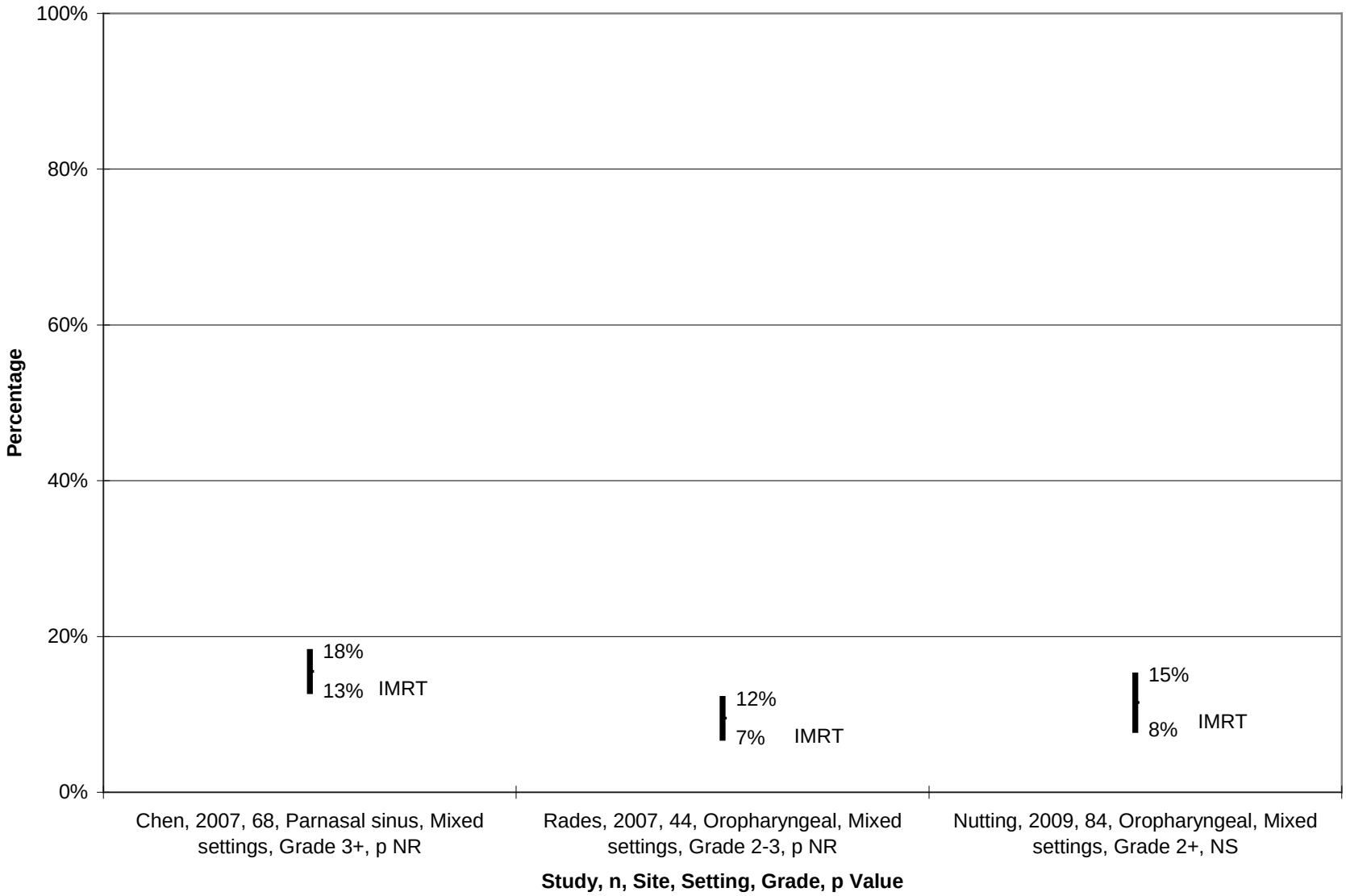


Figure C9. Late osteoradionecrosis/bone toxicity, IMRT vs. 3DCRT

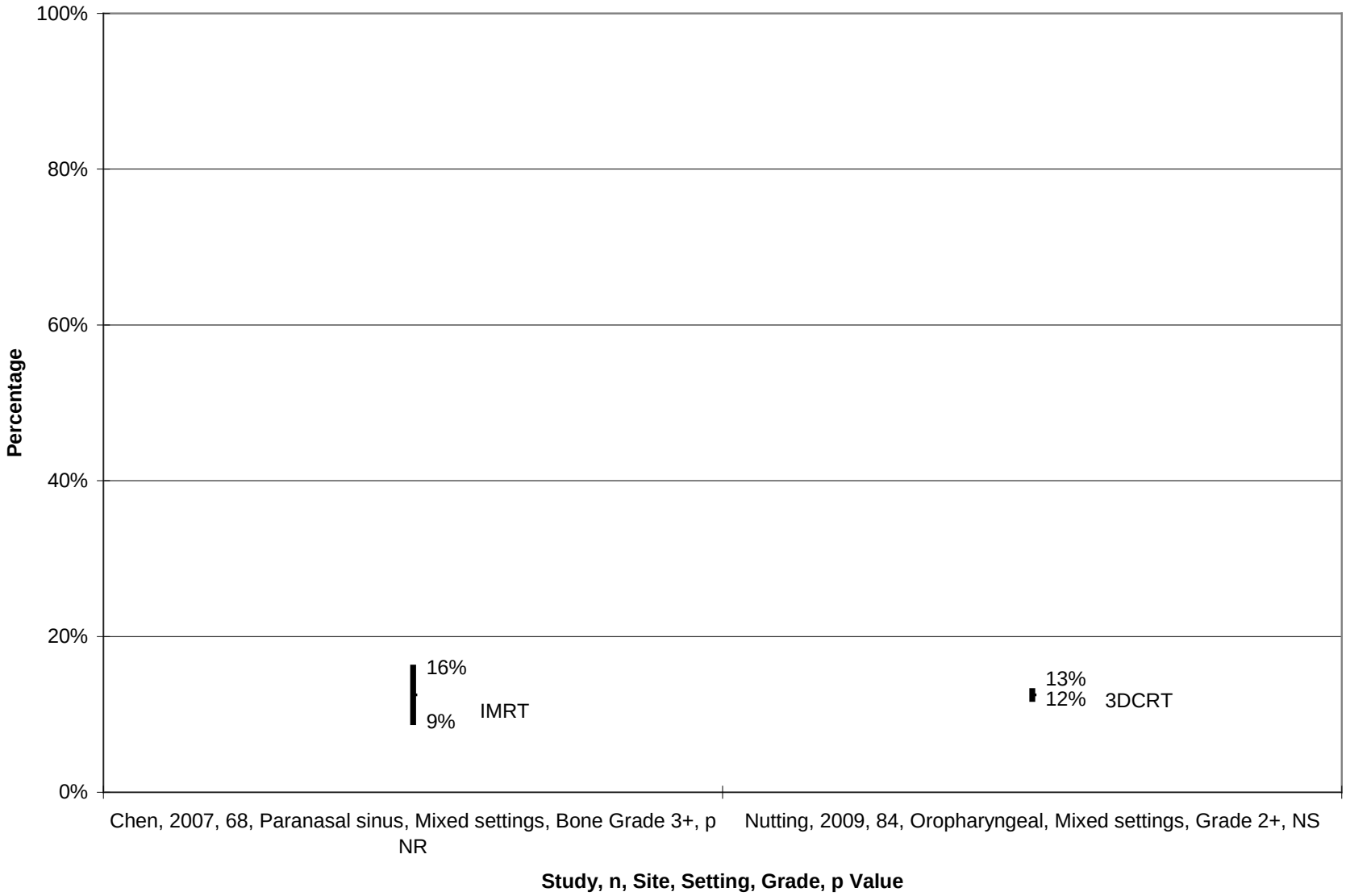


Figure C10. Late xerostomia, 3DCRT vs. 2DRT

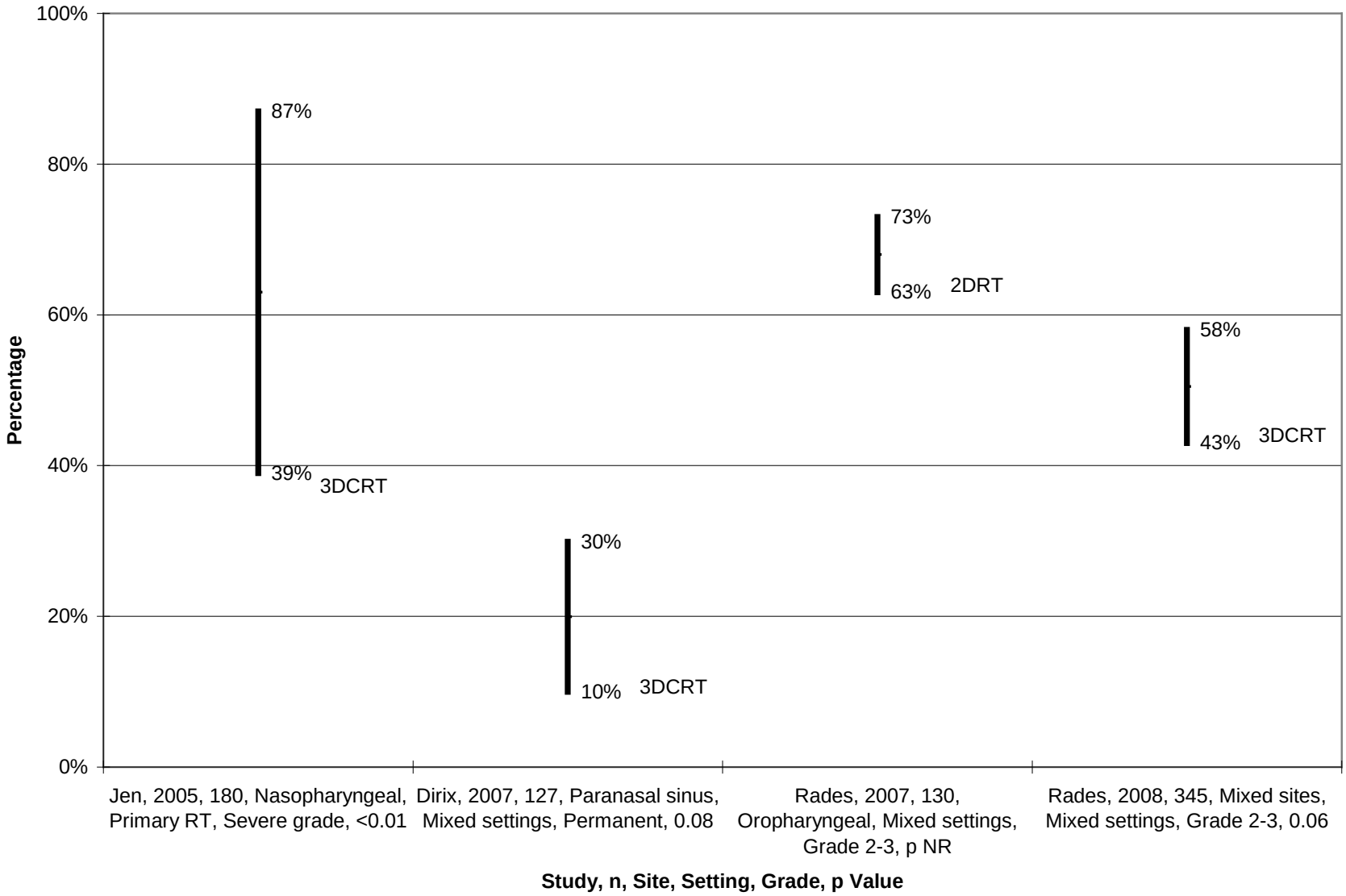


Figure C11. Acute mucositis, 3DCRT vs. 2DRT

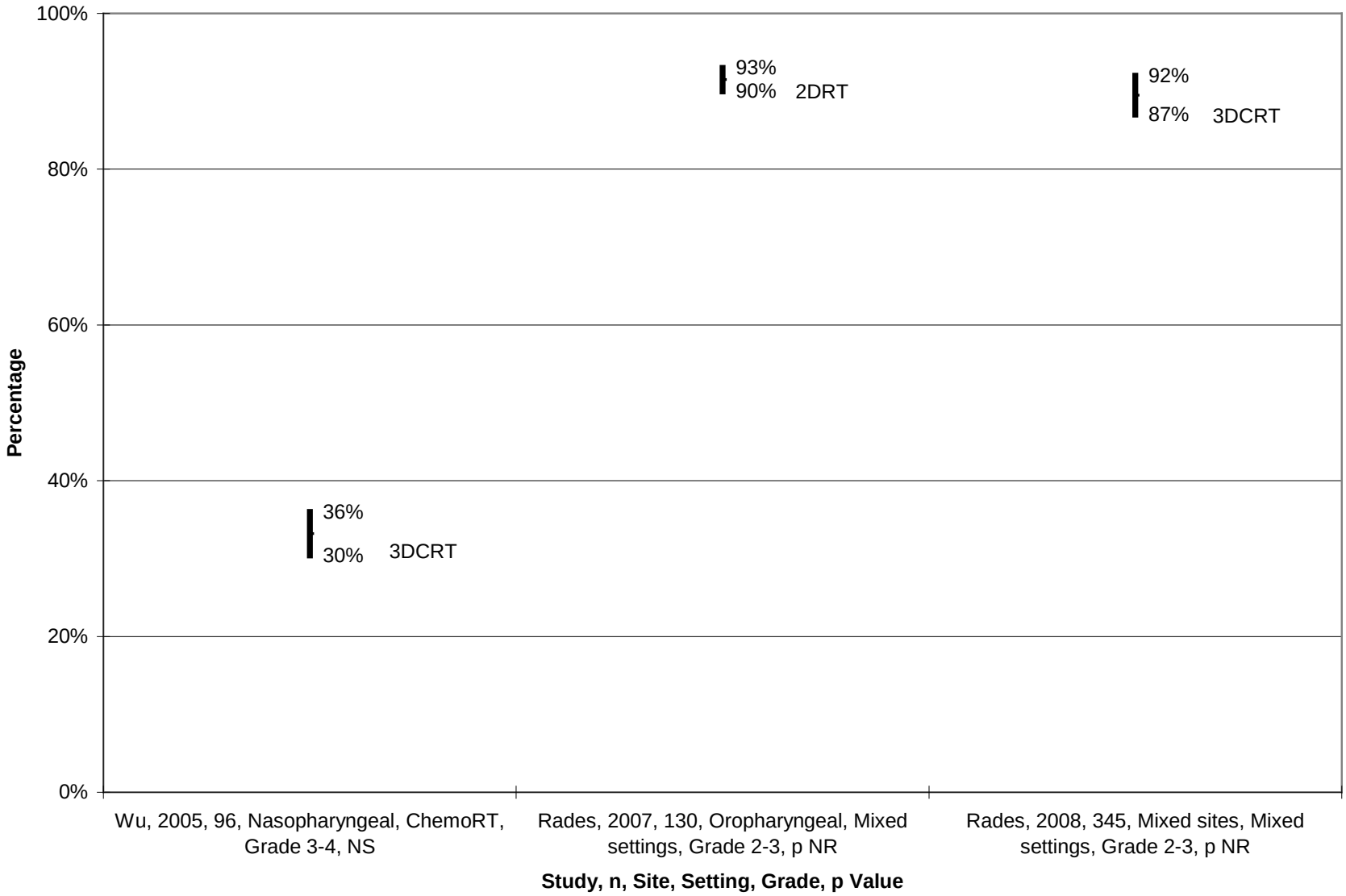


Figure C12. Late mucositis, 3DCRT vs. 2DRT

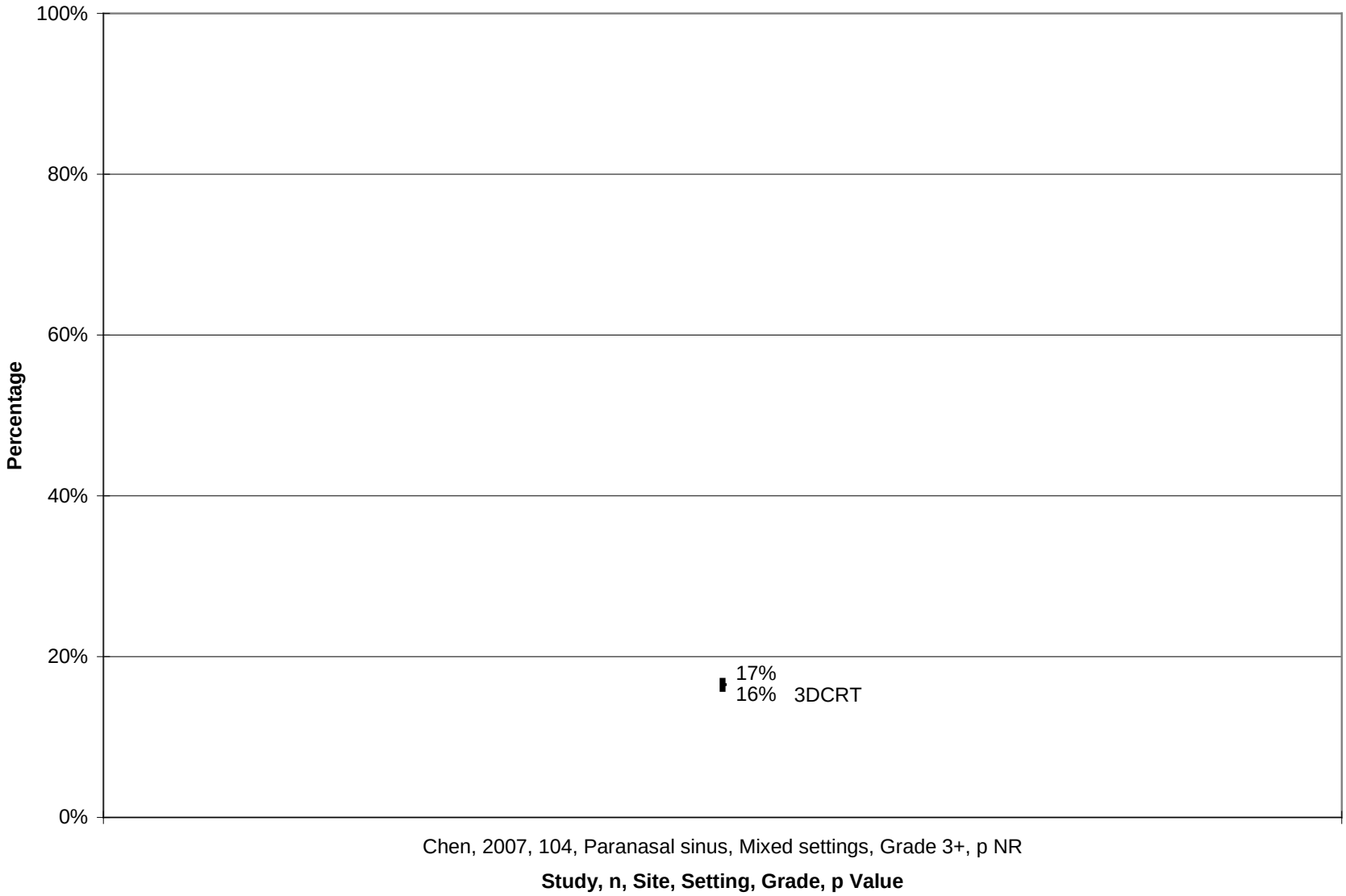


Figure C13. Acute skin toxicity, 3DCRT vs. 2DRT

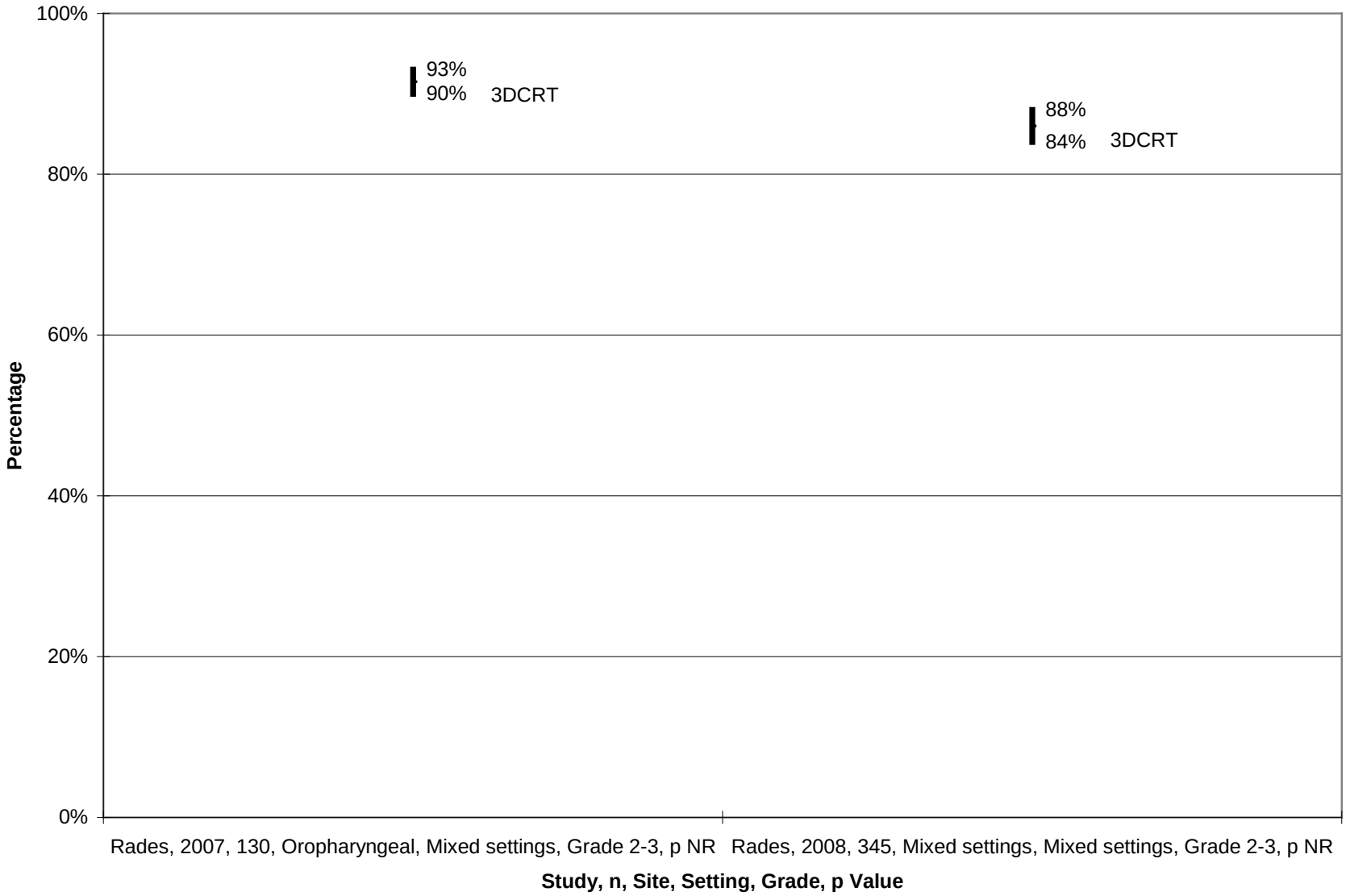


Figure C14. Late skin toxicity, 3DCRT vs. 2DRT

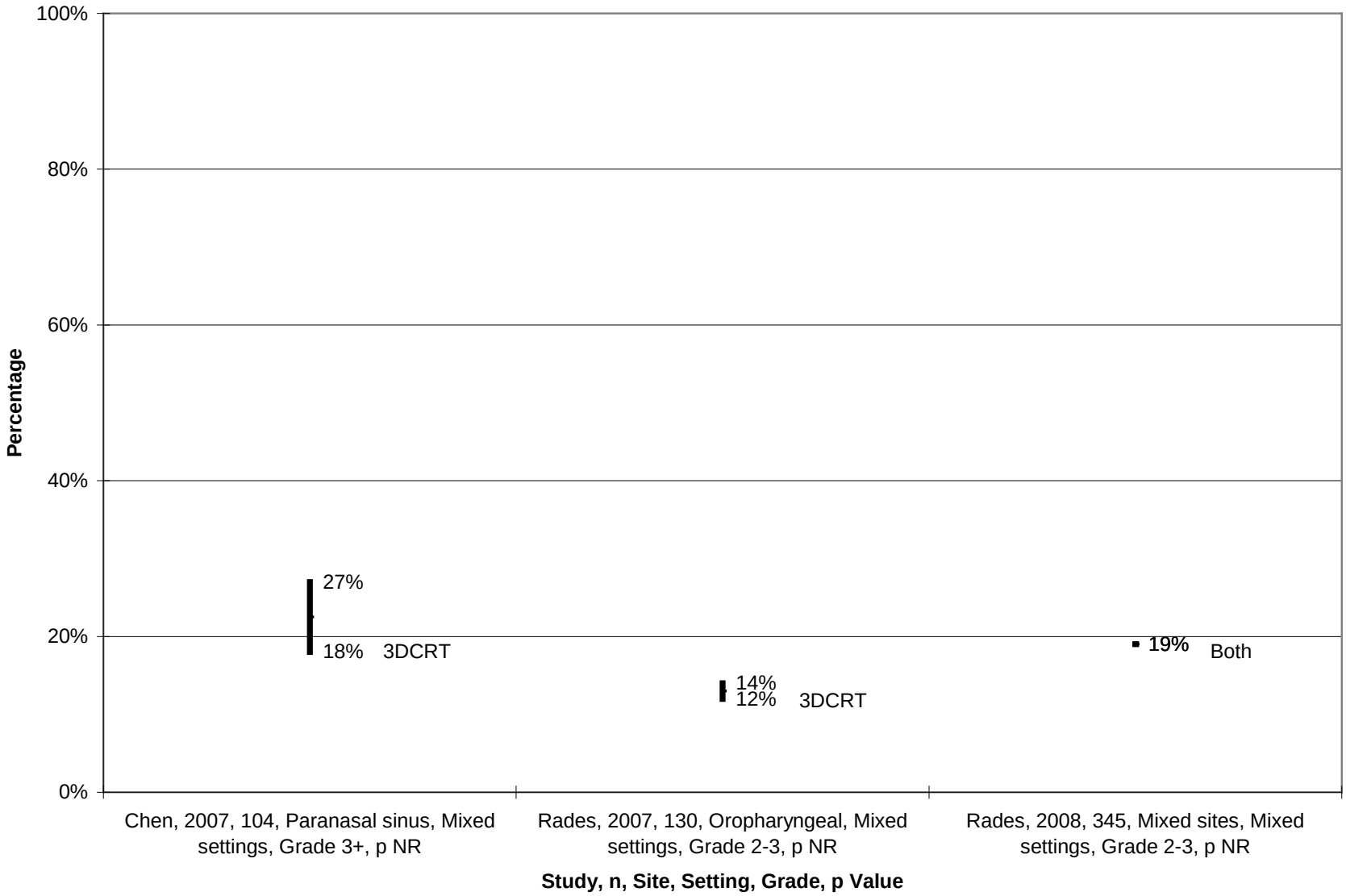


Figure C15. Late osteoradionecrosis/bone toxicity, 3DCRT vs. 2DRT

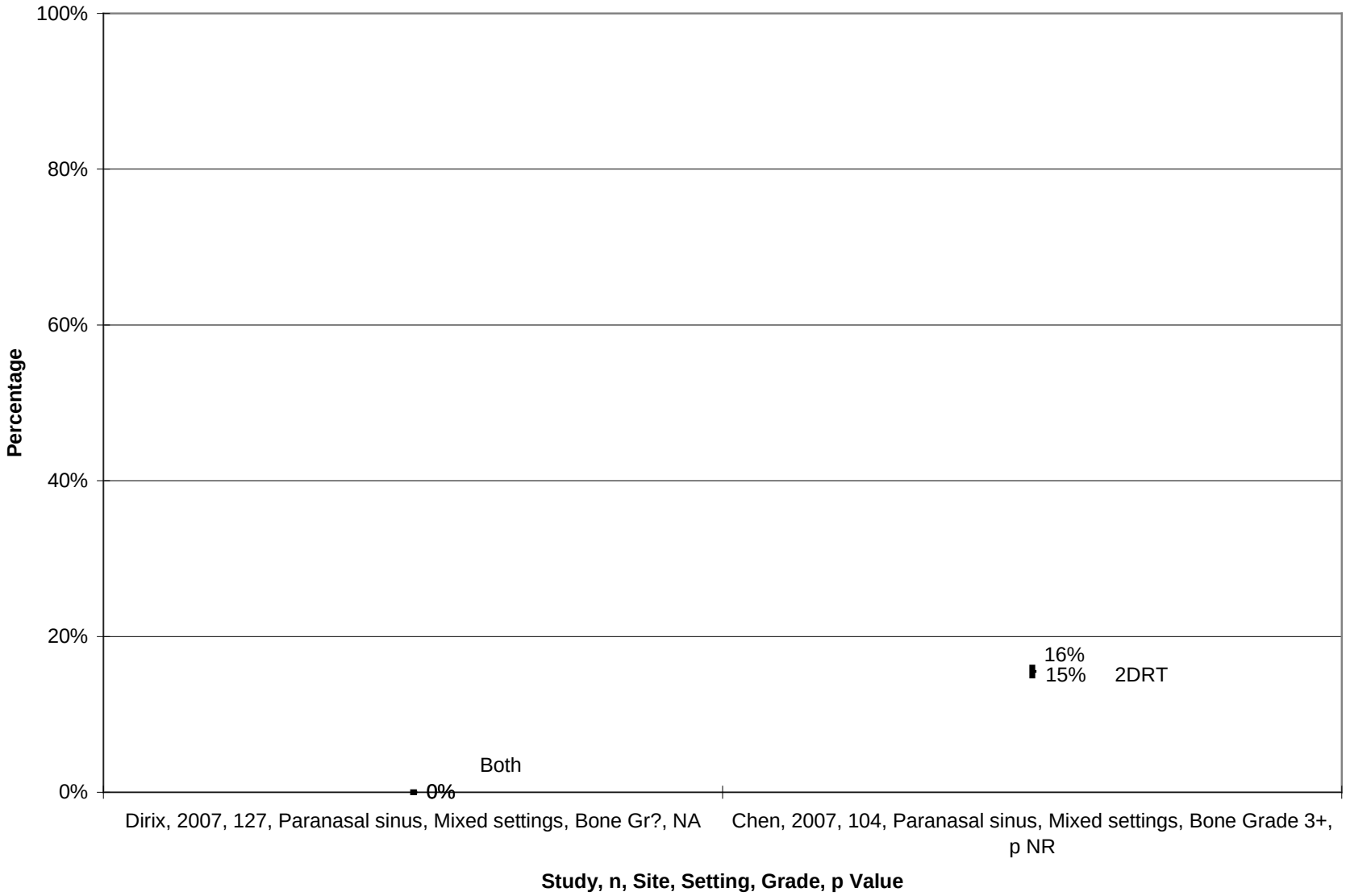


Figure C16. Acute xerostomia, IMRT vs. 2DRT

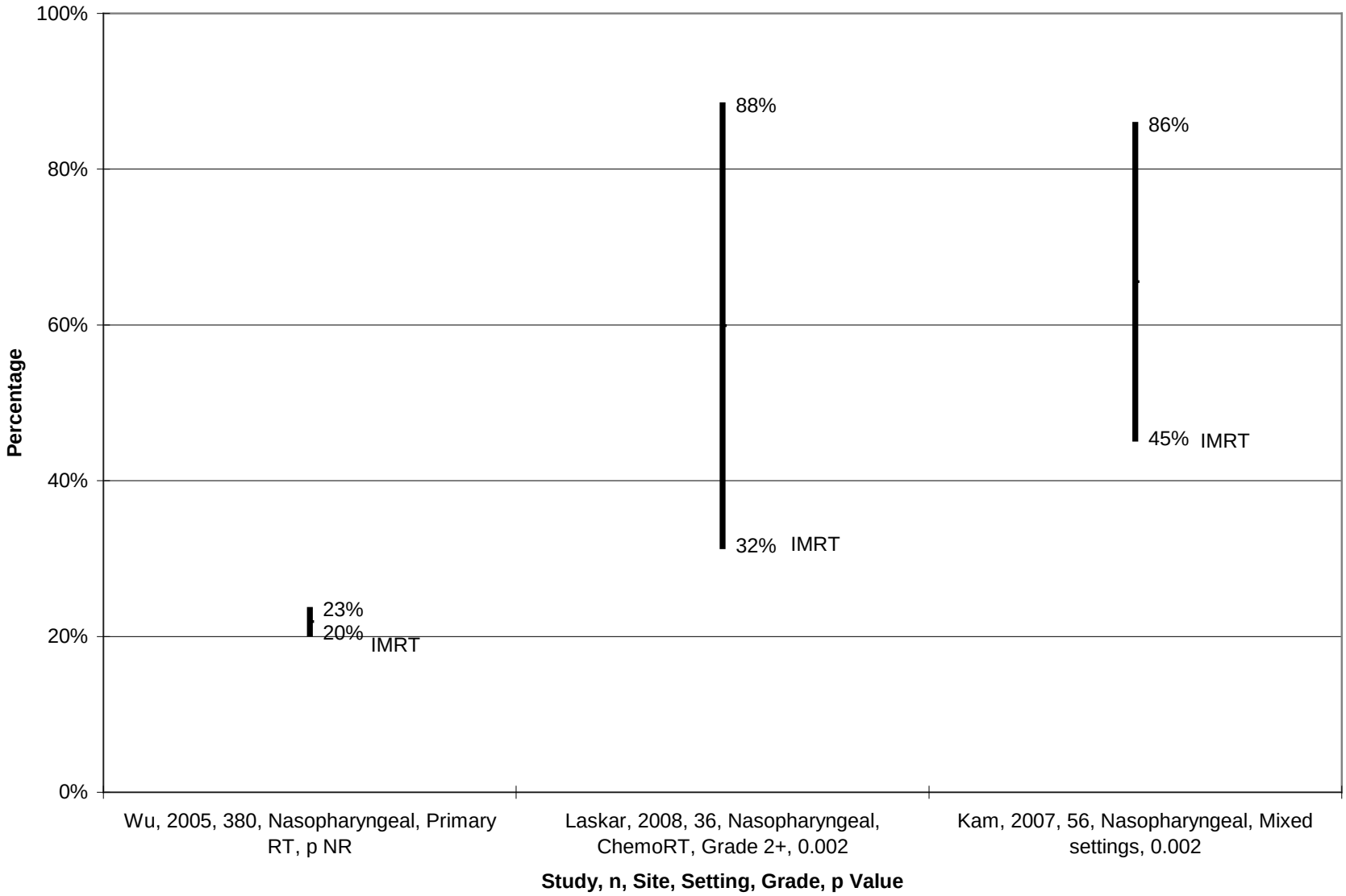


Figure C17. Late xerostomia, IMRT vs. 2DRT

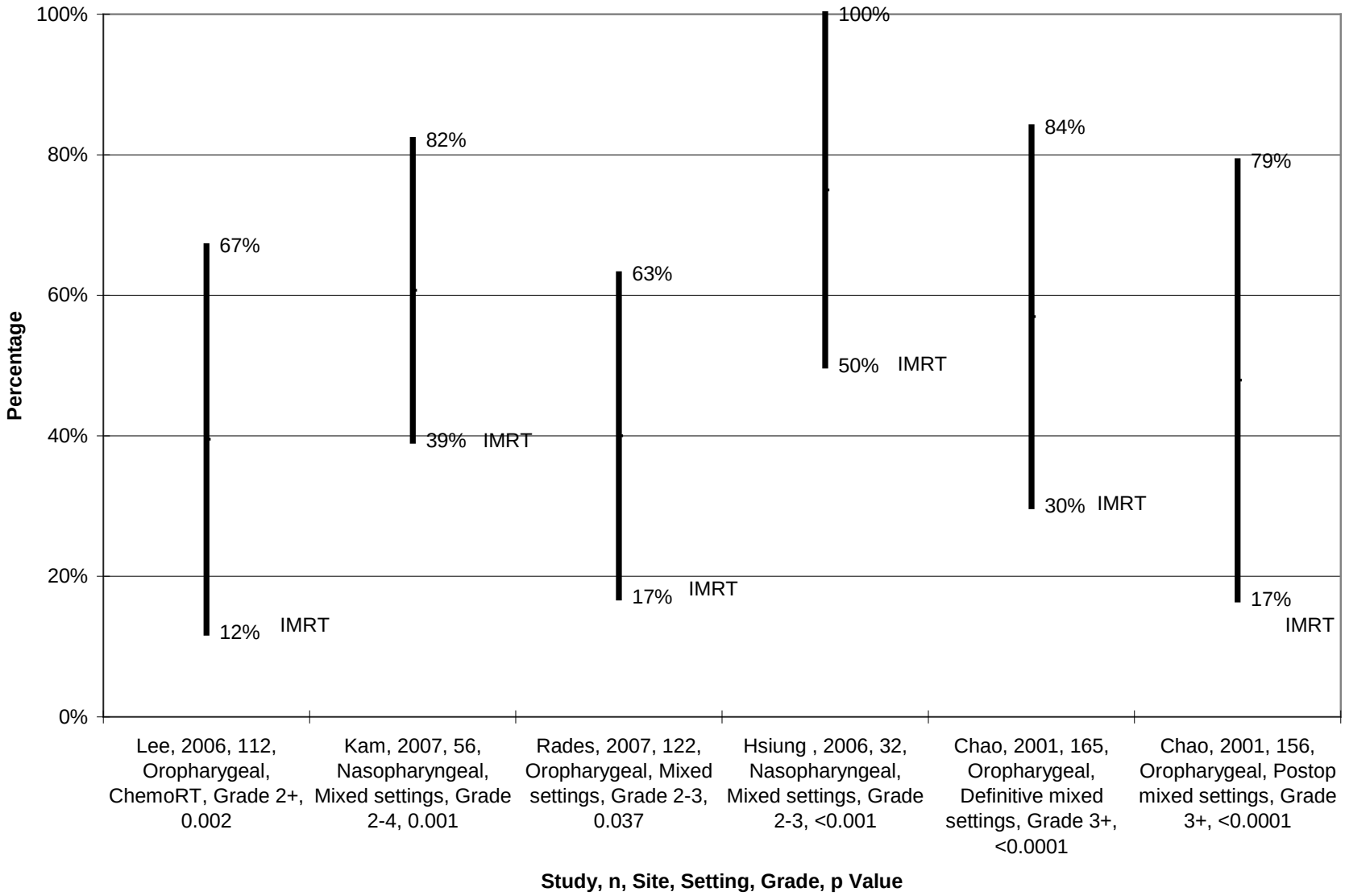


Figure C18. Acute mucositis, IMRT vs. 2DRT

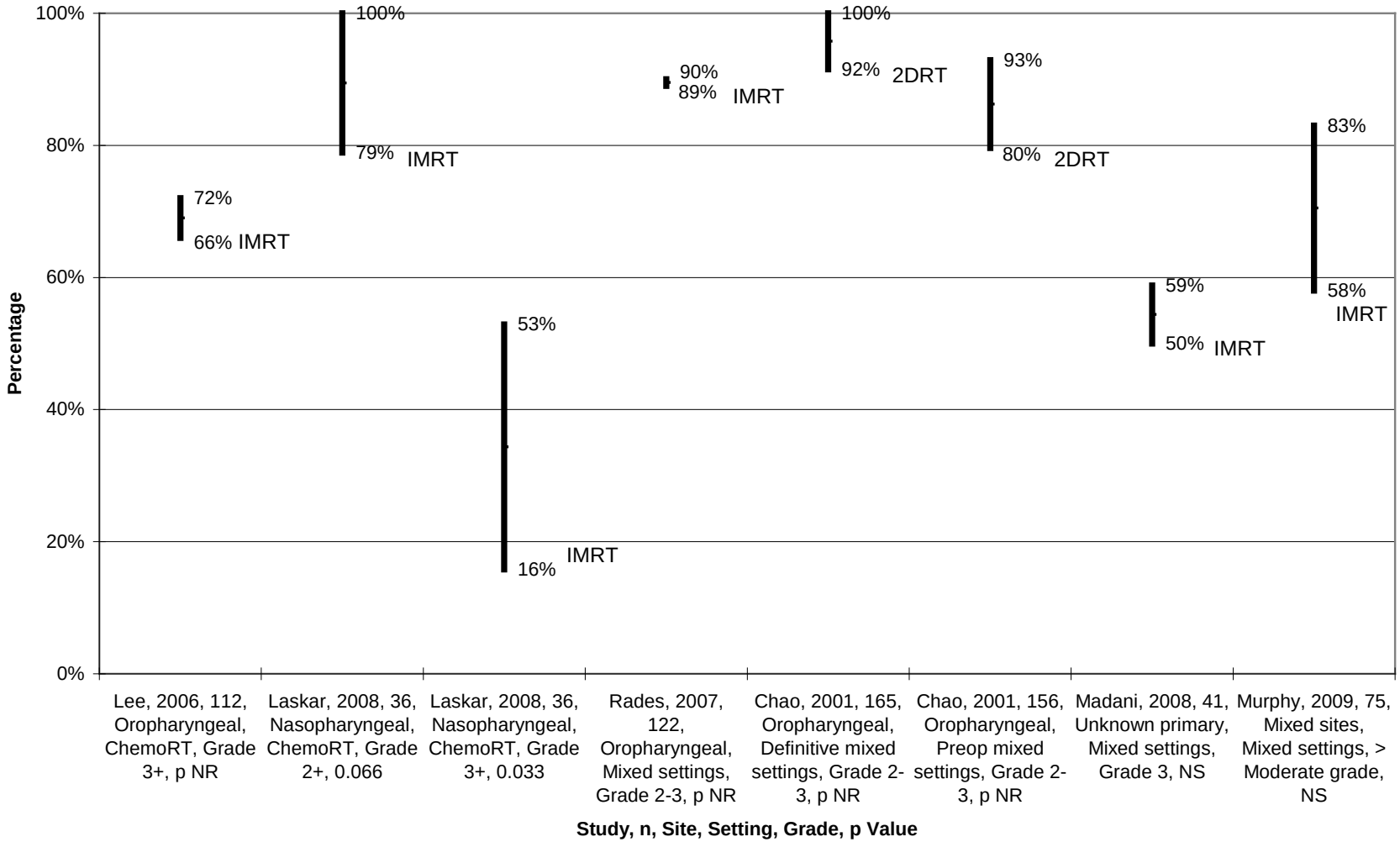


Figure C19. Late mucositis, IMRT vs. 3DRT

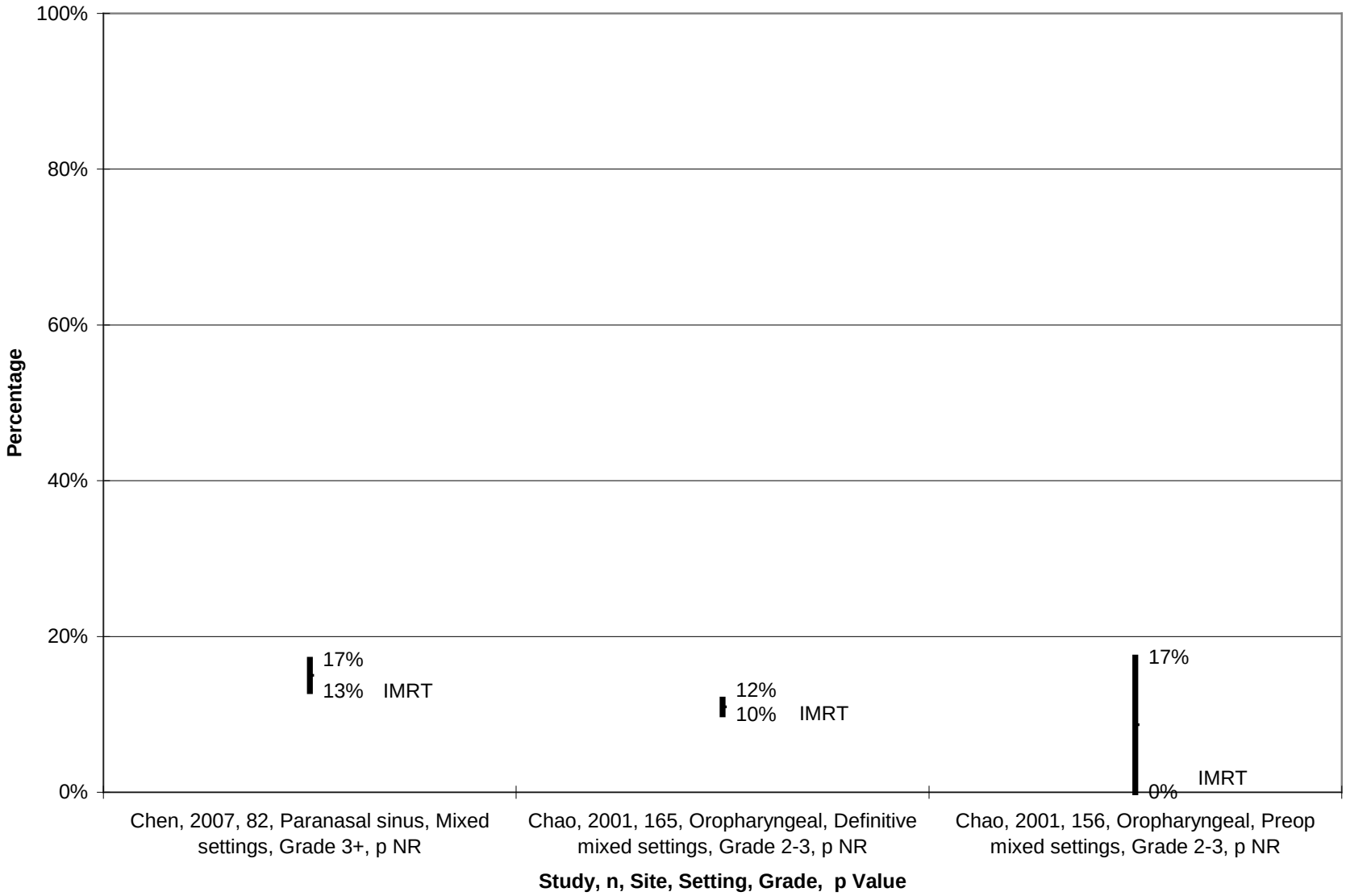


Figure C20. Acute dysphagia, IMRT vs. 2DRT

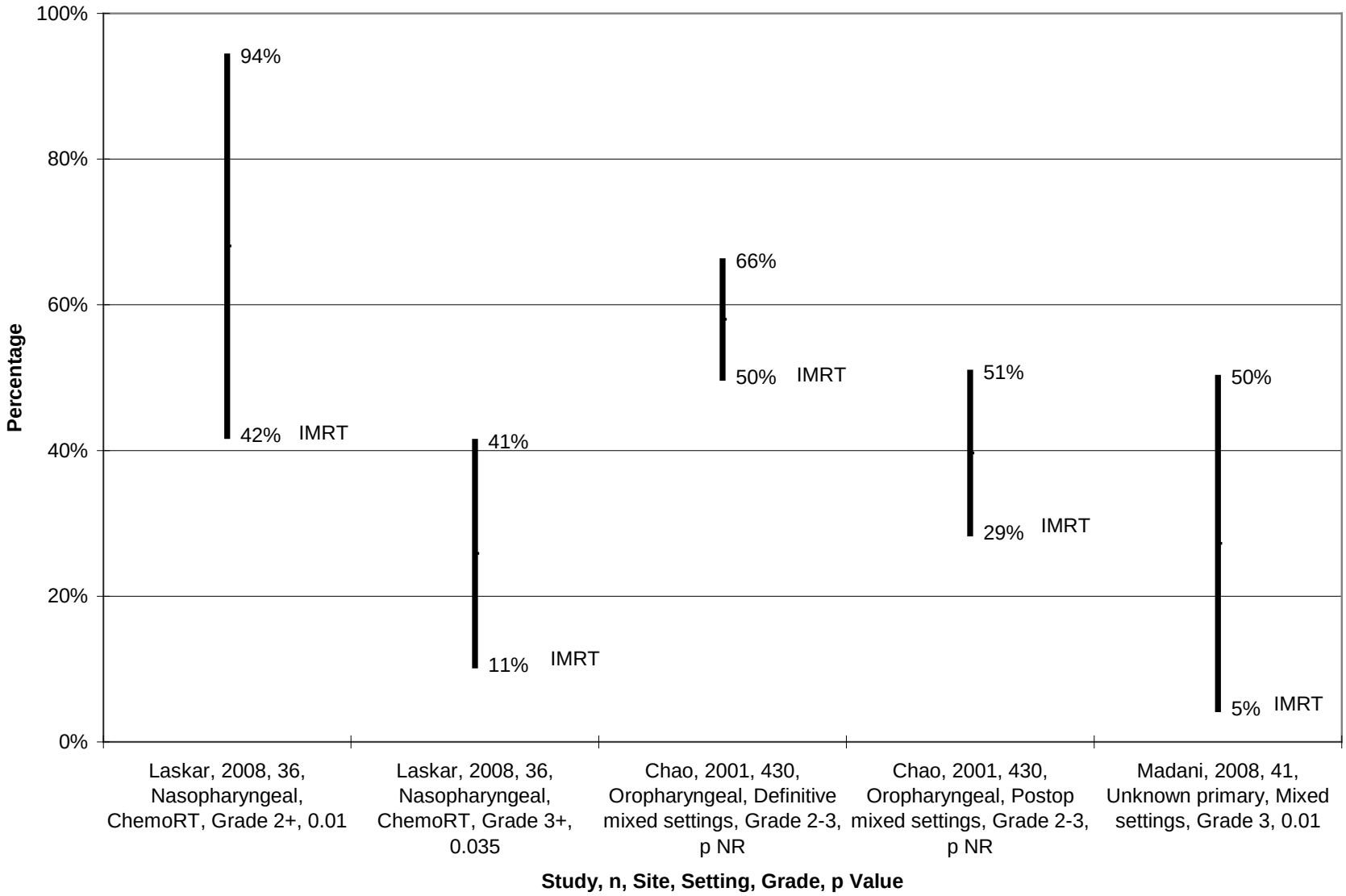


Figure C21. Late dysphagia, IMRT vs. 2DRT

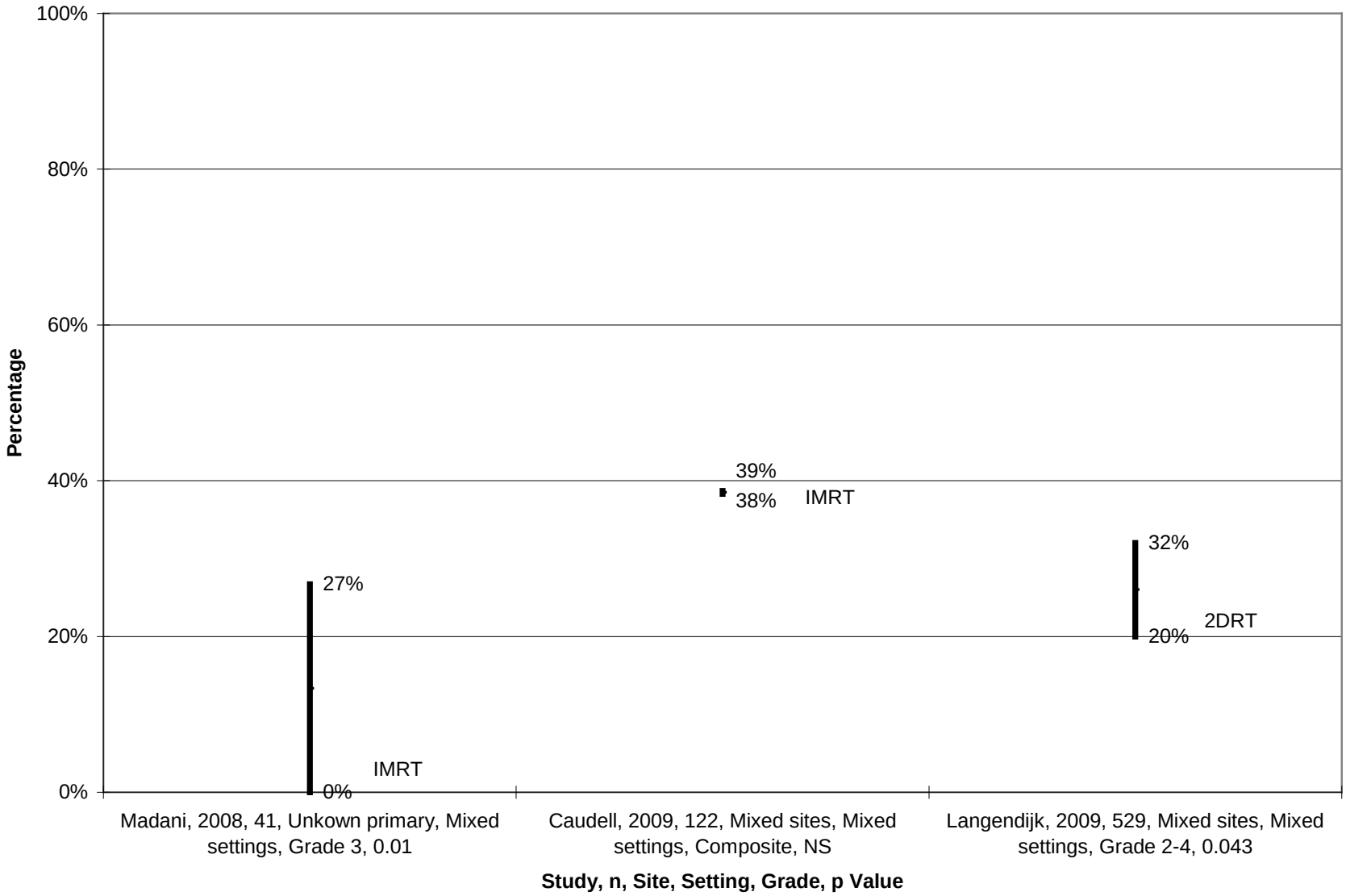


Figure C22. Acute skin toxicity, IMRT vs. 2DRT

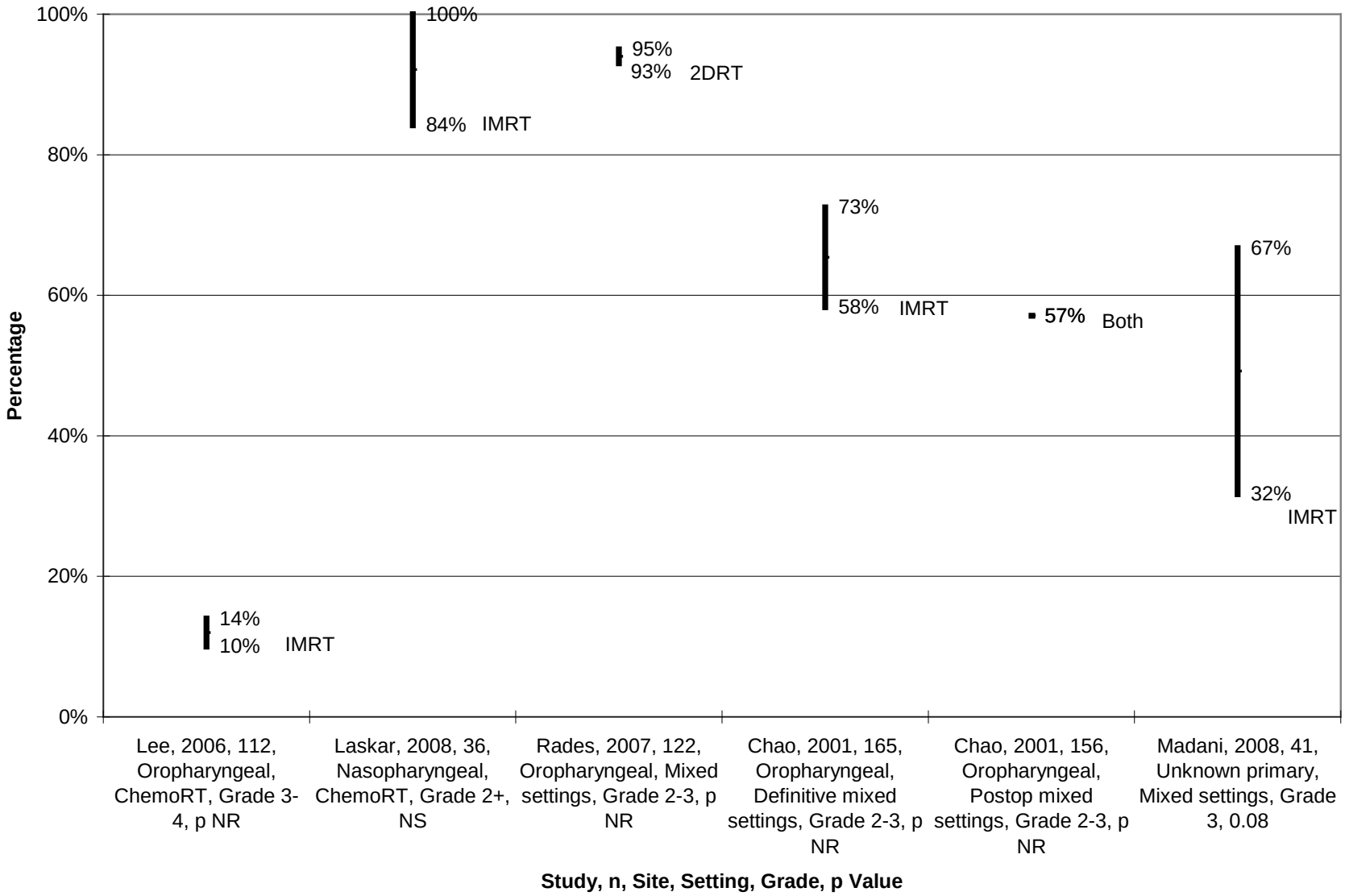


Figure C23. Late skin toxicity, IMRT vs. 2DRT

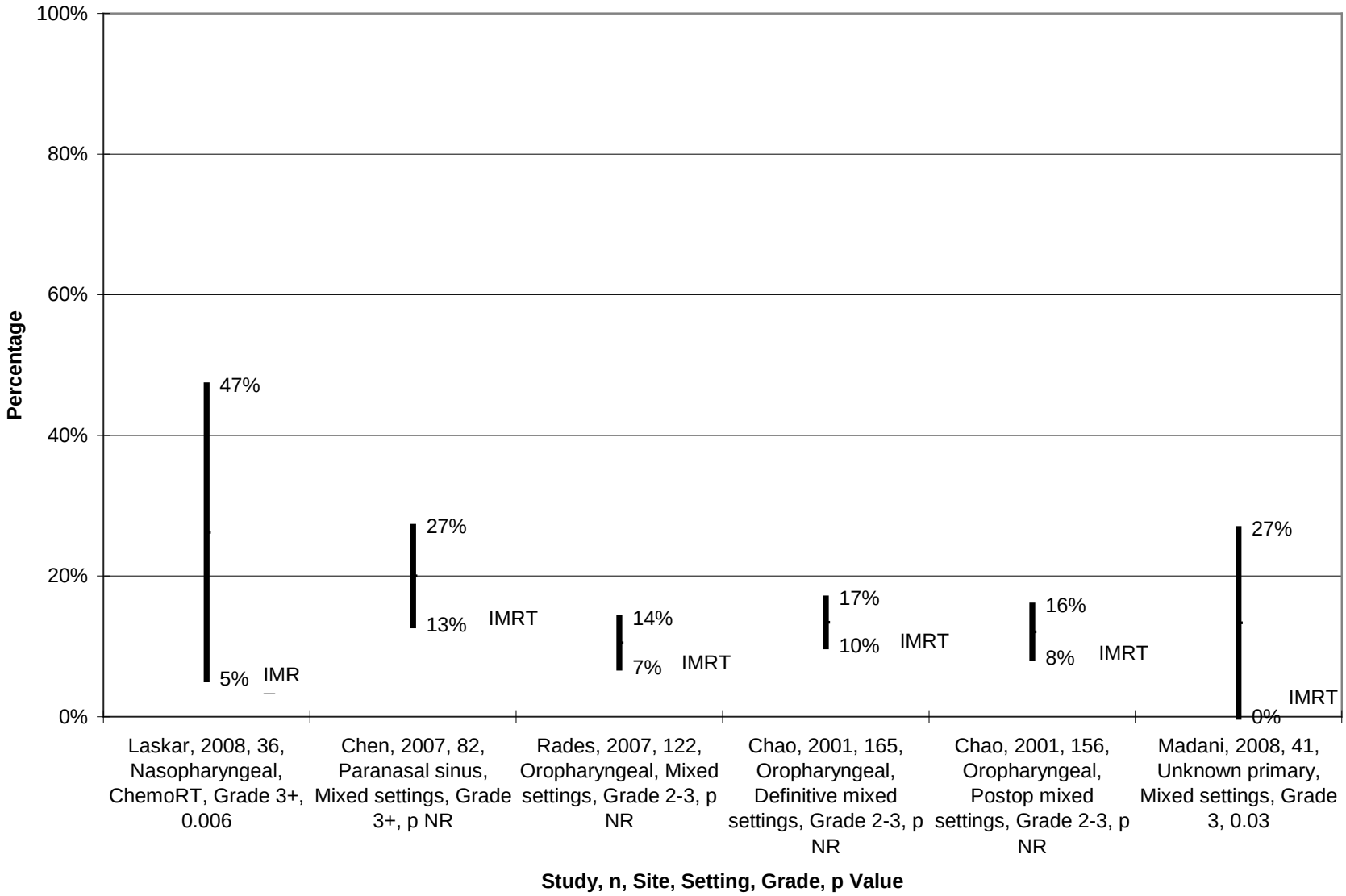
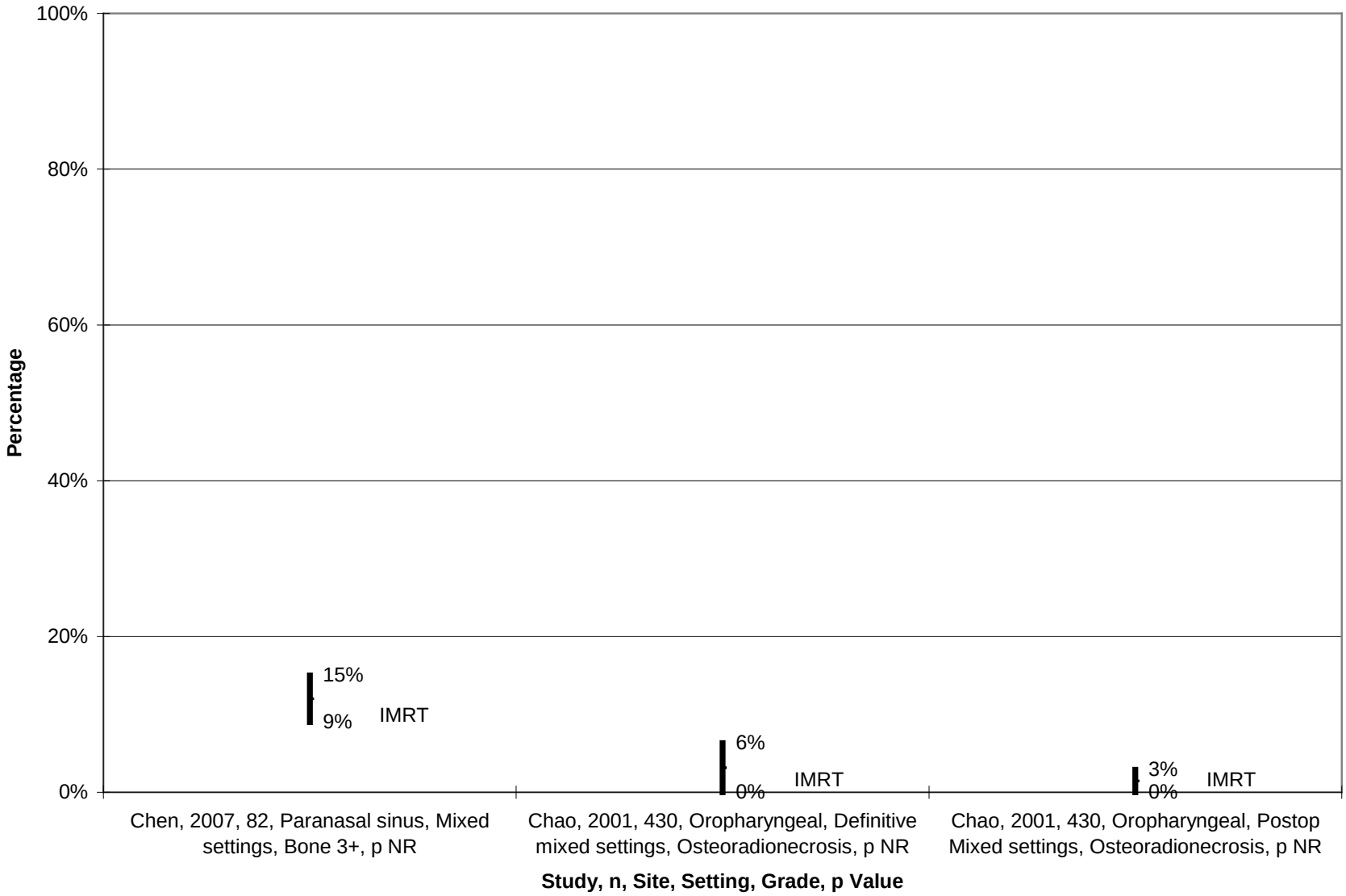


Figure C24. Late osteoradionecrosis/bone toxicity, IMRT vs. 2DRT



Appendix D: Comparative Studies: Full Evidence/Data Abstraction Tables

Table D1a. Nasopharyngeal cancer, outcomes by study

Study	Rec#	No. Pts	Setting	QOL/Adverse Events							Tumor Control			Patient Survival	
				QOL	XST	SF	DYS	MUC	SKN	ORN or BON	LC	LRC	DFS	DSS	OS
1° RT															
3DCRT vs 2DRT															
Jen, 2005	5240	180	1° RT		X										
IMRT vs 2DRT															
Pow, 2006 (RCT)	2340	45	1° RT	X		X									
Wu, 2005	4520	380	1° RT		X	X									
1° RT + split CTx															
3DCRT vs 2DRT															
Wu, 2005 (RCT)	4360	96	1° RT + split CTx					X			X				X
IMRT vs 2DRT															
Laskar, 2008	39050	36	1° RT + split CTx		X		X	X	X			X	X		X
Mixed Settings															
IMRT vs 3DCRT															
Fang, 2007	2250	85	1° RT ± CTx (timing?)	X	X										
Fang, 2008	39090	203	1° RT ± CCTx	X								X			X
3DCRT vs 2DRT															
Fang, 2007	2250	94	1° RT ± CTx (timing?)	X	X										
IMRT vs 2DRT															
Kam, 2007 (RCT)	530	56	1° RT ± ICBRT		X	X									
Fang, 2007	2250	113	1° RT ± CTx (timing?)	X	X										
Hsiung, 2006	3070	32	1° RT± CCTx		X										
Comparisons	11			5	8	3	1	2	1	0	1	2	1	0	3
Studies	9			3	6	3	1	2	1	0	1	2	1	0	3
Total n	1174														

Table D1b. Nasopharyngeal cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Completed RT (%)
1^{o} RT										
3DCRT vs 2DRT										
Jen, 2005	5240	180	1^{o} RT	3DCRT 2DR	15 18	43 (19-80) 44 (18-84)	59.7 58.3	70 (all)	26	100 (all)
IMRT vs 2DRT										
Pow, 2006 (RCT)	2340	45	1^{o} RT	IMRT 2DR	25 19	46 (26-69) 50 (37-75)	0 (all)	68 68-72	NR	NR
Wu, 2005	4520	380	1^{o} RT	IMRT 2DR	32 (all)	38 (15-64) (all)	85.8 (all)	75 70	NR	NR
1^{o} RT + split CTx										
3DCRT vs 2DRT										
Wu, 2005 (RCT)	4360	96	1^{o} RT + split CTx	3DCRT 2DR	35 34	45 (16-68) 44 (18-67)	100 (all)	66-86 (all)	NR	NR
IMRT vs 2DRT										
Laskar, 2008	39050	36	1^{o} RT + split CTx	IMRT 2DR	26 18	14 (5-18) (all)	84.2 94.1	70 (all)	27 (4-42)	100 88
Mixed Settings										
IMRT vs 3DCRT										
Fang, 2007	2250	85	1^{o} RT ± CTx (timing?)	IMRT 3DCRT	33 24	49 51	48.1 48.5	65-76 (all)	NR	NR
Fang, 2008	39090	203	1^{o} RT ± CCTx	IMRT 3DCRT	22 17	NR	52.8 55.9	65-76 (all)	40 (5-57) 46 (10-59)	NR
3DCRT vs 2DRT										
Fang, 2007	2250	94	1^{o} RT ± CTx (timing?)	3DCRT 2DR	24 28	51 51	48.1 50.8	65-76 (all)	46 (10-59)	NR
IMRT vs 2DRT										
Kam, 2007 (RCT)	530	56	1^{o} RT ± ICBRT	IMRT 2DR	25 32	46 50	0 (all)	66 + 18 Gy ICB 66 + 12 Gy ICB	NR	100 (all)
Fang, 2007	2250	113	1^{o} RT ± CTx (timing?)	IMRT 2DR	29 28	49 51	48.5 50.8	60-70 (all)	NR	NR
Hsiung , 2006	3070	32	1^{o} RT± CCTx	IMRT 2DR	31 25	NR	50 37.5	67-70 68-76	24 (14-34)	NR

