

Supplemental Table 1. Cumulative Incidence Estimates of Distant Metastasis

Year	SFX				HFX				AFX-S				AFX-C			
	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk
0	0	--	0	269	0	--	0	263	0	--	0	275	0	--	0	269
1	13.1	9.0-17.1	36	165	10.4	6.7-14.1	27	172	12.1	8.2-16.0	33	169	13.8	9.7-18.0	37	163
2	18.0	13.4-22.6	48	114	16.2	11.7-20.8	42	134	18.7	14.1-23.4	51	119	16.9	12.3-21.4	45	122
3	20.2	15.4-25.1	54	96	19.4	14.5-24.2	50	111	19.1	14.4-23.8	52	100	20.3	15.4-25.1	54	102
4	21.0	16.1-25.9	56	81	21.3	16.3-26.4	55	97	19.5	14.8-24.2	53	87	20.6	15.8-25.5	55	93
5	21.4	16.4-26.3	57	75	21.3	16.3-26.4	55	91	20.2	15.4-25.0	55	77	20.6	15.8-25.5	55	85
10	22.2	17.2-27.2	59	41	22.5	17.4-27.7	58	42	21.0	16.1-25.8	57	48	22.2	17.2-27.3	59	41
15	22.2	17.2-27.2	59	18	23.0	17.8-28.1	59	18	21.4	16.5-26.3	58	18	22.2	17.2-27.3	59	15
Total			59				60				58				59	

Est. = Estimate; CI = Confidence Interval; Cum. = Cumulative.

Supplemental Table 2. Cumulative Incidence Estimates of Second Primary Tumor

Year	SFX				HFX				AFX-S				AFX-C			
	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk
0	0	--	0	269	0	--	0	263	0	--	0	275	0	--	0	269
1	4.1	1.7-6.5	11	173	1.5	0-3.0	6	176	3.3	1.2-5.4	9	177	1.9	0.2-3.5	5	176
2	7.9	4.6-11.1	21	111	8.2	4.8-11.5	21	126	7.7	4.5-10.9	21	116	5.3	2.6-8.0	14	122
3	9.8	6.2-13.3	26	94	10.1	6.4-13.8	26	104	9.9	6.4-13.5	27	89	7.9	4.7-11.2	21	98
4	12.8	8.8-16.8	34	74	11.3	7.4-15.2	29	88	11.4	7.6-15.2	31	77	9.8	6.2-13.5	26	86
5	14.0	9.8-18.1	37	67	12.9	8.7-17.0	33	79	13.3	9.2-17.3	36	68	11.8	7.9-15.7	31	74
10	17.2	12.6-21.8	45	34	18.1	13.3-22.9	46	33	16.8	12.3-21.3	45	39	17.4	12.8-22.1	45	32
15	19.7	14.7-24.6	50	10	19.9	14.9-24.9	50	14	19.0	14.2-23.7	50	16	19.4	14.4-24.3	49	9
Total			51				50				50				49	

Est. = Estimate; CI = Confidence Interval; Cum. = Cumulative.

Supplemental Table 3. Kaplan-Meier Estimates of Disease-Free Survival

Year	SFX				HFX				AFX-S				AFX-C			
	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk
0	100	--	0	269	100	--	0	263	100	--	0	275	100	--	0	269
1	42.7	36.8-48.6	154	114	53.4	47.3-59.4	122	138	46.6	40.7-52.6	146	127	47.0	41.0-53.0	142	124
2	31.0	25.4-36.5	185	82	37.4	31.5-43.3	163	96	33.4	27.8-39.0	182	91	37.2	31.4-43.0	168	98
3	25.7	20.5-30.9	199	68	32.4	26.7-38.1	176	83	27.5	22.2-32.8	198	75	30.7	25.2-36.3	185	81
4	22.3	17.3-27.3	208	59	28.1	22.6-33.6	187	72	24.6	19.5-29.7	206	67	27.7	22.3-33.0	193	72
5	19.3	14.5-24.0	216	51	26.1	20.8-31.5	192	66	22.4	17.5-27.4	212	61	25.3	20.1-30.6	199	64
10	11.3	7.4-15.1	236	25	10.8	7.0-14.6	230	26	14.7	10.5-19.0	232	37	13.0	8.8-17.2	229	29
15	4.2	1.6-6.9	251	7	4.4	1.8-7.0	245	10	7.2	4.0-10.4	250	15	5.5	2.5-8.5	245	8
Total			254				247				256				245	

Est. = Estimate; CI = Confidence Interval; Cum. = Cumulative.

Supplemental Table 4. Kaplan-Meier Estimates of Overall Survival

Year	SFX				HFX				AFX-S				AFX-C			
	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk	Est. (%)	95% CI (%)	Cum. Failures	At Risk
0	100	--	0	269	100	--	0	263	100	--	0	275	100	--	0	269
1	67.5	61.9-73.1	87	180	70.3	64.7-75.9	77	181	66.6	61.0-72.2	91	181	67.1	61.5-72.7	88	177
2	45.6	39.6-51.6	145	121	54.7	48.6-60.8	117	140	46.3	40.4-52.3	146	126	48.9	42.9-54.9	136	129
3	38.5	32.6-44.3	164	102	46.1	40.0-52.2	139	118	37.2	31.4-42.9	171	101	40.9	35.0-46.9	157	108
4	32.0	26.4-37.6	181	83	39.9	33.9-45.8	155	102	33.1	27.5-38.7	182	89	36.4	30.6-42.2	169	95
5	29.3	23.8-34.8	188	76	37.1	31.2-43.0	162	94	29.0	23.6-34.4	193	78	33.7	28.0-39.4	176	86
10	18.3	13.6-23.1	215	41	18.1	13.3-22.9	209	43	19.3	14.5-24.0	218	48	18.1	13.4-22.9	214	41
15	10.1	6.2-13.9	233	18	8.5	4.9-12.0	231	19	9.5	5.8-13.1	241	18	8.8	5.1-12.5	234	15
Total			237				238				248				235	

Est. = Estimate; CI = Confidence Interval; Cum. = Cumulative.

Supplemental Table 5. Number of Patients with a Late Toxicity by Type and Grade

	SFX (n=234) Grade					HFX (n=232) Grade					AFX-S (n=239) Grade					AFX-C (n=232) Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Bone	2	5	1	8	0	1	1	3	5	0	3	3	1	9	0	4	1	2	4	0
Brain	0	0	0	0	0	2	0	0	0	0	5	0	0	0	0	4	0	1	0	0
Joint	12	10	3	0	0	15	11	5	1	0	21	14	4	0	0	21	11	4	0	0
Larynx	56	30	8	1	1	56	32	7	6	0	60	23	6	2	0	54	35	10	2	0
Mucous membrane	51	57	3	7	0	56	61	10	11	0	50	53	4	13	0	55	56	9	13	0
Ototoxicity	13	4	3	0	0	17	14	1	0	0	14	6	1	0	0	18	7	3	0	0
Pharynx & esophagus	47	30	20	6	0	47	47	27	3	0	52	38	25	1	0	51	47	28	2	0
Salivary gland	44	131	12	0	0	38	128	19	1	0	48	120	15	0	0	36	120	23	1	0
Skin	80	35	3	5	0	89	42	1	3	0	81	36	4	3	0	83	46	4	3	0
Spinal cord	3	1	1	0	0	5	1	0	0	0	7	2	0	0	0	8	1	0	0	0
Subcutaneous	61	54	21	1	0	50	78	18	3	0	53	72	11	1	1	64	65	8	3	0
Other	15	9	11	0	1	16	14	4	1	1	20	10	7	1	1	20	15	3	0	1

Supplemental Table 6. Number of Patients with a Late Toxicity by Type and Grade, Limited to Patients with an Oral Cavity Primary Site

	SFX (n=24) Grade					HFX (n=20) Grade					AFX-S (n=27) Grade					AFX-C (n=20) Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Bone	0	2	0	2	0	1	0	0	2	0	0	0	0	2	0	0	1	0	0	0
Brain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Joint	1	1	2	0	0	0	3	0	0	0	0	1	0	0	0	2	1	2	0	0
Larynx	4	1	0	0	0	3	0	0	0	0	1	1	0	0	0	1	1	0	0	0
Mucous membrane	3	5	0	2	0	2	8	2	1	0	3	3	0	4	0	4	3	1	3	0
Ototoxicity	1	1	0	0	0	1	0	0	0	0	1	1	0	0	0	1	1	1	0	0
Pharynx & esophagus	2	2	1	0	0	1	6	1	0	0	2	4	1	0	0	3	2	2	0	0
Salivary gland	3	10	1	0	0	3	7	2	0	0	5	11	1	0	0	3	7	3	0	0
Skin	6	2	1	1	0	5	6	0	0	0	3	4	0	0	0	5	4	2	0	0
Spinal cord	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Subcutaneous	4	3	2	0	0	1	8	1	0	0	1	7	0	1	0	1	9	1	0	0
Other	0	2	1	0	0	2	1	1	0	0	0	1	0	0	0	2	1	0	0	0

Supplemental Table 7. Number of Patients with a Late Toxicity by Type and Grade, Limited to Patients with an Oropharynx Primary Site

	SFX (n=140) Grade					HFX (n=143) Grade					AFX-S (n=139) Grade					AFX-C (n=140) Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Bone	1	2	1	4	0	0	1	3	3	0	1	3	1	7	0	2	0	2	3	0
Brain	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	2	0	1	0	0
Joint	10	9	1	0	0	14	6	5	1	0	17	12	4	0	0	15	9	2	0	0
Larynx	35	13	3	1	0	34	16	2	3	0	35	11	0	0	0	36	13	2	1	0
Mucous membrane	33	37	3	4	0	35	40	7	9	0	31	33	3	8	0	32	35	6	8	0
Ototoxicity	7	2	3	0	0	14	10	1	0	0	8	3	1	0	0	13	5	1	0	0
Pharynx & esophagus	27	20	12	3	0	28	27	20	3	0	35	21	14	0	0	30	27	18	1	0
Salivary gland	25	82	8	0	0	24	80	17	0	0	27	73	12	0	0	20	78	15	1	0
Skin	53	25	1	2	0	57	25	1	2	0	47	21	4	1	0	52	30	1	1	0
Spinal cord	2	1	0	0	0	3	1	0	0	0	3	0	0	0	0	5	1	0	0	0
Subcutaneous	40	35	12	0	0	34	46	13	1	0	33	45	8	0	0	46	36	4	2	0
Other	12	5	8	0	1	8	10	2	1	1	14	7	5	0	1	13	11	3	0	1

Supplemental Table 8. Number of Patients with a Late Toxicity by Type and Grade, Limited to Patients with an Hypopharynx Primary Site

	SFX (n=27) Grade					HFX (n=23) Grade					AFX-S (n=37) Grade					AFX-C (n=35) Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Bone	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0
Joint	1	0	0	0	0	0	0	0	0	0	2	1	0	0	0	2	1	0	0	0
Larynx	6	8	0	0	1	7	3	1	0	0	13	6	1	1	0	8	9	4	0	0
Mucous membrane	5	7	0	1	0	8	4	0	0	0	8	8	0	1	0	6	10	0	0	0
Ototoxicity	1	1	0	0	0	1	2	0	0	0	5	2	0	0	0	1	0	0	0	0
Pharynx & esophagus	7	3	4	1	0	5	3	3	0	0	8	7	4	0	0	7	7	6	0	0
Salivary gland	7	16	1	0	0	3	13	0	0	0	7	17	1	0	0	4	18	0	0	0
Skin	8	2	1	1	0	8	3	0	1	0	13	6	0	0	0	11	3	1	1	0
Spinal cord	0	0	1	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
Subcutaneous	10	5	3	0	0	4	11	0	1	0	9	12	0	0	0	6	12	1	1	0
Other	2	0	1	0	0	2	1	0	0	0	2	1	1	0	0	1	2	0	0	0