Table D1c. Nasopharyngeal cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initl Grps Comp	Bal by Design (Mtch)	BL Chars Clr Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Out-comes Val, Rel, =	Assessors Blind	Txs Clr	Adequate F/U	Analysis: Adj for Confs	USPSTF
1° RT																				
3DCRT vs 2DRT																				
Jen, 2005	5240	180	R	N	N	?	N	Y	?	E	NA	NA	NA	NA	Y	N	Y	md 26	Y/?	Poor
IMRT vs 2DRT																				
Pow, 2006 (RCT)	2340	45	P	Y	Y	Y	Y	Y	Y	?	NA	Y	Y	Y	Y	Y	Y	?	N	Poor
Wu, 2005	4520	380	R	Y	Y	?	N	?	?	?	NA	NA	NA	NA	Y	N	Y	?	N	Poor
1° RT + split CTx																				
3DCRT vs 2DRT																				
Wu, 2005 (RCT)	4360	96	P	Y	Y	?	Y	Y	Y	?	Y	?	Y	Y	Y	N	Y	?	N	Poor
IMRT vs 2DRT																				
Laskar, 2008	39050	36	P	Y	Y	Y	N	Y	Y	A/P	Y	?	Y	Y	Y	?	Y	md 27	Y/?	Poor
Mixed Settings																				
IMRT vs 3DCRT																				
Fang, 2007	2250	85	R	Y	N	Y	N	Y	N	E	?	NA	NA	NA	Y	N	Y	?	N	Poor
Fang, 2008	39090	203	P	Y	Y	Y	N	Y	Y	A/P	Y	?	Y	Y	Y	?	Y	md 40,46	Y/?	Poor
3DCRT vs 2DRT																				
Fang, 2007	2250	94	R	Y	N	Y	N	Y	N	E	?	NA	NA	NA	Y	N	Y	?	N	Poor
IMRT vs 2DRT																				
Kam, 2007 (RCT)	530	56	P	Y	Y	Y	Y	Y	Y	Y	N	?	Y	Y	Y	?	Y	?	Y	Fair
Fang, 2007	2250	113	R	Y	N	Y	N	Y	N	E	?	NA	NA	NA	Y	N	Y	?	N	Poor
Hsiung , 2006	3070	32	R	Y	?	N	N	Y	N	E	N	NA	NA	NA	Y	N	Y	md 24	N	Poor

Table D1d. Nasopharyngeal cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Lrg, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Suffici-ently long F/U	Clear cand var select	Clear appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Valid-ation
1° RT															
3DCRT vs 2DRT															
Jen, 2005	5240	N	N	Y	Y	NA	Y	?	md 26	Y	N	?	?	?	N
1° RT + split CTx															
IMRT vs 2DRT															
Laskar, 2008	39050	Y	N	N	Y	NA	Y	Y	md 27	N	?	?	?	?	N
Mixed Settings															
IMRT vs 3DCRT															
Fang, 2008	39090	Y	N	Y	Y	NA	N	Y	md 40, 46	N	?	?	?	?	N

Table D1e. Nasopharyngeal cancer, quality of life

EORTC QLQ-C30

	Pow, 2006; Rec # 2340				Fang, 2008; Rec # 39090				Fang, 2007; Rec # 2250				
Item	**Mean IMRT n=24**	**Mean 2DRT n=21**	**Mo F/U**	**p Value**	**Mean IMRT n≥79**	**Mean 3DCRT n≥66**	**Mo F/U**	**p Value**	**Mean IMRT n=52**	**Mean 3DCRT n=33**	**Mean 2DRT n=61**	**Mo F/U**	**IMRT vs 3DCRT p value**
Global health	54.9 63.2 63.9	52.8 61.9 63.5	2 6 12 all		41 44 58 61	46 56 63 64	0 3 12 24	<0.05	49	61	64	24-36	NS
Global health-revised	53.8 61.5 62.2	53.6 60.3 62.3	2 6 12 all										NS
Physical function	84.4 86.9 91.1	83.8 88.3 90.5	2 6 12 all		84 79 86 87	87 86 90 91	0 3 12 24		80	87	91	24-36	NS
Role function	94.4 96.5 97.2	94.4 97.6 96.0	2 6 12 all		86 84 90 90	86 88 92 92	0 3 12 24		82	90	92	24-36	NS
Role function-revised	81.9 92.4 100.0	84.9 96.8 95.2	2 6 12 all	<0.05									NS
Emotional function	87.8 91.3 91.7	83.7 89.7 88.9	2 6 12 all						76	84	85	24-36	NS
Cognitive function	86.1 86.8 89.6	85.7 86.5 84.1	2 6 12 all						77	85	85	24-36	NS
Social function	81.3 91.0 93.1	83.3 91.3 92.9	2 6 12 all		72 71 82 82	71 77 81 83	0 3 12 24		75	82	83	24-36	NS

EORTC QLQ-C30 (continued)

	Pow, 2006; Rec # 2340				Fang, 2008; Rec # 39090				Fang, 2007; Rec # 2250				
Item	**Mean IMRT n=24**	**Mean 2DRT n=21**	**Mo F/U**	**p Value**	**Mean IMRT n≥79**	**Mean 3DCRT n≥66**	**Mo F/U**	**p Value**	**Mean IMRT n=52**	**Mean 3DCRT n=33**	**Mean 2DRT n=61**	**Mo F/U**	**IMRT vs 3DCRT p value**
Fatigue	20.4 16.7 13.0	20.1 14.8 13.8	2 6 12 all		36 39 25 24	34 29 24 25	0 3 12 24	<0.05	35	24	25	24-36	NS
Nausea/ vomiting	7.6 0.0 0.7	3.2 0.0 2.4	2 6 12 all		26 15 8 4	22 11 8 4	0 3 12 24		9	4	4	24-36	NS
Pain	7.6 6.3 2.8	7.9 7.1 9.5	2 6 12 all		35 26 10 11	28 18 14 12	0 3 12 24		25	11	12	24-36	NS
Dyspnea	13.9 8.3 4.2	12.7 9.5 3.2	2 6 12 all		11 16 6 6	13 11 7 6	0 3 12 24		17	6	6	24-36	NS
Insomnia	15.3 6.9 6.9	14.3 12.7 11.1	2 6 12 all		27 30 22 19	23 25 22 21	0 3 12 24		27	19	21	24-36	NS
Appetite loss	23.6 8.3 8.3	15.9 7.9 7.9	2 6 12 all		43 32 10 9	41 21 11 8	0 3 12 24		19	9	8	24-36	NS
Constipation	11.1 6.9 5.6	15.9 7.9 11.1	2 6 12 all		16 20 17 15	17 11 13 13	0 3 12 24		17	15	13	24-36	NS
Diarrhea	0.0 4.2 1.4	11.1 7.9 4.8	2 6 12 all	<0.05 0.009	19 16 10 10	14 11 10 11	0 3 12 24		12	10	11	24-36	NS
Financial difficulties	15.3 11.1 5.6	11.1 14.3 11.1	2 6 12 all		25 30 20 22	23 22 22 23	0 3 12 24		26	22	23	24-36	NS