Supplemental Table 9. Number of Patients with a Late Toxicity by Type and Grade, Limited to Patients with an Larynx Primary Site

	SFX (n=43) Grade					HFX (n=46) Grade					AFX-S (n=36) Grade					AFX-C (n=37) Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Bone	1	1	0	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	1	0
Brain	0	0	0	0	0	2	0	0	0	0	2	0	0	0	0	1	0	0	0	0
Joint	0	0	0	0	0	1	2	0	0	0	2	0	0	0	0	2	0	0	0	0
Larynx	11	8	5	0	0	12	13	4	3	0	11	5	5	1	0	9	12	4	1	0
Mucous membrane	10	8	0	0	0	11	9	1	1	0	8	9	1	0	0	13	8	2	2	0
Ototoxicity	4	0	0	0	0	1	2	0	0	0	0	0	0	0	0	3	1	1	0	0
Pharynx & esophagus	11	5	3	2	0	13	11	3	0	0	7	6	6	1	0	11	11	2	1	0
Salivary gland	9	23	2	0	0	8	28	0	1	0	9	19	1	0	0	9	17	5	0	0
Skin	13	6	0	1	0	19	8	0	0	0	18	5	0	2	0	15	9	0	1	0
Spinal cord	1	0	0	0	0	2	0	0	0	0	2	0	0	0	0	3	0	0	0	0
Subcutaneous	7	11	4	1	0	11	13	4	1	0	10	8	3	0	1	11	8	2	0	0
Other	1	2	1	0	0	4	2	1	0	0	4	1	1	1	0	4	1	0	0	0

Supplemental Table 10. Grade 5 Toxicities

Assigned Treatment	Toxicity	Days from Start of Treatment	Days from End of Treatment
SFX	Larynx	4670	4619
	Other (artery)	781	735
HFX	Other (infection)	563	501
AFX-S	Subcutaneous	287	245
	Other (pulmonary aspiration)	4718	4674
AFX-C	Other (artery)	699	657

Supplemental Table 11
Pattern of Failure and Cause of Death

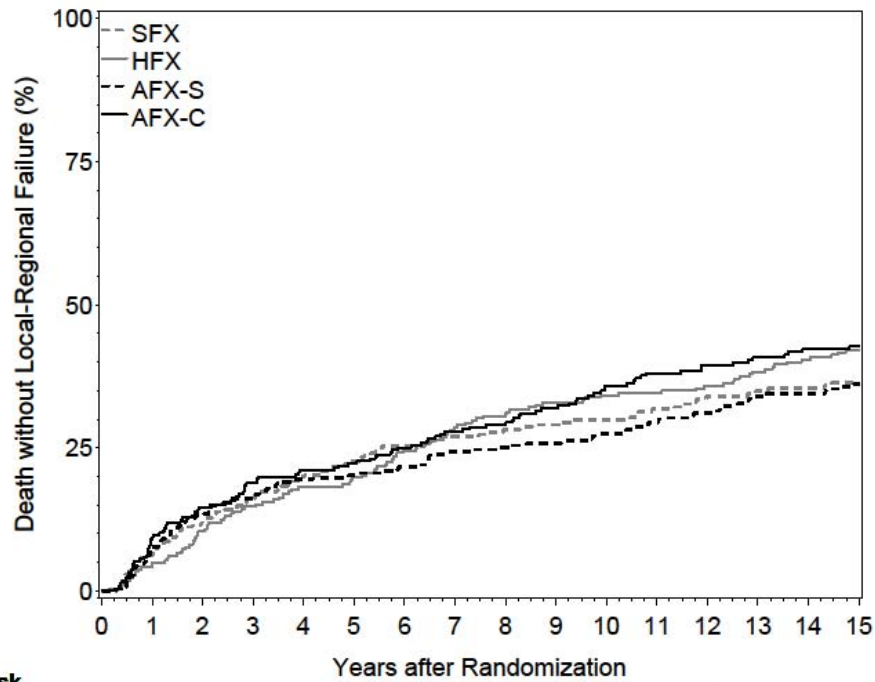
	SFX (n=269)	HFX (n=263)	AFX-S (n=275)	AFX-C (n=269)	Total (n=1076)
First failure, all patients	(n=269)	(n=263)	(n=275)	(n=269)	(n=1076)
Persistent disease	83 (30.9%)	64 (24.3%)	70 (25.5%)	75 (27.9%)	292 (27.1%)
Local relapse	36 (13.4%)	40 (15.2%)	46 (16.7%)	30 (11.2%)	152 (14.1%)
Regional relapse	16 (5.9%)	13 (4.9%)	20 (7.3%)	11 (4.1%)	60 (5.6%)
Local & regional relapse	7 (2.6%)	9 (3.4%)	7 (2.5%)	7 (2.6%)	30 (2.8%)
Local relapse & distant metastases	1 (0.4%)	1 (0.4%)	2 (0.7%)	0 (0.0%)	4 (0.4%)
Regional relapse & distant metastases	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Local & regional relapse & distant metastases	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Local relapse & H&N second primary	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Regional relapse & H&N second primary	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Distant metastases	21 (7.8%)	27 (10.3%)	19 (6.9%)	33 (12.3%)	100 (9.3%)
Distant metastases & non-H&N second primary	1 (0.4%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	3 (0.3%)
H&N second primary	6 (2.2%)	11 (4.2%)	6 (2.2%)	9 (3.3%)	32 (3.0%)
Non-H&N second primary	32 (11.9%)	27 (10.3%)	30 (10.9%)	28 (10.4%)	117 (10.9%)
Dead-NED, COD study cancer	4 (1.5%)	6 (2.3%)	1 (0.4%)	1 (0.4%)	12 (1.1%)
Dead-NED, COD second primary	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.1%)
Dead-NED, COD protocol treatment	0 (0.0%)	1 (0.4%)	4 (1.5%)	0 (0.0%)	5 (0.5%)
Dead-NED, COD other	34 (12.6%)	28 (10.6%)	39 (14.2%)	31 (11.5%)	132 (12.3%)
Dead-NED, COD unknown	9 (3.3%)	16 (6.1%)	10 (3.6%)	19 (7.1%)	54 (5.0%)
Alive-NED	16 (5.9%)	18 (6.8%)	19 (6.9%)	24 (8.9%)	77 (7.2%)
First failure, failures only	(n=253)	(n=245)	(n=256)	(n=245)	(n=999)
Persistent disease	83 (32.8%)	64 (26.1%)	70 (27.3%)	75 (30.6%)	292 (29.2%)
Local relapse	36 (14.2%)	40 (16.3%)	46 (18.0%)	30 (12.2%)	152 (15.2%)
Regional relapse	16 (6.3%)	13 (5.3%)	20 (7.8%)	11 (4.5%)	60 (6.0%)
Local & regional relapse	7 (2.8%)	9 (3.7%)	7 (2.7%)	7 (2.9%)	30 (3.0%)
Local relapse & distant metastases	1 (0.4%)	1 (0.4%)	2 (0.8%)	0 (0.0%)	4 (0.4%)
Regional relapse & distant metastases	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Local & regional relapse & distant metastases	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Local relapse & H&N second primary	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Regional relapse & H&N second primary	2 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Distant metastases	21 (8.3%)	27 (11.0%)	19 (7.4%)	33 (13.5%)	100 (10.0%)
Distant metastases & non-H&N second primary	1 (0.4%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	3 (0.3%)

Supplemental Table 11
Pattern of Failure and Cause of Death

	SFX (n=269)	HFX (n=263)	AFX-S (n=275)	AFX-C (n=269)	Total (n=1076)
H&N second primary	6 (2.4%)	11 (4.5%)	6 (2.3%)	9 (3.7%)	32 (3.2%)
Non-H&N second primary	32 (12.6%)	27 (11.0%)	30 (11.7%)	28 (11.4%)	117 (11.7%)
Dead-NED, COD study cancer	4 (1.6%)	6 (2.4%)	1 (0.4%)	1 (0.4%)	12 (1.2%)
Dead-NED, COD second primary	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.1%)
Dead-NED, COD protocol treatment	0 (0.0%)	1 (0.4%)	4 (1.6%)	0 (0.0%)	5 (0.5%)
Dead-NED, COD other	34 (13.4%)	28 (11.4%)	39 (15.2%)	31 (12.7%)	132 (13.2%)
Dead-NED, COD unknown	9 (3.6%)	16 (6.5%)	10 (3.9%)	19 (7.8%)	54 (5.4%)
Cause of death	(n=235)	(n=236)	(n=248)	(n=235)	(n=954)
Related to or probably related to the cancer under study	127 (54.0%)	128 (54.2%)	125 (50.4%)	128 (54.5%)	508 (53.2%)
Related to or probably related to a second malignancy	18 (7.7%)	22 (9.3%)	31 (12.5%)	24 (10.2%)	95 (10.0%)
Related to or probably related to complications of protocol treatment	1 (0.4%)	0 (0.0%)	3 (1.2%)	0 (0.0%)	4 (0.4%)
Related to or probably related to complications of other treatment	6 (2.6%)	2 (0.8%)	7 (2.8%)	2 (0.9%)	17 (1.8%)
Related to or probably related to complications of protocol and other treatment	2 (0.9%)	1 (0.4%)	2 (0.8%)	2 (0.9%)	7 (0.7%)
Unrelated to or probably unrelated to cancer or treatment	24 (10.2%)	22 (9.3%)	32 (12.9%)	28 (11.9%)	106 (11.1%)
Other	37 (15.7%)	25 (10.6%)	28 (11.3%)	22 (9.4%)	112 (11.7%)
Unknown	20 (8.5%)	36 (15.3%)	20 (8.1%)	29 (12.3%)	105 (11.0%)

H&N = head and neck; NED = no evidence of disease; COD = cause of death.

Supplemental Figure 1. Cumulative incidence of death without local-regional failure



	Patients at Risk															
	Years after Randomization															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
SFX	269	123	94	78	66	58	49	43	39	34	31	27	21	18	17	13
HFX	263	148	113	99	86	80	67	57	51	41	36	35	32	25	20	15
AFX-S	275	133	100	81	73	70	64	56	54	49	45	39	33	25	24	17
AFX-C	269	133	108	91	80	74	66	59	55	46	35	30	27	22	18	14

1. Fu KK, Pajak TF, Trotti A, et al: A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 48:7-16, 2000

2. Cox DR: Regression models and life-tables. Journal of the Royal Statistical Society. Series B (Methodological):187-220, 1972
3. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-70, 1966
4. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. The Annals of statistics:1141-1154, 1988
5. Kalbfleisch J, Prentice R: The Statistical Analysis of Failure Time Data, Wiley, New York, 1980
6. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. Journal of the American statistical association 53:457-481, 1958

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 90-03

A PHASE III RANDOMIZED STUDY TO COMPARE TWICE DAILY HYPERFRACTIONATION, ACCELERATED HYPERFRACTIONATION WITH A SPLIT AND ACCELERATED FRACTIONATION WITH CONCOMITANT BOOST TO STANDARD FRACTIONATION RADIOTHERAPY FOR SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

SCHEMA

S		R	Arm 1: <u>Standard Fractionation:</u> 2 Gy/Fx, Q.D. 5 Days/wk Total Dose: 70 Gy/35 Fx/7 wks
	Site-oral cavity	A	
	T oropharynx hypopharynx larynx	N	Arm 2: <u>Hyperfractionation:</u> 1.2 Gy/Fx, b.i.d. (> 6 hours apart, 5 days/wk Total Dose: 81.6 Gy/68 Fx/7 weeks
		D	
	R	O	Arm 3: <u>Accelerated Hyperfractionation with split:</u> 1.6 Gy/Fx b.i.d. (> 6 hours apart), 5 days/wk Total Dose: 67.2 Gy/42 Fx/6 wks with a 2 week rest after 38.4 Gy
	A Stage- N0 vs. N+	M	
		I	
	T KPS- 90-100 60-80	I	Arm 4: <u>Accelerated fractionation with concomitant boost:</u>
		Z	a. <u>Large Field:</u> 32.4 Gy/18 fx/3 1/2 wks 1.8 Gy/fx/day, 5 days/week
		E	b. <u>Concomitant Boost:</u> - 1.5 Gy/fx/day to boost field for 18.0 Gy/12 fx > 6 hours after large field treatment - Large Field Treatment to receive 21.6 Gy/12 fx, 1.8 Gy/fx
			c. <u>Total Dose:</u> 72.0 Gy/42 fx/6 wks
	I		
	F		
	Y		

Eligible:

Sites: Oral Cavity, Oropharynx, Hypopharynx, Supraglottic Larynx
 Age: ≥ 18
 Histology: Squamous cell or lymphoepithelioma
 Stage: AJC Stage III or IV (Stage II base of tongue and hypopharynx), no distant metastases
 Karnofsky Status: ≥ 60
 Prior Therapy: No prior radiotherapy, chemotherapy or surgery other than biopsy.

Required Sample Size: 1080

4/15/95

1.0 INTRODUCTION

1.1 Treatment Background

Fractionation is one of the most important factors in the outcome of radiotherapy. Conventional radiotherapy using a fractionation scheme of 1.8 to 2.0 Gy per fraction, five daily fractions per week to a total dose of 65.00-75.00 Gy may not be the optimal treatment for some squamous cell carcinomas of the upper respiratory and digestive tracts (*URDT*). On the other hand, treatment with multiple fractions per day can potentially provide a significant improvement in the therapeutic ratio using readily available low LET beams.

Recently, a number of strategies have been used in modifying radiotherapy fractionation schemes:

1. **Accelerated fractionation:** a shortening of the overall treatment duration by giving two or three fractions per day but using similar total dose per fraction as conventional fractionation.
2. **Hyperfractionation:** an increase in the number of fractions, giving two or three fractions per day, with smaller doses per fraction than conventional, higher total dose but same overall time as conventional.
3. **Accelerated hyperfractionation:** a greater fraction number, smaller fraction size and a shorter overall treatment duration than conventional.
4. **Concomitant boost:** a variation of accelerated hyperfractionation, giving a second daily dose of radiation to a reduced "field-within-a-field" during the course of conventional fractionated radiotherapy.

The biological basis and the rationale for altered fractionation schemes has been recently reviewed by Withers, Thames and their colleagues.^{12,19,20} The objective of accelerated fractionation is to reduce the opportunity for tumor cell regeneration during treatment by shortening the overall treatment duration. The objective of hyperfractionation is to increase the therapeutic differential between tumor response and late normal tissue injury through an increased opportunity for tumor cell redistribution and reoxygenation, greater sparing of late reacting normal tissues and a possibly lower oxygen enhancement ratio (*OER*) at low doses. With accelerated hyperfractionation, an increased therapeutic gain can be achieved by combining both a decrease in dose per fraction and a shortening of overall treatment duration. Its main limitation is increased acute toxicity although late normal tissue effects may be the same as or less than conventional fractionation. With the concomitant boost technique, the volume of tissue treated at the accelerated rate is reduced, thereby reducing the severity of mucositis. These different approaches have been tried or are currently under investigation in the treatment of head and neck cancer.^{1-11, 14-18} The relative merits of these different approaches based on available biological and clinical data are discussed in Reference ¹⁰.

Hyperfractionation using doses of 1.1-1.2 Gy per fraction twice daily to 60.00-81.60 Gy have been tested in several studies, including a recently-completed RTOG (79-13) randomized Phase III trial, an EORTC trial, an Indian Trial and an RTOG (83-13) randomized Phase I/II trial.^{2,5,7,25} In the EORTC trial, patients with oropharyngeal carcinoma, Stage T2-T3, N0, N1 less than 3 cm were randomized to receive conventional radiotherapy with 70.0 Gy in 35 fractions in seven weeks or hyperfractionated radiotherapy with 80.5 Gy in 70 fractions (1.15 Gy/fx) in seven weeks. Results thus far show a significantly improved 5-year local-regional control rate in the hyperfractionated radiotherapy arm: 38% vs. 57% ($p = 0.08$). The difference is even more significant ($p=0.01$) in patients with KPS of 90-100. A borderline significant advantage in 5 year survival ($p=0.06$) is seen in the hyperfractionation arm. In the Indian trial, 212 patients with T2, T3, N0 and N1 head and neck cancers were randomized to receive once a day (*OD*) radiotherapy with 2.0 Gy/fraction to 66.0 Gy in 33 fractions over 6.5 weeks or twice a day (*BID*) radiotherapy with 1.2 Gy/fraction to 79.2 Gy in 66 fractions over 6.5 weeks. Of the 176 evaluable patients, those treated with the BID regimen had a significantly better 2-year disease-free rate (62.6% vs. 32.9%, $p < 0.001$) and actuarial survival (71.4% vs. 44.6%, $p < 0.005$).²⁵ However, the total dose (66 Gy) for the standard fractionation arm is lower than that is commonly used for these patients.

In RTOG Phase III randomized trial, in spite of a lower total dose in the two-fractions-a-day arm (60 vs. 66-73 Gy), the actuarial local-regional control rates were similar for the hyperfractionation groups. Acute normal tissue reactions were similar in both groups. Whether an improved local-regional control rate without increased late normal tissue toxicity can be achieved with a higher total dose using the hyperfractionation schedule await phase III testing. Preliminary results of RTOG 83-13 a dose-searching randomized Phase I/II trial of hyperfractionation suggest an increase of local-regional control with an increase of total dose from 67.2 Gy to 81.6 Gy with no increase of late toxicity. The estimated two year local-regional control rates by assigned total doses were 25%, 44%, 43%, and 45% for 67.2, 72.0, 76.8 and 81.6 Gy; the corresponding grade 4 late toxicity rates were 6.7%, 2.7%, 9.0% and 3.6%. The decrease of late toxicity in the 81.6 Gy arm is probably related to the longer interval between the two daily fractions in these patients. Seventy four percent of the patients in the 81.6 Gy arm had an average interval between the two daily fractions > 4.5 hours while only 27%, 52% and 38% of the patients in the 67.2 Gy, 72.0 Gy and 76.8 Gy arms had an average interval between the two daily fractions > 4.5 hours. In the previous RTOG 79-13 randomized trial, patients treated with hyperfractionated radiotherapy with an interval > 4.5 hours between the two daily fractions had less acute and late toxicity than those treated with shorter interfractional intervals.

Accelerated hyperfractionation combines the potential advantages of accelerated fractionation and hyperfractionation. This strategy has been used by C.C. Wang in the treatment of head and neck cancer of

various sites, including the oropharynx, oral cavity, supraglottic larynx and nasopharynx with impressive result¹⁴⁻¹⁸

compared to historical controls. In his twice-daily (*b.i.d.*) program, patients with advanced head and neck cancer receive 1.6 Gy per fraction, two fractions per day with a minimum of four hours between fractions, five days per week for 12 treatment days. After 38.40 Gy, a rest period of two weeks is given to allow recovery from acute radiation reactions. Treatment is then resumed with a reduced field at 1.6 Gy *b.i.d.* to a total dose of 64.00 Gy over six weeks. In some instances, an additional 3.2 Gy in one day is directed to the primary site through a reduced portal as a final boost to a total dose of 67.20 Gy. The spinal cord dose is limited to 38.40 Gy in 2.5 weeks. In 106 patients with supraglottic carcinoma, the three-year actuarial local control rate following the twice-a-day program was 76 percent compared to 50 percent for a historical control group treated with 1.8 Gy per fraction, once a day, five days a week for a total dose of 65.00 Gy in seven weeks. The difference was significant with $p = 0.001$. Survival also appeared to be significantly improved. The three-year actuarial survival was 94 percent for T1 and T2 lesions and 75 percent for T3 and T4 lesions with the *b.i.d.* program compared with 70 and 46 percent using the once-a-day program ($p = 0.05$). In a series of 99 patients with squamous cell carcinoma of the oropharynx, the three-year actuarial local control rate was 58 percent with the *b.i.d.* compared to 45 percent with the once-a-day historical control group ($p = 0.0074$).¹⁰ Similar advantages of the *b.i.d.* program were also seen for patients with oral cavity and nasopharyngeal cancers.^{15,18} In a recent update of 88 patients with T1-4 oropharyngeal carcinoma treated with *b.i.d.* program, the three-year actuarial local control rate was 85%.¹⁷ While the acute effects of the *b.i.d.* program are usually more severe than those of the once-a-day program, the duration of symptoms is shorter and they usually subside after a period of ten days to two weeks. Thus far, late effects after the *b.i.d.* program have been judged to be insignificant.

The major limitation of accelerated hyperfractionation radiotherapy is severe acute mucositis. The concomitant boost technique attempts to overcome this limitation by administering the second daily dose of radiation to a reduced "field-within-a-field" during the course of conventional fractionated radiotherapy, thereby reducing the volume of tissue treated at the accelerated rate. In a series of 53 patients with advanced squamous cell carcinoma of the head and neck treated at the University of Texas M.D. Anderson Hospital,⁶ the concomitant boost was delivered in fractions of 1.2-1.5 Gy separated by three to six hours from the basic daily treatment of 1.8 to 2.0 Gy. The boost treatments were given two to three times a week for three to five weeks, delivering an average of about 17 Gy in 12 fractions. With a median follow-up of 31 months, the two year local regional control rate was 65%, and the survival was 55%. Fourteen (26%) patients developed moderate to severe late complications. Of these, seven had neck dissection after radiotherapy, and one had bilateral neck dissections before radiotherapy.

A recent phase I/II study at M.D. Anderson Hospital compared concomitant boost treatment given twice a week during the basic treatment course with boost treatment given daily during the first or last 2-1/2 weeks of the basic treatment course. Preliminary results suggest that tumor control was best when the boost treatment was given during the last 2-1/2 weeks of the basic course although no difference in overall toxicity was seen.

The objective of this Phase III study is to establish whether any one of the altered fractionation schemas is better than conventional fractionation radiation therapy for advanced squamous cell carcinoma of the head and neck.