SF-36

	Pow, 2006, Rec# 2340			
Domain	**Mean IMRT n=24**	**Mean 2DRT n=21**	**Mo F/U**	**p Value**
Physical function	89.4 92.5 94.4	88.3 92.6 93.8	2 6 12 all	
Role-physical	33.3 60.4 86.5	27.4 48.8 58.3	2 6 12 all	<0.05
Bodily pain	78.0 85.4 89.8	76.2 82.5 75.6	2 6 12 all	<0.05
General health	51.8 55.8 65.7	47.9 52.9 58.7	2 6 12 all	
Vitality	58.1 65.2 70.6	57.6 61.2 63.1	2 6 12 all	
Social functioning	71.4 92.2 91.7	70.2 86.9 92.3	2 6 12 all	
Role-emotional	50.0 77.8 86.1	47.6 55.6 73.0	2 6 12 all	
Mental health	76.5 80.8 84.5	74.5 76.8 80.8	2 6 12 all	

EORTC QLQ-H&N35

	Pow, 2006; Rec # 2340				Fang, 2008; Rec # 39090				Fang, 2007; Rec # 2250				
Item	**Mean IMRT n=24**	**Mean 2DRT n=21**	**Mo F/U**	**p Value**	**Mean IMRT n≥79**	**Mean 3DCRT n≥66**	**Mo F/U**	**p Value**	**Mean IMRT n=52**	**Mean 3DCRT n=33**	**Mean 2DRT n=61**	**Mo F/U**	**IMRT vs 3DCRT p value**
Pain	15.6 9.4 7.3	16.7 15.1 12.7	2 6 12 all		37 27 15 13	34 20 11 10	0 3* 12 24		18	13	10	24-36	NS
Swallowing	9.0 8.7 6.6	13.5 10.7 10.7	2 6 12 all	<0.05 0.022	38 26 23 22	35 21 17 16	0 3* 12 24		30	22	16	24-36	NS
Taste/smell	42.4 27.1 20.1	28.6 17.5 18.3	2 6 12 all	<0.05	36 35 23 22	40 22 21 19	0 3 12 24	<0.05	29	22	19	24-36	NS
Speech	12.5 7.4 3.2	13.2 15.9 10.1	2 6 12 All	<0.05 <0.05 0.053	18 26 14 12	19 17 14 12	0 3 12 24		25	12	12	24-36	NS
Social eating	22.2 11.1 7.3	22.5 13.6 11.5	2 6 12 all		35 27 17 16	37 22 14 13	0 3 12 24		30	16	13	24-36	NS
Social contact	6.4 3.3 0.8	7.6 2.5 2.2	2 6 12 all		15 18 9 9	20 15 10 8	0 3 12 24		18	9	8	24-36	NS
Sexuality	31.1 24.2 22.0	35.6 26.7 25.6	2 6 12 all		27 33 24 24	30 25 19 19	0 3 12 24		27	24	19	24-36	NS
Teeth	8.3 5.6 6.9	5.0 5.0 5.0	2 6 12 all		23 24 23 21	21 20 22 21	0 3 12 24		40	21	21	24-36	NS
Opening mouth	8.3 15.3 12.5	14.3 23.8 19.0	2 6 12 all		24 21 16 15	21 15 15 14	0 3* 12 24		33	15	14	24-36	NS

EORTC QLQ-H&N35 (continued)

	Pow, 2006; Rec # 2340				Fang, 2008; Rec # 39090				Fang, 2007; Rec # 2250				
Item	**Mean IMRT n=24**	**Mean 2DRT n=21**	**Mo F/U**	**p Value**	**Mean IMRT n≥79**	**Mean 3DCRT n≥66**	**Mo F/U**	**p Value**	**Mean IMRT n=52**	**Mean 3DCRT n=33**	**Mean 2DRT n=61**	**Mo F/U**	**IMRT vs 3DCRT p value**
Dry mouth	72.2 59.7 47.2	81.0 69.8 60.3	2 6 12 all	 0.021	54 59 45 44	50 49 41 41	0 3 12 24	 <0.05 	53	44	41	24-36	NS
Sticky saliva	62.5 44.4 40.3	87.3 79.3 66.7	2 6 12 all	<0.05 <0.05 <0.05 <0.001	46 45 34 35	46 44 34 34	0 3 12 24	 	47	35	34	24-36	NS
Coughing	12.5 6.9 4.2	11.1 19.0 12.7	2 6 12 all	 <0.05 	31 30 20 19	27 25 20 20	0 3 12 24	 	27	19	20	24-36	NS
Feeling ill	4.2 4.2 4.2	6.3 9.5 6.3	2 6 12 all	 	38 36 24 23	34 25 20 20	0 3 12 24	 <0.05 	34	23	20	24-36	NS
Pain killers	4.2 4.2 12.5	14.3 4.8 9.5	2 6 12 all	 									
Nutrition supplement	33.3 20.8 20.8	9.5 23.8 28.6	2 6 12 all	 									
Feeding tube	4.2 0.0 0.0	0.0 0.0 0.0	2 6 12 all	 									
Weight loss	25.0 8.3 4.2	9.5 19.0 0.0	2 6 12 all	 									
Weight gain	16.7 25.0 37.5	47.6 23.8 28.6	2 6 12 all	<0.05 									

Table D1f. Nasopharyngeal cancer, xerostomia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1^{o} RT												
3DCRT vs 2DRT												
Jen, 2005	5240	180	1^{o} RT	3DCRT 2DRT	59.7 58.3	RTOG	2-3			OR: 0.55	0.0053	MVA: GEE method
IMRT vs 2DRT												
Wu, 2005	4520	380	1^{o} RT	IMRT 2DRT	85.8 (all)	?	?	20.4 23.4	NR			
1^{o} RT + split CTx												
IMRT vs 2DRT												
Laskar, 2008	39050	36	1^{o} RT + split CTx	IMRT 2DRT	84.2 94.1	RTOG	$\geq$ 2	31.6 88.2	0.002			
Mixed Settings												
IMRT vs 2DRT												
Kam, 2007 (RCT)	530	56	1^{o} RT ± ICBRT	IMRT 2DRT	0 0	RTOG EORTC 6 wk, 6 mo, 1 yr	2-4	45.4 85.7	0.002	75 92.9 39.3 82.1	0.001	
Hsiung , 2006	3070	32	1^{o} RT± CCTx	IMRT 2DRT	50 37.5	RTOG	2-3			50 100	<0.001	

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Scale	Item	Mean	F/U	p value	Comments
Mixed Settings											
IMRT vs 3DCRT											
Fang, 2007	2250	85	1^{o} RT ± CTx (timing?)	IMRT 3DCRT	48.1 48.5	QLQ-H&N35 item	Dry mouth	41 44	2-3 yr	NR	MVA combined IMRT+3DCRT
3DCRT vs 2DRT											
Fang, 2007	2250	94	1^{o} RT ± CTx (timing?)	3DCRT 2DRT	48.5 50.8	QLQ-H&N35 item	Dry mouth	44 53	2-3 yr	<0.05	MVA combined IMRT+3DCRT
IMRT vs 2DRT											
Kam, 2007 (RCT)	530	56	1^{o} RT ± ICBRT	IMRT 2DRT	0 0	6-item XST scale	Total (follow-up minus baseline)	-38.4 -37.2 -30.7 -31.8 -24.3 -33.1	6 wk 6 mo 1 yr 	0.99 0.86 0.32 	
Fang, 2007	2250	113	1^{o} RT ± CTx (timing?)	IMRT 2DRT	48.1 50.8	QLQ-H&N35 item	Dry mouth	41 53	2-3 yr	<0.05	MVA combined IMRT+3DCRT

Table D1g. Nasopharyngeal cancer, salivary flow

Study	Rec#	No. Pts	Setting	Group	% Stage 0/I/II	% Stage III/IV	Mos Post-RT	Stimulated Flow Ratio % of Baseline	Unstimulated Flow Ratio % of Baseline	Comments
1° RT										
IMRT vs 2DRT										
Pow, 2006 (RCT)	2340	45	1° RT	 IMRT 2DRT IMRT 2DRT IMRT 2DRT IMRT 2DRT IMRT 2DRT IMRT 2DRT	 100 100	 0 0	SWS 2 2 6 6 12 12 SPS 2 2 6 6 12 12	(calculated) 0.14 0.08 0.19 0.04 0.26 0.06 0.28 0 0.57 0 1.28 0	NR	Saliva stimulated by chewing on sterile rubber tubing. SWS collected 5 min in cup; SPS collected 15 min w/ Lashley cup & suction over parotid duct on one side. SWS: 2DRT vs IMRT, $p < 0.003$ at 2, 6, 12 mos (ANOVA) SPS: 2DRT vs IMRT, $p < 0.002$ at 2, 6, 12 mos (ANOVA) SEE IF INFO ON DOSE-SLOW FOR THIS AND PREVIOUS ARTICLE
Wu, 2005	4520	380	1° RT	 2DRT IMRT	14.2 (all)	85.8 (all)			% w/ ↓ in parotid 82 70	For static secretion function (rated as a decrease if flow < 0.3 mL/min, i.e., no baseline measure), $p < 0.05$ CF, LCAF vs IMRT for percentage pts decreased post-RT. Measured 3 hrs after last food or mouthwash, then removed from parotid gland w/ catheter for 15 min.

Table D1g. Nasopharyngeal cancer, salivary flow (continued)

Study	Rec#	No. Pts	Setting	Group	% Stage 0/I/II	% Stage III/IV	Mos Post-RT	Stimulated Flow Ratio % of Baseline	Unstimulated Flow Ratio % of Baseline	Comments
Mixed Settings										
IMRT vs 2DRT										
Kam, 2007 (RCT)	530	56	1^{o} RT ± ICBRT					Fractional SWSFR	NR	Measured amount spit out for 5 minutes after stimulated using gum for 1 min: 2DRT vs IMRT $p < 0.01$ at 12 mos (paired t-test).
				IMRT	100	0	1.5	0.32		
				2DRT	100	0	1.5	0.28		
				IMRT			6	0.30		
				2DRT			6	0.20		
				IMRT			12	0.41		
				2DRT			12	0.20		
								Fractional SPFR		Measured amt collected with suction cup from orifice of each parotid duct for 15 min after stimulated w/ lemon candy w/ fixed citric acid content: 2DRT vs IMRT $p < 0.001$ at 1.5, 6, 12 mos (paired t-test)
				IMRT			1.5	0.39		
				2DRT			1.5	0.09		
				IMRT			6	0.70		
				2DRT			6	0.04		
				IMRT			12	0.90		
				2DRT			12	0.05		

Table D1h. Nasopharyngeal cancer, dysphagia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1° RT + split CTx												
IMRT vs 2DRT												
Laskar, 2008	39050	36	1° RT + split CTx	IMRT 2DRT	84.2 94.1	RTOG	≥ 2 ≥ 3	42.0 94.1 10.5 41.2	0.01 0.035			

Table D1i. Nasopharyngeal cancer, mucositis

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1° RT + split CTx												
3DCRT vs 2DRT												
Wu, 2005 (RCT)	4360	96	1° RT + split CTx	3DCRT 2DRT	100 100	?	1-2 3-4	69.6 64.0 30.4 36.0	0.563			
IMRT vs 2DRT												
Laskar, 2008	39050	36	1° RT + split CTx	IMRT 2DRT	84.2 94.1	RTOG	≥ 2 ≥ 3	78.9 100 15.8 52.9	0.066 0.033			

Table D1j. Nasopharyngeal cancer, skin

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1° RT + split CTx												
IMRT vs 2DRT												
Laskar, 2008	39050	36	1° RT + split CTx	IMRT 2DRT	84.2 94.1	RTOG	≥ 2 ≥ 3	84.2 100 5.3 47.1	0.136 0.006			

Table D1k. Nasopharyngeal cancer, oteoradionecrosis/bone

No studies.

Table D1l. Nasopharyngeal cancer, tumor control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
1° RT + split CTx													
3DCRT vs 2DRT													
Wu, 2005 (RCT)	4360	96	1° RT + split CTx	3DCRT 2DRT	100 100	LC	97.8 78.0					0.003	
IMRT vs 2DRT													
Laskar, 2008	39050	36	1° RT + split CTx	IMRT 2DRT	84.2 94.1	LRC		84.2 68.3				0.201	RT tech not entered in MVA
						DFS		67.5 55.8				0.477	RT tech not entered in MVA
Mixed Settings													
IMRT vs 3DCRT													
Fang, 2008	39090	203	1° RT ± CCTx	IMRT 3DCRT	52.8 55.9	LRC	~95 ~98	84.2 ~90	84.2 84.8	84.2 ~83		0.85 (3 yr)	RT tech NS in MVA

Table D1m. Nasopharyngeal cancer, patient survival

Overall Survival

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
1^{o} RT + split CTx													
3DCRT vs 2DRT													
Wu, 2005 (RCT)	4360	96	1^{o} RT + split CTx	3DCRT 2DRT	100 100	OS	100 96					0.17	
IMRT vs 2DRT													
Laskar, 2008	39050	36	1^{o} RT + split CTx	IMRT 2DRT	84.2 94.1	OS		80.8 66.7				0.641	RT tech not entered in MVA
Mixed Settings													
IMRT vs 3DCRT													
Fang, 2008	39090	203	1^{o} RT ± CCTx	IMRT 3DCRT	52.8 55.9	OS	~96 ~98	~90 ~92	85.4 81.7	~79 ~78		0.58 (3 yr)	RT tech NS in MVA

Table D2a. Oropharyngeal cancer, outcomes by study

Study	Rec#	No. Pts	Setting	QOL/Adverse Events							Tumor Control			Patient Survival	
				QOL	XST	SF	DYS	MUC	SKN	ORN or BON	All LC	LRC	DFS	DSS	OS
1° RT + CCTx															
IMRT vs 3DCRT															
Rusthoven, 2008	13200	87	1° RT + CCTx		X			X	X			X	X		X
IMRT vs 2DRT															
Lee, 2006	2350	112	1° RT + CCTx		X			X	X		X		X		X
Mixed Settings															
IMRT vs 3DCRT															
Hodge, 2007	570	195	1° RT ± CCTx		X			X				X		X	X
Rades, 2007	2710	44	postop RT ± CCTx		X			X	X		X				X
Nutting, 2009 (RCT)	41220	84	1° RT/postop ± pre RT CTx		X		X	X	X	X		X			X
3DCRT vs 2DRT															
Rades, 2007	2710	130	postop RT ± CCTx		X			X	X		X				X
IMRT vs 2DRT															
Yao, 2007	1120	53	1° RT ± CTx (timing?)	X											
Rades, 2007	2710	122	postop RT ± CCTx		X			X	X		X				X
Chao, 2001	9940	430	1°/preop/postop RT ± CCTx		X		X	X	X	X		X	X		X
Comparisons	9			1	8	0	2	8	7	2	4	4	3	1	8
Studies	7			1	6	0	2	6	5	2	2	4	3	1	6
Total n	1109														

Table D2b. Oropharyngeal cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
1^o RT + CCTx										
IMRT vs 3DCRT										
Rusthoven, 2008	13200	87	1^o RT + CCTx	IMRT 3DCRT	12 9	NR	100 (all)	70-72 66-70	24 (3-103)	100 97
IMRT vs 2DRT										
Lee, 2006	2350	112	1^o RT + CCTx	IMRT 2DR	12 17	55 (28-78) 56 (33-80)	100 98.6	66-70 70-72	46 (3-93)	100 99
Mixed Settings										
IMRT vs 3DCRT										
Hodge, 2007	570	195	1^o RT ± CCTx	IMRT 3DCRT 3DCRTpre	27 5 29	NR	86 100 78	65-70 60-78	31 (3-166) (all)	NR
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	NR	NR	≥ 50 ≥ 65 balance?	60-70 (all)	NR	NR
Nutting, 2009	41220	84	1^o RT/postop ± preRT CTx	IMRT 3DCRT	28% (all)	58.4 (mn all)	77 (all)	65, 61 64, 61 (1^o, postop)	31.9 (23.5-38.8, all)	NR
3DCRT vs 2DRT										
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DR	NR	NR	≥65 ≥54	60-70 (all)	NR	NR
IMRT vs 2DRT										
Yao, 2007	1120	53	1^o RT ± CTx (timing?)	IMRT 2DR	19.2 18.5	58 53	96.2 85.2	70 (all)	NR	NR
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DR	NR	NR	≥50 ≥54	60-70 (all)	NR	NR
Chao, 2001	9940	430	1^o/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	8 25 14 26 27	56 (50-71) 61 (43-86) 49 (42-76) 60 (30-81) 58 (33-83)	91.7 63.7 85.7 86.7 71.6	70.3 (70.2-72) 70 (60-76) 63.6 (55.1-66.5) 64.8 (50-72) 30 (28-70)	47 (12-276)	NR

Table D2c. Oropharyngeal cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initial Grps Comp	Bal by Design (Mtch)	BL Chars Clear Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Outcomes Val, Rel, =	Assessors Blind	Txs Clear	Adequate F/U	Analysis: Adj for Confs	USPSTF
1° RT + CCTx																				
IMRT vs 3DCRT																				
Rusthoven, 2008	13200	87	R	Y	Y	N	N	N	?	?	N	NA	NA	NA	Y	N	Y	md 24	Y/?	Poor
IMRT vs 2DRT																				
Lee, 2006	2350	112	R	Y	Y	?	N	Y	?	?	Y	NA	NA	NA	Y	N	Y	md 46	N	Poor
Mixed Settings																				
IMRT vs 3DCRT																				
Hodge, 2007	570	195	R	Y	Y	Y	N	Y	Y+N	Y/E	Y	NA	NA	NA	Y	N	Y	md 31	Y/?	Poor
Rades, 2007	2710	44	R	Y	Y	Y	N	Y	?	WL	Y	NA	NA	NA	Y	N	Y	?	Y/?	Poor
Nutting, 2009 (RCT)	41220	84	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	md 32	Y	Good
3DCRT vs 2DRT																				
Rades, 2007	2710	130	R	Y	Y	Y	N	Y	?	WL	Y	NA	NA	NA	Y	N	Y	?	Y/?	Poor
IMRT vs 2DRT																				
Yao, 2007	1120	53	P	Y	Y	N	N	N	N	E	N	NA	Y	Y	Y	?	Y	?	N	Poor
Rades, 2007	2710	122	R	Y	Y	Y	N	Y	?	WL	Y	NA	NA	NA	Y	N	Y	?	Y/?	Poor
Chao, 2001	9940	430	R	Y	Y	N	N	Y	N	E	N	NA	NA	NA	Y	N	Y	?	Y/?	Poor

?: unclear; Adj for Conf: adjustment for confounders; Alloc: allocation; Attr: attrition; B: both concurrent and nonconcurrent control groups; Bal: balanced; BL chars: baseline characteristics; comp: comparable; CR: consecutive retrospective; E: era; F/U: followup; Grps: groups; M: mostly; md: median; Maint: maintenance; Mtch: matched design; N: no; NA: not applicable; Non-diffl: nondifferential; NR: not reported; P/pro: prospective; R/retro: retrospective; Rep: representative; Select: selection; Txs: treatments; W: waiting list; Y: yes; Y/?: multivariate analysis performed of uncertain quality

Table D2d. Oropharyngeal cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Large, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Sufficiently long F/U	Clear cand var select	Clear, appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Validation
1° RT + CCTx															
IMRT vs 3DCRT															
Rusthoven, 2008	13200	N	N	N	Y	NA	Y	NA	md 24	Y	?	?	?	Y	N
Mixed Settings															
IMRT vs 3DCRT															
Hodge, 2007	570	N	N	Y	Y	NA	N	NA	md 31	N	?	?	?	?	N
Rades, 2007	2710	N	N	Y	Y	NA	N	NA	?	Y	N	?	N	?	N
3DCRT vs 2DRT															
Rades, 2007	2710	N	N	Y	Y	NA	N	NA	?	Y	N	?	N	?	N
IMRT vs 2DRT															
Rades, 2007	2710	N	N	Y	Y	NA	N	NA	?	Y	N	?	N	?	N
Chao, 2001	9940	N	N	Y	Y	NA	N	NA	?	N	?	?	?	?	N

Assmpt test: model assumptions tested; Blinded assess pred factor: blinded assessment of predictive factor; Clear, appr model bldg GLs: clear, appropriate model-buliding guidelines followed; Clear cand var select: clear candidate variable selection for multivariate analysis; Cont vars well hndld: continuous variable well-handled; Homog txs, rand/unbiased alloc: homogeneous treatments, randomized or otherwise unbiased allocation to treatment group; Prespec hypoths: prespecified hypotheses relating predicting factor to outcome; well-defd, rep study pop: well-defined, representative study population; pred factor study meths well-descrd: predictive factor study methods well-described; Stand prong vars incld: standard prognostic variables included

Table D2e. Oropharyngeal cancer, quality of life

Head and Neck Cancer Inventory (HNCI)

Mixed Settings *IMRT vs 2DRT*	**Yao, 2007, Rec # 1120**					
Domain	**Mean IMRT n=26**	**Mean 2DRT n=27**	**Mo F/U**	**p Value**	**Difference**	**Magnitude of Clinically Important Difference**
Eating	34.5 42.1 55.4	34.9 31.7 39.0	3 6 12	 0.007	0.4 10.2 16.4	 Small Medium
Speech	83.2	74.3		0.059	8.9	Small
Aesthetics	90.4	79.3		0.069	11.1	Small
Social Disruption	86.1	78.8		0.115	7.3	Small

Table D2f. Oropharyngeal cancer, xerostomia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1^{o} RT + CCTx												
IMRT vs 3DCRT												
Rusthoven, 2008	13200	87	1^{o} RT + CCTx	IMRT 3DCRT	100 100	RTOG	$\geq$ 2			62 100 15 94 6 93	<0.001 <0.001 <0.001	6 mo 12 mo 18 mo
IMRT vs 2DRT												
Lee, 2006	2350	112	1^{o} RT + CCTx	IMRT 2DRT	100 98.6	RTOG/ EORTC	$\geq$ 2			12 67	0.002	
Mixed Settings												
IMRT vs 3DCRT												
Hodge, 2007	570	195	1^{o} RT ± CCTx	IMRT 3DCRT 3DCRT pre	86 100 78	RTOG	mod			56 63 67	0.3	
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	$\geq$50 $\geq$65	RTOG	2-3			17 73	0.037	
Nutting, 2009	41220	84	1^{o} RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	LENT SOM	$\geq$ 2	71 91	0.02	62 83 60 86 39 74 29 71	0.04 0.01 0.004 0.003	late = 3 mo 6 mo 12 mo 18 mo
				IMRT 3DCRT		RTOG	$\geq$ 2			56 78 47 83 41 64 20 81	0.03 0.001 0.05 0.001	late = 3 mo 6 mo 12 mo 18 mo

Table D2f. Oropharyngeal cancer, xerostomia (continued)

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
3DCRT vs 2DRT												
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DRT	≥65 ≥54	RTOG	2-3			73 63		
IMRT vs 2DRT												
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DRT	≥50 ≥54	RTOG	2-3			17 63	0.037	
Chao, 2001	9940	430	1°/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	RTOG	> 2	75 69.3 64.3 63.4 18.3	NR	30 83.9 16.7 79.1 31.7	<0.0001	

Table D2g. Oropharyngeal cancer, salivary flow

No studies.

Table D2h. Oropharyngeal cancer, dysphagia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Nutting, 2009	41220	84	1^{o} RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	CTCAE v3 (acute) LENT SOM (late)	$\geq$ 2	87 98	0.05	13 6	0.44	
IMRT vs 2DRT												
Chao, 2001	9940	430	1^{o}/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	RTOG	2-3	50 66 28.6 50.7 32.1	NR			

Table D2i. Oropharyngeal cancer, mucositis

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1° RT + CCTx												
IMRT vs 3DCRT												
Rusthoven, 2008	13200	87	1° RT + CCTx	IMRT 3DCRT	100 100	CTC	≥ 3	81 78	NR			
IMRT vs 2DRT												
Lee, 2006	2350	112	1° RT + CCTx	IMRT 2DRT	100 98.6	RTOG/ EORTC	3-4	66 72	NR			
Mixed Settings												
IMRT vs 3DCRT												
Hodge, 2007	570	195	1° RT ± CCTx	IMRT 3DCRT 3DCRTpre	86 100 78	RTOG	3	58 75 65	0.2 1.0			pre=preIMRT era
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	≥50 ≥65	CTC	2-3	~89 ~93	NR			
Nutting, 2009	41220	84	1° RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	CTCAE v3 (acute) LENT SOM (late)	≥ 2	91 98	0.18	23 15	0.55	
3DCRT vs 2DRT												
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DRT	≥65 ≥54	CTC	2-3	~93 ~90	NR			
IMRT vs 2DRT												
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DRT	≥50 ≥54	CTC	2-3	~89 ~90	NR			
Chao, 2001	9940	430	1°/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	RTOG	2-3	100 91.5 92.9 79.6 36.8	NR	10 11.90 17.32	NR	

Table D2j. Oropharyngeal cancer, skin

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1^{o} RT + CCTx												
IMRT vs 3DCRT												
Rusthoven, 2008	13200	87	1^{o} RT + CCTx	IMRT 3DCRT	100 100	CTC	$\geq$ 3	34 52	0.002			
IMRT vs 2DRT												
Lee, 2006	2350	112	1^{o} RT + CCTx	IMRT 2DRT	100 98.6	RTOG/ EORTC	3-4	10 14	NR			
Mixed Settings												
IMRT vs 3DCRT												
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	$\geq$50 $\geq$65	Acute-CTC; Late-RTOG	2-3	~95 ~90	NR	~7 ~12	NR	
Nutting, 2009	41220	84	1^{o} RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	CTCAE v3 (acute) LENT SOM (late)	$\geq$ 2	76 93	0.02	8 15	0.46	
3DCRT vs 2DRT												
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DRT	$\geq$65 $\geq$54	Acute-CTC; Late-RTOG	2-3	~90 ~93	NR	~12 ~14	NR	
IMRT vs 2DRT												
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DRT	$\geq$50 $\geq$54	Acute-CTC; Late-RTOG	2-3	~95 ~93	NR	~7 ~14	NR	
Chao, 2001	9940	430	1^{o}/preop/ postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	RTOG	2-3	58.3 72.5 57.1 57.7 27.5	NR	10 16.8 8.3 15.8 5.0	NR	

Table D2k. Oropharyngeal cancer, oteoradionecrosis/bone

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Nutting, 2009	41220	84	1^{o} RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	LENT SOM	$\geq$ 2			13 12	1.00	
IMRT vs 2DRT												
Chao, 2001	9940	430	1^{o}/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	RTOG	2-3			0 6.3 0 2.9 5.9	NR	

Table D2l. Oropharyngeal cancer, tumor control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
1° RT + CCTx													
IMRT vs 3DCRT													
Rusthoven, 2008	13200	87	1° RT + CCTx	IMRT 3DCRT	100 100	LRC	~100 ~87	96 81	96 81	96 81		0.21	MVA IMRT vs 3DCRT+AFxCB HR 5.20 p=0.075
				IMRT 3DCRT		DFS	~90 ~63	79 56	~68 56	~68 ~50		0.18	RT tech NS in MVA
IMRT vs 2DRT													
Lee, 2006	2350	112	1° RT + CCTx	IMRT 2DRT	100 98.6	LC	~100 ~90	95 ~90	95 85	95 85	95 85	0.17	
				IMRT 2DRT		LRC	~100 ~90	~95 ~92	92 82	92 82	92 ~75	0.18	
				IMRT 2DRT		DFS	~92 ~86	~86 ~86	82 76	82 76	82 ~70	0.57	
Mixed Settings													
IMRT vs 3DCRT													
Hodge, 2007	570	195	1° RT ± CCTx	IMRT 3DCRT 3DCRTpre	86 100 78	LRC	96.1 ~87 ~84	96.1 78.1 82.3	96.1 78.1 81.1	96.1 78.1 78.5	78.5		pre=preIMRT era
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	≥ 50 ≥ 65	LC		89 79				0.34	RT tech NS in MVA
Nutting, 2009	41220	84	1° RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	LRC	87.3 88.0					NS	IMRT:3DCRT HR=1.59 (0.67, 3.80)

Table D2l. Oropharyngeal cancer, tumor control (continued)

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
3DCRT vs 2DRT													
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DRT	≥65 ≥54	LC		79 78				0.34	RT tech NS in MVA
IMRT vs 2DRT													
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DRT	≥50 ≥54	LC		89 78				0.34	RT tech NS in MVA
Chao, 2001	9940	430	1°/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	LRC		88 68 100 76 78				NS NS	
				defIMRT def2DRT postopIMRT postop2DRT preop2DRT		DFS		80 58 92 74 68				0.002 0.008	

Table D2m. Oropharyngeal cancer, patient survival

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
1° RT + CCTx													
IMRT vs 3DCRT													
Rusthoven, 2008	13200	87	1° RT + CCTx	IMRT 3DCRT	100 100	OS	~90 ~80	86 73	~72 ~70	~72 ~55		0.48	RT tech NS in MVA
IMRT vs 2DRT													
Lee, 2006	2350	112	1° RT + CCTx	IMRT 2DRT	100 98.6	OS	~100 ~88	~96 ~88	91 81	91 ~70	91 ~70	0.10	
Mixed Settings													
IMRT vs 3DCRT													
Hodge, 2007	570	195	1° RT ± CCTx	IMRT 3DCRT 3DCRTpre	86 100 78	DSS	~99 ~98 ~93	97.7 83.5 87.7	97.7 83.5 79.7	97.7 83.5 ~76	 73.5	NR	
				IMRT 3DCRT 3DCRTpre		OS	~98 ~95 ~90	94.5 81.1 87.7	88.2 81.1 79.7	88.2 81.1 ~56	 54.6	0.02	pre=preIMRT era RT tech NS in MVA (w/ T stage)
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	≥50 ≥65	OS		86 80				0.30	RT tech NS in MVA
Nutting, 2009	41220	84	1° RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	OS	93.6 90.8					NS	IMRT:3DCRT HR=1.05 (0.38, 2.90)
3DCRT vs 2DRT													
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DRT	≥65 ≥54	OS		80 74				0.30	RT tech NS in MVA
IMRT vs 2DRT													
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DRT	≥50 ≥54	OS		86 74				0.30	RT tech NS in MVA
Chao, 2001	9940	430	1°/preop/ postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	OS		100 57 100 71 67				0.001 0.003	

Table D3a. Nasal cavity and paranasal sinus cancer, outcomes by study

Study	Rec#	No. Pts	Setting	QOL/Adverse Events							Tumor Control			Patient Survival	
				QOL	XST	SF	DYS	MUC	SKN	ORN or BON	LC	LRC	DFS	DSS	OS
Mixed Settings															
IMRT vs 3DCRT															
Chen, 2007	1560	68	1°/preop/postop RT± postRT CTx/CCTx					X	X	X	X		X		X
3DCRT vs 2DRT															
Dirix, 2007	1360	127	1°/preop/postop RT		X			X		X	X		X	X	X
Chen, 2007	1560	104	1°/preop/postop RT± postRT CTx/CCTx					X	X	X	X		X		X
IMRT vs 2DRT															
Chen, 2007	1560	82	1°/preop/postop RT± postRT CTx/CCTx					X	X	X	X		X		X
Comparisons	4			0	1	0	0	4	3	4	4	0	4	1	4
Studies	2			0	1	0	0	2	1	2	2	0	2	1	2
Total n	254														

Table D3b. Nasal cavity and paranasal sinus cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
Mixed Settings										
IMRT vs 3DCRT										
Chen, 2007	1560	68	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 3DCRT	40 (all)	61 (27-92) (all)	≥87.4 (all)	66-72 50-73	49 (3-151)	NR
3DCRT vs 2DRT										
Dirix, 2007	1360	127	1^{o}/preop/postop RT	3DCRT 2DR	16 (all)	58 (27-85) (all)	≥93.7 (all)	50-80 (all)	67 (3-307)	100 (all)
Chen, 2007	1560	104	1^{o}/preop/postop RT± postRT CTx/CCTx	3DCRT 2DR	40 (all)	61 (27-92) (all)	≥87.4 (all)	50-73 50-74	49 (3-151)	NR
IMRT vs 2DRT										
Chen, 2007	1560	82	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 2DR	40 (all)	61 (27-92) (all)	≥ 87.4 (all)	66-72 50-74	49 (3-151)	NR

Table D3c. Nasal cavity and paranasal sinus cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initl Grps Comp	Bal by Design (Mtch)	BL Chars Clr Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Out-comes Val, Rel, =	Assessors Blind	Txs Clr	Adequate F/U	Analysis: Adj for Confs	USPSTF
Mixed Settings																				
IMRT vs 3DCRT																				
Chen, 2007	1560	68	R	Y	Y	?	N	?	N	E	?	NA	NA	NA	Y	N	Y	md 49	N	Poor
3DCRT vs 2DRT																				
Dirix, 2007	1360	127	R	Y	Y	?	N	?	N	E	?	NA	NA	NA	Y	N	Y	md 67	Y/N	Poor
Chen, 2007	1560	104	R	Y	Y	?	N	?	N	E	?	NA	NA	NA	Y	N	Y	md 49	N	Poor
IMRT vs 2DRT																				
Chen, 2007	1560	82	R	Y	Y	?	N	?	N	E	?	NA	NA	NA	Y	N	Y	md 49	N	Poor

Table D3d. Nasal cavity and paranasal sinus cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Lrg, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Suffici-ently long F/U	Clear cand var select	Clear appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Valid-ation
Mixed Settings															
3DCRT vs 2DRT															
Dirix, 2007	1360	N	N	Y	Y	NA	N	?	md 67	Y	N	?	N	?	N

Table D3e: Nasal cavity and paranasal sinus cancer, quality of life

No studies.

Table D3f: Nasal cavity and paranasal sinus cancer, xerostomia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
3DCRT vs 2DRT												
Dirix, 2007	1360	127	1^{o}/preop/ postop RT	3DCRT 2DRT	≥93.7 (all)	?	Perm-anent			10.0 29.9	0.08	

Table D3g. Nasal cavity and paranasal sinus cancer, salivary flow

No studies.

Table D3h. Nasal cavity and paranasal sinus cancer, dysphagia

No studies.

Table D3i. Nasal cavity and paranasal sinus cancer, mucositis

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Chen, 2007	1560	68	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 3DCRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			13 16	NR	
3DCRT vs 2DRT												
Dirix, 2007	1360	127	1^{o}/preop/postop RT	3DCRT 2DRT	≥93.7 (all)	?	?				NS	
Chen, 2007	1560	104	1^{o}/preop/postop RT± postRT CTx/CCTx	3DCRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			16 17	NR	
IMRT vs 2DRT												
Chen, 2007	1560	82	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			13 17	NR	

Table D3j. Nasal cavity and paranasal sinus cancer, skin

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Chen, 2007	1560	68	1°/preop/ postop RT± postRT CTx/CCTx	IMRT 3DCRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			13 18	NR	
3DCRT vs 2DRT												
Chen, 2007	1560	104	1°/preop/ postop RT± postRT CTx/CCTx	3DCRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			18 27	NR	
IMRT vs 2DRT												
Chen, 2007	1560	82	1°/preop/ postop RT± postRT CTx/CCTx	IMRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			13 27	NR	

Table D3k. Nasal cavity and paranasal sinus cancer, osteoradionecrosis/bone

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Chen, 2007	1560	68	1°/preop/postop RT± postRT CTx/CCTx	IMRT 3DCRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			9 16	NR	
3DCRT vs 2DRT												
Dirix, 2007	1360	127	1°/preop/postop RT	3DCRT 2DRT	≥93.7 (all)	?	?			0 0		≥ 2 yr
Chen, 2007	1560	104	1°/preop/postop RT± postRT CTx/CCTx	3DCRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			16 15	NR	
IMRT vs 2DRT												
Chen, 2007	1560	82	1°/preop/postop RT± postRT CTx/CCTx	IMRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			9 15	NR	

Table D3l. Nasal cavity and paranasal sinus cancer, tumor control

Local Control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
IMRT vs 3DCRT													
Chen, 2007	1560	68	1°/preop/postop RT ± postRT CTx/CCTx	IMRT 3DCRT	≥87.4 (all)	LC	~85 ~79	~77 ~72	~71 ~66	~65 ~66	65 62	>0.05	
						DFS						0.89	
3DCRT vs 2DRT													
Dirix, 2007	1360	127	1°/preop/postop RT	3DCRT 2DRT	≥93.7 (all)	LC						NS	
Chen, 2007	1560	104	1°/preop/postop RT± postRT CTx/CCTx	3DCRT 2DRT	≥87.4 (all)	LC	~79 ~83	~72 ~62	~66 59	~66 59	62 59	>0.05	
						DFS						0.89	
IMRT vs 2DRT													
Chen, 2007	1560	82	1°/preop/postop RT± postRT CTx/CCTx	IMRT 2DRT	≥87.4 (all)	LC	~85 ~83	~77 ~62	~71 59	~65 59	65 59	>0.05	
						DFS						0.89	

Table D3m. Nasal cavity and paranasal sinus cancer, patient survival

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
IMRT vs 3DCRT													
Chen, 2007	1560	68	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 3DCRT	≥87.4 (all)	OS					47 57	0.60	
3DCRT vs 2DRT													
Dirix, 2007	1360	127	1^{o}/preop/postop RT	3DCRT 2DRT	≥93.7 (all)	OS						NS	
						DSS						NS	
Chen, 2007	1560	104	1^{o}/preop/postop RT± postRT CTx/CCTx	3DCRT 2DRT	≥87.4 (all)	OS					57 51	0.60	
IMRT vs 2DRT													
Chen, 2007	1560	82	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 2DRT	≥87.4 (all)	OS					47 51	0.60	

Table D4a. Unknown primary cancer, outcomes by study

Study	Rec#	No. Pts	Setting	QOL/Adverse Events							Tumor Control			Patient Survival	
				QOL	XST	SF	DYS	MUC	SKN	ORN or BON	LC	LRC	DFS	DSS	OS
Mixed Settings															
3DCRT vs 2DRT															
Beldi, 2007	990	87	1°/postop RT± preRT CTx/CCTx										X		X
IMRT vs 2DRT															
Madani, 2008	37700	41	1°/postop RT ± CTx (timing?)				X	X	X						X
Comparisons	2			0	0	0	1	1	1	0	0	0	1	0	2
Studies	2			0	0	0	1	1	1	0	0	0	1	0	2
Total n	128														

Table D4b. Unknown primary cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
Mixed Settings										
3DCRT vs 2DRT										
Beldi, 2007	990	87	1°/postop RT± preRT CTx/CCTx	3DCRT 2DR	18 (all)	59 (23-88) (all)	100 (all)	45-70 (all)	32	NR
IMRT vs 2DRT										
Madani, 2008	37700	41	1°/postop RT ± CTx (timing?)	IMRT 2DR	26 22	61 (47-85) 58 (38-75)	100 (all)	56-69 66	17 (2-39)	87 100

Table D4c. Unknown primary cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initl Grps Comp	Bal by Design (Mtch)	BL Chars Clr Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Out-comes Val, Rel, =	Assessors Blind	Txs Clr	Adequate F/U	Analysis: Adj for Confs	USPSTF
Mixed Settings																				
3DCRT vs 2DRT																				
Beldi, 2007 2007	990	87	R	Y	Y	?	N	?	N	E	?	NA	NA	NA	Y	N	Y	md 32	Y/N	Poor
IMRT vs 2DRT																				
Madani, 2008	37700	41	R	N	?	N	N	Y	N	E	?	NA	NA	NA	Y	N	Y	md 17	N	Poor

Table D4d. Unknown primary cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Lrg, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Suffici-ently long F/U	Clear cand var select	Clear appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Valid-ation
Mixed Settings															
3DCRT vs 2DRT															
Beldi, 2007 2007	990	N	N	Y	Y	NA	N	Y	md 32	Y	N	?	N	?	N

Table D4e. Unknown primary cancer, quality of life

No studies.