1.2 Quality of Life (added 3/17/92)

1.2.1 Historically, clinical trials have established local-regional tumor control and survival rates to be important indices of treatment outcome. More recently, studies have demonstrated the value of measuring the patients' perceived quality of life (QOL) in clinical trials to identify and describe the effects of the disease and/or its treatment.^{27,28,29,30}

1.2.2 QOL has been defined as the patient's appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be possible or ideal. It is generally agreed, that QOL is a multidimensional concept, requiring assessment of the following domains:

physical function, psychosocial/emotional function, and disease/treatment-related symptomatology.^{31,32,33}

1.2.3 Although it is generally agreed that QOL is an important consideration in the evaluation of current cancer therapies and that conceptually it is multidimensional, review of the current literature reveals that few studies have been conducted to investigate the QOL among head and neck cancer patients.²⁸ In addition, no studies have been conducted which specifically investigate the impact that a definitive course of external beam radiation therapy may have on perceived QOL, performance status and late treatment related morbidity in patients with advanced squamous cell carcinoma of the aerodigestive tract. Therefore, the purposes of this Phase III study are to establish whether any one of the altered fractionation schemas is better than conventional fractionation in relation to local-regional tumor control, survival rates, patients perceived QOL, performance status and late morbidity for the treatment of patients with advanced squamous cell carcinomas of the head and neck. The knowledge gained as a result of this study will assist clinicians to more accurately assess the outcomes of the treatment options proposed in this Phase III randomized clinical trial.

1.2.4 Since QOL is multidimensional, requiring assessment of the physical, psychosocial, emotional functioning and disease/treatment related symptomatology, the researchers have chosen to use the following valid and reliable measurement instruments in the conduction of this study.

2.0 OBJECTIVES

2.1 To determine whether hyperfractionation and/or accelerated fractionation improves the local-regional control rate of advanced squamous cell carcinomas of the head and neck.

- 2.2 To determine the disease-free survival and actuarial survival of patients treated with the different fractionation schemes.
- 2.3 To determine the acute and late toxicity of each fractionation schedule.
- 2.4 To test prospectively whether there exists any difference between the treatment regimens with respect to the Quality of Life endpoints. **(added 3/17/92)**

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Patients with histologically proven squamous cell carcinoma (includes lympho-epithelioma and anaplastic carcinoma) arising in eligible head/neck regions and stages (see Appendix III). Where N + disease is based on presence of nodal disease found only on CT or MRI scans, i.e. not palpable on clinical examination, the size of the node(s) detected with CT or MRI scans must be ≥ 1.0 cm in its minimal axial diameter, or contain necrotic regions regardless of size. Biopsy may be obtained from the primary or regional lymph nodes. **(revised 3/15/93)**
- 3.1.2 General condition: In the estimation of the investigator the patient must be medically able to withstand a course of definitive radiotherapy.
- 3.1.3 The minimum age for entry is 18 years.
- 3.1.4 Karnofsky performance status ≥ 60 (Appendix II).
- 3.1.5 Patients must not have received previous surgery except biopsy, for the tumor under study. Patients with a prior malignancy (other than non-melanoma skin cancer) are ineligible, unless previous cancer was treated 5 years or more prior to the current tumor and patient has remained continually disease free.
- 3.1.6 Patient must sign a study-specific informed consent form.
- 3.1.7 Laboratory values within 2 weeks of entry.

3.2 Ineligibility Criteria

- 3.2.1 Histology other than squamous cell carcinoma, or one of its histologic subtypes (includes lympho-epithelioma/anaplastic). Adenocarcinomas are excluded.
- 3.2.2 Evidence of metastases (below the clavicle or distant) by clinical or radiographic means.
- 3.2.3 Patients with prior or simultaneous primaries (see 3.1.5)
- 3.2.4 Karnofsky status < 60
- 3.2.5 Patients with prior chemotherapy or surgery (other than biopsy) are ineligible.
- 3.2.6 Prior radiotherapy of the head and neck.
- 3.2.7 Patients treated in planned combined pre- or post-operative programs are excluded; however, post RT neck dissections are allowed if lymph nodes are > 3 cm (prior to RT)or persist after treatment. (See Section 8.2). If tumor persists at the primary site 6 weeks following completion of irradiation, salvage surgery, if possible, may be performed.
- 3.2.8 Tumors arising in sites or stages other than those listed in Appendix III; glottic and subglottic sites are ineligible.
- 3.2.9 Patients for whom follow-up is unlikely to be carried out by the member radiation therapist.
- 3.2.10 Patients in whom combined external beam irradiation and interstitial implant boost are planned are excluded.

4.0 PRETREATMENT EVALUATION

4.1 Mandatory Evaluation

- 4.1.1 Complete history and physical exam.
- 4.1.2 Biopsy of primary tumor and/or metastatic lymph node.
- 4.1.3 CBC (within 2 weeks of randomization)
- 4.1.4 Chest x-ray; PA and lateral.
- 4.1.5 CT scan or MRI scan of the head and neck.
- 4.1.6 Diagram of lesion and nodes.
- 4.1.7 Dental evaluation with management according to the guidelines of Daly²⁴.

4.2 Optional Studies

- 4.2.1 Liver scan
- 4.2.2 Bone Scan
- 4.2.3 SMA 12-60

5.0 RANDOMIZATION

- 5.1 Patients must be randomized prior to the start of protocol therapy by calling RTOG Headquarters (215) 574-3191, Monday - Friday, 8:30 a.m. to 5:00 p.m. ET.
- 5.2 The following information must be provided.
 - Name of investigator.
 - Name of patient and ID number.
 - Institution name and number.
 - Treatment start date
 - Eligibility Criteria information.
 - Stratification information.
 - Patient's birthdate, race, sex, social security number, and zip code.
- 5.3 Patients will be assigned to one of the following treatments.
 - Arm 1 -Standard Fractionation:** 2 Gy/Fx, Q.D. 5 Days/wk, Total Dose: 70 Gy/35 Fx/7 wks.
 - Arm 2 -Hyperfractionation:** 1.2 Gy/Fx, b.i.d. (> 6 hours apart), 5 days/wk, Total Dose: 81.6 Gy/68 Fx/7 weeks.

Arm 3 -Accelerated Hyperfractionation with Split: 1.6 Gy/Fx, b.i.d. (> 6 hours apart), 5 days/wk, Total Dose: 67.2 Gy/42 Fx/6 wks with a 2 week rest after 38.4 Gy.

Arm 4 - Accelerated Fractionation with Concomitant Boost: 1.8 Gy/fx/d, 5 days/wk to large field + 1.5 Gy/fx/d to boost field > 6 hours after large field treatment for 12 Fx's during last 2.5 wks, Total Dose: 72.0 Gy/42 Fx/6 wks.

5.4 RTOG Headquarters will assign the protocol therapy arm and a patient case number. This will be confirmed by mail.

6.0 RADIATION THERAPY

6.1 Physical Factors

6.1.1 Equipment: linear accelerators with appropriate photon and electron energies for supplemental boosting to the nodes or Cobalt⁶⁰ machines must be used.

6.1.2 Selection of the appropriate photon energy should be based on optimizing the RT dose distribution within the target volume and minimizing dose to normal tissue. Photon energies > 6 MMV may be utilized in dual energy beam arrangements only if one beam is ≤ 6 MV. **(revised 8/17/92)**

6.1.3 Treatment distance must be ≥ 80 cm S.S.D (or S.A.D for isocentric techniques).

6.2 Localization Requirements

6.2.1 Simulation: Simulation of all fields is mandatory. Patients must be reproducibly immobilized. **Radio-opaque markers should be used to delineate the extent of nodal disease and whenever possible, the primary tumor.** The use of customized blocks to shape the treatment fields is recommended. Simulation films of each field, initial port films, and the calculation form will be sent to RTOG Headquarters in the first week of therapy, together with the treatment prescription for radiation therapy quality assurance review.

6.2.2 Verification: Beam verification (port) films must be obtained for each field. This should be repeated at least every two weeks during treatment and whenever any field adjustments are made. Port films of each field must be submitted to the RTOG Headquarters.

6.3 Target Volume Irradiation Portals

6.3.1 A combination of lateral opposing fields, anterior and lateral wedged fields, or several beam-directed fields, will be used for the primary tumor site at the discretion of the investigator for the case. A single anterior A-P field will be used to treat the neck below the fields for the primary tumor. When there is (are) positive node(s) in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node(s). All fields must be treated on each treatment day. The lower neck and supraclavicular field should abut the primary field at the skin. For oral cavity and oropharynx primaries, a midline block 2 cm wide and at least 2 cm in length on the skin surface will be placed in the anterior lower neck field to shield the larynx and the spinal cord in the junction region. For larynx and hypopharynx primaries, a lower lateral block, 2 cm in height should be placed in the lateral upper neck fields to shield the areas of potential overlap of diverging beams over the spinal cord.

The primary treatment fields should encompass the primary tumors with adequate margins along with sites of known and/or suspected lymph node disease in the upper neck. There should be a minimum of 2-3 cm margin around the primary tumor and positive node(s) and should include upper neck nodes to be irradiated electively for the initial target volume. At least two field reductions are recommended for all four arms. The first field reduction off the spinal cord occurs at 40-44 Gy for arm 1, 45.6 Gy for arm 2 and 38.4 Gy for arm 3. The second field reduction occurs at 50-60 Gy for arm 1, 50.4-60 Gy for arm 2, and 51.2-60.8 Gy for arm 3. A third field reduction at 69.4 Gy is recommended for arm 2. There should be a minimum of 2 cm margin around the initial tumor volume and positive neck node(s) for the first field reduction and a minimum of 1-1.5 cm margin around the initial tumor volume and positive neck node(s) for the second field reduction and a minimum of 1 cm margin for the third field reduction. For arm 4, there should be a minimum of 1-1.5 cm margin around the initial tumor volume and positive neck node(s) for the concomitant boost field beginning at 32.4 Gy. The large field is reduced off the spinal cord at 45 Gy. **(revised 8/17/92)** The primary treatment fields by tumor site and the lower neck field are as follows:

6.3.2 Oral tongue and floor of mouth

6.3.2.1 The lateral fields should include the primary tumor, the submandibular and upper jugular nodes. Irradiation of the posterior chain is not indicated unless there are clinically positive cervical nodes.

6.3.3 Anterior tonsillar pillar and retromolar trigone.

6.3.3.1 The ipsilateral posterior cervical nodes must be irradiated if the primary tumor is T₃ or T₄.

6.3.3.2 Both ipsilateral and contralateral posterior cervical nodes must be irradiated if there are clinically positive nodes in the anterior chain.

6.3.4 Oropharynx

6.3.4.1 The ipsilateral posterior cervical nodes must be irradiated if the primary tumor is T₃ or T₄.

6.3.4.2 Both the ipsilateral and contralateral posterior cervical nodes must be irradiated if there are clinically positive cervical nodes in the anterior chain.

6.3.5 Supraglottic larynx

6.3.5.1 The upper border of the field includes the nodes in the upper jugular region. One cm of the mandible is to be included to obtain adequate coverage.

6.3.5.2 If there is involvement of the pyriform sinus and/or lateral hypopharyngeal wall, the superior border is placed at the base of the skull (above C1) to include the retropharyngeal nodes.