Table D4f. Unknown primary cancer, xerostomia

No studies.

Table D4g. Unknown primary cancer, salivary flow

No studies

Table D4h. Unknown primary cancer, dysphagia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 2DRT												
Madani, 2008	37700	41	1°/postop RT ± CTx (timing?)	IMRT 2DRT	100 100	Acute-RTOG Late-LENT/ SOMA	≤ 2 3	95.5 50 4.5 50	0.003	100 72.3 0 26.7	0.01	

Table D4i. Unknown primary cancer, mucositis

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 2DRT												
Madani, 2008	37700	41	1°/postop RT ± CTx (timing?)	IMRT 2DRT	100 100	RTOG	≤ 2 3	50 41.2 50 58.8	0.82			

Table D4j. Unknown primary cancer, skin

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 2DRT												
Madani, 2008	37700	41	1°/postop RT ± CTx (timing?)	IMRT 2DRT	100 100	Acute-RTOG Late-LENT/ SOMA	≤ 2 3	68.2 33.3 31.7 66.7	0.08	100 73.3 0 26.7	0.03	

Table D4k, Unknown primary cancer, osteoradionecrosis/bone

No studies.

Table D4l. Unknown primary cancer, tumor control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
3DCRT vs 2DRT													
Beldi, 2007 2007	990	87	1°/postop RT± preRT CTx/CCTx	3DCRT 2DRT	100 100	DFS					48.3 15.2	<0.01	RT tech NS in MVA

Table D4m. Unknown primary cancer, patient survival

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
3DCRT vs 2DRT													
Beldi, 2007 2007	990	87	1^{o}/postop RT± preRT CTx/CCTx	3DCRT 2DRT SCC only	100 100	OS					69.1 26.3 69.1 30.8	<0.01 <0.05	RT tech NS in MVA
IMRT vs 2DRT													
Madani, 2008	37700	41	1^{o}/postop RT ± CTx (timing?)	IMRT 2DRT	100 100	OS	74.8 61.1					0.97	

Table D5a. Laryngeal cancer, outcomes by study

				QOL/Adverse Events							Tumor Control			Patient Survival	
Study	Rec#	No. Pts	Setting	QOL	XST	SF	DYS	MUC	SKN	ORN or BON	LC	LRC	DFS	DSS	OS
1° RT															
3DCRT vs 2DRT															
Zouhair, 2004	7400	122	1° RT								X				
Comparisons	1			0	0	0	0	0	0	0	1	0	0	0	0
Studies	1			0	0	0	0	0	0	0	1	0	0	0	0
Total n	122														

Table D5b. Laryngeal cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
1° RT										
3DCRT vs 2DRT										
Zouhair, 2004	7400	122	1° RT	3DCRT 2DR	13 (all)	62 (35-92) (all)	0 (all)	60-74 (all)	85 (12-178)	NR

Table D5c: Laryngeal cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initl Grps Comp	Bal by Design (Mtch)	BL Chars Clr Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Out-comes Val, Rel, =	Assessors Blind	Txs Clr	Adequate F/U	Analysis: Adj for Confs	USPSTF
1° RT																				
3DCRT vs 2DRT																				
Zouhair, 2004	7400	122	R	Y	Y	N	N	?	N	E	Y	NA	NA	NA	Y	N	Y	md 85	Y/?	Poor

Table D5d. Laryngeal cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Lrg, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Suffici-ently long F/U	Clear cand var select	Clear appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Valid-ation
1° RT															
3DCRT vs 2DRT															
Zouhair, 2004	7400	N	N	Y	Y	NA	Y	NA	md 85	N	?	?	?	?	N

Table D5e. Laryngeal cancer, quality of life

No studies.

Table D5f. Laryngeal cancer, xerostomia

No studies.

Table D5g. Laryngeal cancer, salivary flow

No studies.

Table D5h. Laryngeal cancer, dysphagia

No studies.

Table D5i: Laryngeal cancer, mucositis

No studies.

Table D5j: Laryngeal cancer, skin

No studies.

Table D5k: Laryngeal cancer, osteoradionecrosis/bone

No studies.

Table D5l. Laryngeal cancer, tumor control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
1^{o} RT													
3DCRT vs 2DRT													
Zouhair, 2004	7400	122	1 setting: 1^{o} RT	3DCRT 2DRT	0 (all)	LC					86 81	0.55	RT tech NS in MVA

Table D5m. Laryngeal cancer, patient survival

No studies.

Table D6a. Mixed head and neck cancer, outcomes by study

Study	Rec#	No. Pts	Setting	QOL/Adverse Events							Tumor Control			Patient Survival	
				QOL	XST	SF	DYS	MUC	SKN	ORN or BON	LC	LRC	DFS	DSS	OS
1° RT															
IMRT vs 3DCRT															
Golen, 2007	14200	40	1° RT		X										
Mixed Settings															
IMRT vs 3DCRT															
Marchal, 2004	5580	87	1°/postop/repeat RT ± pre/post RT CTx/CCTx		X								X		X
Chao, 2001	10470	41	1°/postop RT ± postRT CTx/CCTx			X									
Gomez, 2008	13390	32	1°/postop RT± CTx (timing?)										X		X
Palazzi, 2008	13850	116	1°/postop RT ± CCTx/CCTx + preRT CTx		X		X	X	X						
Langendijk, 2009	39950	529	1°/postop RT± CTx (timing?)				X								
Vergeer, 2008	38540	141	1°/postop RT ± CCTx	X	X			X	X						
3DCRT vs 2DRT															
Kuhnt , 2005	4840	33	1°/postop RT			X									
Rades, 2008	13180	345	1°/postop RT± CCTx		X			X	X			X			X
Gomez, 2008	13390	42	1°/postop RT± CTx (timing?)										X		X
Palazzi, 2008	13850	137	1°/postop RT ± CCTx/CCTx + preRT CTx		X		X	X	X						
IMRT vs 2DRT															
Sanguineti, 2007	1740	66	1° RT ± CTx (timing?)												
Daly, 2007	2470	69	1°/postop RT ± CCTx/CTx (timing?)		X										
Jabbari, 2005	4480	106	1°/postop RT ± CTx (timing?)	X	X										
Pacholke, 2005	4830	210	1°/postop RT ± CTx (timing?)		X										
Kent, 2008	13300	40	1°/postop RT ± CTx (timing?)												
Gomez, 2008	13390	44	1°/postop RT± CTx (timing?)										X		X
Palazzi, 2008	13850	45	1°/postop RT ± CCTx/CCTx + preRT CTx		X		X	X	X						
van Rij, 2008	38520	162	1°/postop RT ± CCTx		X										
Caudell, 2009	39420	122	1° RT ± preRT CTX and/or CCTx				X								
Murphy, 2009	40430	75	1°/postop RT± CTx (timing?)					X							
Comparisons	**21**			**2**	**11**	**2**	**5**	**6**	**5**	**0**	**0**	**1**	**4**	**0**	**5**
Studies	**17**			**2**	**9**	**2**	**3**	**4**	**3**	**0**	**0**	**1**	**2**	**0**	**3**
Total n	**2274**														

Table D6b. Mixed head and neck cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
1° RT										
IMRT vs 3DCRT										
Golen, 2007	14200	40	1 setting: 1° RT	IMRT 3DCRT	28 (all)	NR	40 (all)	62-72 (all)	NR	NR
Mixed Settings										
IMRT vs 3DCRT										
Marchal, 2004	5580	87	1°/postop/repeat RT ± pre/post RT CTx/CCTx	IMRT 3DCRT			≥19.5 ≥21.7			
Chao, 2001	10470	41	1°/postop RT ± postRT CTx/CCTx	IMRT 3DCRT	29 (all)	58 (36-75) (all)	82.9 (all)	50-70 (all)	NR	100 (all)
Gomez, 2008	13390	32	1°/postop RT± CTx (timing?)	IMRT 3DCRT	59 (all)	52 (15-85) (all)	≥47.4 (all)	52-70 (all)	71 (6-180)	100 (all)
Palazzi, 2008	13850	116	1°/postop RT ± CCTx/CCTx + preRT CTx	IMRT 3DCRT	22 (all)	57 (27-94) (all)	87 (all)	60-70 (all)	NR	NR
Vergeer, 2008	38540	141	1°/postop RT ± CCTx	IMRT 3DCRT	44 31	NR	77 62	54-70 46-70	NR	NR
Langendijk, 2009	39950	529	1°/postop RT± CTx (timing?)	IMRT 3DCRT	25 (all)	60 (all)		70 (all)	≥ 6 mo	NR
3DCRT vs 2DRT										
Kuhnt , 2005	4840	33	1°/postop RT	3DCRT 2DR	23 20	56 (44-68) 60 (41-74)	NR	?	?	?
Rades, 2008	13180	345	1°/postop RT± CCTx	3DCRT 2DR	25 29	NR	100 (All)	60-72 60-70	NR	NR
Gomez, 2008	13390	42	1°/postop RT± CTx (timing?)	3DCRT 2DR	59 (all)	52 (15-85) (all)	≥47.4 (all)	52-70 (all)	71 (6-180)	100 (all)
Palazzi, 2008	13850	137	1°/postop RT ± CCTx/CCTx + preRT CTx	3DCRT 2DR	22 (all)	57 (27-94) (all)	87 (all)	60-70 (all)	NR	NR

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
IMRT vs 2DRT										
Sanguineti, 2007	1740	66	1^{o} RT ± CTx (timing?)	IMRT 2DR	18 (all)	54 (35-85) (all)	≥75.8 (all)	60-78 60-72	17 (0.4-50)	NR
Daly, 2007	2470	69	1^{o}/postop RT ± CCTx/CTx (timing?)	IMRT 2DR	10 13	58 (39-73) 58 (35-80)	96.6 96	66 NR	25 (10-60)	NR
Jabbari, 2005	4480	106	1^{o}/postop RT ± CTx (timing?)	IMRT 2DR	23 30	53 (29-85) 53 (28-81)	100 (all)	60-78 63-77	NR	NR
Pacholke, 2005	4830	210	1^{o}/postop RT ± CTx (timing?)	IMRT 2DR	NR	NR	NR	> 50 (all)	NR	NR
Kent, 2008	13300	40	1^{o}/postop RT ± CTx (timing?)	IMRT 2DR	NR	NR	NR	NR	NR	100 (all)
Gomez, 2008	13390	44	1^{o}/postop RT± CTx (timing?)	IMRT 2DR	59 (all)	52 (15-85) (all)	≥47.4 (all)	52-70 (all)	71 (6-180)	100 (all)
Palazzi, 2008	13850	45	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	IMRT 2DR	22 (all)	57 (27-94) (all)	87 (all)	60-70 (all)	NR	NR
van Rij, 2008	38520	162	1^{o}/postop RT ± CCTx	IMRT 2DR	28 36	59 (all)	100 (all)	≥ 60 (all)	NR	NR
Caudell, 2009	39420	122	1^{o} RT ± preRT CTX and/or CCTx	IMRT 2DR	24 (all)	55 (18-83) (all)	100 (all)	65-79 (all)	32 (12-73)	NR
Murphy, 2009	40430	75	1^{o}/postop RT± CTx (timing?)	IMRT 2DR	19 (all)	mn 59 (40-86) (all)	84 (all)	NR	1.4	

Table D6c. Mixed head and neck cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initl Grps Comp	Bal by Design (Mtch)	BL Chars Clr Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Out-comes Val, Rel, =	Assessors Blind	Txs Clr	Adequate F/U	Analysis: Adj for Confs	USPSTF
1° RT																				
IMRT vs 3DCRT																				
Golen, 2007	14200	40	R	N	?	?	N	?	Y	R	Y	NA	NA	NA	Y	N	Y	?	N	Poor
Mixed Settings																				
IMRT vs 3DCRT																				
Marchal, 2004	5580	87	P	N	?	?	N	?	Y	?	?	?	?	?	Y	?	N	?	N	Poor
Chao, 2001	10470	41	P	N	?	?	N	?	Y	?	?	Y	Y	Y	Y	?	Y	?	Y/?	Poor
Gomez, 2008	13390	32	R	Y	Y	?	N	?	N	?	?	NA	NA	NA	Y	N	Y	md 71	Y/?	Poor
Palazzi, 2008	13850	116	P	Y	?	?	N	?	N	E	?	?	?	?	Y	?	Y	?	Y/?	Poor
Vergeer, 2008	38540	141	P	Y	Y	N	N	N	N	E	N	NA	?	?	Y	?	Y	?	Y/?	Poor
Langendijk, 2009	39950	529	P	Y	N	?	N	?	?	?	?	?	?	?	Y	?	Y	6	Y/N	Poor
3DCRT vs 2DRT																				
Kuhnt , 2005	4840	33	P	Y	Y	?	N	?	Y	?	?	?	Y	Y	Y	?	Y	?	N	Poor
Rades, 2008	13180	345	R	Y	Y	Y	N	Y	Y	?	Y	NA	NA	NA	Y	N	Y	?	Y/N	Poor
Gomez, 2008	13390	42	R	Y	Y	?	N	?	N	?	?	NA	NA	NA	Y	N	Y	md 71	Y/?	Poor
Palazzi, 2008	13850	137	P	Y	?	?	N	?	N	E	?	?	?	?	Y	?	Y	?	Y/?	Poor
IMRT vs 2DRT																				
Sanguineti, 2007	1740	66	R	Y	N	?	N	?	?	?	?	NA	NA	NA	Y	N	Y	md 17	Y/N	Poor
Daly, 2007	2470	69	R	N	?	Y	N	Y	?	?	Y	NA	NA	NA	Y	N	Y	md 25	N	Poor
Jabbari, 2005	4480	106	P	N	?	?	Y	Y	Y	Risk	Y	N	N	?	Y	?	N	?	N	Poor
Pacholke, 2005	4830	210	R	Y	Y	?	N	?	?	?	?	NA	NA	NA	Y	N	N	?	Y/?	Poor
Kent, 2008	13300	40	R	Y	N	?	N	?	?	?	?	NA	NA	NA	Y	N	N	?	N	Poor
Gomez, 2008	13390	44	R	Y	Y	?	N	?	N	?	?	NA	NA	NA	Y	N	Y	md 71	Y/?	Poor
Palazzi, 2008	13850	45	P	Y	?	?	N	?	N	E	?	?	?	?	Y	?	Y	?	Y/?	Poor
van Rij, 2008	38520	162	R	Y	Y	?	N	N	N	?	N	NA	NA	NA	Y	N	N	md 31	Y/?	Poor
Caudell, 2009	39420	122	R	Y	Y	?	N	?	?	?	?	NA	NA	NA	Y	N	Y	md 32	Y/N	Poor
Murphy, 2009	40430	75	P	Y	Y	?	N	?	Y	?	?	?	?	?	Y	?	N	1.4	N	Poor

Table D6d. Mixed head and neck cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Lrg, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Suffici-ently long F/U	Clear cand var select	Clear appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Valid-ation
Mixed Settings															
IMRT vs 3DCRT															
Gomez, 2008	13390	N	N	Y	Y	NA	N	NA	md 71	Y	?	?	?	?	N
Palazzi, 2008	13850	Y	N	Y	Y	NA	N	N	?	N	?	?	?	?	N
Vergeer, 2008	38540	Y	N	Y	Y	NA	N	?	?	N	?	?	?	?	N
3DCRT vs 2DRT															
Rades, 2008	13180	N	N	Y	Y	NA	N	NA	?	N	N	?	N	?	N
Gomez, 2008	13390	N	N	N	Y	NA	N	NA	md 71	Y	?	?	?	?	N
Palazzi, 2008	13850	Y	N	Y	Y	NA	N	N	?	N	?	?	?	?	N
IMRT vs 2DRT															
Sanguineti, 2007	1740	N	N	N	Y	NA	N	NA	md 17	N	N	?	N	?	N
Pacholke, 2005	4830	N	N	N	Y	NA	?	NA	?	N	?	?	?	?	N
Gomez, 2008	13390	N	N	N	Y	NA	N	NA	md 71	Y	?	?	?	?	N
Palazzi, 2008	13850	Y	N	Y	Y	NA	N	N	?	N	?	?	?	?	N
van Rij, 2008	38520	N	N	Y	Y	NA	N	NA	?	N	?	?	?	?	N
Caudell, 2009	39420	N	N	Y	Y	NA	N	NA	md 32	N	N	?	N	?	N

Table D6e. Mixed head and neck cancer, quality of life: head and neck cancer-related quality of life (HNQOL)

EORTC QLQ-C30

	Vergeer, 2008, Rec # 38540			
Item	**Mean IMRT n=91**	**Mean 3DCRT n=150**	**Mo F/U**	**p Value Linear-l Quadratic-q**
Global health	76.0 79.2	64.9 65.6	1.5 6 all	 <0.004-l
Physical function	77.4 80.7	73.3 74.4	1.5 6 all	
Role function	81.5 82.1	65.6 70.8	1.5 6 all	 0.042-l
Emotional function	78.2 85.3	73.5 73.2	1.5 6 all	
Cognitive function	87.8 93.6	83.9 84.6	1.5 6 all	 0.033-l
Social function	82.7 92.0	76.1 76.5	1.5 6 all	 <0.001-l
Fatigue	30.9 24.2	40.5 40.4	1.5 6 all	 0.026-l
Nausea/ vomiting	12.8 6.4	13.6 8.4	1.5 6 all	
Pain	14.1 19.2	25.2 23.3	1.5 6 all	 0.042-q
Dyspnea	11.9 10.7	19.1 22.4	1.5 6 all	
Insomnia	27.4 16.7	26.3 30.1	1.5 6 all	 0.021-l
Appetite loss	19.8 12.3	32.5 24.2	1.5 6 all	 0.018-l
Constipation	10.7 10.7	17.1 12.1	1.5 6 all	
Diarrhea	11.5 2.6	7.8 8.5	1.5 6 all	
Financial difficulties	16.7 15.4	12.6 14.8	1.5 6 all	

EORTC QLQ-H&N35

	Vergeer, 2008, Rec # 38540			
Item	**Mean IMRT n=91**	**Mean 3DCRT n=150**	**Mo F/U**	**p Value Linear-l Quadratic-q**
Pain	19.9 18.9	33.0 28.3	1.5 6 all	 0.030-l 0.046-q
Swallowing	35.5 21.1	36.1 33.7	1.5 6 all	 0.042-l
Taste/smell	32.7 16.7	34.0 26.8	1.5 6 all	
Speech	23.0 19.8	31.2 29.9	1.5 6 all	
Social eating	23.0 15.9	35.7 30.9	1.5 6 all	 0.011-l
Sexuality	30.7 13.3	45.5 38.1	1.5 6 all	 0.003-l
Teeth	4.3 7.2	19.6 24.3	1.5 6 all	 0.015-l
Opening mouth	8.6 17.3	27.1 30.2	1.5 6 all	 0.026-q
Dry mouth	43.2 48.1	62.2 68.6	1.5 6 all	 <0.001-l
Sticky saliva	41.3 32.0	61.3 56.9	1.5 6 all	 0.001-l
Coughing	35.8 27.2	33.3 35.4	1.5 6 all	
Feeling ill	21.0 6.2	1.1 19.1	1.5 6 all	 0.011-l

	Jabbari, 2005, Rec # 4480						
Domain	**Median IMRT n=30**	**IMRT Trend for Improvement p Value**	**Median 2DRT n=10**	**2DRT Trend for Improvement p Value**	**F/U**	**Difference Adjusted for Baseline**	**p Value**
Total	~31 ~31 ~20 17 ~13 ~7	 0.04	~31 ~32 ~58 68 ~4 ~47	 0.97	1 3 6 12 18 24 all	 19.2	 NS
Communication		0.11		0.56	all		
Eating		0.07		0.78	all		
Emotion		0.04		0.11	all		
Pain		0.05		0.38	all		

Table D6f. Mixed head and neck cancer, xerostomia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Marchal, 2004	5580	87	1°/postop/repeat RT ± pre/post RT CTx/CCTx	IMRT 3DCRT	≥21.7 ≥19.5	RTOG	≥ 2 ≥ 3	23 24		42 50 7 18	0.06	
Palazzi, 2008	13850	116	1°/postop RT ± CCTx/CCTx + preRT CTx	IMRT 3DCRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Vergeer, 2008	38540	141	1°/postop RT ± CCTx	IMRT 3DCRT	77 62	RTOG ? mn QLQ-H&N35 XST item RTOG	2 12 wk 6 mo mod-sev ≥ 2 6 mo	~25 ~42	0.014	 41 67 32 56	 <0.001 <0.01 0.002	p<0.02 at 3, 4, 5 wk; NS at 0, 1, 2, 6, 7, 8 wk; 6 mo MV ORa (95% CI): 0.27 (0.13, 0.54); IMRT<3DCRT at end RT, 6 wk, 6mo, 12 mo MV ORa (95% CI): 0.24 (0.12, 0.51)
3DCRT vs 2DRT												
Rades, 2008	13180	345	1°/postop RT± CCTx	3DCRT 2DRT	100 100	RTOG	2-3			43 58	0.06	
Palazzi, 2008	13850	137	1°/postop RT ± CCTx/CCTx + preRT CTx	3DCRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
IMRT vs 2DRT												
Palazzi, 2008	13850	45	1°/postop RT ± CCTx/CCTx + preRT CTx	IMRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Scale	Item	Mean	F/U	p value	Comments
1° RT											
IMRT vs 3DCRT											
Golen, 2007	14200	40	1 setting: 1° RT	IMRT 3DCRT	40 (all)	CTC SOMA-LENT	Mean grade by group	~2.75 ~2.4 ~2.4 ~2.6 ~2.25 ~2.5 ~2.25 ~2.25 ~2.25 ~2.2 ~2.5 ~2.0 ~5.0 ~5.4 ~4.3 ~5.2 ~4.3 ~5.0 ~3.9 ~4.8 ~3.6 ~3.8 ~2.5 ~4.1	3 mo 6 mo 12 mo 18 mo 24 mo 30 mo 3 mo 6 mo 12 mo 18 mo 24 mo 30 mo	NR NR	
Mixed Settings											
IMRT vs 2DRT											

Daly, 2007	2470	69	1°/postop RT ± CCTx/CTx (timing?)	IMRT 2DRT	96.6 96.0	XQ	Talking difficult Chewing difficult Swallow difficult Sleeping problems Dry w/ eating Dry w/o eating Freq sipping w/ eat Freq sipping w/o eat Total	3.0 4.8 3.9 5.3 5.2 6.0 3.0 2.8 4.7 6.0 3.8 5.0 5.5 7.8 3.8 5.9 33.0 43.7	> 6 mo	0.003 0.03 0.16 0.76 0.02 0.03 0.002 0.0006 0.006	
Jabbari, 2005	4480	106	1°/postop RT ± CTx (timing?)	IMRT 2DRT	100 100	XQ	Total	~3 ~7 ~39 ~58 ~53 ~68 ~43 ~58 32 67 ~35 ~23 ~28 ~88	Pre 1 mo 3 mo 6 mo 12 mo 18 mo 24 mo	0.7	at 12 mo, adjusting for baseline, IMRT-2DRT difference NS (p=0.2)
Pacholke, 2005	4830	210	1°/postop RT ± CTx (timing?)	IMRT IMRT>26Gy IMRT≤26Gy 2DRTbilat-tot 2DRTbilat-par		XQ	Total above or below median	36 50 34 64 53	> 1 yr		RT tech p<0.001 on MVA

van Rij, 2008	38520	162	1°/postop RT ± CCTx	IMRT 2DRT	100 100	Blend of EORTC H&N35 & XQ XST in rest XST during meals	Mean in rest	7.6 10.3	med 2.6 yrs	UVA	MVA p value
							↓/much ↓ saliva	78 85		0.07	0.008
							↓/much ↓ Δ saliva	22 27		1.0	0.7
							F/A dry not eating	36 61		0.004	0.001
							F/A probs gumbs	13 13		0.3	0.2
							F/A probs speaking	29 57		<0.0001	<0.0001
							F/A drink H_2O day	55 79		0.001	0.001
							F/A trouble sleeping	20 25		0.5	0.2
							F/A drink H_2O night	28 47		0.05	0.03
							Mean during meals	7.2 11.5			
							F/A probs solid food	29 62		<0.001	<0.001
							F/A probs grnd food	14 34		<0.001	0.001
							F/A swallow solid	30 61		<0.001	<0.001
							F/A swallow grnd	19 36		0.007	0.02
							F/A dry meals	25 55		<0.001	<0.001
							F/A H_2O to swallow	38 71		<0.001	<0.001
							F/A eat w/ others	19 34		0.006	0.02
							Grnd/liquid diet	9 22		0.03	0.3
							Swallow more freq	34 21		0.2	0.2

Table D6g. Mixed head and neck cancer, salivary flow

Study	Rec#	No. Pts	Setting	Group	% Stage 0/I/II	% Stage III/IV	Mos Post-RT	Stimulated Flow Ratio % of Baseline	Unstimulated Flow Ratio % of Baseline	Comments
Mixed Settings										
IMRT vs 3DCRT										
Chao, 2001	10470	41	1°/postop RT ± postRT CTx/CCTx	IMRT post op IMRT definitive 3DCRT post op 3DCRT definitive	14.6 (all)	82.9 (all)	6	0.70±.35 0.61±.30 0.38±.28 0.67±.25	0.50±.40 0.39±.21 0.22±.20 0.38±.10	UWS: After swallowing let saliva drip into cup for 5 min. SWS: Chewed on paraffin strip for 2 min, then collected saliva for 5 min in cup while still chewing. RT technique did not independently influence stimulated whole salivary flow.
3DCRT vs 2DRT										
Kuhnt , 2005	4840	33	1°/postop RT	3DCRT 2DRT 3DCRT 2DRT 3DCRT 2DRT 3DCRT 2DRT 3DCRT 2DRT			0.7 1.4 2.3 6 12	~0.69 ~0.55 ~0.42 ~0.19 ~0.43 ~0.19 ~0.64 ~0.21 ~0.50 ~0.25		P<0.1 for difference between treatment groups in salivary flow rate at 10 wks.

Table D6h. Mixed head and neck cancer, dysphagia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Palazzi, 2008	13850	116	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	IMRT 3DCRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Langendijk, 2009	39950	529	1^{o}/postop RT± CTx (timing?)	IMRT 3DCRT		RTOG	2-4			31.5 19.5	0.043	
3DCRT vs 2DRT												
Palazzi, 2008	13850	137	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	3DCRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
IMRT vs 2DRT												
Palazzi, 2008	13850	45	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	IMRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Caudell, 2009	39420	122	1^{o} RT ± preRT CTX and/or CCTx	IMRT 2DRT	100 100	Long-term PEG dependence/ aspiration pneumonia/ pharyngeal-esophogeal stricture/ stenosis	any (com-posite)			38.3 38.7	0.97	RT tech NS in MVA (p=0.68)

Table D6i. Mixed head and neck cancer, mucositis

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Palazzi, 2008	13850	116	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	IMRT 3DCRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Vergeer, 2008	38540	141	1^{o}/postop RT ± CCTx	IMRT 3DCRT	77 62	RTOG	$\geq$ 3 12 wk	~0 ~4	NS			p<0.05 at 3, 4, 5, 6, 7 wk; NS at 0, 1, 2, 8 wk
3DCRT vs 2DRT												
Rades, 2008	13180	345	1^{o}/postop RT± CCTx	3DCRT 2DRT	100 100	CTC	2-3	~87 ~92	NR			
Palazzi, 2008	13850	137	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	3DCRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
IMRT vs 2DRT												
Palazzi, 2008	13850	45	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	IMRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Murphy, 2009	40430	75	1^{o}/postop RT± CTx (timing?)	IMRT 2DRT	84 (all)	MTS	> mod	58 83	0.175			

Table D6j. Mixed head and neck cancer, skin

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Palazzi, 2008	13850	116	1°/postop RT ± CCTx/ CCTx + preRT CTx	IMRT 3DCRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Vergeer, 2008	38540	141	1°/postop RT ± CCTx	IMRT 3DCRT	77 62	RTOG	2 7 wk	86 74	0.03			
3DCRT vs 2DRT												
Rades, 2008	13180	345	1°/postop RT± CCTx	3DCRT 2DRT	100 100	Acute-CTC; Late-RTOG	2-3	~84 ~88	NR	~19 ~19	NR	
Palazzi, 2008	13850	137	1°/postop RT ± CCTx/ CCTx + preRT CTx	3DCRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
IMRT vs 2DRT												
Palazzi, 2008	13850	45	1°/postop RT ± CCTx/ CCTx + preRT CTx	IMRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute

Table D6k. Mixed head and neck cancer, oteoradionecrosis/bone

No studies.

Table D6l. Mixed head and neck cancer, tumor control

Local Control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
IMRT vs 3DCRT													
Marchal, 2004	5580	87	1^{o}/postop/repeat RT ± pre/post RT CTx/CCTx	IMRT 3DCRT	≥21.7 ≥19.5	DFS	88 85					NS	
Gomez, 2008	13390	32	1^{o}/postop RT± CTx (timing?)	IMRT 3DCRT	≥47.4 (all)	DFS						NS	RT tech not entered in MVA
3DCRT vs 2DRT													
Rades, 2008	13180	345	1^{o}/postop RT± CCTx	3DCRT 2DRT	100 100	LRC	76 82	71 72	68 65			0.71	
Gomez, 2008	13390	42	1^{o}/postop RT± CTx (timing?)	3DCRT 2DRT	≥47.4 (all)	DFS						NS	RT tech not entered in MVA
IMRT vs 2DRT													
Gomez, 2008	13390	44	1^{o}/postop RT± CTx (timing?)	IMRT 2DRT	≥47.4 (all)	DFS						NS	RT tech not entered in MVA

Table D6m.: Mixed head and neck cancer, patient survival

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
IMRT vs 3DCRT													
Marchal, 2004	5580	87	1°/postop/repeat RT ± pre/post RT CTx/CCTx	IMRT 3DCRT	≥21.7 ≥19.5	OS	90 87					NS	
Gomez, 2008	13390	42	1°/postop RT± CTx (timing?)	IMRT 3DCRT	≥47.4 (all)	OS						NS	RT tech not entered in MVA
3DCRT vs 2DRT													
Rades, 2008	13180	345	1°/postop RT± CCTx	3DCRT 2DRT	100 100	OS	75 84	62 66	57 62			0.15	
Gomez, 2008	13390	32	1°/postop RT± CTx (timing?)	3DCRT 2DRT	≥47.4 (all)	OS						NS	RT tech not entered in MVA
IMRT vs 2DRT													
Gomez, 2008	13390	44	1°/postop RT± CTx (timing?)	IMRT 2DRT	≥47.4 (all)	OS						NS	RT tech not entered in MVA

Appendix E: Single-Arm Studies

Questions 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-A. Design, participant selection and enrollment

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
560, Biagioli et al., 2007	Retrospective	Histologically proven locoregionally recurrent or second primary HNC with no distant metastases (01/2001-11/2006)	Definitive or salvage IMRT plus CTx Cisplatin or carboplatin with or w/out docetaxel or 5-FU, induction or concurrent	62	41 Ctx 54 21 excluded (n = 4 treated 2x daily; n = 2 no records available; n = 15 treated w/non-IMRT method)	1 Died during tx 7 did not complete prescribed RT course
580, Dirix et al., 2007	Prospective	Histologically proven AJCC stage T2-T4 primary sinonasal malignancy (01/2003-03/2007)	Adjuvant IMRT	43	25 18 excluded for recurrence (n = 3); melanoma or sarcoma (n = 7); too short F/U (n = 8)	0
1010, Urbano et al., 2007	Prospective dose-escalation	Histologically proven locally advanced stage T2-4, N1-3, M0 laryngeal or hypopharyngeal SCC (02/2002)	Definitive IMRT plus CTx Neoadjuvant cisplatin and 5-FU plus concurrent cisplatin during IMRT	30 (15 per dose cohort)	30 Neoadjuvant CTx 15 DL1 13 DL2 Concurrent CTx 15 DL1 14 DL2	0
1420, Feng et al, 2007	Prospective	Stage III/IV oropharyngeal or nasopharyngeal cancer	Definitive IMRT plus CTx Concurrent carboplatin and taxane (oropharynx) or cisplatin (nasopharynx)	36	36 CTx 36	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
1430, Scrimger et al., 2007	Prospective	Histologically proven AJCC stage I-IV SCC at various head and sites (07/2000-12/2004)	Definitive or adjuvant IMRT with or w/out concurrent CTx Usually platinum-based CTx	64	47 CTx 12	17 incomplete salivary flow data or lost to F/U
1500, Lee et al., 2007	Retrospective	Histologically proven AJCC stage III-IV laryngeal and hypopharyngeal SCC (01/2002-06/2005)	Definitive IMRT plus CTx Concurrent cisplatin alone, carboplatin plus 5-FU, or carboplatin plus paclitaxel	37	31 CTx 37	6 2 had early-stage disease 3 had postoperative IMRT 1 refused CTx
1770, Yao et al., 2007 (see 4630, Yao et al., 2005)	Retrospective	Histologically proven AJCC stage T0-4, N2-3 SCC at various head and neck sites (12/1999-07/2005)	Definitive IMRT alone or plus CTx Concurrent or induction cisplatin Neck dissection in 13 pts	100	90 CTx 74	10 4 with NPH carcinoma 5 with pre-RT neck dissection, 1 lost to F/U
1780, Lee et al., 2007	Retrospective	Histologically proven recurrent cancer of the head and neck (07/1996-09/2005)	Definitive or adjuvant IMRT with or w/out CTx Induction, concurrent, or adjuvant mostly platinum-based regimens	155	105 CTx 45	5 did not complete prescribed RT 6 lost to F/U

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
1900, Ben-David et al., 2007	Retrospective	Histologically proven AJCC stage I-IVB or recurrent head and neck cancer at various sites (03/1996-03/2005)	Definitive or adjuvant IMRT, with or w/out CTx Concurrent cisplatin, carboplatin or carboplatin plus paclitaxel	188	176 CTx 108	12 5 lost to F/U at < 6 mos 2 died of pneumonia or trauma 2 died of lung metastases 3 did not complete RT course
1990, Yao et al., 2007	Retrospective	Histologically proven AJCC stage I-IV SCC of the oral cavity (05/2001-07/2005)	Definitive or adjuvant IMRT, with or w/out CTx Concurrent, adjuvant, or neoadjuvant cisplatin	55 CTx 6	55	0
2180, Daly et al., 2007	Retrospective	Histologically proven AJCC stage Tis-T4 malignancies of the nasal cavity and paranasal sinuses (04/1998-12/2004)	Definitive or adjuvant IMRT, with or w/out CTx CTx not described	45 CTx 8	36	9 3 excluded received boost IMRT after CRT 3 treated for recurrent disease 3 had inadequate F/U
2290, Yao et al., 2006	Retrospective	Histologically proven AJCC stage I-IV oropharyngeal SCC (01/2000-07/2004)	Definitive or adjuvant IMRT, with or w/out CTx Cisplatin alone or with 5-FU	69	66 Ctx 46	3 2 presented with metastatic disease 1 lost to F/U after 6 mos. of tx

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
2370, Garden et al., 2007	Retrospective	Histologically proven AJCC stage T1-x primary SCC of the oropharynx (10/2000-06/2002)	Definitive or adjuvant IMRT, with or w/out CTx CTx not described	54	51 CTx 5	3 1 received IMRT to boost field only 1 received boost with CRT 1 switched from IMRT to CRT
2430, Vosmik et al., 2006	Prospective	Histologically proven stage I-IV (staging system not identified) carcinoma of the head and neck region with regional nodal involvement (12/2003-09/2005)	Definitive or adjuvant IMRT, with or w/out concurrent CTx Cisplatin	41	38 CTx 5	3 RT terminated early due to toxicity and inability to continue
2770, Cheng et al., 2006	Prospective	Histologically proven AJCC stage T1-4, N0-3b, M0 primary NPC with regional nodal involvement (04/1990-12/2002)	Definitive 3DCRT with or w/out CTx Concurrent cisplatin plus 5-FU	719 CTX 586	630	89 48 presented with metastatic disease 9 did not receive full RT dose 32 had no MRI data for F/U analysis
3080, Meirovitz 2006	Prospective cross-sectional	Pts with H & N cancer txd with IMRT at a single institution (11/2001-10/2003)	IMRT Adjuvant or definitive Concurrent CTx	38 Definitive 20 (15 also rec'd concurrent CT) Post op RT 18 (1 rec'd concurrent CT)	38	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
3220, Portaluri et al., 2006	Prospective	Histologically proven locally advanced AJCC staged, previously untreated SCC of the head and neck (2001-2003)	Definitive or adjuvant 3DCRT with or w/out CTx Cisplatin alone or plus 5-FU	49	49 CTx 13	0
3340, Studer 2006	CS with historical controls (3DCRT)	Consecutive patients with HYP cancer (01/2002-07/2005)	SIB IMRT Adjuvant or definitive Concurrent CTx	29 definitive 25 adjuvant 4 CTx cisplatin-based 25	29	0
3400, Studer 2006	CS with historic controls (IMRT v 3DCRT)	OPH or oral cancer	IMRT with simultaneously integrated boost (SIB) Adjuvant or definitive Concurrent CTx	123 21 adjuvant 52 definitive CTx cisplatin-based 56	73 73 considered “at risk” for ORN (defined as receiving >60Gy for primary OPH or oral cancer) OPH (n=55) Oral cancer (n=18)	0
3570, Saarilahti 2006	Cohort	Cohort with stage 2 or higher primary squamous ca H & N and at least one parotid gland spared from PTV. (07/2000-04/2004)	IMRT Adjuvant or definitive Concurrent CTx	36 Definitive 16 Adjuvant 20 CTx 16	36 (evaluated as whether or not the contralateral submandibular gland was spared [n=18] or not [n=18]).	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
3790, Ozsahin et al., 2006	Retrospective	Histologically proven IUAC locally advanced cancer of the head and neck with regional nodal involvement (11/2000-01/2003)	Definitive or adjuvant 3DCRT with or w/out CTx Concurrent cisplatin plus 5-FU	33	33 CTx 26	0
3820, McMillan 2006	Prospective, longitudinal	Histologically confirmed NPC Stage 1 and 2	IMRT with parotid sparing	32	32	0
4290, Lau et al., 2006	Retrospective	Histologically proven AJCC stage I-IV primary, non-nasopharyngeal SCC of the head and neck (09/2000-12/2002)	Definitive or adjuvant 3DCRT with or w/out CTx Concurrent cisplatin	57	56 CTX 57	1 Died with MI 1 wk after CRT
4430, Kwong 2006	CS	Histologically proven NPC, locally advanced (skull base involvement or intracranial extension by CT scan). No evidence distant mets. (09/2000-06/2004)	IMRT with dose escalation. Concurrent, adjuvant or induction CTx	50 CTx cisplatin plus 5-FU 34	50	0
4630, Yao	CS	H & N squamous ca txd at one institution (U of Iowa) (10/1999-04/2004).	IMRT Concurrent or induction CTx	151 Definitive n=99 Post op n=51 Concurrent or induction cisplatin-based CTx 68	150	1 (lost to f/u p 2 mos.)