6.3.5.3 The lower border of the field encompasses the larynx usually at or below the level of C5.

- 6.3.5.4 The ipsilateral posterior nodes should be treated for T3 and T4 lesions.
- 6.3.5.5 Both ipsilateral and contralateral posterior nodes should be treated if there are clinically positive nodes in the anterior chain.
- 6.3.6 **Hypopharynx**
- 6.3.6.1 The superior border is placed at the base of skull (above C1) to include the retropharyngeal nodes. Nodes in the upper jugular region and posterior triangle are included. One cm of the mandible is to be included to obtain adequate coverage.
- 6.3.6.2 The lower border of the field encompasses the lower border of the cricoid cartilage.
- 6.3.7 **Lower neck**
- 6.3.7.1 A single anterior lower neck field will be used to treat the neck and the supraclavicular fossa below the fields for the primary tumor. When there is (are) positive node (s) in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node (s). (See Section 6.3.1)
- 6.3.7.2 The lower border of the field will be just below the clavicle or 1 cm below the clavicle when there are positive nodes in the supraclavicular fossa.
- 6.3.7.3 For all patients with clinically positive nodes greater than 6 cm, positive supraclavicular nodes, or pyriform sinus tumors that are T3 or T4 or have clinically positive nodes, a mediastinal T field should be used.(8/17/92) The lateral limbs of the T extend to 1 cm below the clavicle and the central portion of the field extends 5 cm more inferiorly to include the upper mediastinum.
- 6.4 Dose Calculation**
- 6.4.1 Dose to the supraclavicular field is calculated at 3 cm depth and to the upper mediastinum at 5 cm depth. Complete isodose curves are required. Lithium fluoride dosimetry is recommended as a further check on tumor dose. Cumulative isodose distributions at the level of tumor center, and a copy of the treatment record indicating cumulative doses, and boost field simulation and portal films must be submitted at the completion of radiotherapy. The specification of the target dose is in terms of a dose to a point at or near the center of target volume. The following portal arrangement are specified for photon beams:
- 6.4.1.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
- 6.4.1.2 For arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.
- 6.4.1.3 Other or complex treatment arrangements: at the center of the target area (Note: there may be several target areas).
- 6.4.2 Tissue equivalent compensators should be used to ensure homogeneity of dose distribution so that variation within the target volume does not exceed 10% of the target dose.
- 6.4.3 Boost doses will be specified at the actual site(s) of gross primary and nodal disease.
- 6.5 Dose Fractionation**
- 6.5.1 **Standard Fractionation (Arm 1) (revised 8/17/92, 3/15/93)**
Treatment to the primary tumor and upper neck will be given at 2.0 Gy per fraction, once a day, five days a week to a total dose of 70 Gy in 35 fractions in seven weeks. Fields must be reduced to exclude the spinal cord at 40 -44 Gy at the midplane. However the entire neck must be irradiated to a dose of 44 Gy (even in N0 stage) at anatomical levels of lymph node spread usually 2-4 cm below the skin surface. Clinically positive neck nodes should receive a minimum dose of 70 Gy in 35 fractions in 7 weeks. To supplement the dose to the posterior neck and clinically positive nodes, boost techniques may include additional electron beam (≥ 9 MeV) to the posterior neck, wedge pair or oblique fields. Initially clinically negative posterior neck should receive a minimum dose of 44 Gy at 3 cm depth.
The anterior lower neck field will be treated at 2 Gy per fraction at 3 cm depth, once a day, to a total dose of 44 Gy in 22 fractions in 4.5 weeks. The total dose to the primary tumor and clinically positive nodes will be 70 Gy in 35 fractions in 7 weeks.
- 6.5.2 **Hyperfractionation (Arm 2) (revised 3/15/93)**
Treatment to the primary and upper neck will be given at 1.2 Gy per fraction, twice a day with a minimum of a 6 hour interval, 5 days a week, to a total dose of 81.6 Gy in 68 fractions in 7 weeks. Fields must be reduced off the spinal cord at 45.6 Gy at the midplane. Clinically positive nodes should receive a minimum dose of 81.6 Gy. To supplement the dose to clinically positive neck nodes, boosts technique may include additional electron beam (≥ 9 MeV) to the posterior neck, wedge pair or oblique fields. Initially clinically negative posterior neck should receive a minimum dose of 45.6 Gy at 3 cm depth.
The anterior lower neck field will be treated with 1.2 Gy per fraction at 3 centimeter depth, twice a day, with a minimum of 6 hour intervals to a total dose of 45.6 Gy in 38 fractions in 4 weeks. The total dose to the primary and clinically positive nodes will be 81.6 Gy in 68 fractions in 7 weeks. The exact time and date of each treatment should be clearly documented on the treatment record.
- 6.5.3 **Split Course b.i.d. (Arm 3) (revised 3/15/93)**
Treatment to the primary tumor and the upper neck will be given at 1.6 Gy per fraction, twice a day with a minimum of 6 hour interval, five days a week to a dose of 38.4 Gy in 24 fractions delivered in 2 1/2 weeks. This is followed by a rest period of 14 days. Subsequently, treatment will resume to deliver 1.6 Gy twice a day, with a minimum of 6 hour interval, to a reduced boost volume encompassing the primary tumor and clinically positive nodes for an additional dose of 28.8 Gy. The total tumor dose will be 67.2 Gy in 42 fractions in 6 weeks. Fields must be reduced off the spinal cord at 38.6 Gy at the midplane. Clinically positive nodes should receive a minimum dose of 67.2 Gy. To supplement the dose to clinically positive neck nodes, boost techniques may include additional electron beam (≥ 9 MeV) to the posterior neck wedge pair or oblique fields. Initially clinically negative posterior neck should receive a minimum dose of 43.2 Gy at 3 cm depth.

The anterior lower neck field will be treated only during the first segment of the therapy with 1.8 Gy per fraction at 3 cm depth, twice a day, with a minimum of 6 hour interval, to a total dose of 43.2 Gy in 24 fractions in 2 1/2 weeks. The exact time and date of each treatment should be clearly documented on the treatment record.

6.5.4 Concomitant Boost (Arm 4) (revised 3/15/93)

The large field treatment will be given at 1.8 Gy per fraction, once a day, five days a week to deliver 54 Gy in 30 fractions over 6 weeks to the primary tumor and upper neck nodes. After 32.4 Gy/18 Fx/3-1/2 weeks to the large field, start concomitant boost with 1.5 Gy/Fx/day to the boost field at least 6 hours after the large field treatment. Treat the boost field daily during the last 12 treatment days. The reduced boost volume should encompass the primary tumor and clinically positive nodes. The total tumor dose will be 72.0 Gy in 42 fractions in 6 weeks. The primary treatment fields must be reduced off the spinal cord at 45 Gy.

Clinically positive nodes should receive a minimum dose of 72 Gy. To supplement the dose to clinically positive nodes, boost techniques may include additional electron beam (≥ 9 MeV) to the posterior neck wedge pair or oblique fields. Initially clinically negative posterior neck should receive a minimum dose of 50.4 Gy at 3 cm. **(4/15/95)**

The anterior lower neck field will be treated with 1.8 Gy per fraction at 3 cm depth to a total dose of 50.4 Gy in 28 fractions in 5.6 weeks. All treatment times must be documented on the treatment record.

6.5.5 Time and Dose Modifications:

6.5.5.1 Standard Fractionation Program: Treatment breaks must be clearly indicated in the treatment record. Treatment breaks if necessary should not exceed five treatment days at a time and ten treatment days total and should be allowed only for healing of severe normal tissue reactions. If the total treatment interruptions exceed ten treatment days, the case will be considered a protocol deviation.

6.5.5.2 Hyperfractionation Program: Treatment breaks must be clearly indicated in the treatment record. Treatment breaks if necessary should not exceed five treatment days at a time and ten treatment days total and should be allowed only for healing of severe normal tissue reactions. If the total treatment interruptions exceed ten treatment days the case will be considered a protocol deviation.

6.5.5.3 Accelerated Hyperfractionation with Split: Treatment breaks must be clearly indicated in the treatment record. Treatment breaks other than the planned 14 day rest period for healing of severe normal tissue reactions such as confluent radioepithelitis (mucositis). If unplanned treatment interruptions exceed 5 treatment days total, the case will be considered a protocol deviation.

6.5.5.4 Concomitant Boost Program: Treatment breaks must be clearly indicated in the treatment record. Treatment breaks, if necessary should not exceed one week and should be allowed only for healing of severe mucositis. If treatment interruptions exceed five treatment days total, the case will be considered a protocol deviation.

6.5.6 Fraction Interval: Documentation of interfraction interval must be provided on the daily treatment record.

6.5.7 Neck Dissection: If a neck dissection is planned for lymph nodes which were > 3 cm prior to RT, the dose to the involved lymph nodes may be limited to 44-50 Gy in the standard fraction arm, 50.4 in the hyperfraction arm, 38.4-43.2 Gy in the split course b.i.d. arm and 50.4 Gy in the concomitant boost arm. This information must be clearly documented in the treatment record.

6.5.8 Boost Doses:
Additional boost doses may be given through reduced fields to persistent primary tumor and or clinically positive nodes. The boost dose should not exceed 5.0 Gy for each of the fractionation schemes.

6.6 Anticipated Side Effects and Toxicities

6.6.1 Suggested maximum doses to critically sensitive normal structures:

<u>Organ</u>	<u>Dose</u>
Spinal Cord	44.0 Gy/22 fx/4 weeks (Arm 1) (revised 8/17/92) 45.6 Gy/38 fx/4 weeks (Arm 2) 38.4 Gy/24 fx/2.5 wks (Arm 3) 45.0 Gy/25 fx/5 wks. (Arm 4)

6.6.2 Reversible radioepithelitis of oropharyngeal mucosa is expected and its timing with dose and severity should be noted and graded according to the RTOG Acute Radiation Morbidity criteria for mucous membrane (Appendix IV).

6.6.3 Also expected will be epilation of treated areas and various degrees of skin reaction in the treated area. These should be graded according to the RTOG Acute Radiation Morbidity Criteria for skin. (Appendix IV)

6.6.4 Other expected acute reactions include xerostomia, hypogeusia, and dysphagia. Unusual severity of either of these should be noted, especially if supplemental feeding tube is required. See RTOG Toxicity Criteria for Acute and Late Effect grading (Appendix IV).

6.6.5 Late effects include permanent xerostomia in almost all patients and occasionally persistent dysphagia. Mandibular osteoradionecrosis will occur in 5% or less of the patients, but can be reduced by thorough dental evaluation before irradiation, which is recommended. Pretherapy extraction of badly diseased teeth should be carried out with conservation of restorable teeth where possible. At least 10 days should be allowed for healing of gingivae post-extraction.

6.6.6 Radiation-induced myelopathy can occur in less than 1% of patients providing cervical spinal cord dose remains below 40 Gy in 20 fractions in 4 weeks in Arm 1, 45.6 Gy in 38 fractions in 4 weeks in Arm 2, 38.40 Gy in 24 fractions in 2 1/2 weeks in Arm 3 or 45 Gy in 25 fx in 5 weeks in Arm 4. However, special attention should be

directed in follow-up exams to any numbness, parasthesia, or L'hermitte's signs, particularly in the first 6-12 months of follow-up.

6.7 Adverse Reaction Reporting

6.7.1 Since this protocol utilizes altered fractionation radiation therapy, RTOG Headquarters and the study chairman must be notified by telephone of all fatal and life threatening toxicities (those \geq grade 4). See RTOG Toxicity Reporting Guidelines for details. (Appendix VI).

7.0 DRUG THERAPY

Not applicable to this protocol.

8.0 SURGERY

8.1 Surgical Removal (salvage) of the primary tumor

Surgical removal (salvage) of the primary tumor should be performed only when biopsy proven persistent cancer confirms failure in the clinically abnormal site at least six weeks after completion of radiotherapy (i.e., arbitrary biopsies in clinically negative sites will not constitute reason for surgical resection). The extent of resection will be dictated by the extent of tumor at the time of the initial evaluation. The primary lesion must be widely excised utilizing accepted criteria for adequate excision depending upon region involved.

Frozen section should be taken from the patient and not the surgical specimen. Marking the surgical margin in ink at the site corresponding to where the frozen section was obtained for the patient is recommended to determine if there was a sampling error in obtaining clear margins. If grossly visible palpable tumor remains unresectable at a margin that is histologically positive or when gross tumor removal is not performed, the patient will be considered to have gross residual disease. In the absence of gross residual disease, if the tumor extends within 5 mm of surgical margin the case would be considered to have close margins.

8.2 Neck Dissection

Surgical removal of the cervical lymph nodes in place of supplemented doses of irradiation may be undertaken for nodes $>$ 3 cm prior to RT in diameter at the discretion of the surgeon/radiotherapist team. If a neck dissection is planned the dose to the involved lymph nodes may be limited to 50.0 Gy in standard fractionation arm, 50.4 Gy in hyperfractionation arm, 38.4-43.2 Gy in the split course b.i.d. arm and 50.4 Gy in the concomitant boost arm. Preservation of the accessory nerve and protection of the carotid artery will be at the discretion of the surgeon.

8.3 Closure

Primary closure with surgical defect is to be accomplished whenever possible. Reconstruction or closure with grafts, local or regional skin flaps when required is allowed at the discretion of the responsible surgeon. Close suction drainage will be routinely employed.

8.4 Operative Report

The operative report must accurately and completely describe the precise location and the extent of the primary lesion and cervical lymph node metastasis. Assessment of the completeness of the resection and results of intra-operative frozen section should be included. Any type of closure utilized should be specified as to the primary, pedicle flap or dermal graft.

9.0 OTHER THERAPY

Not applicable to this protocol.

10.0 PATHOLOGY

10.1 Institutional Preparation of Tumor Sections (4/14/95)

10.1.1 Paraffin blocks of tumor will have an H and E stained section prepared of the block face. The section will be examined to select an area of tumor that is free of necrosis, inflammation and most benign elements. This area will be marked on the slide and outlined on the block face prior to sectioning. Only this region will be subjected to analysis. If unacceptable results are obtained (such a high coefficient of variation or lack of sufficient cell numbers for analysis), another area will be selected. Sections 10.2 to 10.5 describe Dr. Hammond's analysis.

10.1.2 Institutions not able to submit paraffin blocks of pretreatment biopsies may submit 10-15 unstained slides instead.

10.1.3 Pathology slides, blocks, and reports must be accompanied by an RTOG Pathology Submission form and sent to:

Pathology Coordinator
RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107

10.2 Preparation of Nuclear Suspensions.

10.2.1 Two 40-micron-thick sections from the scored area of the paraffin block are placed in a 10-ml glass centrifuge tube.

10.2.2 The tissue is deparaffinized in xylene and rehydrated with sequential graded ethanols: 100%, 100%, 95%, 75% and 50% for 10 minutes each and washed with distilled water.

10.2.3 For tissue dissociation, the tissue is incubated in 1 ml of 0.5% pepsin in saline, at a pH of 1.5 adjusted with 2N hydrochloric acid for 30 minutes at 30°C with brief vortexing. The reaction is terminated by placing the tubes on ice and treat with 0.5 ml of 0.5 mg/ml of pepstatin.

10.2.4 The nuclei are then filtered through a 37-mm nylon filter and washed twice with 8 ml of BME:HEPES buffer separated by 3-minutes centrifugations at 250 g.

10.2.5 The nuclei are re-suspended in 8 ml of BME:HEPES and maintain at 4°C for approximately 18 hours prior to staining.

10.3 p105 Antibody and DNA Staining

10.3.1 The nuclei are resuspended at 2.0×10^6 in 1 ml of 3% Triton X100 in phosphate buffered saline for 3 minutes.

10.3.2 Following centrifugation, the supernatant is decanted and the nuclei are resuspended in 1 ml of appropriately diluted mouse monoclonal antibody (780-3) against p105 antigen for one hour.

10.3.3 Following centrifugation, the nuclei are washed with 3% Triton X 100 and re-suspended in 0.33 ml of 1:20 goat antimouse-IgM-fluorescence isothiocyanate for 30 minutes.

10.3.4 For DNA staining the nuclei are re-suspended in 1 ml of RNAase (200 U/ml) for 20 minutes at 30°C, centrifuged and re-suspended in 1 ml of propidium iodide (50 mg/ml) and incubated at 4°C for 1 hour in the dark.

10.4 Flow Cytometry

10.4.1 Data are acquired in listmode on an EPICS 752D flow cytometer (Coulter) with use of the 488 nm line of an argon ion laser at 350mW power. Typically, listmode files of 20,000 events containing data on forward-angle light scatter (size), right-angle light scatter (granularity), green fluorescence (FITC stained anti-p105), red fluorescence (propidium iodide stained DNA), and a computer generated time signal are obtained.

10.4.2 For standardization of propidium iodide staining, calf thymocytes are stained with propidium iodide and the peak is recorded at approximately channel 200 on a 1024-channel histogram.

10.4.3 Instrument alignment and standardization of green fluorescence is performed using 10 um of Full-bright Fluorosphere beads seta at green channel 56 on a 64-channel log-linear histogram. A total of 2×10^4 nuclei are run for each case with a flow rate of approximately 102 nuclei per second.

10.4.4 Quality Control of Flow-cytometry

Standard calibration of instruments will be performed daily. Monthly comparisons of histograms generated in the two major flow laboratories in Salt Lake City, Utah showed that the variation in results over the past two years has been negligible. Controls to be run with each batch of tumor samples include: 1) Positive control: proliferal blood lymphocytes from normal donors stimulated with PHA, and 2) Negative control: proliferal blood lymphocytes from normal donors without stimulation. Positive and negative controls will be treated exactly like the test samples with propidium iodide and p105 prior to assay.

10.5 Data Analysis

10.5.1 Fluorescences results are analyzed on a microcomputer using the PARA 1.1 program (Coulter Electronics). This program assumes a Gaussian distribution of G0G1 and G2M peaks and applies the quick estimate (peak reflect) method to calculate the cell cycle phases. Graphic representation of the data will be prepared with the use of VERITY:ISOCONTOUR software.

10.5.2 The DNA index is determined as the ratio of the aneuploid mean channel divided by the diploid G0 G1 mean channel number. The Coefficient of Variation of the diploid DNA peak must be less than 5% or the sample will be discarded and a new one obtained.

10.5.3 Immunofluorescence for p105 is determined by the mean channel number on the log scale and recorded as arbitrary fluorescence units for each cell cycle phase: G0, G1, S, and G2M. These phases of the cycle are determined from the DNA histogram. Numbers of cells in each phase which label with antibody to p105 will be recorded.

10.5.4 A labelling index (LI-C) for p105 will be calculated as follows:

$$\text{LI-C} = \frac{\text{number of cells p105 positive G1, S and G2M phases}}{\text{Total number of cells counted}}$$

This LI will be calculated independently for the diploid as well as aneuploid DNA (if present) in each sample.

10.5.5 A labelling index (LI-S) analogous to that obtained with BUdR labelling can be calculated as follows:
number of p105 positive cells in S phase

$$\text{LI-S} = \frac{\text{Total number of cells counted}}{\text{Total number of cells counted}}$$

10.5.6 Antigen density (AD) of p105 positive cells will be calculated as the mean channel fluorescence recorded on a log scale.

10.5.7 Data to be collected and sent for correlation with clinical parameters will include:

1. LI-S p105
2. LI-C p105
3. AD p105
4. % DNA diploid
5. % DNA aneuploid
6. DNA Index of aneuploid peak

10.6 Fixed Tumor Repository Study (Optional) (4/14/95)

10.6.1 Patients entered on this study are also eligible for the Fixed Tumor Repository.

10.6.2 To receive an additional case credit, the following must be provided to RTOG:

10.6.2.1 One additional paraffin block of tumor or 15 unstained slides (*maximum thickness of 5 microns each*). Block/slides must be clearly labeled with the pathology identification number that agrees with the Pathology Report.

10.6.2.2 Pathology report documenting that submitted block or slides contain tumor.

10.6.2.3 A Pathology Submission Form must be included and must clearly identify the enclosed materials as being for the Fixed Tumor Repository.

10.6.3 To encourage compliance, your Pathology Department could be reimbursed for obtaining blocks or cutting slides.

10.6.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).

10.6.5 Materials will be sent to:

Pathology Coordinator
RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107

11.0 PATIENT ASSESSMENTS (revised 9/21/92)

11.1 Summary of the study parameter requirements is as shown:

	Prior to xrt	1 mo after xrt	1st 18 mos, every 3 mos	18 mos through year 3, every 4 mos	every 6 mos. 3-5 years
History + Physical	x	x(a)	x(a)	x(a)	x(a)
CBC	x				
Calcium	x(b)				
Serum glucose	x(b)				
Chest x-ray	x				
Biopsy of primary	x		x		
		(no earlier than 6 wks after RT & only if persistence suspected)			
CT scan or MRI of primary and neck	x	x(b)	x(b)	x(b)	

a) To include scoring of acute and late radiation effects

b) As indicated

11.2 Tumor Clearance:

Response of tumor should be documented as gauged by caliper or ruler measurements, measuring longest diameter and at right angles to it, by inspection and by palpation (use photography when applicable), should be made before therapy, weekly during therapy, and subsequently at each follow-up. Failure of clearance (persistence) will thus be documented. Time of apparent beginning regrowth will be noted. Clinically suspected persistence or recurrence should be biopsied when feasible.

11.3 Local Reaction of skin and mucous membranes should be scored (using criteria in Appendix IV) at least weekly during radiotherapy and postradiotherapy until clearance. Note concomitant use of alcohol, tobacco, or other irritants.

11.4 Survival

Record survival from start of radiation with or without local, regional or metastatic disease.

11.5 Late Effects:

At each follow-up visit, note condition of tissues (nerves, mucosa, skin, subcutaneous) and signs of soft tissue change or bony necrosis. Record any change or abnormality in CNS and/or peripheral nervous system.

11.6 Tumor assessment will be as follows: (revised 9/21/92)

Weekly during radiotherapy and the 2 week rest period.

4 weeks postradiotherapy

Every three months for first 1-1 1/2 yrs.

Every 4 months from 18 months through 3 years

Every 6 months in years 3-5 then annually thereafter until death

11.7 QOL Measurement Instruments (added 3/17/92) DISCONTINUED 12/13/00

The Quality of Life (QOL) component for this study will use three measurement instruments; two to be completed by the investigator/data manager/nurse participant and one self-report questionnaire to be completed by the patient. Each of these instruments is described below. Additional instructions for the investigator/data manager/nurse participant and patient will be included with the data forms.

11.7.1 List Performance Status Scale: (LPSS)

The LPSS is an instrument developed by List et al.²⁷ in collaboration with experts in the fields of otolaryngology, surgical oncology, and speech and swallowing rehabilitation science to measure performance status of the head and neck cancer patient in terms of three separate areas of functioning: (1) eating, (2) speaking, and (3) diet. Its intended use was to make effective assessments of treatment outcome, development of rehabilitation program and to gain a better understanding of the functional status of the head and neck cancer patient after a course of cancer therapy.