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
5020, Nishimura et al., 2005	Retrospective cohort study assessing Xerostomia incidence after IMRT w/ boost	33 patients with pharyngeal cancer (32 SCC, 1 Non-Hodgkin lymphoma) treated w/ whole neck IMRT Stage II, III, IV	Definitive , Postoperative RT Definitive RT, Postop RT 45, 55 Concurrent Chemotherapy: Cisplatin, Docetaxel, None 30, 39, 30	33	33	0
5120, Wolden et al., 2006	Retrospective 2-arm 3DCRT vs. IMRT	Histologically proven stage I-IV NPC (AJCC) T1-T4/N0-N3, without prior treatment or distant metastasis (07/1998-11/2004)	Definitive RT	109	109 (3DCRT: 35, IMRT: 74)	6 1 refusal T3N0 5 not receiving chemotherapy due to stage I
5210, Duthoy et al., 2005	Prospective cohort comparing postoperative IMRT to historic 3DCRT control	Patients treated w/ postoperative IMRT for adenocarcinoma or SCC of the paranasal sinuses or nasal cavity. T2, T3, T4a, T4b	Postoperative RT	39	39	2
5310, Zheng et al., 2005	Prospective	Histologically proven locally recurrent AJCC T1-4, N0-2 NPC (07/1997-03/2003)	Salvage 3DCRT with or w/out CTx	86	86 CTx 46	0
5330, Lu et al., 2005	Prospective	Histologically proven AJCC stage II nasopharyngeal squamous cell carcinoma (SCC) (08/2001-02/2003)	Definitive 3DCRT	25	24	1 Declined to participate due to inconvenience
5420, Pan et al., 2005	Prospective	Histologically proven stage I-IV head and neck cancer at various sites	Definitive or adjuvant 3DCRT with or w/out CTx Concurrent cisplatin	40	35 CTx 4	5 Did not participate in hearing tests

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
5740, Thorstad et al., 2004	Prospective	Histologically proven AJCC staged, previously untreated SCC of the head and neck	Adjuvant IMRT	27	25	2 Discontinued treatment
6430, Kwong et al, 2004	Prospective cohort of	Newly diagnosed NPC treated w/ IMRT T1, N0-N1, M0	Definitive RT	30	30	0
7090, Chao et al., 2004	Retrospective cohort	TIV, TII, TII, TI SCC of oropharynx were treated w/ IMRT	Definitive and postoperative RT	74	74	0
7110, Sze et al., 2004	Retrospective	Histologically proven AJCC T1-T4 NPC (11/1998-06/2001)	Definitive 3DCRT with or w/out CTx Concurrent cisplatin Induction cisplatin plus 5-FU	308	308 CTx 128	1 Discontinued treatment
7370, Lu et al., 2004	Prospective	Histologically or clinically diagnosed 1992 Fuzhou, China staging system I-IV locoregional recurrent NPC (01/2001-02/2002)	Definitive IMRT with or w/out adjuvant CTx Cisplatin plus 5-FU	49	49 CTx 3	0
7570, Levendag et al., 2004	Prospective	Histologically proven AJCC node-positive or node-negative primary squamous cell carcinoma (SCC) of the head and neck (12/1998-03/2001)	Definitive or adjuvant 3DCRT	57	46	11 Received brachytherapy boost to primary tumor and ipsilateral neck dissection

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
7750, Liu et al., 2003	Prospective	Histologically proven AJCC I-IV nasopharyngeal carcinoma (NPC) (06/1999-04/2003)	Definitive IMRT with or w/out concurrent CTx Cisplatin alone or plus 5-FU	103	83 CTx 63	20 6 distant metastasis 7 local recurrence with previous RT 7 did not complete RT
8250, Munter et al., 2003	Prospective	Histologically proven AJCC staged carcinoma of the head and neck (10/1999-04/2002)	Definitive or adjuvant IMRT with or w/out CTx	48	48 CTx 9	1 Did not complete RT
8270, Braaksma 2003	CS, prospective	Consecutive pts with LN negative histologically proven squamous ca of the LAR, for whom elective LN irradiation was indicated (07/1998-01/2000)	3DCRT	26	26	0
8370, Padovani 2003	Prospective	Consecutive patients with PNS CA (01/1995-07/2001)	3DCRT CTx Resection	25 CTx 7 Resection 22	25	0
8400, Amosson 2003	CS	Histologically confirmed H & N cancer (01/1996-06/2000) No evidence of mets	SMART boost technique with IMRT	30	30	0
9290, Teh 2002	CS	28 pts with primary H & N cancer	IMRT with SMART boost with parotid preservation. No chemotx	28	28	0
9330, Kovacs 2002	CS	Histologically proven primary squamous cell ca of the OC or OPH	Adjuvant 3DCRT Concurrent CTx	73 Concurrent CTx	50 CTx 42	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
9510, Jian 2002	Prospective phase 2	T3 or T4 histologically proven NPH Ca with apparent base of skull and intracranial disease. ECOG PS 0-1 Adeq renal and BM fxn (01/1992112/1998)	3DCRT and concomitant and adjuvant CT	48	48	0
10740, Pommier et al, 2000	Retrospective review 3D CRT	Primary tumor including the paranasal sinuses and undergoing CRT	Definitive(10) or Postoperative (30) RT	40	40	3
11650, Kuppersmith et al., 1999	Retrospective	Histologically proven AJCC staged primary or recurrent cancer of the head and neck (03/1994-04/1997)	Definitive or palliative IMRT	28	28	0
13270, Lawson 2008	CS Retrospective	Pts who underwent definitive RT for BOT SCC using SMART and CT (01/2003-08/2005)	Definitive IMRT (SMART) and platinum-based CT	34	34	0
13340, Ikushima et al, 2008	Retrospective cohort study SIC and CRT	Stage III and IV SCC of the oral cavity treated with CRT and Superselective intra-arterial infusion chemotherapy (SIC)	Preoperative RT	40	40	0
16840, Wu et al, 2006	Retrospective cohort study IMRT	Histologically confirmed nasopharyngeal carcinoma patients treated with modulated accelerated radiation therapy boost technique.	Definitive RT	75	75	0
26140 , Scorsetti 2001	CS	Relapsed H & N cancer (04/1993-06/2000)	3DCRT	58	58	0
24330, Pfreunder et al., 2003	Prospective Cohort paclitaxel/cisplatin induction chemotherapy (ICHT) and RT	Patients eligible for total laryngectomy (TL) and TL plus partial pharyngectomy (TLPP) were enrolled in an ICHT RT study	Postoperative RT	50	50	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
37660, Wendt et al, 2006	Prospective cohort study examining tissue sparing of 3D-c-IMRT w/ compensators	SCC of HnN using 3D conformal IMRT	Definitive, Postoperative, concomitant RT	39	38	1
38290, Anand et al., 2008	Prospective	Histologically proven AJCC staged locoregionally advanced cancer of the head and neck (12/2002-12/2004)	Definitive or adjuvant IMRT with or w/out CTx Concurrent cisplatin alone, or cisplatin ifosphamide, and 5-FU	67	62 CTx 29	5 Did not complete RT 13 had interruption of RT
38530, Studer et al., 2008	Retrospective	Histologically proven stage pT1-pT4, N0-N2c recurrent SCC of the head and neck (04/2003-09/2008)	Definitive or adjuvant salvage IMRT with or w/out CTx Concurrent cisplatin or cetuximab	44	44 CTx 32	0
38640, Studer et al., 2008	Prospective	Histologically proven AJCC staged Tx-T4, N0-N3 primary or recurrent head and neck cancer at various sites (01/2002-12/2007)	Definitive or adjuvant IMRT with or w/out CTx Concurrent cisplatin or cetuximab	409	409 CTx 343	0
38840, Seung 2008	CS Retrospective	Histologically proven cancer of NPH or OPH (04/2003-04/2007)	All with curative intent. Concurrent CTx	69 definitive 60 adjuvant 9 CTx 45	69	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
38850, Caglar 2008	CS Retrospective	Consecutive pts with newly dxd HNSCC between Excluded if had distant mets, previous RT, sal gl tumor or did not have pharynx in the field. (09/2004-08/2006)	IMRT Concurrent or induction CTx	96 definitive 82 adjuvant 14 Induction CTx 28 Concurrent CTx 59	96	0
39000, Sanguineti 2008	CS	Pathologically proven OPH SCC, no surgery x pretx tonsillectomy (05/2002-02/2006)	Definitive IMRT	50	50	0
39020, Rosenthal 2008	CS Retrospective	Consecutive pts for OPH cancer (09/2002-11/2006)	IMRT definitive or IMRT with concurrent CTx	160 IMRT alone 93 Concurrent cisplatin 40 Other concurrent CTx 27	160	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
39300, Hoppe et al., 2008	Retrospective	Histologically proven AJCC staged recurrent or primary T1-T4, N0-N2 head and neck cancer at various sites (11/1999-06/2006)	Adjuvant IMRT with or w/out CTx Concurrent or adjuvant platinum containing regimens	151	37 CTx 6	114 39 received RT at different center 29 received definitive RT or CRT only for stage 4B disease 7 treated with 3DCRT 7 treated with IMRT boost 5 had prior RT for paranasal sinus cancer 27 had melanoma 1 did not complete RT (received 40 Gy)
39390, Worden et al., 2008	Prospective	Histologically confirmed, previously untreated stage III-IV SCC of the oropharynx (01/2000-11/2002)	Definitive IMRT with CTx Neoadjuvant cisplatin or carboplatin plus 5-FU, concurrent cisplatin or carboplatin	66	53 CTx 53 concurrent	13 11 did not respond to induction CTx prior to RT 1 died due to CTx toxicity 1 died from disease prior to RT

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-B. Participant characteristics

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
560, Biagioli et al., 2007	med 63 rng 19-82		10	Recurrent	SCC 85 Malignant neoplasm 4 Adenoid cystic carcinoma 2 Adenocarcinoma 2 Mucoepidermoid 2 Small cell carcinoma 2 Larynx 29 Oropharynx 29 Parotid 15 Oral cavity 12 Paranasal sinuses 5 Unspecified 5 Nasopharynx 2 Hypopharynx 2		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
580, Dirix et al., 2007	med 65 rng 39-82		20	T2 16 T3 32 T4 52 None had evidence of LN or DM at diagnosis	Adenocarcinoma 68 Neuroendocrine 16 Esthesioneuroblastoma 8 SCC 8 Ethmoid sinus 72 Nasal cavity 16 Maxillary sinus 12		
1010, Urbano et al., 2007	63 Gy cohort med 59 rng 37-77 67.2 Gy cohort med 66 rng 60-85		30	T1 3.3 T2 20 T3 53.3 T4 23.3 N0 40 N1 20 N2a 3.3 N2b 16.7 N2c 16.7 N3 3.3	SCC Laryngeal 47 Hypopharyngeal 53		
1420, Feng et al, 2007	56 ± 9		17	T1 6 T2 31 T3 25 T4 39 N0 8 N1 11 N2 72 N3 8	Oropharyngeal 31 Nasopharyngeal 5 Tongue base 53 Tonsil 33 Nasopharynx 14		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
1430, Scrimger et al., 2007	≤ 50 n = 16 > 50 n = 31		21	T0 4 T1 15 T2 43 T3 26 T4 13 N0 32 N1 26 N2 40 N3 1 AJCC I 4 II 23 III 23 IV 49	SCC 100 Oral cavity 42 Nasopharynx 21 Oropharynx 19 Larynx/hypopharynx 13 Unknown primary 4	Current 28 Past 49 Never 17 Unknown 6	
1500, Lee et al., 2007	med 57 rng 36-78		32	T1-2 26 T3 42 T4a 29 T4b 3 N0 23 N1 23 N2 54 AJCC III 29 IVA 68 IVB 3	SCC 100 Larynx 65 Hypopharynx 35		KPS 90 65 70-80 35
1770, Yao et al., 2007 (see 4630, Yao et al., 2005)	med 57 rng 36-85		19	T0 2 Tx 7 T1 11 T2 34 T3 20 T4 26 N2a 12 N2b 43 N2c 31 N3 13	SCC 100 Oropharynx 71 Larynx 13 Hypopharynx 3 Oral cavity 3 Sinus/nasal 2 Unk primary 7		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
1780, Lee et al., 2007	med 58 (rng 31-84)		34	Recurrent	SCC 86 Adenoid cystic 5 Mucoepidermoid 5 Adenocarcinoma 4 Nasopharynx 20 Neck 20 Paranasal sinus 17 Oropharynx 15 Larynx 10 Oral cavity 8 Parotid 6 Hypopharynx 4		Neck dissection pre-RT 10
1900, Ben-David et al., 2007	med 55 rng 29-86	white 98 Black 1 Asian 1	48	AJCC I 1 II 4 III 23 IVA 65 IVB 7 Rec 1	Oropharynx 68 Oral cavity 18 Hypopharynx 7 Larynx 4 Other 2		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
1990, Yao et al., 2007	med 62 rng 26-90		40	T0 4 T1 14 T2 25 T3 11 T4 45 N0 31 N1 33 N2A 4 N2B 27 N2C 5	SCC 100 Tongue 36 Mouth floor 27 Buccal mucosa 11 Retromolar trigone 11 Alveolar ridge 11 Lip 4		
2180, Daly et al., 2007	≤ 60 n = 19 > 60 n = 17		53	Tis 3 T1 3 T2 3 T3 22 T4 69	SCC 33 Esthesio 19 Adeno 14 Adenoid cystic ca 14 Sinonasal undiff ca 14 Mucoepidermoid 3 Neuroendocrine ca 3		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
2290, Yao et al., 2006	med 53 rng 36-84		12	T1 20 T2 39 T3 12 T4 29 N0 12 N1 6 N2A 11 N2B 38 N2C 20 N3 14 AJCC I 2 II 6 III 4 IV 88	Tonsil 47 Tongue base 39 Oropharynx 9 Oropharyngeal wall 3 Soft palate 1		
2370, Garden et al., 2007	med 54 rng 30-75		14	T1 37 T2 35 Tx 27 N0 16 N1 14 N2A 20 N2B 27 N2C 2 N3 4 Nx 18	Tonsil 65 Tongue base 31 Pharyngeal wall 4		> 10 drinks/wk 20 1-10 drinks/wk 43 Rare/never drink 37

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
2430, Vosmik et al., 2006	med 55 rng 25-83		16	I 3 II 18 III 29 IV 50	SCC 92 Other 8 Oropharynx 34 Larynx 21 Hypopharynx 16 Nasopharynx 13 Maxillary sinus 10 Nasal cavity 5		
2770, Cheng et al., 2006	≤ 40 223 > 40 407		30	T1 25 T2a 7 T2b 19 T3 22 T4 27 N0 11 N1 23 N2 55 N3a 4 N3b 6	WHO 1 3 WHO 2 21 WHO 3 76		Parapharyngeal space extension 60 Cranial nerve involvement 12 LDH ≥ 410 13 LDH < 410 87
3080 Meirovitz 2006			n=8 (21%)	Stage I n=2 II n=4 III n=6 IVA n=24 IVB n=2	OPH n=26 OC n=9 LAR n=1 HYP n=1 UNP n=1		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
3320, Portaluri et al., 2006	med 61 rng 37-81		25	AJCC II 12 III 31 IVA 33 IVB 4	SCC 100 Larynx 36 Oropharynx 24 Oral cavity 24 Nasopharynx 12 Other 4		
3340 Studer 2006	Mean 60.8 (34-87 years)		F:M ratio 1:5 (6:23)	T1N2a n=1 T1N3 n=1 T2N0 n=3 T2N2a n=1 T2N2b n=8 T2N2c n=2 T3N0 n=1 T3 N1 n=1 T3N2a n=1 T 3N2b n=2 T3N2c n=1 T4N0 n=1 T4N1 n=2 T4N2b n=2 T4N2c n=2 Stage 1 n= (%) Stage 2 n= (%) Stage 3 n= (%) Stage 4 n= (%)	HYP cancer (100%)		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
3400 Studer, 2006	Mean 60.2 (41-85)		14(19.2%)	Locally advanced stage ¾ n=37 T1/2N2c n=5 Recurrent dz n=6 T1-2 N0-2b N=25	OPH (75%) Oral cavity (25%)		
3570 Saarilahti 2006	Submandibular gland spared Mean 55.4 (29-78) Not spared 52.0 (36-68)		21/36 (58%)	Tumor stage Submand gl spared: T0: n=1 (6) T1-2: n=12 (67) T3-4: n=5 (28) Submand gl not spared: T0: n=0 (0) T1-2: n=10 (56) T3-4: n=8 (44) Nodal stage NPH Submand gl spared: N0: 1 N1: 1 N2: 1 Submand gl not spared: N0: 2 N1: 2 N2: 1 OPH Submand gl spared: N0: 1 N1: 3 N2a: 3 N2b: 0 N2c: 0 N3: 0	NPH 8/36 (22.2%) OPH 28/36 (77.8%)		WHO PS Subgl spared 0 n=10 1 n=8 Subgl not spared 0 n=9 1 n=9

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
				Submand gl not spared: N0: 2 N1: 2 N2a: 0 N2b: 5 N2c: 3 N3: 2			
3790, Ozsahin et al., 2006	med 54 rng 39-76		18	T1-2 30 T3-4 70 N0-1 45 N2-3 55	Oropharynx 34 Oral cavity 27 Nasopharynx 15 Hypopharynx 12 Larynx 12		
3820 McMillan 2006	Mean 45.9 (28-63)	Southern Chinese	n=13 (40.6%)	AJCC Tumor stage 1: n=15(47%) 2: n=17 (53%)	NPH (100%)		
4290, Lau et al., 2006	med 58 (rng 38-77)		25	Tx 12 T1 14 T2 27 T3 25 T4 21 N0 18 N1 20 N2 59 N3 3 AJCC X 12 II 7 III 20 IV 61	SCC Oropharynx 48 Hypopharynx 18 Larynx 16 Unknown primary 12 Oral cavity 5		KPS 90-100 75 70-80 21 ≤ 60 4

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
4430 Kwong 2006	Median 48 (24-74 years)		n=11 (28%)	T3 (n=16) T4 (n=34) Stage III (n=14) Stage IVA-B (n=36) No evidence distant mets.	NPC either poorly or undifferentiated (100%)		
4630 Yao	56 (20-90)		n=32 (21%)	AJCC Stage I n=1 II n=10 III n=25 IV n=103 Unk n=11	NPH n=5 OPH n=56 LAR n=33 OCL n=29 HYP n=8 PNS n=8 UNP n=11		
5020, Nishimura et al., 2005	57 (35 – 81)		21	UICC II, III, IV 27, 15, 58	Nasopharynx, Oropharynx, Hypopharynx: 39, 30, 30		Performance Status: 0, 1, PS2 67, 30, 3
5120, Wolden et al., 2006	Med (rng) 48 (13-79)	Caucasian, Asian, Black, Hispanic, Other 3DCRT 43, 29, 11, 6, 11 IMRT 35, 32, 19, 8, 5	3DCRT 26 IMRT 28	AJCC I, IIB, III, IV A/B 3DCRT 0, 20, 31, 49 IMRT 7, 16, 30, 47 T1,2,3,4 3DCRT 11, 23, 29, 37 IMRT 20, 28, 20, 31 999N0, 1, 2, 3 3DCRT 9, 40, 13, 5 IMRT 22, 31, 23, 24	NPC		LCC at 3-yr negatively influenced by increasing T stage p=.001

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
5210, Duthoy et al., 2005	IMRT Group: 62 (30-78)			IMRT: T1=0, T2=13, T3=4, T4=11 Historic 3DCRT Cohort: T1=2, T2=8, T3=9, T4=11	IMRT: Adenocarinoma: 31 SCC: 8 Ethmoid Sinus: 30 Maxillary Sinus: 6 Nasal Cavity: 3		IMRT Group: 2 patients treated for recurrent tumor 24 patients w/ history of occupational wood exposure 3 patients w/ neurological symptoms 5 patients w/ cheek swelling 14 patients w/ epitaxis 26 patients w/ nasal obstruction
5310, Zheng et al., 2005	med 47 (rng 25-71)		30	T1 18 T2 31 T3 28 T4 23 N0 91 N1-2 9	WHO II 13 WHO III 87		Complications at dx Grade0/1 61 Grade 2 31 Grade 3 8
5330, Lu et al., 2005	med 44 ≥ 60 5 (20) < 60 20 (80)		36	T1 52 T2 48 N0 16 N1 84	WHO I 4 WHO II 8 WHO III 88		KPS ≥ 70 100
5420, Pan et al., 2005	mn 58 (SD 16)		49	Nonmalignant 9 I/II 20 III 23 IV 49	Oral cavity 31 Paranasal 26 Salivary gland 23 Nasopharynx 11 Skin 9 Oropharynx 3		Hypertension 31 Diabetes mellitus 15

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
5740, Thorstad et al., 2004	> 18				SCC Oropharynx Hypopharynx Larynx Paranasal sinus		KPS > 70 100
6430, Kwong et al, 2004	43 (29-74)		51.5	T1, T2, T3 94, 3, 3% N0, N1 81.8, 18.2%	NPC 100%		Two patients found not to be T1 stage after MRI (1 T2, 1 T3)
6530 Zheng 2004	≤45 n=26 >45 n=28		N=15 (28%)	AJCC Stage 1 n=5 (9.3) Stage 2 n=16 (29.6) Stage 3 n=18 (33.3) Stage 4 n=15 (27.8) rT1 n=15 rT2 n=25 rT3 n=14 T1 n=7 T2 n=16 T3 n=18 T4 n=13 N0 n=15 N1 n=17 N2 n=17 N3 n=5	NPC (100%) WHO type 2 n= 6 (11%) type 3 n=48 (89%)		
7090, Chao et al., 2004	55 (35-76)		17.6	T1, T2, T3, T4: 22, 35, 19, 26 N0, N1, N2, N3: 17, 22, 58, 6	Tonsil, base of tongue, soft palate: 70, 25, 5		
7110, Sze et al., 2004	med 48 rng 17-83		29	T1 9 T2 41 T3 35 T4 21	WHO II-III 99 Nasopharynx		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
7370, Lu et al., 2004	med 45 rng 28-70		24	T1 8 T2 18 T3 22 T4 51 N0 94 N1 4 N2 0 N3 2 AJCC I 8 II 18 III 20 IV 51	Carcinoma 100		
7570, Levendag et al., 2004	mn 61 rng 41-82		21	N0 72 N+ 28 AJCC stage III/IV reported in 75% of all cases	SCC 100 Larynx 48 Oropharynx 39 Hypopharynx 11 Oral cavity 2		
7750, Liu et al., 2003	med 48 rng 25-85		16	T1 23 T2 42 T3 7 T4 28 N0 23 N1 33 N2 30 N3 14 AJCC I 7 II 30 III 24 IV 39	WHO I 2 WHO II 56 WHO III 42		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
8250, Munter et al., 2003	med 55 rng 21-78		33	AJCC I-IVB T1-T4 N0-N1 M0-M1 (not clearly compiled)	SCC 54 Adenoid cystic carcinoma 38 Adenocarcinoma 8 Salivary glands 38 Maxillary sinus 19 Oropharynx 19 Nasopharynx 17 Larynx/hypophar 4 Unknown primary 4		
8270 Braaksma 2003	Median 62 (42-81)		n=6 (23.1%)	T1 n=6 (23.1) T2 n=10 (38.5) T3 n=9 (34.6) T4 n=1 (3.8)	Squamous ca (100) Well diff n=3 (11.5) Mod diff n=15 (57.7) Poor diff n=4 (15.4) Unk n=4 (15.4)		
8370 Padovani 2003	67 (34-86)			T4 n=17 T3 n=4 T2 n=4 (disease was recurrent in 4 pts)	25 PNS CA (18 ETH and 7MAX) 13 adenoca and 12 sq ca		Major adverse px fx was initial involvement of CNS (n=3) or base of skull or dura mater (n=8) and mets to LNs.

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
8400 Amosson 2003	Mean 60.5 Median 63.0 Range 43-73		20%	Stage 1 n=3 (10.0%) Stage 2 n=7 (23.3%) Stage 3 n=9 (30.0%) Stage 4 n=9 (30.0%) Recurrent n=1 (3.3%)	OPH n=16 (53.3) NPH n=4 (13.3) OC n=2 (6.7%) LAR n=4 (13.3) HYP n=1 (3.3) PNS n=2 (6.7) UNP n=1 (3.3) Included squamous cell ca, adenoca and adenoid cystic ca (numbers not provided)		
9290 Teh 2002					NPH n=7 (25%) OPH n=12 (43%) HYP n=3 (11%) LAR n=4 (14%) OC n=2 (7%)		
9330 Kovacs 2002	Ave 59.6		27% *note= these numbers include all 73 pts and are not broken out for the pts who rec'd RT vs. those that did not	Stage 1 n=12 (16.4%) Stage 2 n=19 (26.1%) Stage 3 n=10 (13.7%) Stage 4 n=32 (43.8%) *note= these numbers include all 73 pts and are not broken out for the pts who rec'd RT vs. those that did not	OPH n=10 (14%) OC n=63 (86%) *note= these numbers include all 73 pts and are not broken out for the pts who rec'd RT vs. those that did not		ECOG status 0: 84% I: 15% II: 1% *note= these numbers include all 73 pts and are not broken out for the pts who rec'd RT vs. those that did not
9510 Jian 2002	n (%) ≤40 n=14 (29.2) 41-50 n=16 (33.3) 51-60 n=7 (14.6) >60 n=11 (22.9)		8 (16.7)	T3 n=11 (23) T4 n=37 (77)	NPC (100) WHO type 2 n=17 (35.4) WHO type 3 n=31 (64.6)		
10740, Pommier et al, 2000	67 (28 – 86)		35%		Paranasal Sinuses: 70% Nasal cavities: 10% Hard Palate: 20%		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
13270 Lawson 2008	Mean 61 (34-76)		11 (32)	AJCC Stage 1 0(0) Stage 2 2 (6) Stage 3 3 (9) Stage 4 29 (85) T1N0-3 n=10 T2N0-3 n=10 T3N0-3 n=4 T4N0-3 n=10	BOT SCC 100%	24 (71)	
11650, Kuppersmith et al., 1999	med 55 rng 10-92		14	T1-T4 N0-N2C M0	SCC 64 Other 36 Nasopharynx 25 Maxillary sinus 14 Base of tongue 14 Other 47		
13340 Ikushima et al, 2008	63.1 (27-81)		35	III,IV 33, 77	Tongue, gingiva, bucca mucosa, oral floor, soft palate 35, 47.5, 10, 5, 4		SIC chemotherapy
16840, Wu et al, 2006	52 (24-82)		28	I, II, III, IV 5.3, 38.6, 38.6, 17.3 WHO type 1,2,3 2.6, 88, 9.3			
26140 Scorsetti 2001	46 (20-71)		20 (34.5)		Undiff NPC n=16 (27.6%) Squamous cell ca n=10 (17.2) Adenoid cystic ca n=9 (15.5) Adenocarcinoma n=8 (13.8) Various n=15 (25.9)		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
24330, Pfreunder et al., 2003	58 (42-77)		16	T2N0, T3N0, T3N1, T3N2a, T3N2c, T4n), T4N1, T4N2b, T4N2c, T4N3 2, 28, 8, 2, 2, 6, 18, 10, 6, 14, 4%	Resectable carcinomas of the glottic (T3-T4) and supraglottic larynx/hypopharynx (T2-T4, N0-N3, M0)		
38840 Seung 2008	Median 56 yrs (35-89)		14 (20)	AJCC stage I n=2 (3) II n=11 (16) III n=16 (23) IV n=40 (58)	NPH n=11 (16) BOT n=18 (26) Tonsil n=40 (58) n=66 (95.7) SCC n=2 (2.9) LELCarc n=1 (1.4) undiff carc		
38850 Caglar 2008	Median 55 (20-87)	White n=70 (73) Nonwhite n=9 (9) Unk n=17 (18)	17 (18%)	Stage I n=1 (1) II n=3 (3) III n=23 (24) IV n=69 (72)	OPH n=43 (45%) NPH 11(11) OC 13(14) HYP 17(18) MAX 2(2) UNP 10(10)	Yes n=48 (50%) No 48 (50)	
39000 Sanguineti 2008				Stage 1 n=1 (2%) 2 n=5 (10%) 3 n=15 (30%) 4 n=29 (58%)	Tonsil n= 34 (68%) BOT n=8 (16) Pharyngeal wall 2 (4) Soft palate 6 (12)		
39020 Rosenthal 2008	Median 58 (34-81)		21 (13.1)	T1N0-3 n=48 T2N0-3 n=72 T3N0-3 n=21 T4N0-3 n=19	BOT n=78 (48.8) Tonsil n=80 (50) OPH n=2 (1.2)		
37660, Wendt et al, 2006	57 (37-76)		10%		Nasopharynx, oropharynx, oral cavity/tongue, hypopharynx/supraglottic larynx, CUP-syndrome 10, 51, 23, 13, 3%		Radical RT alone: 26% Postoperative RT: 74% RT without simultaneous chemotherapy: 51 RT with simultaneous cDDP: 49

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
38290, Anand et al., 2008	med 56 rng 27-85		23	AJCC I 6 II 16 III 27 IVA 39 IVB 11	SCC 89 Adenoid cystic carcinoma 6 Mucoepidermoid carcinoma 3 Adenocarcinoma 2 Nasopharynx 24 Larynx 21 Oropharynx 16 Tongue 14 Hypopharynx 13 Alveolus 6 Paranasal sinus 5		
38530, Studer et al., 2008	mn 64 rng 35-87		36	pT1 32 pT2 52 pT3 2 pT4 7 T unk 7 N0 59 N1 11 N2a/b 20 N2c 5 N unk 5	SCC 100 Oral cavity 66 Glottic 18 Oropharynx 9 Sinonasal 5 Skin 2		Grade 1 5 Grade 2 34 Grade 3 27 unk 25

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
38640, Studer et al., 2008	mn 60 rng 21-87		22	Tx 1 T1 11 T2 31 T3 17 T4 28 N0 17 N1 12 N2a/b 32 N2c 27 N3 5 Recurrent 17	SCC 95 Lymphoepithelial carcinoma 5 Oropharynx 40 Oral cavity 19 Hypopharynx 15 Larynx 12 Nasopharynx 10 Sinonasal 2 Unknown 1		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
39300, Hoppe et al., 2008	med 55 rng 15-88	White 73 Asian 11 Black 11 Other 5	49	T1 0 T2 17 T3 17 T4 55 N0 90 N1 10 Kadish A 0 B 66 C 33	SCC 46 Sarcoma 14 Adenoid cystic 11 Undifferentiated 8 Adenocarcinoma 8 Esthesioneuroblastoma 8 Myoepithelial 5 Maxillary sinus 54 Nasal cavity 27 Ethmoid sinus 11 Lacrimal gland 3 Sphenoid sinus 3 Frontal sinus 3		KPS med 90 (rng 70-100)
39390, Worden et al., 2008	Male med 55 rng 37-77 Female med 61 rng 50-74		23	T1 8 T2 26 T3 35 T4 32 N0 18 N1 23 N2 50 N3 9	SCC 100 Base of tongue 61 Tonsil 39	Never 24 Past 42 Current 33	HPV titer pos 41 neg 23 unk 36 KPS 80 9 90 20 100 71

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-C. Treatment characteristics

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
560, Biagioli et al., 2007	CT	Yes (Nomos.)	Photons (6-MV)	60 Gy, 2 Gy/frac, 5 frac/wk Lifetime dose to spinal cord ≤ 60 Gy			GTV = gross tumor volume PTV = GTV and areas at risk of microscopic disease expanded by 5-20-mm margin	
580, Dirix et al., 2007	CT, MRI	Yes (Helios, Cadplan, Eclipse)	Photons (6-MV)	60 Gy 2 Gy/frac, 5 frac/wk IMRT boost 6 Gy, 2 Gy/frac in 10 pts In regions where PTV and OAR overlapped (optic structures) underdosage of the PTV was tolerated No elective irradiation of cervical LNs	Non-coplanar 6-field arrangement consisting of 5 fields of 6-MV photons and 1 filed of 10 or 18 MV photons from LA	3-point fixation thermoplastic mask	CTV included GTV plus margin (not defined) to account for microscopic disease at margin, encompassing resection cavity plus all paranasal sinuses that were invaded PTV included CTV plus 5-mm margin	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1010, Urbano et al., 2007	CT	Yes (Helios, Cadplan, Eclipse or Helax-TMS and Pinnacle)	Photons (6-MV)	Dose level (DL) 1: Primary tumor site 63 Gy, 2.25 Gy/frac Elective nodal areas 51.8 Gy, 1.85 Gy/frac With IMRT SIB DL 2: Primary tumor site 67.2 Gy, 2.4 Gy/frac Elective nodal areas 56 Gy, 2 Gy/frac Mn Tx time: DL1 = 39±3 days DL2 = 38±1 days Maximum mean dose to parotids 24 Gy where possible	5- and 7-beam arrangements	Custom-made cabulite head and neck mask	CTV1 = entire larynx and hypopharynx complex, including thyroid cartilage, from 1 cm above the tip of the epiglottis to below the cricoid cartilage; adjacent sites invaded by tumor as well as all involved nodal areas and retropharyngeal nodes were included; CTV2 = elective nodal volume, including uninvolved levels 2-5 and supraclavicular fossa nodes bilaterally; PTV1/PTV2 = CTV1/CTV2 plus 3-mm margin	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1420 Feng et al, 2007	CT	Yes (in-house system)		70 Gy, 2.0 Gy/frac to gross disease 59-63 Gy, 1.7-1.8 Gy/frac to low- and high-risk subclinical targets Maximal mandibular dose < 72 Gy Mean parotid gland dose ≤ 26 Gy Mean noninvolved oral cavity dose ≤ 30 Gy	Inverse-planned beamlet (not further described)		CTV = primary tumor and include lateral retropharyngeal (RP) nodes PTV = CTV plus a 3-mm margin Targets in low neck were included I IMRT plans, but anterior low neck fields abutting upper neck plans were not used	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1430, Scrimger et al., 2007		Yes (Helax v.6.02)	Photons	2 Gy/frac, 5 frac/wk initially, then 1.8-2.2 Gy/frac in SIB protocol Planning goal to keep RT dose to spared portion of parotids as low as possible (mean dose to spared portion of parotid 18.4 Gy Mean dose to all parotid tissue 27.1 Gy	7 gantry angles, 128-leaf MLC		In most patients, the CTV was immediately adjacent to the deep lobe of the parotid; entire target volume, including low neck, treated as 1 volume with no separate supraclavicular field PTV = CTV plus 5-mm margin PTV66 = areas of gross disease PTV60 = high-risk operative bed PTV54 = low-risk operative bed or undissected nodal regions	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1500, Lee et al., 2007	CT with contrast	Yes (MSKCC tx planning system)	Photons (6-MV)	70-72 Gy, 1.64-2.12 Gy/frac, once daily with concomitant boost (n = 4) or SIB (n = 27) When possible, a mean parotid dose of ≤ 26 Gy was achieved; efforts were made to prevent unwarranted hot spots within the glottic larynx	7-field	Thermoplastic head, neck, and shoulder mask	GTV = any visible tumor on imaging studies and/or physical examination CTV = GTV plus 5-10-mm margin, including levels II-IV nodal regions in the neck, retropharyngeal region in pts with clinically involved neck nodes, levels I-II in pts with node-positive disease at level II, and pts who had a primary hypopharyngeal tumor PTV = GTV or high-risk CTV plus a 3-mm margin In some cases a low-risk CTV and corresponding low-risk PTV involved the clinically uninvolved contralateral neck and base of skull	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1770, Yao et al., 2007 (see 4630, Yao et al., 2005)	CT, MRI	Yes (Corvus v.3.0, Nomos.)	Photons	50-74 Gy, 1.2-1.25 Gy/frac, once daily (n = 83), twice-daily (n = 5), 2 with accelerated fractionation with noncomitant boost	Multivane, intensity-modulating collimator	Thermoplastic facemask	CTV1 = primary tumor and involved lymph nodes with margins CTV2 = high-risk areas harboring microscopic disease, including soft tissue surrounding CTV1 and lymphatic areas with high risk of metastasis CTV3 = areas with intermediate risk of microscopic disease	
1780, Lee et al., 2007	CT with or w/out contrast	Yes (MSKKC in-house)	Photons (6-MV)	30-70 Gy med 59 Gy Dose constraints: Spinal cord 50 Gy	Beams chosen to ensure at least 95% of dose encompassed the target volume	Thermoplastic mask	GTV = any visible evidence of disease CTV = at minimum the preoperative GTV and postop tumor bed PTV = GTV and CTV plus 10-20-mm margins	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1900, Ben-David et al., 2007	CT	Yes	Photons	70 Gy, 2 Gy/frac to gross tumor, 56-64 Gy, 1.6-1.8 Gy/frac to low- and high-risk targets Maximal mandibular dose < 72 Gy Mean parotid gland dose ≤ 26 Gy Mean noninvolved oral cavity dose ≤ 30 Gy	Static multisegmental or inverse-planned beamlet (not further described)		CTV = not described PTV = CTV plus 5-mm margin	Radiation guards used in all pts with metallic dental restorations to reduce electron backscatter to adjacent soft tissue