The LPSS consists of three separate subscales: (1) normalcy of diet, (2) understandability of speech, and (3) eating in public. The Normalcy of Diet subscale assesses the degree to which a patient is able to eat a normal diet. Ten food categories are arranged from easy-to-eat at the low end to hard-to-eat at the high end. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. Scores are computed by assessing the highest ranking food the patient is able to eat. The Understandability of Speech subscale is a five-item scale which assesses the mechanism used by the patient to communicate. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. The scores are computed by assessing the degree to which the observer is able to understand the patient's speech. The Eating in Public subscale was designed to assess the degree to which the patient eats in the presence of others. There are five categories describing the patients eating patterns. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. Scores are computed based upon patients report of who he eats with and in what type of setting. Therefore, each patient studied will receive a total of three scores, one on each subscale. The investigator/data manager/nurse participant will determine the score on each of the subscales by performing a clinical evaluation and unstructured interview format.²⁷

11.7.2 Dische Morbidity Scoring Tool (DMST)

The DMST instrument was developed by Dische³⁴ to measure treatment-related morbidity in head and neck cancer patients who have received a definitive course of external beam radiation

therapy. Areas to be assessed include: (1) symptoms: pain, dysphagia, and taste impairment, (2) mucous membrane: erythema, ulceration, edema, thinning of the mucosa, pallor of the mucosa and telangiectasia, pigmentation-decrease, hair loss and thinning of the epidermis, and (4) temporomandibular joint and salivary gland function: trismus, dryness of the mouth, salivary consistency, time to fill in and ease of filling in. Its intended use is to objectively measure treatment related morbidity in head and neck cancer patients after receiving a course of external beam radiation therapy.

11.7.3 The Functional Assessment of Cancer Therapy for Head and Neck Questionnaire (F.A.C.T. - H&N)

This self-report questionnaire, developed by Cella et al.,^{31,32} is a 47 item inventory. Of the 47 items on this questionnaire, 38 are summarized into five sub-test scores representing the following four domains of QOL to be measured; physical, social, emotional well being and relationship with their doctor. The remaining nine items are specific to the head and neck site of treatment.

12.0 DATA COLLECTION (revised 3/17/92, 9/21/92, 4/14/95, 10/15/96, 12/13/00)

QOL DATA COLLECTION WAS DISCONTINUED, 12/13/00

12.1 Data will be submitted to Headquarters on the following schedule:

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of randomization.
Initial Evaluation/On-Study form (I1)	
Diagram/Staging Worksheet, Primary Site (I6)	
Diagram/Staging Worksheet, Nodes, (I7)	
Pathology Report (P1)	
Pathology Blocks/Slides (P2)	
List Performance Status Scale (QP)	
Dische Morbidity Scoring Tool (F2)	
F.A.C.T. - H&N (FA)^a	
<u>For Fixed Tumor Repository (See Section 10.6)</u>	Within 4 weeks of randomization
Pathology Report (P6)	
Pathology Block/Slides (P7)	
<u>Initial Radiotherapy Data:</u>	Within 1 week of commencement of treatment
Treatment Prescription Form (T2)	
Initial Field Localization (simulation & portal) (T3)	
Calculation Form (T4)	
Radiotherapy Form (T1)	Within 1 week of completion of treatment
F.A.C.T. - H&N (QF)^a	
<u>Final Radiotherapy/Dosimetry Data:</u>	Four weeks after treatment completed, then List every 3 months for the first 1 1/2 years, F.A.C.T - H&N (QF)^a every four months
Copy of Complete Treatment Record (T5)	
Isodose Distribution (T6)	
Simulation and Portal Boost Films of Primary & Nodes (T8)	
Follow-up Form (F1)	months in years 3-5 then annually. At progression and death.
Performance Status Scale (PF)	
through year 3, every six	
Dische Morbidity Scoring Tool (F3)^b	
Surgery Form (S1)	When applicable
Operative Path Report (S5)	
Surgical Report (S2)	

- a. and form-specific cover sheet
- b. with the 6,12,18,22 month post-tx F1 form then with every other F1 form

- 12.2 Patients are not eligible for the Quality Life Component unless the initial pretreatment F.A.C.T form is completed. Eligibility for the LPSS or Dische Component is based upon having completed the initial pretreatment form of each component.
- 12.3 Evaluability will be determined by successful completion and submission of follow-up forms in the QOL companion study.
- 12.4 Failure to participate in one or all components QOL or ancillary, will not affect eligibility or evaluability of the overall case status for inclusion in the treatment component of the study.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

- 13.1.1 To determine whether at least one of the "experimental" treatments, (hyperfractionation (Arm 2), accelerated hyperfractionation with split course (Arm 3), or accelerated hyperfractionation with concomitant boost (Arm 4), provides improved local-regional control of advanced squamous cell carcinoma of the head and neck, as compared to the local-regional control provided by standard fractionation radiotherapy (Arm 1). The primary site and nodal disease will be scored separately.
- 13.1.2 To examine overall and disease-free survival patterns associated with each of the fractionation schemes.
- 13.1.3 To determine the acute and late radiotherapy toxicity associated with each of the fractionation schedules.
- 13.1.4 To determine whether there exists any differences among the four treatment regimens with respect to Quality of Life **(added 3/17/92)**
- 13.1.2 To examine overall and disease-free survival patterns associated with each of the fractionation schemes.
- 13.1.3 To determine the acute and late radiotherapy toxicity associated with each of the fractionation schedules.
- 13.1.4 To determine whether there exists any differences among the four treatment regimens with respect to Quality of Life **(added 3/17/92)**

13.2 Sample Size (4/15/95)

The external RTOG Data Monitoring Committee(DMC) reviewed this protocol at the February 1994 RTOG meeting when over 50% of the originally targeted accrual was reached. The DMC voted to continue patient accrual on all four treatment options. The DMC, however, expressed concern that the magnitude(20%) of the difference sought between each of the experimental arms and the control arm was unrealistic and felt that the study should have sufficient statistical power (.80) to detect a smaller difference, say 15%, in the two year local regional failure. During the discussion, it was pointed out that the local regional failure rate used when the study was designed was 75% at two years. The analysis of its immediate successor study, RTOG 85-27, found a two year rate of 60% for standard once-a-day fractionation radiotherapy arm. If that rate held true with the 90-03 study, there would be a loss in statistical power to detect the difference. By consensus, it was decided that the statistical section, be revised to detect a smaller difference and to account for possibly a lower failure rate for the standard arm. In the original statistical considerations, there was no allowance made for patients who died before two years without a local regional failure. In the revised statistical section adjustment was made for them. The protocol called for twice testing for early termination of the trial. Another test was added and now there are tests to be done after 324, 648, and 1080 patients have then entered. The section on early termination has been revised to test only on local control failure rates since it was the primary endpoint for the study.

Since this study will involve the comparison of three "experimental" treatments to a single "control" treatment, the analyses will require correction for multiple comparisons using appropriate statistical procedures.²² The sample sizes were therefore calculated using methods of

sample size estimation that account for overall power and Type I error rates being affected by implementation of such multiple comparison procedures.²³

Based on the recent analysis of its immediate successor study RTOG 85-27, a two-year local-regional control rate of 0.40 is now expected for the standard fractionation patients.²⁶ In this study, we would like to detect with a probability (*power*) of 0.80, a difference in local-regional control rates of $\geq 15\%$ at two years between the control group and one of the experimental treatment groups. We would also like to keep the probability of erroneously drawing a conclusion that there is a significant difference in local-regional control rates between patients on the control group and patients on any one of the experimental treatments to 5% (*Type I error rate*). In order to accomplish this we will need to accrue 223 eligible and analyzable patients to each of the four treatment groups. From the closed head and study RTOG 85-27, it was projected that 10% of patients will die without local regional failure. The sample size was initially increased by 10%. To also guard against an ineligibility rate of up to 10% the sample size was again increased by another 10% to 270 patients on each treatment arm. **Thus a total of 1080 patients will be required on the study.**

13.3 Patient Accrual (4/15/95)

As of 12/1/94, 600 patients were entered on the study. Average monthly patient accrual over the last year and over the entire study have been 15.6 and 15.8 cases respectively. Using 15.6 cases per month, it will take approximately 31 months to the complete new total accrual of 1080 cases. Thus, the patient accrual period over the entire study is estimated to be 5.75 years. If the average monthly accrual rate is less than 10 cases per month, the study will be re-evaluated for feasibility.

13.4 Randomization Scheme

Patients will be randomized to one of four treatment schedules in order to avoid any patient selection biases. The treatment allocation will be done using a randomized permuted block design within strata to balance for patient factors other than institution. Based on analyses of previous RTOG inoperable head and neck studies, three factors (site: oral cavity, oropharynx, larynx, or hypopharynx; nodal status: N0 or N+; and KPS: 90-100 or 60-80) will be used as stratifying variables.

13.5 Analyses Plans (3/17/92, 4/15/95)

13.5.1 Background

With the increased sample size, another test for early termination of the trial was added. So now tests will be performed after approximately 324, 634, and 1080 patients have then entered. Early termination will be solely based on local control failure rates because it is primary endpoint for the study. The DMC's role has been clearly delineated. More details about the analyses have been added.

13.5.2 Interim Analyses to monitor the study progress:

Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. The interim reports will typically contain information about the patient accrual rate with a projected completion date, data quality, compliance rate of treatment delivery with the distributions of important prognostic baseline variables and the frequencies and severity of the toxicities by treatment arm. If these analyses suggest the occurrence of unexpected toxicities or unacceptable protocol compliance in one or more treatment arms, corrective action will be considered. This may result in modifications of treatment regimen(s) or possibly its termination due to toxicity. These reports will not contain any results from the treatment comparisons with respect to the efficacy endpoints. (Local regional control, disease free survival, absolute survival)

13.5.3 Significance testing for early termination

In order to ensure that patients entered on this protocol are not being randomized to an inferior treatment or being denied an obviously superior treatment, significance testing of all treatment outcomes will be conducted at the earliest point in the study that meaningful differences can be ascertained. The primary endpoint for this study is local regional failure rates at two years. This endpoint will be tested three times for early termination of the trial. First significance test was performed for the first RTOG meeting after the first 324 patients (30% of the revised total sample size of 1080) have been entered. No significant differences were reported to DMC and the trial continued as planned.

The second significance tests will be performed after 648 patients (60% of 1080 patients) have been entered into the protocol. If any experimental treatment arm shows significant inferiority to the control arm at $p < 0.001$ in a pairwise comparison, termination of patient accrual to that treatment arm would be recommended. If all experimental arms show a highly significant advantage over the control arm at $p < 0.001$ in the pairwise comparisons, termination of the study will be recommended. The results from the tests will be then reported to the RTOG DMC for their consideration. If any of experimental treatment arm(s) is discontinued, case accrual will continue until the required sample size of 270 patients is reached for the remaining arms. At this time, there will be interim analysis of the data from the QOL and the Dische Late Morbidity tool components. The results will be presented to the DMC for their consideration of terminating further patient accrual to these components.

The third significance tests will be performed after all 1080 patients have been entered into the protocol and have been potentially followed for at least six months. If all the pairwise tests show that all the experimental arms are either superior or inferior to the control, the recommendation will be made to publish the results immediately. The results from the tests will be then reported to the RTOG DMC for their consideration. If the study is not terminated here, it will continue as planned.

13.5.4 Analysis for Reporting the Initial Treatment Results:

This major analysis will occur after each patient has been potentially followed for a minimum of 24 months unless the study is stopped earlier. The usual components of this analysis are:

- 1) tabulation of all cases entered and any excluded from the analyses with the reasons for such exclusions;
- 2) reporting of institutional accrual;
- 3) distribution of the important prognostic baseline variables by assigned treatment group;
- 4) observed results with respect to the primary study endpoints.

The primary hypotheses for the study are whether each of the experimental arms has different effect on two-year local regional failure rate than the control arm. All eligible patients randomized will be included in the pairwise comparison. All eligible patients randomized will be grouped by assigned treatment arm in the analysis. Then, a treatment difference will be considered statistically significant at a nominal alpha level of 0.047 to preserve an overall Type I error rate of 0.05 because of the three earlier tests.