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1990, Yao et al., 2007	CT	Yes	Photons	50-70 Gy, 2 Gy/frac Definitive IMRT pts received additional SIB of 10 Gy, 2 Gy/frac High-risk postoperative sites (extracapsular extension, positive or close margins, tumor involvement of soft tissue or bone) received additional SIB of 4-6 Gy, 2 Gy/frac No SIB given for intermediate-risk sites (w/out extracapsular extension, no positive or close margins, no soft tissue or bone involvement)			CTV1 = tumor bed, including preoperative primary tumor volumes and involved LNs CTV2 = high-risk areas harboring microscopic disease, including normal structures immediately surrounding CTV1 with high risk of local tumor invasion (primary tumor CTV2) and high-risk lymphatic regions (lymphatic CTV2) CTV3 = intermediate-risk lymphatic areas PTV = CTV plus 5-8-mm margin	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
2180, Daly et al., 2007	CT	Yes (Nomos.)	Photons	60-70 Gy, 1.8-2.12 Gy/frac, once daily Dose constraints: 1% of brainstem and optic nerves volume 54 Gy < 1% temporal lobes volume 60 Gy Half the contralateral parotid gland 25 Gy Upper neck or high-risk subclinical region 60 Gy Low neck and supraclavicular region 50-54 Gy	Continuous course RT delivered using an auto-sequence MLC	Perforated, thermoplastic head mask	GTV = gross extent of tumor CTV = GTV plus margin of 10-20 mm for microscopic disease PTV = CTV plus 3-5-mm margin to account for patient setup error Elective neck radiation administered at the discretion of the treating physician (n = 10) Two methods used to treat neck: Primary tumor and upper neck above vocal cords treated with IMRT, anterior field for lower neck and supraclavicular fossae Extended field IMRT for primary tumor plus all regional LNs including supraclavicular	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
2290, Yao et al., 2006	CT	Yes (Nomos.)	Photons	Definitive IMRT: 70-74 Gy to PTV1, 60 Gy tp PTV2, 50-54 Gy to PTV3 Adjuvant IMRT: 60-66 Gy to PTV1, 60 Gy to PTV2, 50-54 Gy to PTV3	Multivane intensity modulating collimator		CTV1 = primary tumor and involved cervical LNs CTV2 = high-risk areas harboring microscopic disease CTV3 = intermediate-risk lymphatic areas PTV 1-2 = CTV 1-3 plus 5-mm margin	
2370, Garden et al., 2007	CT	Yes (CORVUS v.4.0, Nomos.)	Photons (6-MV)	66-70 Gy, 1.8-2.2 Gy/frac to CTV1 57-64 Gy, 1.9-2.1 Gy/frac to CTV2 54 Gy, 1,8 Gy/frac to CTV3 Concomitant boost 15-18 Gy in10 frac in 4 pts Dose constraints: Parotid glands 26 Gy Larynx 30-40 Gy	MLC		CTV1 = gross disease with minimum 5-mm margin CTV2 = CTV1 with additional margin CTV3 = subclinical sites in both sides of upper neck Lower neck treated with anterior field matched to inferior borders of IMRt delivery	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
2430, Vosmik et al., 2006	CT (with or w/out contrast), MRI in some cases	Yes (CadPlan, Helios)	Photons	54-66 Gy, 1.8-2.2 Gy/frac, 6 wks 66 Gy to PTV66 60 Gy to PTV60 54 Gy to PTV54 With IMRT simultaneous integrated boost (SIB) Dose constraints: Spinal cord maximum dose < 44 Gy Brain stem maximum dose < 54 Gy mean dose < 28 Gy Larynx (if not part of PTV) 67% volume < 50 Gy	Dynamic MLC, 2x26 leafs	Thermoplastic mask	CTV, GTV, PTV defined according to ICRU Report 50 GTV = all macroscopic disease CTV = gross disease plus 0.5-20-mm margin for microscopic disease PTV = CTV plus 0.5-20-mm margin for setup errors	
2770, Cheng et al., 2006	CT	Yes	Photons (6-MV and 18-MV)	70 Gy, 2 Gy/frac, 5 frac/wk 74.4 Gy, 1.2 Gy/frac, 2 frac daily, 10 frac/wk Dose constraints: Spinal cord 43-44 Gy	Opposed fields with or w/out anterior field		Bilateral, off-cord or posterior cord boost, separate anterior field for low neck and supraclavicular fossa	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
3080 Meirovitz 2006				Tumor dose NR Mean dose to contra and ipsilateral parotid ave 22 Gy (SD 5 Gy) and 53 Gy (SD 7 Gy) Mean dose to contra and ipsilat submandibular gland 57 Gy (SD 8) and 65 Gy (SD 7)			Bilateral neck in all 38	
3320, Portaluri et al., 2006	CT with or w/out contrast	Yes (Eclipse)	Photons (6-MV)	44-64 Gy to PTV1, 2 Gy/frac, 5 frac/wk Boost to CTV2 Dose constraints: Median Dmax (overall population) Spinal cord 44 Gy Ipsilateral parotid 48 Gy Contralateral parotid 42 Gy	Multileaf collimator with 80 leaves, 11 fields (minimum 10, maximum 14)	Head-and-shoulder mask	CTV1 = tumor bed and bilateral LN levels depending on tumor site and stage CTV2 = tumor bed and involved LNs PTV1 and PTV2 = CTV1 and CTV 2 plus 4-mm margin	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
3340 Studer 2006	CT, MRI and PET	Varian treatment-planning system (Eclipse®, Version 7.3.10, Varian Medical Systems, Hansen Way, Palo Alto CA, USA)	6 MV photon beams	Simultaneous integrated boost (SIB) doses between 60 and 71 Gy (five fractions/week) with 2.0 (n = 8), 2.11 (n = 17), and 2.2 Gy (n = 4)/fraction to the boost volume (planning target volume, PTV1) were applied. Organs at risk: Sp cd max <45 Gy, parotids mean <26 Gy, OC mean <35 Gy, nuchal tissue mean <45 Gy. Mean total treatment time was 45.4 days (32–58 days).	5-field equiangular.	Commercially available thermoplastic mask	GTV with a margin of 10–15 mm was included in the SIB volume. Elective lymph node regions (PTV2, 50–57 Gy) level 2–5 were included bilaterally.	
3400 Studer 2006		IMRT: Varian Treatment planning system (Eclipse®, version 7.3.10, Varian medical system, Hansen Way, Palo Alto, CA, USA)	IMRT: 6-MeV photon beams	In all patients, SIB-IMRT technique was performed using the following schedules: • 30 × 2.2/1.8 Gy to 66 Gy (PTV1)/54 Gy (PTV2; n = 28); • 33 × 2.11/1.64 Gy to 69.6 Gy/54	Most were 5-field arrangements (n=61) 6-fields (n=5) 7-fields (n=7) Sliding window MLC			Doses delivered to partial volumes of mandibular bone using IMRT with doses between 60-75Gy (mean 67) on

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
				Gy (n = 25); • 30 × 2.11/1.8 Gy to 63.3/54 Gy (n = 3); • 30–35 × 2.0 Gy to 60–70 Gy (n = 16 postoperative patients). In one case with large necrotic nodes, a higher SIB dose of 2.35 Gy per fraction to 75.2 Gy to the nodal GTV was chosen. Dose to spinal cord, parotids, TMJ, brain, OC outside of PTV, nuchal tissue: Max <45 Gy, mean ≤26, <50, <40, mean <35, mean <45				average 7.8, 4.8, 0.9 and 0.3 cm^3 were exposed to doses >60, 65, 70 and 75 Gy respectively. [mean mandibular bone volume 58.4 cm^3 (33-88cm^3)

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3570 Saarilahti 2006		IMRT: Helios inverse treatment planning software with Cadplan® system version 6.27(Varian Medical Systems, Helsinki, Finland)	IMRT: 6 MV photon beam	IMRT: Parotids excluded from PTV: Max 25 Gy 1st 5 patients and 16-20 Gy in rest of patients. Dose constraints for spared submandibular glands varied 20-25 Gy. Mean total dose to parotids and submand gl not treated as OAR was 49 Gy(45-54)		Conventional thermoplastic mask for immobilization in 1st 10 patients (Posicast®, Sinmed BV, EM Reenwijk, the Netherlands). Remaining pts stereotactic H & N immobilization device (BrainLab, Heinstetten, Germany).		Both parotids spared in 7 (19%) patients, one contralateral parotid in 29 (81%). Contralateral submandibular spared in 18 (50%) of patients.
3790, Ozsahin et al., 2006	CT, MRI		Photons (6-MV) and electrons	Definitive tx: 70 Gy, 2 Gy/frac, 6 wks Adjuvant RT: 66 Gy, 2 Gy/frac, 5 wks, 3 days RT delivered as concomitant-boost accelerated schedule in single daily fracs M-Th, 2 frac on F Parotids received ≥ 50 Gy in all pts		Thermoplastic mask	Surgical margins, extracapsular nodal infiltration, regional nodes	Amifostine 500 mg sc prior to each RT frac except Friday pm session

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
3820 McMillan 2006	CT	Corvus system (version 3.0)		IMRT: To PTV 66-68 Gy (included deep lobe of parotid and posterior ½ of submandibular) To GTV 68-72 Gy 34 fractions over 7 weeks		Cast	IMRT: CTV= GTV + 1 cm PTV added 2 mm margin and included level 2 and 4 Cx LNs.	
4290, Lau et al., 2006	CT w/contrast	Yes (Pinnacle3)	Photons (6-MV) and electrons	70 Gy, 2 Gy/frac, 7 wks 50 Gy to areas of microscopic spread Dose constraints: Spinal cord 36-40 Gy	Shaped lateral opposed fields, matching anterior low-neck field 0.5-cm multileaf collimator (MLC)	Hard plastic immobilization shell	GTV = primary tumor and involved LNs Upper and lower neck	

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4430 Kwong 2006	CT	Inverse planning Corvus System version 3.0 (NOMOS. Corp, Sewickley, PA)		Prescribed dose: GTV: 76 Gy. Nodal GTV: 72 PTV:70 35 fractions over 7 weeks. Fractional dose PTV: 2 Gy daily GTV: 2.17 Gy daily (SMART boost technique) Dose to lower neck 60 Gy if N0, 66 Gy if node-positive in 2 Gy daily fractions.	9 coplanar equally spaced beam angles	Tailor-made thermoplastic cast from head to shoulders with neck support and mouth bite.	IMRT: GTV includes whole NP, tumor extending out of NP, any skull-base erosion and intracranial disease. GTV_n: enlarged neck nodes CTV: in some cases, just GTV (if close to critical structures), some were GTV + 5mm-1.5 cm. If palpable residual neck node present after IMRT completion, boost dose of up to 10 Gy may have been given.	
4630 Yao	CT, MRI, FDG-PET	Corvus treatment planning system, NOMOS Version 3.0		<u>Definitive IMRT</u> Prescribed dose PTV1 70-74 Gy PTV2 60 PTV3 50-54 <u>Postop high risk</u> Prescribed dose PTV1 64-66 PTV2 60 PTV3 50-54 <u>Postop intermediate risk</u> PTV1 60 PTV2 60 PTV3 50-54 Total (daily) dose SEB=sequential boost <u>Definitive IMRT:</u>		Thermoplastic face mask	CTV_1: GTV with 5-10 mm margins CTV_2: high-risk areas harboring microscopic disease (incl normal structures immediately surrounding CTV with high risk of local tumor invasion and high risk lymphatic regions. CTV_3: Intermediate-risk lymphatic areas.	

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				SIB: CTV1/CTV2: 60 (2) CTV3: 54 (1.8) SEB: CTV1:10-14 (2) <u>High risk post op</u> SIB: CTV1/CTV2: 60 (2) CTV3: 54 (1.8) SEB: CTV 1: 4-6 (2) <u>Intermed risk postop</u> SIB: CTV 1/CTV 2: 60 (2) CTV 3: 54 (1.8) SEB: CTV1: no Max to normal tissues: Sp cd 45 Gy Br stm 54 Optic n/chiasm 54 Retina 50 Temp lobes 60 Glottic larynx 2/3 < 50 Mandible 70 Parotid mean <30 or 50% of either <30.				

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
5020, Nishimura et al., 2005	CT	IMRT treatment planning done by Cadplan Helios, Varian associates, Palo Alto, CA; Eclipse, Varian Medical Systems International Inc, Baden, Switzerland) Treatment delivery by: Clinac-600C accelerator (Varian Associates)	4MV X-Ray	Whole neck irradiation with 46 to 50 Gy in 23-25 frac IMRT boost to PTV to a total dose of 56 to70Gy in 28-35 frac (med, 68 Gy) Dose constraints to spinal cord, brain, ipsilateral parotid gland, contralateral parotid glad: 40, 50, 25-30, 20-25 Gy	5 or 7 co-planar beams: angles of 60-75, 105-115, 135-150, 180, 210-225, 245-255m 285-300	Type-S theromoplastic based system (med-tec, Orance City, IA)	Bilateral and submandibular (Ib) and jugular chain (level II-IV) nodes were included in CTV. The planning organ at risk volume a 3mm margin was added for the spide with no margin to parotid	.
5120, Wolden et al., 2006	CT, MRI	3DCRT (not specified) IMRT (not specified)		IMRT 70 Gy total dose; accelerated fractionation/ 59 patients treated with hyperfractionated concomitant boost/ 15 patients dose painting (PTVm 1.8 Gy/frac 54 Gy total and PTVg 2.34 Gy/frac 70.2 Gy)	IMRT Multiple beams tailored to patient anatomy and NPC distribution using dynamic multileaf collimators	Aquaplast masks for IMRT	IMRT PTVg included GTV w/ 1-cm margin increase with the exception of posterior dimension to the primary tumor where a 5-mm margin was added. PTVm consisted of PTVg plus the area encompassing the nasopharynx and all cervical lymph nodes w/ a 5-mm margin.	Limitation of parotid gland mean dose limited to 26 Gy when possible; cochlea dose reduced as much as possible

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
5210, Duthoy et al., 2005	CT/MRI			IMRT: End dose of 60 Gy in 4 patients, 66 Gy in 6 patients and 70 Gy in 29 patients all in 35 frac. Prescribed dose not reached in 2 patients (1 death after 21 frac and 1 was stopped due to liver mets) 3DCRT: 19 patients had 65Gy (61-70Gy) 1.8Gy/ frac 11 patients had noncoplanar beam w/ median dose of 66 Gy (54-66Gy) 2Gy/frac	3DCRT: 19 patients had coplanar beams 10 had non-coplanar	‘	No elective radiation of cervical lymph nodes (ELNI) 3mm margin used for expansion from CTV to PTV	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
5310, Zheng et al., 2005	CT, MRI		Photons (6-MV)	66-72 Gy, 2 Gy/frac, once daily 5 days/wk, 6-7 wks Dose constraints: Mean Dmax Gy (rng) Brainstem 32 (19-45) Spinal cord 24 (13-42) Temporal lobe I 42 (17-68) Temporal lobe C 23 (7-47) Optic nerve I 36 (7-67) Optic nerve C 31 (6-56) Optic chiasm 31 (6-56) Eyeball I 21 (2-39) Eyeball C 15 (1-22)	5-7 static coplanar or noncoplanar beams with 3-7-mm block aperture margin from the PTV boundary, with wedges to improve dose conformity and homogeneity as needed		GTV = primary tumor CTV = GTV plus extent of subclinical microscopic disease, usually 5-10-mm margin For high risk subclinical sites (eg, skull base, parapharyngeal space, oropharynx) 8-10 mm of CTV margin was delineated PTV = CTV plus 2.5-mm margin PRV (planning risk volume) = 2.5-mm margin around organs at risk	

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5330, Lu et al., 2005	CT	Yes		Total to CTV 72 Gy, 1.7 Gy/frac, 6 wks Initial dose to GTV 54 Gy, 1.8 Gy/frac, 5 frac/wk, 6 wks Accelerated boost added 1.5 Gy/frac as second daily frac for 12 days Dose constraints: Spinal cord 39.6 Gy			GTV = primary tumor plus draining anterior neck LNs Clinically involved and uninvolved posterior neck Boost target volume included primary tumor plus involved LNs plus 2-cm margin Supraclavicular fossae	
5420, Pan et al., 2005	CT	Yes (UMPlan in-house)		40-70 Gy med 64 Gy			Primary tumor Unilateral neck	
5740, Thorstad et al., 2004	CT	Yes (Nomos.)	Photons (6-MV)			Aquaplast face mask	CTV1 = preop gross tumor volume plus 10-2—cm margin, including resection bed with invasion, or extracapsular extension by metastatic neck LNs CTV2 = uninvolved cervical LNs	Amifostine 500 mg sc prior to each RT frac

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
6430, Kwong et al, 2004	CT	IMRT delivered with Mimic (NOMOS. Corporation) Inverse planning by Corvus v3.0 (NOMOS. Corporation)	4 or 6 MV	GTV: 68-70Gy to at least 95% and 70 Gy to macroscopically enlarged nodes in 2-2.06Gy/ 34 frac PTV:66-68Gy to 95% 1.9-2.0Gy/frac 60-66Gy 2Gy daily frac from neck caudal to the chin or caudal to the most distal enlarged lymph node. Organ at risk Gy are listed in rightmost column. Dose constraints to organs at risk: Spinal cord, [Eye, optic nerve, optic chiasm, temporal lobes, brain], brainstem, parotid glands, pituitary glands, [inner ears, middle ears, tempromandibular joints] – 40, 50, 50, 20, 25, 50 Gy	9 co-planar beam angels equally spaced. 0, 40, 80, 120, 160, 200, 240, 280, 320, 360 degrees	Custom thermoplastic cast from head to shoulders	Potential sites of local infiltration 1mm from GTV were included in CTV. CTV included: sphenoid sinus caudal to the base of pituitary fossa, cavernous sinuses on both sides, base of skull, including petrous temporal bones and excluding internal auditory canals and cochleae, inferior orbital fissures, foramen ovale and foramen spinosum, anterior half of the clivus and posterior third nasal cavity and antrum, medial pterygoid muscles and parapharyngeal space up to the styloid process and anterior one-half of the arch of the cervical vertebrae (C1) and prevertebral muscles inferior to C1. Enlarged cervical lymph nodes were localized as separate GTV	

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6530 Zheng 2004	CT/MRI	3D planning (AcQPlan 3D RTP, Marconi Medical Systems)		Salvage dose ranged from 16-38 Gy (median 24) with 2 Gy/fraction, one fraction daily, 5d/wk. (Initial external beam RT doses: median to NPH 70 Gy, to negative neck 50, and to positive neck 68, fraction 2.0/d).			PTV= persistent disease + 5mm margin	
7090, Chao et al., 2004	CT	i		70 + or – 1.1 Gy to CTV1 definitive, 66.3 + or – 3.6Gy, CTV for definitive patients was 64+ or -4.2 Gy, and 66.3 + or – 3.6 Gy. 1.9 to 2.0 Gy /frac 5 frac/wk			CTV1 encompassed GTV and region adjacent to GTV, the surgical bed w/ soft-tissue invasion, and regions with extracapsular extension by metastatic neck nodes, CTV2 was primarily prophylactically treated nodal stations. Dose to each target volume was normalized to 80-90% of maximal isodose reference point.	

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7110, Sze et al., 2004	CT w/out contrast	Yes (Helax TMS)		70 Gy, 2 Gy/frac, 5 or 6 frac/wk, 7 wks 70 Gy to grossly enlarged LNs 50-60 Gy to supraclavicular fossae med 46 days (rng 36-55 days	5-7 beams	Rigid immobilzation device	GTV-P = gross tumor volume plus adjoining involved retro-pharyngeal LNs PTV = GTV-P and whole nasopharynx, plus 7-12-mm margin Parapharyngeal spaces, posterior nasal fossae and maxillary sinuses, sphenoid and posterior ethmoid sinuses, base of skull and cavernous sinuses	
7370, Lu et al., 2004	CT, MRI	Yes (Nomos.)		66-70 Gy, 1.8-2.8 Gy/frac, 5 frac/wk 60 Gy to positive LNs in neck Dose constraints: According to ICRU 50 guidelines Brainstem mn dose 28 Gy Optic chiasm mn dose 22 Gy Optic nerves mn dose 19 Gy Lens mn dose 4 Gy	Dynamic multivane intensity modulating collimator (MIMiC) using segmental tomotherapy techniques		GTV = gross extent of tumor shown on imaging studies CTV = GTV plus 5-10- and 10-15-cm margins	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
				Temporal lobes mn dose 22 Gy Temporomandib 28 Gy Mandible mn dose 20 Gy Pituitary mn dose 33 Gy				
7570, Levendag et al., 2004	CT	Yes (3D Cadplan)	Photons (6-MV)	70 Gy to gross primary tumor and involved neck LNs 46 Gy to uninvolved neck LNs	Dynamic multileaf collimator, abutted AP portal with midline shield for lower neck	PVC head cast	CTV = primary tumor plus neck PTV = CTV plus 5-mm margin Unilateral and bilateral neck	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
7750, Liu et al., 2003	CT, MRI	Yes (Pinnacle3)	Photons (6- or 15-MV)	60-77 Gy, 1.8 Gy/Frac, 5 frac/wk 70-77 Gy to primary tumor and positive neck LNs 60-65 Gy to CTV 50 Gy to clinically negative neck Limit dose to 1% of volume of critical structures as follows: Brainstem and optic nerves 50 Gy Spinal cord and optic chasm 45 Gy Temporal lobes 60 Gy 50% of contralateral parotid 25 gy	Static multisegmental multileaf collimator Split-beam technique for anterior lower neck field		GTV = gross extent of tumor, including nasopharyngeal primary and retropharyngeal lymphadenopathy CTV = GTV plus margin of potential microscopic spread	
8250, Munter et al., 2003	CT, MRI	Yes (KonRad, VIRTUOS)	Photons (6- or 15-MV)	55-72 Gy to primary PTV, GTV, positive LNs, 1.6-2.0 Gy/frac or 1.6-2.0 Gy/ frac IMRT boost or	Integrated multileaf collimator, 5-9 beams (med 7)	Scotch-Cast mask	GTV = visible tumor in imaging studies CTV = GTV plus 5-mm margin; in postop cases GTV included surgical bed and margins according to	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
				integrated boost also used 50-65 Gy to secondary PTV Dose constraints: Cervical spinal cord 50 Gy Brainstem 60 Gy Optic nerve and chiasm 54 Gy Protected parotid < 26 Gy			assessed risk Primary PTV = CTV plus 3-mm margin to compensate internal organ motion and setup variability Secondary PTV = LNs or surgical neck levels at risk of subclinical disease, including LN level II-V (depending on tumor site), retropharyngeal LNs, and in some cases level I All pts with ipsilateral LN involvement also had contralateral neck RT Tumor suspicious LNs and LN levels with radiographic evidence were defined as a target volume	

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8270 Braaksma 2003	CT	Non commercial inverse planning module "Optimize" Computer planning purposes: Cadplan versions 2.7.9 and 3.1.2, Varian-Dosetek, Finland.	10 MV	3DC 46 Gy to primary tumor and LN levels of neck (PTV1); then boosted to cumulative dose of 70 Gy primary tumor (PTV2). Mean dose to R and L parotids was 29.2 and 28.7, respectively.			PTV= CTV + 5mm margin	
8370 Padovani 2003		Focus logical, CMS, St Louis, MO	6-18 MV	3DC RT delivered in doses of 2 Gy/fraction at 5 fractions weekly. Median dose PTV was 63 Gy (range 30-70). Ipsilateral neck 60 Gy Max dose to chiasma and CNS limited to 54 and 60 Gy, respec, ipsi optic n and retina 60 Gy.	Noncoplanar	Thermoplastic face mask	CTV = pretx GTV and microscopic extension PTV= CTV plus additional uniform 5 mm expansion Ipsi Cx LN in 5 pts; contra Cx LN in 1 pt.	

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8400 Amosson 2003	CT	NOMOS. Peacock	10 MV	Ipsilat and contralat parotids had threshhold limits of 35 Gy and 25 Gy, respectively. (ave mean doses to ipsilat and contralat parotids were 24.2 and 19.1 Gy, respectively) No attempt made to avoid submandibular glands. Sp cd 40 Mandible 58		n=13 with "Talon" fixation device n=17 Reinforced Aquaplast mask.		
9290 Teh 2002				Daily fractions of 2.4 and 2 Gy to primary and secondary targets to a total dose of 60 and 50 Gy, respectively. Overall tx course was five weeks (daily tx). Dose to parotids limited- for midline tumors to 25 Gy, for unilateral tumors the ipsilat parotid was limited to 30-35 and contralat 25 Gy.				

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9330 Kovacs 2002		HELAX TMS	6 MeV	Prescription dose 51.3 Gy with 1.9 Gy/d		Mask fixation	Planning included pretherapeutic tumor extension and cx LN bilaterally	
9510 Jian 2002	CT	FOCUS (computerized medical systems, Inc., St Louis, MO)	6MV, 18MV and 9MeV	40.8-43.2 Gy @ 1.2/frac, 2 frac/day, 6 hr interval betw doses with 6 MV. After 1 wk brk, off-cord 16.8-19.2, 1.2/frac, 2 frac/d with 18MV. Finally, an additional 14.4 Gy in 12 fracs off brnstm. Boost to upper neck by electron beam if necessary. Total dose to primary tumor 74.4 Gy, to involved neck nodes 68-74.4 and to uninvolved neck nodes 50-60 Gy. Dose constraints: Brstm 60-65 Gy Sp cd 50 Gy			NPH and upper neck	

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10740, Pommier et al, 2000	CT	Elektra linear accelerator w/ multileaf collimator	Mixed X-ray 6 to 18 MV	63.5 Gy (56-68) 2 Gy frac/ 5 frac wk	6 to 15 (median 11)portals w/ multileaf collimation field shaping	Thermoplastic face mask	PTV including CTV plus 5 mm expansion Ipsilateral lymph nodes treated In 7 patients	Palatine prosthesis to protect floor of mouth Dose limited to 12 Gy for contralateral eye, 56 Gy to optic chiasm and contralateral optic nerve, 60 Gy to frontal CNS
11650, Kuppersmith et al., 1999	CT with contrast	Yes		14-71 Gy, 1.5-4.0 Gy/frac, 1 frac/day Dose constraints: Parotid glands 30 Gy	Dynamic multivane collimator, 40 beams	Screws in skull vertex attached top docking device		

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
13270 Lawson 2008	CT and PET	Eclipse (Varian Medical Systems)	6 MV	Mean (median, range) total dose to gross dz: 70.14 Gy (70.29, 69.3-70.4). Per fraction to gross dz: 2.13 (2.13, 2.1-2.2). To remainder of clinically involved neck: 61.05 (63.03, 54.4-63.03). Per fraction to clinically invol neck: 1.85 (1.91, 1.7-1.95). Clinically uninvolved neck: 58.34 (57.75, 54.4-63.03). Per fraction to clinically uninvolved neck: 1.77 (1.75, 1.7-1.91). 5 daily fractions per week, to median (range) of 33 fractions (31-35).			CTV= PTV + 1-1.5 cm margins.	
13340 Ikushima et al, 2008	CT MRI	Clinac 2100C, Arian Alpatro	4 and 10 MV	30 Gy, 2.0 Gy daily frac	Three to five ports with a 1.5 cm margin to CTV			

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16840, Wu et al, 2006	CT, MRI		Electron beam	Simultaneous modulated accelerated RT-GTV, CTV 70/2.5 Gy frac, 56/ 2.0 Gy frac With 28 frac within 6 weeks	IMRT using split-beam technique w/ middle and lower neck fields treated with single anterior field joined by CRT Coplanar means positioned every 40 degrees from the posterior and lateral directions	BrainLAB noninvasive thermoplast mask and localizer frame	CTV plus areas of potential microscopic spread including: nasopharynx, retropharyngeal nodes, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus, posterior third of the nasal cavity and maxillary sinuses. Included ipsilateral and contralateral neck nodes of level 1,2,3, 5	Brainstem, spinal cord, parotid glands, and lens specified at risk for inverse planning with different weights.
24330, Pfreunder et al., 2003	CT		5 MV linear accelerator	HnN compartments and lymphatic drainages were irradiated with 50.4 Gy/1.8 frac 5 frac/ wk GTV received 2nd 1.4 Gy frac after wk 4 of RT resulting in total 69.9 Gy in 5.5 weeks to GTV and 50.4 total to lymphatic drainage	Static wedge fields	Individualized masks for patient fixation		

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26140 Scorsetti 2001			6MV	1-18 fractions (med 8) at median dose of 30 Gy (range 6-54). Second boost of 10-30 Gy to reduced target volume if good responders.			PTV= GTV + 2-10 mm margin.	
37660, Wendt et al, 2006	CT	Mevatron KD2, Siemens Medical Solutions, Germany Inverse planning software: Helax TMS, Nucletron, Europe w/ KonRad, Siemens		5 frac/wk Median parotid gland dose 30 Gy or less in 37 or 39 patients and less than 26 in 29 patients rng 21-52.8 Gy.	Bilateral 3D-C-IMRT using standard 7-portal arrangement. Each portal modified by # D metallic compensator Lower neck and supraclavicular fossae (region II, IV, IV B) used single anterior field		Tumors of the nasopharynx, oropharynx, oral cavity, floor of mouth, gross primary tumor bed and lymph node down to the level of hyoid bone were irradiated	Median dose to one parotid gland at aimed at 26Gy or less
38290, Anand et al., 2008	CT, MRI	Yes (Plato ITPc or Primus)	Photons (6-MV)	Definitive IMRT 66 Gy, 1.9-2.0 Gy/frac, 33-35 frac to CTV1 and 70 Gy, 2.0-2.1 Gy/frac , to GTV for pts receiving CTx 70 Gy, 1.9-2.0 Gy/frac, 35-37 frac for pts	Multileaf collimator or compensators, 7-9 fields Separate low anterior field with midline laryngeal block	Thermoplastic mask for head and neck	GTV = primary tumor volume and metastatic LNs CTV1 = GTV plus 10-12-mm margin CTV2 = ipsilateral high risk but clinically negative LNs CTV3 = contralateral	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
				receiving IMRT alone Adjuvant IMRT 56-62 Gy toCTV1, 50-54 Gy to CTV2 and CTV3 50-52 Gy to supraclavicular region Dose constraints: Median Dmax Gy (rng) Spinal cord 45 (37-48) Brainstem 51 (33-58) Optic nerve 24 (1-61) Optic chiasm 26 (2-62) Cochlea 42 (0.5-53) Mandible 72 (28-77)			uninvolved LNs CTV1 for adjuvant IMRT included preop GTV and 15-20-mm margin to encompass surgical bed with soft tissue or bone invasion, or metastatic neck node regions with extracapsular extension PTV = CTV1 plus 5-mm margin	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
38530, Studer et al., 2008	CT			Definitive IMRT 69-72 Gy, 2.0-2.2 Gy/frac, 5 frac/wk Postop IMRT 66 Gy, 2 Gy/frac, 5 frac/wk All schedules based on SIB delivery				
38640, Studer et al., 2008	CT			Definitive IMRT 70-73 Gy, 2.1-2.2 Gy/frac, 33-35 frac to boost PTV 73 Gy, 2,2 Gy/frac, 33 frac to large GTVs 70 Gy, 2 Gy/frac, 35 frac in pts with CNS structures in the PTV Adjuvant IMRT 60-66 Gy, 2 Gy/frac, 30-33 frac to boost PTV Elective dose 54 Gy in most pts, 60-66 Gy prescribed for higher risk pts All schedules based on SIB delivery			GTV = primary or total gross tumor volume	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
38840 Seung 2008	CT	ADAC Pinnacle version 7.4; Phillips/ADAC	6 MV	SIB Median prescribed dose 69.96 Gy (66-70) to PTV70/66; 59.4 Gy (59.4-60) to PTV59.4; and 54 (54-54.12) to PTV 54. Median dose per frac: 2.12 (2.12-2.2) to PTV70/66; 1.8 (1.8-2.0) to PTV59.4 and 1.64 (1.64-1.8) to PTV54. Normal tissue dose limitation max ≤45 to sp cd, and ≤54 brstm. Mean to parotids ≤26.	7-9 equally placed coplanar beams	Aquaplast mask	Primary tumor and upper neck above VCs GTV:gross extent of tumor and LNd > 1cm diameter. CTV70:GTV plus margin for potential microscopic spread. CTV59.4 (highrisk CTV):CTV70 + retropharyngeal nodes and levels IB-V on LN positive side. PTV: CTV + margin 0.3-1 cm	
38850 Caglar 2008		ECLIPSE (Varian Medical Systems)		IMRT 70 Gy at 2Gy/fraction to GTV, 64 to high-risk CTV, and 60 to low-risk CTV. Post op cases 64 Gy. Parotid glands mean dose 26 Gy. Sp cd dose 46 Gy.		thermoplastic	GTV: for definitive cases = tumor and involved LNs High-risk CTV for definitive = GTV plus margin for subclinical dz and neck nodal regions at greatest risk of subclinical involvemt. Low risk CTV included uninvolved Cx LNs. PTV: CTV + 5 mm margin.	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
39000 Sanguineti 2008	CT	Pinnacle[3]	6 MV	Early stage lesions (stage 1-2) hypofractionated schedule. Adv stage dz acc/hyperfrac 78 Gy to PTV1 at 1.3 Gy twice daily. Others rec'd conventional frac at 2 Gy/frac to PTV1.		Thermoplastic	CTV1=CTV + GTV CTV2=included tissue at high risk of containing microscopic dz. CTV3=included tissue at low risk of microsc dz. PTV1, PTV2 and PTV3 expanded the corresponding CTV by 5mm.	
39020 Rosenthal 2008		ADAC Pinnacle		To primary site: 60-63/30 fx n=5 66/30 fx n=79 66-68/33 fx n=5 70/33 fx n=56 72/40 fx (concomitant boost) n=15				

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
39300, Hoppe et al., 2008	CT, MRI	Yes (MSKKC system)	Photons (6-MV)	70 Gy, 2.1 Gy/frac to PTV1 60 Gy, 2 Gy/frac to PTV2 54 Gy, 1.8 Gy/frac to PTV3 54 Gy to involved neck All treated once daily, 5 days/wk Dose constraints: Brainstem < 50 Gy Spinal cord < 45 Gy Cochlea < 50 Gy Retina/eye < 45 Gy Optic nerve < 54 Gy Optic chiasm < 54 Gy	Dynamic multileaf collimator with dynamic leaf sequencing	Custom Aquaplast mask that also immobilizes shoulders when neck is treated	CTV1 = clinical tumor volume included gross disease with 3-5-mm margin CTV2 = surgical bed and areas at high risk of microscopic disease CTV3 = LN regions at risk PTV1, 2, 3 = CTV 1, 2, 3 plus 5-10-mm margin, expanded 1-mm in areas adjacent to critical normal structures Bilateral or ipsilateral neck irradiation for involved LNs	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
39390, Worden et al., 2008	CT, PET			70 Gy, 2 Gy/frac daily, 5 frac/wk to gross disease and 10-20-cm margins 59-63 Gy, 1.7-1.8 Gy/frac to tissue volumes at risk of harboring subclinical disease			Gross tumor volume plus 10-20-cm margins Bilateral neck	

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT
Single-Arm Studies

Table E-D. Outcome assessment

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
560, Biagioli et al., 2007	Tumor response, DFS, PFS, OS, LRRFS	Acute and late toxicities	CR = NED after tx PR = ≥ 50% reduction of tumor SD = < 50% reduction to 25% enlargement of tumor PD = > 25% tumor enlargement		med 14 mos. (rng 1-53 mos.)
580, Dirix et al., 2007	2-yr LC, OS, DFS Acute and late toxicities, in particular ocular				Baseline, every 2 mos. in first 2 yrs, every 3 mos. in third yr, every 4 mos. in fourth yr, every 6 mos. in fifth yr, annually thereafter med 24 mos. (rng 7-47 mos.)
1010, Urbano et al., 2007	Acute and late toxicities, in particular laryngeal	Tumor control	CR: No evidence of disease (clinical, radiographic, or pathologic		Acute toxicity: 2.5 mos. after commencement of CRTx (1.5 mos. of Tx plus 1 mo after) and at wk 14 (2mos. post Tx) Late toxicity: 3, 6, 12, 18, 24 mos, yearly thereafter Tumor response: 1-1.5 mos. post-Tx
1420 Feng et al, 2007	Dysphagia measures	Patient-reported QoL Acute and late observer-assessed toxicity			Baseline, weekly during therapy, 1 (acute) and 3 (late) mos. after therapy
1430, Scrimger et al., 2007	Salivary function, QoL	QoL, late salivary gland and other toxicities			
1500, Lee et al., 2007	2-yr LPFS, LRPFS, RPFS, DMFS, OS, laryngectomy-free survival	Tracheostomy tube placement, acute and late toxicities			Weekly during treatment, every 1-2 mos. for first 2 yrs, every 4-6 mos. thereafter
1770, Yao et al., 2007 (see 4630, Yao et al., 2005)	LRFS, RRFS, DMFS, OS				1 mo after treatment, every 1.5-2 mos. for first yr, every 2-3 mos. in second yr med 29 mos. (rng 0.2-74 mos.)

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
1780, Lee et al., 2007	2-yr LRPFS				Baseline, every 1-2 mos. post-RT for first 2 yrs, then every 4-6 mos med 35 mos (rng 2-80 mos.)
1900, Ben-David et al., 2007	Mandibular osteoradionecrosis (ORN)				Every 1.5-2 mos. during first 2 yrs after therapy, every 3-4 mos. thereafter
1990, Yao et al., 2007	OS, DSS, LRFS, LRRFS, DMFS				1 mo post-RT, every 1.5-2 mos. in first yr, every 2-3 mos. in second yr med 17 mos. (rng 0.3-59 mos.)
2180, Daly et al., 2007	OS. LPFS, DFS	Acute and late toxicities			Every 1-2 mos. for first 6 mos. post RT, every 3 mos. for next 6-12 mos, every 4-6 mos. from 18-36 mos, annually thereafter med 39 mos. (rng 6-82 mos.)
2290, Yao et al., 2006	OS, LPFS, LRC, DMFS, DFS	Acute and late toxicities			1 mo post RT, every 1.5-2 mos. in the first yr, every 2-3 mos. in the second yr
2370, Garden et al., 2007	OS, LRC, RFS	Acute and late toxicities			med 45 mos. (rng 15-63 mos.)
2430, Vosmik et al., 2006	Acute toxicities				
2770, Cheng et al., 2006	5-yr LRC, DMFS, OS				med 58 mos
3080 Meirovitz 2006	XST SLF				At 6-24 months (median 12 mos.) after completion of therapy same
3320, Portaluri et al., 2006	Xerostomia				med 18 mos. (rng 16-19 mos.)
3340 Studer 2006	LC Distant control Nodal control Overall DFS	SKN MUC DYS LX SPN QOL (weight loss)			Mean 16 months (4-44 months) During treatment, pts clinically assessed at weekly intervals, and at 2 weeks and 2 months after completion of treatment.
3400 Studer, 2006	ORN	LRC			

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
3570 Saarilahti 2006	XST and SLF	MUC LRC			XST: 2-3 month intervals after IMRT SLF: measured before therapy (baseline), and 6 and 12 months after last date of RT. LRC: median F/U 31 months (14-62 mos.)
3790, Ozsahin et al., 2006	Acute and late toxicities	OS, LRC,			med 36 mos. (rng 8-37 mos.)
3820 McMillan 2006	QoL SLF XST				SLF assessed baseline, then 2,6, and 12 months after IMRT.
4290, Lau et al., 2006	OS, DSS, LRRFS	Acute toxicities	CR according to physical examination with or w/out imaging		Every mo during first yr, every 2 mos. in second yr, every 3-4 mos. in third yr med 16 mos
4430 Kwong 2006	LRC MFS PFS OS	MUC SKN			Median follow-up 25 months (3-55.5 months) Assessed weekly during treatment. At 6 and 8 weeks after completion of IMRT, biopsied to assess dz remission. After IMRT completion, f/u q month during 1st yr, q 2 mos. during 2nd yr, then q 3-6 mos. afterwards.
4630 Yao	LC LRC MFS OS				Median time from tx completion to LR recurrence was 4.7 mos. (1.8-15.6 mos.)
5020, Nishimura et al., 2005	Xerostomia and parotid dose volume				
5120, Wolden et al., 2006	3-yr LC, LRC, MFS, PFS, OS	Other acute and late toxicities			Median follow up 35 mos. (3-74)
5210, Duthoy et al., 2005	OS, DFS, DSS, LC	Toxicity			
5310, Zheng et al., 2005	OS, LFFS	Major late toxicities			med 35 mos. (rng 9-71 mos.)
5330, Lu et al., 2005	LC, LRC, DFS, OS	Acute and late toxicities	PCR defined as no evidence of malignant cells in tumor bed biopsy 4 mos. after completion of RT		Every 2-3 mos. for first 3 yrs post RT, every 4-6 mos. for next 2 yrs, annually thereafter med 24 mos. (rng 15-31 mos.)

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
5420, Pan et al., 2005	Hearing loss				Baseline, 1, 6, 12, 24, 36 mos
5740, Thorstad et al., 2004	Salivary function	Acute nonhematologic toxicities			Baseline, 6 mos, 12 mos
6430, Kwong et al, 2004	Salivary Function	Dose Volume			Weekly during RT, 6-8 wks after RT completion. Every month of 1st year, every 2 months 2nd year, 3-6 mo thereafter
6530 Zheng 2004	LFFS (local failure free survival) DSS OS	Radiation induced toxicities			After salvage tx completion, q 2-3 months for first 2 yrs, then q 4-6 mos. thereafter. Median f/u58 mos. (12-95)
7090, Chao et al., 2004	DMFS, LRC, DFS, Gross tumor volume	Toxicity			
7110, Sze et al., 2004	LFFS, PFS, OS				med 23 mos. (rng 1-47 mos.)
7370, Lu et al., 2004	LRC	Acute toxicities			med 9 mos. (rng 3-13 mos.)
7570, Levendag et al., 2004	3-yr RRFS, LRRFS, OS, DFS				med 29 mos
7750, Liu et al., 2003	OS, DFS, DSS	Acute and late toxicities			Every 1-2 mos. post-RT for first yr, every 3 mos. for second yr, every 6 mos. thereafter med 17 mos. (rng 3-42 mos.)
8250, Munter et al., 2003	2-yr OS, LC	Acute and late toxicities			1.5 mos. post-RT, every 3 mos. for first yr, every 6 mos. thereafter med 14 mos. (rng 3-34 mos.)
8270 Braaksma 2003	SLF XST	LRC DFS OS			Median f/u 18 mos. (2.4-39.6)
8370 Padovani 2003	PFS OS	Acute and late toxicities			Med f/u 25 mos. (4-51 mos.) **Note: ?? should we abstract the number of local relapses??**
8400 Amosson 2003	XST				

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
9290 Teh 2002	QOL TAE XST				Median f/u 11.5 months
9330 Kovacs 2002	Toxicities and survival				
9510 Jian 2002	LRC DFS OS	acute toxicity (MUC and QOL incl weight loss)			q 2 mos. 1st 2 yrs q 3-6 mos. yrs 3-5 and 1 yr intervals thereafter
10740, Pommier et al, 2000	OS, LPFS, LPFR,	Toxicity			
11650, Kuppersmith et al., 1999	Acute toxicity				
13270 Lawson 2008	LC LRC MFS OS	Acute and late toxicities (MUC, ESO, LAR, sal gl, SKN, SUB, blood cnt)			Mean (median, range) 22.2 mos. (20.1, 3.6-42.8) F/U 1 month p tx, then q 1-3 mos.
13340 Ikushima et al, 2008	SR, cause of death	Toxicity			
16840, Wu et al, 2006	Local regional FS, OS	Toxicity			
24330, Pfreunder et al., 2003	OS, LTC, larynx preservation	Toxicity			
26140 Scorsetti 2001	OS TAE				
37660, Wendt et al, 2006	RTOG toxicity				Median FU 21 mo
38290, Anand et al., 2008	2-yr LRC, OS	Acute and late toxicities			Baseline, 3 mos, 6 mos med 19 mos. (rng 6-36 mos.)
38530, Studer et al., 2008	LC, DSS, DFS				med 21 mos. (rng 3-67 mos.)
38640, Studer et al., 2008	3-yr LC, LRC, DFS, OS, DMFS				med 20 mos. (rng 3-72 mos.)
38840 Seung 2008	LC OS Cause specific survival (CSS)	Acute and late toxicities			p RT, q 2-3 mos. for first 2 yrs, then q 3-6 mos. thereafter.

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
38850 Caglar 2008	DYS	Aspiration (*I did not abstract this intermediate outcome)			Median 10 mos
39000 Sanguineti 2008	Local and regional failure LC LRC				Q 2-3 mos. dur 1st 2 yrs, then q 3-4 mos. dur yrs 3-5.
39020 Rosenthal 2008	Acute toxicities				
39300, Hoppe et al., 2008	2-yr LPFS, OS	Acute and late toxicities			1-2 mos. post-RT, every 3 mos. for the next 3 yrs, annually thereafter med 28 mos. (rng 11-57 mos.)
39390, Worden et al., 2008	Tumor response, DSS, OS	Acute and late toxicities	Biopsy-proven residual disease		2 mos. post-RT for initial assessment med 64 mos

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-E. Time to event outcomes

Study	Outcome	Grp	N	Med (mos.)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%CI)	Comments
560, Biagioli et al., 2007	OS		41	18	77	49	~ 40	~ 34					
	OS w/CR		24	33									
	OS w/PR		7	12									
	OS w/SD		4	12									
	OS w/PD		6	7									
	OS w/resect		17	31	~ 77	~ 66	~ 66	~ 66		M-C	0.14		
	OS w/out resect		24	23	~ 69	~ 36	~ 28	~ 18					
	OS + cisplatin		15	32	~ 70	~ 63	~ 48	~ 48		M-C	0.17		
	OS + carboplatin		26	13	~ 44	~ 39	~ 39	~ 29					
	OS w/induction CTx		13	13	~ 60	~ 37	~ 37			M-C	0.4		
	OS w/out induction Ctx		28	19	~ 70	~ 44	~ 34						
	DFS (CR only)		24	27	~ 60	48	~ 48	~ 48					
	PFS (CR only)		24	11	~ 42	38	~ 38	~ 38					
580, Dirix et al., 2007	LC		25	nr	~ 88	81	~ 80						
	DFS		25	nr	~ 85	77	~ 78						
	OS		25	nr	~ 93	88	~ 88						
	DMFS		25	nr		88							
1010, Urbano et al., 2007	OS	DL1	15	17 (12-37)									
		DL2	15	8 (1-14)									
	TTR	DL1/DL2	30	9 (6-13)									

Study	Outcome	Grp	N	Med (mos.)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%CI)	Comments
1420 Feng et al, 2007													
1430, Scrimger et al., 2007													
1500, Lee et al., 2007	LPFS		31		~88	86	86	86	86				
	LRPFS				84	84	84	84					
	RPFS						94						
	DMFS						92						
	OS						63						
	OS	larynx pts	20		~84	69	69						
		hypopharynx	11		~82	53	53	53					
	laryngectomy-FS				~92	89	89	89					
1770, Yao et al., 2007 (see 4630, Yao et al., 2005)	LRFS		90		~98	96	96	~96	~96				
	RRFS				~95	95	95	~95	~95				
	DMFS				~88	82	80	~80	~80				
	OS				~88	80	68	~68	~68				
1780, Lee et al., 2007	2-yr LRPFS	IMRT		28		52				L-R	< 0.001		Not comparative study but gave separate data for IMRT and non-IMRT
		non-IMRT		~4		20							
1900, Ben-David et al., 2007													

Study	Outcome	Grp	N	Med (mos.)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%CI)	Comments
1990, Yao et al., 2007													
	OS		55		~70	68	68	68	68				
	DSS				~75	74	74	74	74				
	LRFS				~85	85	85	85	85				
	LRRFS				~84	82	82	82	82				
	DMFS				~94	89	89	89	89				
2180, Daly et al., 2007													
	OS		36	~48	~100	69	~69	~45	45				
	LPFS				~84	62	~62	~58	58				
	DFS				~84	62	~60	~60	55				
2290, Yao et al., 2006													
	OS		66		~96	91	78	~80	~80				
	LPFS				~98	98	92	~92	~92				
	LRC				~98	98	92	~92	~92				
	DMFS				~87	88	80	~80	~80				
	DFS				~92	84	64	~64	~64				
2370, Garden et al., 2007													
	OS		51		100	93	87	87	~80				
	LRC				~95	93	93	93	93				
	RFS				~93	87	84	~82	~82				
2430, Vosmik et al., 2006													

Study	Outcome	Grp	N	Med (mos.)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%CI)	Comments
2770, Cheng et al., 2006	LRC	overall	630						89				
		T1 dis	155		~98	96	~96	~95	95	L-R	0.001		
		T2 dis	163		~98	97	~96	~96	91				
		T3 dis	140		~98	92	~91	~90	87				
		T4 dis	172		~96	91	~92	~85	81				
		< 40 yrs	223		~98	97	~96	~95	93	L-R	0.018		
		> 40 yrs	407		~95	93	~90	~88	87				
		WHO I, II	148		~92	89	~85	~82	81	L-R	1E-04		
		WHO III	482		~98	96	~94	~92	91				
		LDH < 410	548		~98	95	~93	~92	91	L-R	3E-04		
		LDH > 410	82		~95	89	~85	~81	75				
		AG2 < 2 sites	373		~98	96	~95	~94	93	L-R	< 0.0001		
		AG2 > 2 sites	257		~95	91	~89	~83	81				
		RS0 (low)	96		~100	100	~100	~100	100	L-R	< 0.0001		
		RS1 (int-low)	266		~98	96	~95	~95	93				
		RS2 (int-high)	184		~98	94	~91	~87	83				
		RS>3 (high)	84		~90	81	~78	~73	71				
	MFS	RS0 (low)	96		~98	97	~97	~95	95	L-R	0.002		
		RS1 (int-low)	266		~95	88	~86	~86	85				
		RS2 (int-high)	184		~95	85	~81	~80	78				
		RS>3 (high)	84		~88	81	~78	~76	73				
	OS	RS0 (low)	96		~100	100	~98	~96	94	L-R	< 0.0001		
		RS1 (int-low)	266		~98	93	~89	~88	87				
		RS2 (int-high)	184		~96	93	~86	~83	76				
		RS>3 (high)	84		~90	83	~70	~63	63				

Study	Outcome	Grp	N	Med (mos.)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%CI)	Comments
3320, Portaluri et al., 2006													
3340, Studer, 2006	Local DFS				~90	90	~90						
	Regional DFS				~93	93	~93						
	Distant DFS				~93	93	~93						
5120, Wolden et al., 2006	LC	IMRT 3DCRT	74 35	35	~95 ~95	~93 ~82	91 79	~91 ~74	~84 ~74		.11 .11		P=.11
	LRC	IMRT											
	MFS	IMRT					78						
	PFS	IMRT					67						
	OS	IMRT			~97	~87	83	~79	~73				

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-F. Time to event outcome regression modeling

Study	Design/ Outcome /Model	Candidate predictors/Method for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/ Methods for Selecting Predictors for Multivariate Model	Proportional Hazards Assumption Assessed?/ Interactions Considered	Multivariate Model Results, Variable (p value)	Discrimination/Validation Methods/Results	Calibration/Goodness of Fit
4290, Lau et al., 2006	OS	age, initial Hb, KPS, % CTX (< 50%, > 50%), T, N, overall stage, tumor site	age, initial Hb, < 50% CTx, T, N stage (< 0.07, 2-tailed)	age, initial Hb, KPS, % CTx, T, N, overall stage		CTX, N stage (<0.07, 2-tailed)		
	LRRFS	same	age, KPS, CTX, T, N stage (< 0.07. 2-tailed)					

Study	Design/ Outcome /Model	Candidate predictors/Method for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/ Methods for Selecting Predictors for Multivariate Model	Proportional Hazards Assumption Assessed?/ Interactions Considered	Multivariate Model Results, Variable (p value)	Discrimination/Validation Methods/Results	Calibration/Goodness of Fit
5020, Nishimura et al., 2005	Dose to parotid correlated w/ incidence of Xerostomia grade Mean and median parotid dose decreased significantly from CT1-CT2	Initial Volume of parotid glands CT-1 43.1+ or – 15.2 ml CT-2 (3-4 wks of IMRT) 32 + or – 11.4ml	0.04 P<0.0001 (regression rate of parotid glands not significantly correlated w/ grade of xerostomia p=.186)					

Study	Design/ Outcome /Model	Candidate predictors/Method for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/ Methods for Selecting Predictors for Multivariate Model	Proportional Hazards Assumption Assessed?/ Interactions Considered	Multivariate Model Results, Variable (p value)	Discrimination/Validation Methods/Results	Calibration/Goodness of Fit
5310, Zheng et al., 2005	OS LFFS	age, sex, histo, mn dose primary RT, vol irrad primary RT, T stage, GTV local recurrence, int initial RT to dx recur, late tox from prev RT, CTx, simultan RR	T stage, GTV (< 0.01)	same		T stage (< 0.01)		
6430, Kwong et al, 2004								

Study	Design/ Outcome /Model	Candidate predictors/Method for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/ Methods for Selecting Predictors for Multivariate Model	Proportional Hazards Assumption Assessed?/ Interactions Considered	Multivariate Model Results, Variable (p value)	Discrimination/Validation Methods/Results	Calibration/Goodness of Fit
7090, Chao et al., 2004	Univariate analysis of 4 yr estimate DFS, LRC, DMFS	Gender	.7, .5, .9	Definitive IMRT Group DFS, LRC, DMFS	Gross tumor volume, nodal gross tumor volume	DFS:		
						GTV .03		Standard Error
		Subsite	.5, .6, .6			nGTV .05		0.01
								0.03
		IMRT(Postop/Definitive)	.02, .07, .2			LRC		
						GTV .03		
		Chemotherapy				nGTV .01		0.07
			.6, .7, .8					0.01
		T stage				DMFS		
						GTV .03		
		Nodal status	.14, .4, .2					0.009
		AJCC stage	.56, .4, .9					
		Fraction size	.2, .3, .4					
			.14, .5, .2					

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT, and 2DRT

Table E-G. Tumor response

Study	Group	N	CR	PR	SD	PD	NE	Test	p	Comments
560, Biagioli et al., 2007		41	24(58)	7(17)	4(10)	6(15)				
1010, Urbano et al., 2007	DL1 DL2	15 15	80 87							
4290, Lau et al., 2006		56	82							
4430 Kwong 2006										2 pts had persistent NP disease after IMRT. (both received salvage stereotactic radiosurgery – 1 remained well, 1 died of progressive local dz) 3 pts relapsed 14-37 mos. after dx and all died of progressive dz.
4630 Yao										11 LR failures 7 local failures 3 regional failures 1 failure at both the primary and reg LN 16 patients failed distantly
5330, Lu et al., 2005		25	96							
7370, Lu et al., 2004		49	100(at 3 mo f/u)							
8370 Padovani 2003	3DRT					N=2 during RT				
9290 Teh 2002			n=25 (89%)	n=3 (11%)						
38840 Seung 2008	All	69								Of 69, 1 had persistent local dz after tx.
39390, Worden et al., 2008	CRT	53	92			8				

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT, and 2DRT

Table E-H. Quality of life

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
1420 Feng et al, 2007	UWQOL	1 swallowing question w/ 5 answers	Pre-RT, 3mos	Overall		36	Med10 (rng 10-30), 20 (10-50)	P<0.001
	HNQOL	2 questions related to dysphagia with 5 answers each		Liquids			Med 0(rng 0-3), 1 (0-3)	P<0.001
				Solids			Med 0 (rng 0-3), 2 (0-4)	P<0.001
1430, Scrimger et al., 2007	UWQOL	9 health-related questions, total score reported	Pre-RT, 3, 6, 12 mos	NPH OPH OC LAR UKP All pts		10 9 20 6 2 47	92.5, 77.5, 82.0, 78.5 71.0, 73.0, 71.0. 78.0 73.0, 76.0, 76.5, 79.0 83.5, 85.0, 86.5, 85.5 80.5, 79.5, 83.0, 82.5 ~79, ~76, ~78, 80	
	Xerostomia QOL	9 questions related to oral moisture, total score reported	Pre-RT, 3, 6, 12 mos	All pts		47	~.6, ~ 1.4, ~1.4, ~1.2	
	RTOG late xerostomia score	0-5 scale total score	Pre-RT, 3, 6, 12 mos	All pts		47	0, ~1.2, ~1.0, ~1.0	
3340 Studer 2006	SOMA-LENT and RTOG/EORTC radiation morbidity score used to assess toxicity.							Feeding tube inserted in 9 patients (30%). Mean body weight loss at 1 yr after tx was 3.3% (+11% to -11%)
3820 McMillan 2006	Medical outcomes short form (SF-36) Scale of 0-100 (higher score better health status)				BL, 2, 6, 12	32	Mean (SD) BL, 2 mo, 6 mo, 12 mo/p value all 4 visits, BL vs. 2 mo, BL vs. 6 mo, BL vs. 12 mo Physical function 94.4 (9.0) 89.4 (6.3) 92.3 (6.2) 92.7 (8.6) <.001 .001 .028 .190 Role—physical 64.8 (35.3) 32.0 (38.2) 55.5 (41.5) 72.7 (40.3) <.001 .001 .291 .330 Bodily pain 88.2 (20.3) 75.6 (26.9) 84.6	

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
	EORTC QLC-30 questionnaire Scale of 0-100 (higher score higher/healthier level of functioning)						(20.0) 81.1 (28.3) .387 .023 .498 .166 General health 57.2 (21.1) 48.3 (19.4) 52.7 (22.5) 62.0 (23.3) .014 .049 .163 .172 Vitality 72.7 (16.8) 55.9 (20.2) 64.4 (18.9) 67.7 (19.6) .006 .001 .012 .138 Social functioning 82.4 (24.4) 71.5 (26.8) 89.1 (19.8) 89.5 (19.9) .001 .049 .123 .085 Role—emotional 61.5 (38.0) 52.1 (47.1) 71.9 (40.7) 78.1 (37.5) .009 .462 .207 .073 Mental health 71.0 (17.7) 75.1 (19.1) 77.25 (16.8) 80.3 (19.0) .089 .121 .073 .036 Mean (SD) BL, 2 mo, 6 mo, 12 mo/p value all 4 visits, BL vs. 2 mo, BL vs. 6 mo, BL vs. 12 mo <u>Global health status/QOL</u> Global health status 55.5 (19.6) 54.7 (15.4) 65.9 (19.6) 67.2 (20.3) .001 .989 .004 .004 Global health status(revised) 57.6 (18.9) 54.9 (13.4) 65.6 (18.2) 66.7 (19.6) .011 .474 .013 .006 <u>Functional scales</u> Physical functioning (revised) 92.7 (9.5) 83.3 (7.2) 88.5 (9.6) 89.6 (10.7) <.001 <.001 .027 .082 Role functioning 97.9 (7.0) 92.7 (10.3) 94.3 (10.0) 96.4 (8.2) .004 .002 .020 .180 Role functioning (revised) 85.9 (15.3) 81.3 (16.8) 90.1 (14.0) 92.2 (13.4) .008 .112 .290 .089 Emotional function 80.5 (15.5) 86.5 (12.3) 87.8 (15.0) 88.8 (15.2) .097 .036 .034 .014 Cognitive function 86.5 (15.5) 83.9 (19.2) 83.3 (13.4) 85.9 (16.5) .729 .533 .530 1.000 Social function 82.8 (21.8) 77.1 (21.5) 91.1 (13.4) 90.6 (16.9) <.001 .118 .016 .095 <u>Symptom scales</u> Fatigue 14.2 (15.5) 25.7 (17.3) 16.0 (13.5) 14.9 (16.6) <.001 .002 .479 .743 Nausea/vomiting 3.1 (6.6) 7.8 (15.3) 1.0 (4.1) 1.0 (4.1) .032 .101 .157 .157 Pain 7.8 (12.7) 8.3 (14.0) 8.3 (12.0) 7.3 (16.4) .685 .715 .793 .593	

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
	EORTC QLQ-H&N35 Score of 1-100 (higher score higher/healthier level of functioning)						Symptom items Dyspnea 10.4 (17.8) 10.4 (19.7) 9.4 (15.2) 8.3 (14.7) .949 1.000 .763 .593 Insomnia 24.0 (31.9) 15.6 (23.9) 13.5 (23.7) 13.5 (20.5) .141 .118 .049 .062 Appetite loss 15.6 (20.7) 24.0 (22.8) 6.3 (13.2) 5.2 (12.3) <.001 .103 .013 .008 Constipation 5.2 (12.3) 8.3 (14.7) 6.3 (13.2) 9.4 (19.4) .447 .180 .655 .157 Diarrhea 5.2 (12.3) 2.1 (8.2) 9.4 (17.4) 7.3 (14.0) .120 .180 .248 .527 Financial difficulties 17.7 (25.4) 12.5 (20.3) 7.3 (14.0) 6.3 (15.7) .012 .218 .019 .005 Mean (SD) BL, 2 mo, 6 mo, 12 mo/p value all 4 visits, BL vs. 2 mo, BL vs. 6 mo, BL vs. 12 mo Pain 8.3 (9.0) 18.5 (14.3) 14.8 (11.9) 9.1 (12.2) .001 <.001 .016 .797 Swallowing 1.6 (3.3) 11.5 (9.6) 9.6 (7.7) 9.6 (9.3) <.001 <.001 <.001 <.001 Senses problem 6.7 (15.2) 42.2 (22.4) 25.0 (18.5) 17.7 (19.8) <.001 <.001 .002 .048 Speech problem 6.3 (10.2) 12.8 (15.5) 11.1 (10.6) 8.7 (12.5) .006 .010 .008 .129 Trouble social eating 2.3 (6.1) 20.1 (16.0) 12.5 (12.5) 9.4 (11.3) <.001 <.001 <.001 .006 Trouble social contact 1.5 (5.3) 8.3 (11.0) 5.0 (7.4) 3.1 (7.8) <.001 .001 .003 .044 Less sexuality 16.1 (19.7) 35.1 (36.1) 23.0 (26.9) 25.0 (30.6) .017 .001 .194 .087 Teeth 5.2 (12.3) 9.7 (17.6) 8.3 (14.7) 9.4 (15.2) .712 .285 .366 .102 Open mouth 0.0 (0.0) 9.4 (15.2) 17.7 (18.9) 10.4 (15.7) <.001 .003 <.001 .002 Dry mouth 13.5 (20.5) 82.3 (20.7) 64.6 (26.7) 47.9 (29.3) <.001 <.001 <.001 <.001 Sticky saliva 4.2 (11.2) 63.9 (38.0) 40.7 (31.1) 34.6 (25.3) <.001 <.001 <.001 <.001 Coughing 19.8 (20.5) 14.6 (20.6) 11.5 (21.8) 10.4 (15.7) .742 .766 .315 .479 Felt ill 6.3 (13.2) 8.3 (14.7) 5.2 (12.3) 6.3	

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
							(13.2) .767 .068 .436 .238 Pain killers 9.4 (29.6) 0.0 (0.0) 12.5 (33.6) 3.1 (17.7) .141 .083 .655 .317 Nutrition supplement 18.8 (39.7) 28.1 (45.7) 25.0 (44.0) 25.0 (44.0) .809 .317 .564 .564 Feeding tube 0.0 (0.0) 0.0 (0.0) 0.0 (0.0) 0.0 (0.0) - - - - Weight loss 31.2 (47.1) 40.6 (49.0) 12.2 (33.6) 9.4 (29.6) .005 .467 .083 .020 Weight gain 15.6 (36.9) 15.6 (36.9) 21.9 (42.0) 40.6 (49.9) .050 1.000 .480 .033	
9290 Teh 2002	RTOG							23 of 28 pts (82%) lost 10% or less of pre-tx weight. 13 of 28 (46%) required IV fluids and/or tube-feeding.

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
9510 Jian 2002	NCI toxicity criteria 1-4	Weight loss	Concomitant phase	CDDP		31	Grade 1 32.3% Grade 2 22.6% Grade 3 0 Grade 4 0	
				CDDP/5-FU		17	Grade 1 17.6 Grade 2 47.1 Grade 3 0 Grade 4 0	
		Vomiting	Concomitant phase	CDDP		31	Grade 1 25.8 Grade 2 35.5 Grade 3 6.5 Grade 4 3.2	
				CDDP/5-FU		17	Grade 1 23.5 2 52.9 3 11.8 4 0	
		Vomiting	Adjuvant phase	CDDP		28	1 25.0 2 25.0 3 7.1 4 7.1	
				CDDP/5-FU		16	1 37.5 2 25.0 3 0 4 0	
		Leukopenia/Hb/Plt	Concomitant phase	CDDP		31	1 35.5/48.4/16.1 2 22.6/9.7/0 3 0/3.2/0 4 0/0/0	
				CDDP/5-FU		17	1 35.3/47.1/0 2 5.9/11.8/0 3 0/0/0 4 0/0/0 1 10.7/50.0/21.4	

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
		Leukopenia/Hb/Plt	Adjuvant phase	CDDP		28	2 42.9/25.0/0 3 7.1/0/0 4 0/0/0	
				CDDP/5-FU		16	1 31.3/50.0/18.8 2 31.3/6.3/0 3 0/0/0 4 0/0/0	
		Tube feeding rate		CDDP		31	64.5%	
			Concomitant phase	CDDP/5-FU		17	35.3%	
			Concomitant phase					

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-I. Response/adverse event regression modeling

Study	Design/ Outcome/ Model	Candidate Predictors/ Method for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/ Methods for Selecting Predictors for Multivariate Model	Interactions Considered?	Multivariate Model Results, Variable (p value)	Discrimination/ Validation Methods/ Results	Calibration/ Goodness of Fit
5310, Zheng et al., 2005	Major late tox	age, sex, histo, mn dose primary RT, vol irrad primary RT, T stage, GTV local recurrence, int initial RT to dx recur, late tox from prev RT, CTx, simultan RR	T stage, GTV (< 0.01)	same		GTV (< 0.04)		

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-J. Xerostomia incidence

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
580, Dirix et al., 2007	NCI CTC (v3.0) RTOG/EORTC	0, 1, 2 0, 1, 2, 3, 4	acute 6 mos			20, 4, 1, 9, 9	40, 56, 4 80, 16, 4, 0, 0		
1010, Urbano et al., 2007	NCI CTC (v2.0)	2, 3	12 mos 6 mos	DL1 DL2	10, 14, 1	15 15	60/0 73/7		
1500, Lee et al., 2007	NCI CTC (v 2.0)	0-1 2	12 mos			25 1	81 3		
1780, Lee et al., 2007	NCI CTC						100 pre-RT		
2430, Vosmik et al., 2006	RTOG	0,1,2,3,4				0, 15, 23, 0, 0	0, 39, 60, 0		
3080 Meirovitz 2006	RTOG/EORTC XST questionnaire (0-100 with higher number representing greater levels of XST)	0-3			6-24 (med 12) 6-24 (med 12)	38 38	100 100	Mean score of 3 observers 0.34 (SD 0.48) Range 0-2 Mean 37.3 (SD 24.4) Median 35 Range 0-86	
3320, Portaluri et al., 2006	RTOG/EORTC	0,1,2,3		38pts		12, 9, 14, 3	32, 24, 37, 8		

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
3570 Saarilahti 2006	XST: LENT-SOMA scale (reported both by patient [subjective] and by radiotherapist [objective].				12	36	100	<u>Subj XST Subman gl spared</u> Y N Grade 0/1 14 (78) 7 (39) Grade 2/3 4 (22) 11(61) p=0.018 <u>Obj XST Subman gl spared</u> Y N Grade 0/1 14 (78) 9 (50) Grade 2/3 4 (22) 9 (50) P=0.083 <u>Managemt of XST Subman gl spared</u> Grade 0/1 13 (72) 7 (39) (none needed) Grade 2/3 5 (28) 11 (61) (occ/freq) P=0.044	
3790, Ozsahin et al., 2006	RTOG/EORTC	0, 1, 2, 3, 4				33	13, 36, 36, 15, 0		

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
5020, Nishimura et al., 2005	RTOG	G0,1,2,3	3-4mo after start IMRT			33		3, 55, 36, 6%	
5120, Wolden et al., 2006	NCI	0 1 2 3		IMRT	12 mo	59	80	25 42 32 0	
5310, Zheng et al., 2005	RTOG	1, 2, 3	acute			45, 41	52, 48		
5330, Lu et al., 2005	RTOG	1, 2, 3, 4	<90 days >90 days			1, 3, 1, 0 5, 9, 0, 0	4, 12, 4, 0 20, 36, 0 ,0		
7090, Chao et al., 2004		Grade 1,2		IMRT		32,9		43, 12%	
7370, Lu et al., 2004	RTOG	0, 1, 2, 3	9 mos			0, 26, 23, 0	0, 53, 47, 0		
7750, Liu et al., 2003	RTOG	1, 2, 3, 4	> 90 days			0, 3,0, 0	0, 4, 0, 0		
8250, Munter et al., 2003	RTOG	0, 1, 2, 3	acute			23, 9, 10, 6	48, 19, 21, 12		

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
8270 Braaksma 2003	VAS score (10-point scale) 0=no complaints 10=severe complaints				BL End of RT 1 3 6 12 24	21 17 15		Mean [25th to 75th percentile] 0 6.1 [~3.7-~8.8] ~4.5 [~2.4-~6.8] 7.0 [~1.0-~7.8] ~6.8 [~2.0-~7.6] 3.2 [~1.8-~6.4] 5.2 [~1.7-~8.2]	
8400 Amosson 2003/ 8600 Amosson 2002	Subjective questionnaire RTOG/EORTC Visual analog scale (VAS)	1-4		IMRT with SMART boost	Median time from completion of IMRT 38.5 months (mean 39.9- range 16.6-71.4 months)	30	100	A questionnaire was used to assess long-term xerostomia. Thirty patients responded to the 10 question questionnaire for subjective assessment of mouth dryness. Questions with significant correlation to dosimetric parameters 1. "What is the overall comfort of your mouth?" n=9 (30%) felt that their mouth was very comfortable. n=11 (36.7%) had slight dryness (RTOG	Should we report p values from table 8??

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
								Grade 1) n=6 (20%) had moderate dryness (RTOG Grade 2) n=4 (13.3%) developed severe dryness (RTOG Grade 3). 2: “Does your mouth feel dry when eating?” n=9 (30%) no n=12 (40%) mild n=5 (16.7%) moderate n=4 (13.3) severe 3: “do you have difficulty swallowing any foods?” n=19 (63.3) yes n=11 (36.7%) no 4: “ do you need to sip liquids to swallow dry food?” n=23 (76.7%) yes n=7 (23.3%) no 6. “do you feel like the amount of saliva in your mouth is… n=14 (46.7%) too little n=16 (53.3%) adequate	

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
								n=0 (0%) too much 9. “has your taste changed due to salivary gland function?” n=13 (43.4%) yes n=17 (56.7%) no <u>Questions without significant correlation to dosimetric parameters</u> 5. “do you feel thirsty all the time?” n=6 (20%) n=24 (80%) 7. “do you have problems with speech b/c of dry mouth?” n=10 (33.3) yes n=20 (66.7%) no 8. “does dry mouth interfere with your ability to sleep all the time?” n=17 (56.7%) no n=10 (33.3%) occasionally n=3 (10%) frequently 10. “do you need to carry a water bottle	

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
								daily?" n=15 (50%) no n=4 (13.3%) occasionally n=4 (13.3%) frequently n=7 (23.3%) all the time	
9290 Teh 2002	Subjective (none, mild, moderate and severe or complete) RTOG	0 1 2				2 13 13	7 46 46		
9330 Kovacs 2002	CTC v. 2.0	0 1 1-2 2 2-3 3 3-4 4				4 7 0 32 0 6 0 0	8 14 65 12		n=49 I'm not clear which population this is- in the text they report that 42 pts who rec'd RT got concomitant CT, but the table (4) adds up to 49.
11650, Kuppersmith et al., 1999	RTOG					2	7	Not defined	
13340 Ikushima et al, 2008	RTOG	0, 1, 2, 3, 4	75	IMRT	36mo			20, 49.3, 18.7, 12%	
24330, Pfreunder et al., 2003	RTOG	1,2,3,4	50	ICHT				22, 65, 12, 0%	
37660, Wendt et al, 2006	RTOG	0,1,2,3,4	38	IMRT	21mo	38		~18, ~41, ~28, ~13, 0%	
38290, Anand et al., 2008	NCI CTC v3.0	0, 1, 2	3 mos 6 mos			31, 24, 4 35, 18, 4	52, 41, 7 61, 32, 7		

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
38840 Seung 2008	RTOG	0 1 2 3 4 0 1 2 3 4	Acute Late (f/u at least 1 yr)			0 0 29 40 0 0 27 17 0 0	0 0 42 58 0		
39300, Hoppe et al., 2008	RTOG	0, 1, 2, 3, 4	<3 mos > 3 mos			7, 23, 7, 0, 0 30, 3, 3, 0, 0	19, 62, 19, 0, 0 83, 8, 8, 0, 0		

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-K. Salivary flow

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Salivary Flow	Comment
3080 Meirovitz 2006	Stimulated (ml/min)			IMRT	6-24 (med 12)	38	100	Mean 0.55 (SD 0.27) Median 0.57 (0.01-2.42)	
	Unstimulated (ml/min)				Same	38	100	Mean 0.10 (SD 0.16) Median 0.13 (0-0.96)	
	% stimulated (relative to pretx)				Same	38	100	Mean 40 (SD 32) Median 30 (0-140)	
	% unstimulated (relative to pretx)				same	38	100	Mean 32 (SD 27) Median 18 (0-243)	

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Salivary Flow	Comment
3570 Saarilahti 2006	SLF: LENT-SOMA score (percent of pretreatment value)				12 months after last RT			Basal SLF Subman gl spared Y N Grade 0 or 1 (76-100% of pretx value) 10 (56) 3 (17) Grade 2,3 or 4 (0-75% of pretx value) 8 (44) 15 (83) p=0.015 Stimulated SLF Subman gl spared Y N Grade 0 or 1 10 (56) 7 (39) Grade 2,3 or 4 8 (44) 11 (61) P=0.32 Six months following RT, mean unstimulated SLF was 57% of the BL value among the patients who had one submandibular gland spared and 27% among those who did not. Values 12 months after RT were 60 and 25%, respectively (p=0.006). One patient (6%) with contralateral submandibular gland sparing had severe (grade 4) reduction in the unstimulated SLF (to 0–25% of the pre-treatment value) 12 months after completion of IMRT as compared to 7 (39%) of the rest of the patients (p=0.016).	

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Salivary Flow	Comment
3820 McMillan 2006	Stimulated whole salivary (SWS) flow rate (ml/min) Stimulated parotid Salivary (SPS) flow rate (ml/min)				BL,2,6,12 BL,2,6,12	32 32	100 100	Mean (SD) .91 (.53), .10 (.08), .18 (0.16), .28 (.27) p<.001 for all 4 visits, BL vs. 2 mo, BL vs. 6 mo and BL vs. 12 mo. .06 (.09), .01 (.02), .02 (.03), .06 (.10) p=.005 for all 4 visits, <.001 for BL vs. 2 mo and BL vs. 6 mo, .217 for BL vs. 12 mo	
6430, Kwong et al, 2004	Mean flow mL/min		0,2,6,12,18,24 mo	IMRT	19 patients @ baseline 17 patients @ 12 mo, 7 patients @ 24 mo.	19, 17, 7		Stimulated Whole Saliva (mL/min) 0,2,6,12,18,24 mo: 4.78, .47, .92, 1.33, 1.42, 2.73 Stimulated parotid saliva (mL/min) 0,2,6,12,18,24 mo: .92, .16, .21, .59, .62, .69	
8270 Braaksma 2003	Stimulated whole saliva flow measurements (WS)- mL/min as a % of BL before RT.				BL, weekly during RT, and at regular intervals after (1-3-6-12-24 mos.) Median BL,1,3,6,12,24 (25^{th} to 75^{th} %)	18	69	Pretx median SLF 1.96 mL/min (range .06-6.25). SLF decreased to 35% of BL (at 6 mos. post RT) and 37% (at 12 mos.). Partial recovery observed with a median of 48% of pretx SLF at 2 yrs post tx in 9 pts. 1.96 mL/min (~1.3-2.75), ~.80 (~.4-~1.25),~.85 (~.3-~.9), ~.80 (~.5-~.9), ~.82 (~.25-~1.1), ~1.2 (~.4-~1.9)	

Question 1-3: Toxicity, Efficacy, and Differences in Comparative Effects of IMRT, 3DCRT, PBT, and 2DRT

Table E-L. Dysphagia incidence

Study	Definition/Scale	Grade	F/U	Group	Mos. post Tx	n	%	Comment
580, Dirix et al., 2007	NCI CTC (V 3.0)	0, 1, 2, 3, 4	Acute			17, 7, 1, 0, 0	68, 28, 4, 0, 0	
1010, Urbano et al., 2007	NCI CTC (v 2.0)	2,3	12 mos 6 mos	DL1 DL2		15 15	20, 67 13, 87	
1500, Lee et al., 2007	NCI CTC (v 3.0)	3	12 mos			6	19	
2370, Garden et al., 2007	Chronic	Mild				3	6	
2430, Vosmik et al., 2006	RTOG	0, 1, 2, 3, 4				0, 10, 14, 14, 0	0, 26, 37, 37, 0	
2770, Cheng et al., 2006								
3320, Portaluri et al., 2006								
3340 Studer 2006	SOMA-LENT and RTOG/EORTC radiation morbidity score	0/1 3/4				24/27 n=2		
3790, Ozsahin et al., 2006	NCI CTC v 2.0	0, 1, 2, 3, 4				0, 4, 16, 13, 0	0, 12, 49, 39, 0	
4290, Lau et al., 2006	RTOG	0, 1, 2, 3, 4				1, 13, 22, 20, 0	2, 23, 39, 36, 0	
5210, Duthoy et al., 2005	RTOG	G0,1,2, 3	31	IMRT		39	18, 54, 28, 0%	
16840, Wu et al, 2006	Dysphagia					0	0	
24330, Pfreunder et al., 2003	Dysphagia	1, 2, 3,4				6, 25, 17, 0	12, 51, 35, 0	
338850 Caglar 2008	Swallowing Performance Scale (1-7)	1 2 3 4 5 6 7		IMRT (all)	1-2	~32 ~6 ~22 ~14 ~9 ~4 ~9	33.3 6.25 22.9 14.6 9.4 4.2 9.4	

Study	Definition/Scale	Grade	F/U	Group	Mos. post Tx	n	%	Comment
37660, Wendt et al, 2006	RTOG	0,1,2,3	38	IMRT	21		~14, ~38, ~32, ~17	
38290, Anand et al., 2008	NCI CTC V 3,0	0, 1, 2	3 mos 6 mos			41, 7, 11 44, 6, 7	69, 12, 19 77, 10, 12	
38840 Seung 2008	RTOG	0 1 2 3 4 0 1 2 3 4	Acute Late			0 11 52 6 0 0 40 25 4 0	0 15.9 75.4 8.7 0 58.0 36.2 5.8 0	

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-M. Other toxicities to head and neck, e.g., osteoradionecrosis, radiation-induced caries

Study	Toxicity Type	Definition/Scale	Grade	F/U	Group	Mos. post Tx	n	%	Comment
3400 Studer 2006	ORN		3		IMRT	6	1	1.4	Total dose of 66 Gy for T3N2b BOT cancer.
5020, Nishimura et al., 2005									
6430, Kwong et al, 2004									
6530 Zheng 2004	ORN mandible				3DC		0	0	
7090, Chao et al., 2004	Trismus Jaw discomfort		1 2		IMRT IMRT		3 1		

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT, and 2DRT

Table E-N. Other adverse events

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
TRM	5310, Zheng et al., 2005		39		11	13			
	7750, Liu et al., 2003		7, 10		1,1	1,1			
	8370, Padovani et al., 2003	Acute infectious complication leading to death			2	8			
Skin	560, Biagioli et al., 2007	RTOG Grade 3-4	14		2				
	580, Dirix et al., 2007	NCI CTC (v 3.0) dermatitis 0,1,2,34 RTOG/EORTC 0,1,2,3,4,5	Acute 6		3, 17, 5, 0, 0 21, 3, 1, 0, 0	12, 68, 20, 0, 0 84, 12, 4, 0,0			
	1010, Urbano et al., 2007	NCI CTC (v.2.0) Grade 2-3 RTOG Grade 1 LENT SOM	12/6 12/6 12/6	DL1 DL1 DL1	15 11 11	67/20 18 27	DL2 DL2 DL2	15 10 10	47/20 20 40
	1500, Lee et al., 2007	NCI CTC (v.3.0) Grade 0, 1, 2, 3	12 Acute		1 4, 20, 6, 1	3 13, 64, 19, 3			
	2430, Vosmik et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 24, 12, 2, 0	0, 63, 32, 5, 0			
	3340, Studer et al., 2006	"mild to moderate" (no number provided)							
	4430, Kwong et al., 2006	Grade 3			23	46			
	3790, Ozsahin et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 9, 10, 14, 0	0, 27, 30, 43, 0			
	4290, Lau et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 15, 24, 16, 1	0, 27, 43, 29, 2			
	5210, Duthoy et al., 2005	Radiodermatitis G1,2,3	31			64, 31, 5%			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	5310, Zheng et al., 2005	RTOG Grade 1, 2, 3	Acute		40, 2	47, 2			
	5330, Lu et al., 2005	RTOG Grade 1, 2, 3, 4	<90 days >90 days		4, 12, 6, 0 5, 1, 0, 0	16, 48, 24, 0 20, 4, 0, 0			
	5740, Thorstad et al., 2004	Grade 1/2; 3/4	Acute		22, 5 8, 2	82, 18 29, 7			
	7090, Chao et al., 2004	Acute toxicity G1, G2, G3, G4 Late toxicity G1,2		IMRT IMRT		42,35, 15, 5% 3, 1%			
	7370, Lu et al., 2004	RTOG Grade 0, 1, 2, 3	9 mos		29, 19, 1, 0	59, 39, 2, 0			
	8250, Munter et al., 2003	RTOG 0, 1, 2, 3	Acute		0, 25, 21, 2	0, 52, 44, 4			
	9290, The et al., 2002	18 of 28 (64%) grade 1 10 of 28 (36%) grade 2							
	9330, Kovacs et al., 2002	0 1 1-2 2 2-3 3 3-4 4		n=49 I'm not clear which population this is- in the text they report that 42 pts who rec'd RT got concomitant CT, but the table (4) adds up to 49.	5 9 0 31 0 3 0 1	10 18 63 6 2			
	10740, Pommier et al, 2000								
	11650, Kuppersmith et al., 1999	RTOG (not defined)	Acute		3	11			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	13270, Lawson et al., 2008	Acute 1 2 3 4 Late 1 2 3 4			 16 11 0 0 3 0 0 0				
	13340 Ikushima et al, 2008	Dermatitis G 0, 8, 4	36 mo	CRT	28, 8, 4	70, 20, 10			
	16840, Wu et al, 2006	Grade 0, 1, 2, 3, 4	36 mo	IMRT	35, 31, 6, 3, 0	46.7, 41.3, 8, 4, 0%			
	24330, Pfreunder et al., 2003	RTOG 1, 2, 3 4		ICHT	16, 29, 3, 0	32, 58, 6, 0%			
	37660, Wendt et al, 2006	Dermatitis G 1, 2	21	IMRT		~38, ~62			
	38290, Anand et al., 2008	NCI CTC (v.3.0) Grade 1, 2, 3	3 mos		0, 8, 2	0, 13, 3			
	38840, Seung et al., 2008	0 1 2 3 4		All	0 32 32 5 0	0 46.4 46.4 7.2 0			
	39020, Rosenthal et al., 2008	NCI's common toxicity criteria (v3.0)		IMRT alone		28	IMRT + CT		35
	39300, Hoppe et al., 2008	RTOG Grade 0, 1, 2, 3, 4	<3 mos >3 mos		4, 23, 7, 3, 0 33, 2, 1	11, 62, 19, 8, 0 92, 6, 3			
Subcutaneous Tissue	6530, Zheng et al., 2004	Neck fibrosis			1	1.9			
	7750, Liu et al., 2003	RTOG grade 1, 2, 3, 4	> 90 days		0, 0, 0, 0	0, 0, 0, 0			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	13270, Lawson et al., 2008	Late 1 2 3 4			 3 5 0 0				
	16840, Wu et al, 2006	Fibrosis G 1, 2, 3, 4	36	IMRT	14,1,0,0	18.6, 1.3,0,0			
	24330, Pfreunder et al., 2003								
	37660, Wendt et al, 2006								
Mucous Membrane	560, Biagioli et al., 2007	RTOG Grade 3-4	14		2	5%			
	580, Dirix et al., 2007	NCI CTC (v. 3.0) Grade 0, 1, 2, 3, 4 RTOG/EORTC 0, 1, 2, 3, 4	Acute 6		7, 12, 6, 0, 0 17, 7, 1, 0, 0	28, 48, 24, 0, 0 68, 28, 4, 0, 0			
	1010, Urbano et al., 2007	NCI CTC (v.2.0) Grade 2/3 RTOG Grade 1 LENT SOM Grade 1	12/6 12/6 12/6	DL1 DL1 DL1	15 11 11	33/67 9 36	DL2 DL2 DL2	15 10 10	47/40 60 30
	1420, Feng et al., 2007	NCI CTC Grade 0-4	1	Highest score	Med 3(rng 2-3), mean 2.6 + or – 0.5				
	1500, Lee et al., 2007	NCI CTC (v.3.0) Grade 0, 1, 2, 3	Acute		3, 13, 8, 7	10, 42, 26, 23			
	2180, Daly et al., 2007	RTOG/EORTC Grade 1, 2, 3	Acute		19, 11, 6	53, 30, 17			
	2430, Vosmik et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 4, 23, 11, 0				
	3340, Studer et al., 2006	Grade 2 (n=13) Grade 3 (n=6)							

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	3570, Saarilathti et al., 2006	Grade 1: 3 Grade 2: 11 Grade 3: 19 Grade 4: 3							
	3790, Ozsahin et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 5, 14, 14, 0	0, 16, 42, 42, 0			
	4290, Lau et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 16, 23, 16, 1	0, 29, 41, 29, 2			
	4430, Kwong et al., 2996	Grade 3			39	78			
	5210, Duthoy et al., 2005	Mucositis G1,2,3	31			54, 28, 18%			
	5310, Zheng et al., 2005	RTOG Grade 1, 2,3	Acute		34, 24, 5	40, 28, 6			
	5330, Lu et al., 2005	RTOG Grade 1, 2, 3, 4	<90 days > 90 days		1, 17, 5, 2 0, 2, 0, 0	4, 68, 20, 8 0, 8, 0, 0			
	5740, Thorstad et al., 2004	Grade 1/2, 3/4	Acute		19, 8	70, 30			
	7090, Chao et al., 2004	Acute mucosal toxicity G1, G2, G3, G4 Late mucositis G1		IMRT IMRT		12, 46, 38, 3% 4%			
	7370, Lu et al., 2004	RTOG Grade 0, 1, 2, 3	9 mos		16, 10, 21, 2	33, 20, 43, 4			
	7750, Liu et al., 2003	RTOG Grade 1, 2, 3,4	<90 days		26, 39, 7, 0	31, 47, 9, 0			
	8250, Munter et al., 2003	RTOG 0, 1,2, 3	Acute		8, 10, 21, 9	16, 21, 44, 19			
	9290, The et al., 2002	1 of 28 (3%) grade 1 5 of 28 (18%) grade 2 22 of 28 (79%) grade 3							

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	9330, Kovacs et al., 2002	0 1 1-2 2 2-3 3 3-4 4		n=49 I'm not clear which population this is- in the text they report that 42 pts who rec'd RT got concomitant CT, but the table (4) adds up to 49.	4 6 2 12 7 16 1 1	8 12 4 24.5 14 33 2 2			
	9510, Jian et al., 2002	 1 2 3 4 1 2 3 4		concomitant CDDP Adjuvant CDDP		0.0 22.6 67.7 9.7 25.0 32.1 21.4 10.7	CDDP/5-FU CDDP/5-FU		0.0 11.8 82.4 5.9 31.3 25.0 18.8 12.5
	10740, Pommier et al, 2000	NCI CTC (v.2.0) Grade 2, 3, 4, 5							
	11650, Kuppersmith et al., 1999	RTOG (not defined)	Acute		7	25			
	13270, Lawson et al., 2008	Acute 1 2 3 4 Late 1 2 3 4			 12 19 3 0 4 0 0 0				

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	13340 Ikushima et al, 2008	Mucositis G I, II, III	36 mo	CRT	14,22, 4	35, 55, 10			
	16840, Wu et al, 2006	Mucositis G 0, 1, 2, 3, 4	35mo	IMRT	7, 31, 30, 7	9.3, 41.4, 40, 9.3			
	24330, Pfreunder et al., 2003	Mucositis G 1, 2, 3, 4		ICHT	10, 23, 16, 0	20, 47, 33, 0			
	26140, Scorsetti et al., 2001	"transient"			NR				
	37660, Wendt et al, 2006	Mucositis G, 1, 2, 3	21mo	IMRT		~28, ~60, ~12			
	38290, Anand et al., 2008	NCI CTC (v.3.0) Grade 0, 1, 2, 3	3 mos		2, 27, 33	3, 44, 53			
	38840, Seung et al., 2008	0 1 2 3 4	Acute	All	0 8 33 28 0	0 11.6 47.8 40.6 0			
	38850, Caglar et al., 2008	0 1 2 3 4		IMRT	3 7 34 50 2	3 7 36 52 2			
	39020, Rosenthal et al., 2008	NCI's common toxicity criteria		IMRT alone		9	IMRT + CT	22	
	39300, Hoppe et al., 2008	RTOG Grade 0, 1, 2, 3, 4	< 3 mos >3 mos		2, 18, 12, 5, 0 36, 0 ,0 ,0, 0	5, 49, 32, 14, 0 100,0, 0, 0, 0			
	39390, Worden et al., 2008		acute		21, 42, 3	32, 64, 4			
Hematologic	560, Biagioli et al., 2007	RTOG Grade 3-4	14		5	12			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	4290, Lau et al., 2006	CTC 0, 1,2, 3, 4 Hb WB Neutrophils Platelets Creatine	Acute		25, 25, 2, 1, 1 36, 9, 8, 1, 0 42, 8, 2, 1, 1 49, 4, 1, 0, 0 49,2, 1, 0, 0	45, 45, 4, 2, 2 64, 16, 14, 2 75, 14, 4, 2, 2 88, 7, 2, 0, 0 88, 4, 2, 0, 0			
	38290, Anand et al., 2008	NCI CTC (v.3.0) Grade 1, 2, 3 Anemia Neutropenia thrombocytopenia	3 mos		 3, 2, 0 5, 4, 4 2, 1, 1	 5, 3, 0 8, 6, 6 3, 2, 2			
	39390, Worden et al., 2008	NCI CTC (v.2.0) Grade 2, 3, 4, 5 Anemia Leukopenia Neutropenia Thrombocytopenia Febrile neutropenia	 Acute Late Acute Late Acute Late Acute Late Acute Late		 5, 0, 0, 0 5, 1, 0, 0 44, 0, 0, 0 6, 0, 1, 0 1, 9, 1, 0 12, 4, 2, 0 6, 1, 0, 0 1, 1, 0, 0 0,0,2, 0 0,0,1,0	 8,0, 0, 0 7, 1, 0, 0 66, 0, 0, 0 9, 0, 1, 0 1, 14, 1, 0 18, 6, 3, 0 9, 1, 0, 0 1, 1, 0, 0 0, 0, 3, 0 0, 0, 1, 0			
Nausea/Vomiting	560, Biagioli et al., 2007	RTOG Grade 3-4	14		3	7			
	5330, Lu et al., 2005	RTOG grade 1, 2, 3, 4	<90 days		0, 1, 3, 0	0, 4, 12, 0			
	5740, Thorstad et al., 2004	Grade ½, ¾	Acute		23, 0 12, 0	85, 0 44, 0			
	39390, Worden et al., 2008	NCI CTC (v 2.0) grade 2, 3, 4, 5	Acute		8, 2, 0, 0 5, 3, 0, 0	12, 3, 0, 0 8, 4, 0, 0			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
Brain	580, Dirix et al., 2007	NCI CTC (v. 3.0) Grade 0, 1, 2, 3, 4 RTOG/EORTC Grade 0,1, 2, 3, 4 (headache, other braine)	Acute 6		10, 11, 4, 0, 0 11, 11, 3, 0, 0	40, 44, 16, 0 ,0 44, 44, 12, 0, 0			
	5210, Duthoy et al., 2005	Brain necrosis	31			5%9			
	5310, Zheng et al., 2005	RTOG Grade 3, 4 Temporal lobe necrosis	39 mos		11, 2	13, 2			
Spinal Cord	5310, Zheng et al., 2005	Tog grade 3 or higher, cranial neuropathy	39 mos		25	29			
	5330, Lu et al., 2005	RTOG 1, 2, 3, 4 L'hermitt's syndrome	>90 days		1, 0,0,0	4,0,0,0			
	8370, Padovani et al., 2003	Acute purulent keratoconjunctivitis Uveitis Retinopathy	 17 mos 23 mos		2 1 1				
	13340 Ikushima et al, 2008	Neurology G 0, II	36	CRT	39, 1	97.5, 2.5			
	16840, Wu et al, 2006	Neuropathy G 1, 2, 3, 4	36mo	IMRT	0,2,1,0	0, 2.6, 1.3, 0 %			
	24330, Pfreunder et al., 2003	Vertigo CTC 1, 2, 3, 4 Headache CTC 1, 2, 3, 4 Sensorial disorder CTC 1,2,3,4 Motoric Disorder CTC 1,2,3,4		ICHT	17, 1, 0, 0 1, 5, 0, 0 10, 1, 0 ,0 23, 0 ,0 ,0	34, 2,0 ,0 % 2,10, 0, 0% 20, 2, 0, 0% 46, 0, 0 ,0%			
	39390, Worden et al., 2008	NCI CTC (v 2.0) Grade 2, 3, 4, 5	Acute Late		8,2, 0, 0 2, 7, 0, 0	12, 3, 0 ,0 3, 14, 0 ,0			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
Eye	580, Dirix et al., 2007	NCI CTC (v. 3.0) Grade 0, 1, 2, 3, 4 : conjunctivitis NCI CTC (v. 3.0) Grade 0, 1, 2, 3, 4: tearing RTOG/EORTC Grade 0, 1, 2, 3, 4: tearing	Acute Acute 6		5, 10, 10, 0 7, 11, 7, 0,0 14, 11, 0,0,0	20, 40, 40, 0 28, 44, 28, 0, 0 56, 44, 0, 0, 0			
	2180, Daly et al., 2007	RTOG/EORTC Grade 1,2,3 Xeropthalmia Lacrimal stenosis Gyru rectus necrosis	 Acute Chronic Chronic		 18, 10, 1 1 1	 50, 28, 3 3 3			
	5210, Duthoy et al., 2005	Keratitis G2 Photophobia G2, 3 Blurred Vision G2,3 Tearing G0, 1,2,3 Dry Eye G1,2,3 Conjunctivitis G1,2,3	31			8% 8, 3% 10, 3% 13, 62,23,3% 92, 8,0 % 59, 38, 3%			
	11650, Kuppersmith et al., 1999	RTOG (not defined) Irritation	Acute		1	4			
	39300, Hoppe et al., 2008	RTOG grade 0 ,1 ,2, 3, 4 Ipsilateral contralateral	<3 mos >3 mos <3mos >3mos		27, 3, 2, 0, 0 32, 0 ,0 ,0, 0 36, 1, 0, 0, 0 36, 0, 0, 0, 0	73, 8, 5, 0, 0 100, 0, 0, 0, 0 97, 3, 0, 0, 0 100, 0, 0, 0, 0			
Visual Acuity	2180, Daly et al., 2007		Chronic	30 pts	0	0			
Ear	2180, Daly et al., 2007	Vestibular symptoms	Chronic	30 pts	3	10			
	5330, Lu et al., 2005	RTOG Grade 1,2, 3, 4 Ottis media	<90 days >90 days		1, 2, 0, 0 0, 0, 3, 0	4, 8, 0, 0 0, 0, 12, 0			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	6530, Zheng et al., 2004	Hearing loss			3	5.6			
	9510, Jian et al., 2002	1 2 3			12 26 2				
	16840, Wu et al, 2006	Hearing Loss Grade 1, 2, 3	36	IMRT	5, 2, 1	6.6, 2.6, 1.3			
	38290, Anand et al., 2008	Otitis media	3 mos		3	5			
	39300, Hoppe et al., 2008	NCI CTC v 2.0 grade 2, 3, 4, 5 Otitis medius	< 2 wks of RT Post RT		4 3	11 8			
	39390, Worden et al., 2008	tinnitus	Acute		5, 2, 0, 0, 0	8, 3, 0, 0, 0			
Auditory Acuity	5310, Zheng et al., 2005	RTOG Grade 3: hearing loss	Med 39mo						
	5330, Lu et al., 2005	RTOG Grade 1, 2, 3, 4 hearing loss	<90days >90days						
	5420, Pan et al., 2005	hearing loss > or = 10 Db	1 mo 6 mo 12 mo 24 mo 36 mo 1 mo 6 mos 12 mos 24 mos 36 mos	8000 Hz 4000 Hz	19 16 14 10 2 23 20 14 12 3	47 44 46 29 6 14 14 20 34 9			
	7750, Liu et al., 2003	RTOG 1, 2, 3, 4 hearing impairment	< 90days		0, 2, 1, 0	0, 2, 1, 0			
	38290, Anand et al., 2008	hearing impairment	3 mos		1	2			
	39300, Hoppe et al., 2008	hearing impairment	6 mos 4 yrs		1 1	3 3			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
Larynx	1010, Urbano et al., 2007	RTOG Grade 1-2 LENT SOM Grade 1-2	12/6 12/6	DL1 DL1	11 11	27 27	DL2 Dl2	10 10	20 20
	1500, Lee et al., 2007	NCI CTC (v.3.0)	12		3	10			
	3340, Studer et al., 2006	Grade 4 laryngeal fibrosis (n=1) "Laryngeal preservation maintained in all 23 locally controlled patients who underwent definitive IMRT , ultimate organ preservation in 96% (26/27).							
	5740, Thorstad et al., 2004	Grade 1/2, ¾	Acute		11, 2	41, 7			
	13270, Lawson et al., 2008	Acute 1 2 3 4 Late 1 2 3 4			 3 1 0 0 6 0 0 0				
	38840, Seung et al., 2008	0 1 2 3 4		all	12 51 6 0 0	17.4 73.9 8.7 0 0			
Lung									
Heart									
Esophagus	560, Biagioli et al., 2007	Late	14		1	2			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	1010, Urbano et al., 2007	RTOG Grade 2-3 LENT SOM	12/6 12/6	DL1 DL1	11 11	9 18	DL2 DL2	10 10	10 10
	1420, Feng et al., 2007	NCI CTC RTOG/EORTC	1 3 (late)	Highest score Highest score	Med2 (rng 2-3) Med 1 (rng 0-3)	Mean 2.3 + or - .5 Mean 1.0 + or – 1.1			
	2290, Yao et al., 2006	Stenosis (not defined)			3	4			
	5740, Thorstad et al., 2004	Grade 1/2, 3/4	Acute		23, 2	85, 7			
	8250, Munter et al., 2003	RTOG Grade 0, 1, 2, 3	Acute Late		6, 8, 26, 8 0, 0, 1, 1	12, 17, 54, 17 0,0 ,0, 2, 2			
	13270, Lawson et al., 2008	Acute Grade 1 Grade 2 Grade 3 Grade 4 Late Grade 1 Grade 2 Grade 3 Grade 4			 13 19 1 0 13 3 6 (*note # different than text) 0				

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	38850, Caglar et al., 2008	Stricture (doses significantly associated with stricture development = 54 Gy to mean inferior constrictor muscle [p=.02]; dose to LAR NS). Minimal dose rec'd by 60% of inf constrictor and % volume receiving ≥50 Gy correlated with stricture development [p=.03 and .02, respectively]. NS for larynx.		IMRT	36	37			
Bone	8250, Munter et al., 2003	RTOG Grade 0, 1, 2, 3	late		1	2			
	39390, Worden et al., 2008	NCI CTC (v.2.0) Mandibular necrosis	Late		3	5			
Joint	5310, Zheng et al., 2005	RTOG Grade 3, 4 trismus	Med 39 mos		12, 4	14, 5			
	5330, Lu et al., 2005	RTOG Grade 1,2, 3, 4 Trismus	>90days		10, 3, 0, 0	40, 12, 0,0			
	7750, Liu et al., 2003	RTOG Grade 1,2, 3, 4 trismus	>90days		0, 1, 0, 0	0, 1, 0, 0			
Teeth	1900, Ben-David et al., 2007	NCI CTC (v.3.0) Grade 1-4 Osteoradionecrosis	Med 35(rng 6-129)		0	0			
	2290, Yao et al., 2006	Mild (not define) Osteoradionecrosis			4	6			
	2370, Garden et al., 2007	Not defined Osteoradionecrosis			1	2			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
Pain	560, Biagioli et al., 2007	RTOG Grade 3 – 4	14		4	10			
	1010, Urbano et al., 2007	NCI CTC (v 2.0) grade 2-3	12/6	DL1	15	47/27	DL2	15	53/40
Other	560, Biagioli et al., 2007	Late: fistula carotid hemorrhage persistent PEG tube	14		 2 1 2	 5 2 5			
	580, Dirix et al., 2007	NCI CTC (v. 3.0) Grade 0, 1, 2 sense of smell taste disturbance NCI CTC (v. 3.0) Grade 0, 1, 2, 3, 4 fatigue	Acute		 10, 5, 10 8, 8, 15 4, 10, 11, 0, 0	 40, 20, 40 32, 32, 60 15, 40, 44, 0, 0			
	1420, Feng et al., 2007	PEG insertion	Pre-RT During Tx		2 11				
	1500, Lee et al., 2007	NCI CTC (v.3.0) Grade 2, 3: pharyngitis PEG dependence	 Acute 12		 27, 4 6, 19	 87, 13			
	2180, Daly et al., 2007	keratitis cellulitis dacryocystitis parotiditis	ACUTE		1 1 1 1	3 3 3 3			
	2290, Yao et al., 2006	PEG dependence Tracheotomy	Chronic		10 3	15 4			
	2370, Garden et al., 2007	RTOG/EORTC Grade 0, 1, 2, 3, 4: PEG insertion Fibrosis	 <1yr Late		 21 7, 23, 2, 0, 0	 40 21, 70, 3, 0,0			
	3790, Ozsahin et al., 2006	PEG insertion nasogastric tube wt loss			18 8 Med 4.5kg (rng 0-13kg)	55 24			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	4290, Lau et al., 2006	PEG insertion NG tube	Overall/chronic		13/7 10/2	23/12 18/4			
	5120, Wolden et al., 2006								No cases of temporal lobe necrosis, osteoradionecrosis or clinical hypopituitarism
	5330, Lu et al., 2005	RTOG Grade 1,2, 3, 4 taste disturbance olfactory disturbance	<90 days >90 days > 90 days		1, 4, 0, 4 1, 3, 1, 0 1, 1, 1, 0	4, 16, 0, 16 4, 12, 4, 0 4, 4, 4, 0			
	5740, Thorstad et al., 2004	Grade 1/2, ¾ asthenia fever hypotension salivary weight loss	Acute		 12, 0 2, 0 0,0 27, 0 15, 0	 44, 0 7, 0 0,0 100, 0 56, 0			
	6530, Zheng et al., 2004	Soft tissue necrosis of NPH Cranial neuropathy Trismus Temporal lobe necrosis Endocrine dysfxn		3DC	1 4 2 1 3	1.9 7.4 3.7 1.9 5.6			
	8250, Munter et al., 2003	PEG insertion	Acute		6	13			
	8370, Padovani et al., 2003	Nasal cartilage necrosis- limited			1				
	9290, The et al., 2002	6 of 28 (21) grade 1 pharyngitis 10 of 28 (36) grade2 pharyngitis 12 of 28 (43%) grade 3 pharyngitis							

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	9510, Jian et al., 2002	1 Pharyngitis 2 3 4		Concomitant CDDP		9.7 35.5 48.4 3.2	Concomitant CDDP/5-FU		23.5 47.1 29.4 0
	9510, Jian et al., 2002	1 neurologic deficits			3	6			
	13270, Lawson et al., 2008	Grade 1 salivary gland toxicity Grade 2 salivary gland toxicity WBC 1 2 3 4 Hct/Hb 1 2 3 4 Upper GI 1 2 3 4			18 10 4 10 6 2 13 6 0 0 3 18 2 0	53 29			
	13340 Ikushima et al, 2008	Hematoxicity Grade 0,I, II, III, IV Renal dysfunction G 0,I, II, III, IV	36 mo	CRT	16,13,10,1	40,32.5,25, 2.5, 0 92.5, 2.5, 5, 0 , 0			
	16840, Wu et al, 2006	Trismus	36	IMRT	0	0			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	24330, Pfreunder et al., 2003	Weight loss RTOG G 1, 2 CTC GRADED: Hypotension G 1, 2 Hypertension G1 Alopecia G 3 Fever G 1, G2, Myalgia, Arthralgia G1, 2 Nausea G1,2 Vomiting, G1, 2 Gastritis G1, Diarrhea G1 Constipation G2 Creatine G 1, 2, 3 Urea nitrogen G, 1, 2, 3 Bilirubin G 2, 3 Trans-aminases G 1, 2, 3 Hemoglobin G1, 2, 3 Leucocytes G1, 2, 3 Thrombocytes G 1, 2, 3	75	ICHT	19, 4 6, 8 3 50 3, 1 13, 1 7, 19 4, 12 8 7 2 17, 6, 1 18, 9, 2 17, 1 14, 6, 1 9, 7, 2 17, 7, 2 4, 2, 2	39, 8 12, 16 6 100 6, 2 26, 2 14, 28 8, 24 16 14 4 34,12, 2 36, 28, 4 34, 2 28, 12, 2 18, 14, 4 34, 14, 4 8, 4, 4			
	38290, Anand et al., 2008	enteral tube feeding iv fluids	3 mos		22 27	35 44			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	39020, Rosenthal et al., 2008	NCI's common toxicity criteria Nausea Grade 0 1 2 3 4 (p value for IMRT alone vs. with CT for grades 0-4 <.004) Vomiting Grade 0 1 2 3 4 (p value for IMRT alone vs. with CT for grades 0-4 <.04) Occipital scalp epilation Headache		IMRT alone		 76 24 33 38 5 0 38 63 16 18 3 0 40 10	IMRT + CT	 98 2 22 58 18 0 68 32 18 38 12 0 25 30	
	39390, Worden et al., 2008	elevated creatinine enteral tube feeding	NCI CTC (v.2.0) Grade 2, 3, 4, 5	Acute Acute	3, 0, 0, 0, 0 21	4, 0, 0 ,0, 0 32			

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-O. Case series/single arm trial study quality ratings

Study	Clearly Defined Question	Well-Described Study Population	Well-Described Intervention	Use of Validated Outcome Measures (Indepen-dently Assessed)	Appropriate Statistical Analysis	Well-Described Results	Discussion/ Conclusions Supported by Data	Funding/ Sponsorship Source Acknow-ledged
580, Dirix et al., 2007	Y	Y	Y	Y/N	Y	Y	Y	N
1010, Urbano et al., 2007	Y	Y	Y	Y/N	Y	Y	Y	N
3080 Meirovitz 2006	Y	N	N	U	Y	Y	Y	Y
3340 Studer 2006	Y	Y	Y	U	Y	Y	Y	Y
3400 Studer 2005	Y	Y	Y	U	Y	Y	Y	N
1420 Feng et al, 2007	Y	Y	N	Y	Y	Y	Y	Y
1430, Scrimger et al., 2007	Y	Y	Y	Y/N	?	Y	?	N
1500, Lee et al., 2007	Y	Y	Y	Y/N	Y	Y	Y	N
3570 Saarilahti 2006	Y	Y	Y	U	Y	Y	Y	N
1770, Yao et al., 2007	Y	Y	N	Y	Y	Y	N	N
1780, Lee et al., 2007	Y	Y	N	Y	Y	N	U	N
3820 McMillan 2006	Y	Y	Y	U	Y	Y	Y	Y
1900, Ben-David et al., 2007	Y	Y	N	Y	U	Y	Y	Y
1990, Yao et al., 2007	Y	Y	N	Y	Y	Y	Y	N

Study	Clearly Defined Question	Well-Described Study Population	Well-Described Intervention	Use of Validated Outcome Measures (Indepen-dently Assessed)	Appropriate Statistical Analysis	Well-Described Results	Discussion/ Conclusions Supported by Data	Funding/ Sponsorship Source Acknow-ledged
2180, Daly et al., 2007	Y	Y	Y	Y	Y	Y	Y	N
2290, Yao et al., 2006	N	Y	N	Y	Y	N	Y	N
2370, Garden et al., 2007	Y	Y	N	Y	Y	Y	N	Y
4430 Kwong	Y	Y	Y	Y	Y	Y	Y	Y
2430, Vosmik et al., 2006	Y	Y	Y	Y	U	N	N	N
4630 Yao 2005	Y	Y	Y	U	Y	Y	Y	N
2770, Cheng et al., 2006	Y	Y	N	Y	Y	Y	Y	Y
3320, Portaluri et al., 2006	Y	Y	Y	Y	U	N	U	N
3790, Ozsahin et al., 2006	N	Y	N	Y	Y	N	U	N
4290, Lau et al., 2006	Y	Y	Y	Y	Y	Y	Y	N
6530 Zheng 2004	Y	Y	Y	Y	Y	Y	Y	N
5020, Nishimura et al., 2005	Y	Y	Y	Y	Y	N	Y	Y
5210, Duthoy et al., 2005	Y	Y	Y	Y	Y	Y	Y	Y
5310, Zheng et al., 2005	Y	Y	Y	Y	Y	Y	Y	N
5330, Lu et al., 2005	Y	Y	N	Y	Y	Y	U	N
5420, Pan et al., 2005	Y	Y	N	Y	U	Y	U	N
5740, Thorstad et al., 2004	Y	N	N	U	N	N	U	Y

Study	Clearly Defined Question	Well-Described Study Population	Well-Described Intervention	Use of Validated Outcome Measures (Indepen-dently Assessed)	Appropriate Statistical Analysis	Well-Described Results	Discussion/ Conclusions Supported by Data	Funding/ Sponsorship Source Acknow-ledged
8270 Braaksma 2003	Y	Y	Y	U	Y	Y	Y	N
8370 Padovani 2003	Y	N	Y	U	Y	Y	Y	N
8400 Amosson 2003	Y	Y	N	U	Y	Y	Y	N
6430, Kwong et al, 2004	Y	Y	Y	Y	Y	Y	Y	N
7090, Chao et al., 2004	Y	Y	Y	Y	Y	Y	Y	N
7110, Sze et al., 2004	Y	N	Y	Y	Y	N	U	N
9290 Teh 2002	Y	N	Y	U	U	Y	Y	N
9330 Kovacs 2002	Y	Y	Y	U	Y	N	Y	N
7370, Lu et al., 2004	Y	Y	Y	U	U	N	U	N
9510 Jian 2002	Y	Y	Y	U	Y	Y	Y	Y
7570, Levendag et al., 2004	N	N	N	Y	U	N	U	N
7750, Liu et al., 2003	Y	Y	Y	Y	Y	Y	Y	N
8250, Munter et al., 2003	Y	Y	Y	Y	U	N	U	N
10740, Pommier et al, 2000	Y	Y	Y	Y	Y	Y	Y	N

Study	Clearly Defined Question	Well-Described Study Population	Well-Described Intervention	Use of Validated Outcome Measures (Indepen-dently Assessed)	Appropriate Statistical Analysis	Well-Described Results	Discussion/ Conclusions Supported by Data	Funding/ Sponsorship Source Acknow-ledged
13270 Lawson 2008	Y	Y	Y	U	Y	Y	Y	Y
11650, Kuppersmith et al., 1999	N	N	N	U	U	N	U	N
13340 Ikushima et al, 2008	N	N	Y	Y	Y	Y	Y	N
16840, Wu et al, 2006	Y	N	Y	Y	Y	Y	Y	N
26140 Scorsetti 2001	Y	N	Y	U	Y	Y	Y	N
24330, Pfreunder et al., 2003	Y	N	Y	Y	Y	Y	Y	N
38840 Seung 2008	Y	Y	Y	U	Y	Y	Y	N
38850 Caglar 2008	Y	Y	Y	U	Y	Y	Y	N
39000 Sanguineti 2008	Y	N	Y	U	U	Y	Y	N
39020 Rosenthal 2008	Y	Y	Y	U	Y	Y	Y	Y
37660, Wendt et al, 2006	Y	N	Y	Y	Y	Y	Y	N
38290, Anand et al., 2008	Y	Y	Y	Y	Y	Y	Y	N
38530, Studer et al., 2008	Y	N	N	U	U	N	U	N
38640, Studer et al., 2008	Y	Y	N	Y	Y	N	U	N
39300, Hoppe et al., 2008	Y	Y	Y	Y	Y	Y	Y	N

Study	Clearly Defined Question	Well-Described Study Population	Well-Described Intervention	Use of Validated Outcome Measures (Indepen-dently Assessed)	Appropriate Statistical Analysis	Well-Described Results	Discussion/ Conclusions Supported by Data	Funding/ Sponsorship Source Acknow-ledged
39390, Worden et al., 2008	Y	Y	N	Y	Y	N	U	Y