The primary hypothesis of benefit with each of experiment arm will be tested using the Cox proportional hazard model with the stratification factors of primary site, N-stage, and KPS included as covariates in addition to treatment (an experimental arm vs the control arm). The benefit for an experimental arm on disease free survival, local control rate, and absolute survival will be analyzed in a similar fashion.

Further subgroup analyses may be conducted (depending on sample sizes of the defined subgroups) for the purpose of identifying differing patterns of treatment responses in such patient subgroup.

13.5.5 Analysis of Quality of Life

Data accrual from the Functional Assessment of Cancer Therapy (F.A.C.T. - H&N) will be analyzed using both fixed time point and quality adjusted survival methodologies. List Performance Status Scores (LPSS) will be correlated with the Karnofsky Performance Status and the two will be analyzed for sensitivity and responsiveness. The LPSS results will be compared by treatment and with subscales of the F.A.C.T. - H&N. The Dische Late Morbidity tool will be correlated with the RTOG late effects scoring system and compared for differences in the treatment arms.

14.0 ADDITIONAL THERAPY

- 14.1** Additional surgical treatment of the local-regional disease is allowed for head and neck if 6 weeks or more following radiotherapy, the patient manifests persistent or recurrent tumor. Systemic chemotherapy may be given at the discretion of the cancer management team for either loco-regional or distant failure. Details of any chemotherapy given must be included in the appropriate follow-up forms. Although retreatment with radiotherapy is not encouraged, irradiation may be utilized when appropriate for tumor extensions outside of the previously treated regions or for palliation of distant metastatic cancer.

REFERENCES

1. Ang KK, and Peters LJ: Concomitant boost radiotherapy schedules in the treatment of carcinoma of the oropharynx and nasopharynx. Int J Radiation Oncol Biol Phys - 19:1339-1345, 1990.
2. Cox JD, Pajak TF, Marcial VA, Hanks GE, Mohiuddin M, Fu KK, Byhardt RW, and Rubin P: Dose-response for local control with hyperfractionated radiation therapy in advanced carcinomas of the upper aerodigestive tracts: preliminary report of the Radiation Therapy Oncology Group. Radiation Oncol Biology Phys (submitted).
3. Gray AJ: Treatment of advanced head and neck cancer with accelerated fractionation. Int J Radiation Oncology Biol Phys, 12:9-12, 1986.
4. Horiot J-C: EORTC prospective trials of altered fractionation using multiple fractions per day (MFD) Sonderb-Strahlenther-Onkol, 81:135-140, 1987.
5. Horiot JC, LeFur R, Nguyen T, Schraub S, Chenal C, Alfonsi, Gardani G, van der Schueren: Hyperfractionation versus conventional fractionation in curative radiotherapy of oropharynx carcinoma: updated results of a randomized EORTC trial. Presented at the Seventeenth International Congress of Radiology, July 1989.
6. Knee R, Shields RS, Peters LJ: Concomitant boost radiotherapy for advanced squamous cell carcinoma of the head and neck. Radiotherapy and Oncology, 4:1-7, 1985.
7. Marcial VA, Pajak TF, Chang,C et al.: Hyperfractionated photon radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity, pharynx, larynx and sinuses using radiation therapy as the only planned modality: (preliminary report) by the Radiation Therapy Oncology Group (RTOG). Int J Radiation Oncology Biol Phys, 13:41-47, 1987.
8. Parsons JT, Mendenhall WM, Cassisi NJ, Issacs JH, Million RR: Hyperfractionation for Head and Neck Cancer. Int Radiat Oncol Biol Phys 14:649-658, 1988.
9. Peracchia G and Salti C: Radiotherapy with thrice-a-day fractionation in a short overall time: clinical experiences. Int J Radiation Oncology Biol Phys, 7:99-104, 1981.
10. Peters LJ, Ang KK, Thames HD: Accelerated fractionation in the treatment of head and neck cancer: A critical comparison of different strategies. Acta Radiologica, 27:185-94, 1988.
11. Saunders MI, Dische S, Hong N, Grosch EJ, Fermont DC, Ashford RFU, Maher EJ: Continuous hyperfractionated accelerated radiotherapy in locally advanced carcinoma of the head and neck region. Int J Radiat Oncol Biol Phys 17:1287-1293, 1989.
12. Thames HD, Peters LJ, Withers HR, et al: Accelerated fractionation vs. hyperfractionation: rationales for several treatments per day. Int J Radiation Oncology Biol Phys. 9:127-138, 1983.
13. Van den Bogaert W, Schueren E, Horiot J-C, et al.: Early results of the EORTC randomized clinical trial on multiple fractions per day (MFD) and misonidazole in advanced head and neck cancer. Int J Radiation Oncology Biol Phys, 12:587-591, 1986.
14. Wang CC: Improved local control for advanced oropharyngeal carcinoma following twice-daily radiation therapy. Am J Clin Oncol (CCT), 8:512-516, 1985.
15. Wang CC, Blitzer PH and Suit HD: Twice-a-day radiation therapy for cancer of the head and neck. Cancer, 55:2100-2104, 1985.
16. Wang CC, Suit HD and Blitzer PH: Twice-a-day radiation therapy for supraglottic carcinoma. Int J Radiation Oncology Biol Phys, 12:3-7, 1986.
17. Wang CC: Local control of oropharyngeal carcinoma after two accelerated hyperfractionation radiation therapy schemes. Int J Radiat Oncol Biol Phys 14:1143-1146, 1988.
18. Wang CC: Accelerated hyperfractionation radiation therapy for carcinoma of the nasopharynx: techniques and results. Cancer 63:2461-2467 (1989).

19. Withers HR: Biologic basis for altered fractionation schemes. Cancer, 55:2086-2095, 1985.
20. Withers HR, Taylor JNG, Maciejewski B: The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncologica 27:131-146, 1988.
21. Pajak TF, Marcial VA, Davis LW, Durbin LM. Final dosimetry review in head and neck trials: Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 15: 135-136, 1988.
22. Dunnet CW: A multiple comparison procedure for comparing several treatments with a control. J Am Stat Assoc 50:1096-1121, 1955.
23. Briston DR: Designing clinical trials for two-sided multiple comparisons with a control. Controlled Clinical Trials 10:142-152, 1989.
24. Daly TE: Dental Care in the Irradiated Patient in: Textbook of Radiotherapy. Fletcher GH ed. 3rd. Edition, Lea & Febiger, Philadelphia PA, pp 229-237, 1980.
25. Datta NR, Choudhry AD, Gupta S, Rose AR: Twice a day versus once a day radiation therapy in head and neck cancer. Int J Radiat Oncol Biol Phys 17 (supplement 1): 132-133, 1989
26. Lee D, Pajak T, Marcial V, et al. F.: Results of an RTOG Phase III Trial (RTOG 85-27) Comparing Radiotherapy Plus Etanidazole (SR-2508) with Radiotherapy Alone for Locally Advanced Head and Neck Carcinomas. Proceeding of ASTRO, In J Radiat Oncol Biol Phys 30 (Supplement 1): 212, [102], 1994.
27. List MA, Ritter-Sterr C, Lansky SB: A Performance Status Scale for Head and Neck Cancer Patients. Cancer 66:564-569, 1990.
28. Rathmall AJ, Ash DV, Howes M, Nichols J: Assessing the Quality of Life in Patients Treated for Advanced Head and Neck Cancer. Clinical Oncology 3:6-10, 1991.
29. Strain JJ: The Evolution of Quality of Life Evaluation in Cancer Therapy. Oncology 4:22-26, 1990.
30. Moinpour C: Use of QOL Endpoints in Cancer Clinical Trials: Review and Recommendations. Position Paper, March 1988.
31. Cella DF, Cherin EA: Quality of Life During and After Cancer Treatment. Comprehensive Therapy 14:69-75, 1988.
32. Cella DF, Tutsky DS: Measuring Quality of Life Today. Oncology 4:29-37, 1990.
33. Schipper H: Guidelines and Caveats for Quality of Life Measurement in Clinical Practice and Research. Oncology 4:51-57, 1990.
34. Dische S, Warburton MF, Jones D, Lartigan E: The Recording of Morbidity Related to Radiotherapy. Radiotherapy and Oncology 16:103-108, 1989.

3/17/92, 4/15/95

APPENDIX I

A PHASE III RANDOMIZED STUDY TO COMPARE TWICE DAILY HYPERFRACTIONATION, ACCELERATED HYPERFRACTIONATION WITH A SPLIT AND ACCELERATED FRACTIONATION WITH CONCOMITANT BOOST TO STANDARD FRACTIONATION RADIOTHERAPY FOR SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

RTOG 90-03 PATIENT CONSENT FORM

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

Purpose of the Study

I understand that my diagnosis is a malignant squamous cell tumor of my head and neck and that further treatment is recommended. The standard therapy in the management of cases such as mine would be radiotherapy. Radiotherapy is the treatment of tumors by means of x-rays. I understand that in the past radiation therapy has been conventionally administered in daily doses 5 days per week for 6-8 weeks. Previous studies have shown that alternate ways of administering the radiation therapy may produce greater tumor control, however this has not been proven through randomized clinical trials. Therefore the purpose of this study is to determine which of four possible treatment plans described below is the most effective treatment for tumors such as mine. In addition, this study will attempt to determine how I perceive the quality of my life before treatment, at the end of treatment and at subsequent evaluations.

Description of Procedures (4/14/95)

Since, it is currently uncertain which is the best treatment for tumors such as mine, the treatment selection will be made by computer. I will be assigned to one of four treatment schedules by computer selection. The chances of my receiving treatment are approximately equal. If I receive the standard fractionation treatment (Arm 1) each radiation treatment will be administered once a day, five days a week to a total dose of 70.0 Gy in 35 treatments in seven weeks.

If I receive the hyperfractionation treatment (Arm 2) two radiation treatments will be administered each day at least 6 hours from each other. Treatment will be administered five days a week to total dose of 81.6 Gy in 68 treatments in seven weeks.

If I receive the split treatment (Arm 3) two radiation treatments will be administered each day at least 6 hours from each other. Treatment will be administered five days a week for 2-1/2 weeks, then a rest period of 14 days followed by another 1-1/2 weeks of treatment for a total dose of 67.2 Gy in 42 treatments over a total treatment time of six weeks.

If I receive the concomitant boost treatment (Arm 4) each radiation treatment will be administered once a day. Treatment will be administered five times weekly for six weeks without a rest period. During the last two-and-one-half weeks, I will receive a second daily treatment at least 6 hours after the first treatment for a total dose of 72.0 Gy in 42 treatments in six weeks.

The experimental aspect of this study is the use of two fractions of irradiation daily. The total dose of irradiation administered is also being investigated in the current study.

For pre-treatment evaluation, a blood count (CBC), chest X-ray, and a CT scan or MRI scan or bone scan and additional blood tests may be performed when indicated. These tests may be repeated to monitor my disease status during or following completion of my treatments when indicated. In addition, I will be asked to complete questionnaires which will evaluate the quality of my life at different time points. I will complete the questionnaires before and after my radiation and at certain followup visits. The questionnaires will take approximately 15-20 minutes of my time for each session and will monitor my disease status and how I feel about the quality of my life. All my answers will be kept strictly confidential.

Also, at the time of my diagnosis by biopsy, all or some of my tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, remaining tumor samples were

stored in the pathology department. I am being asked for permission to use the remainder of the tumor for additional tests. Since this tissue was removed at the time of surgery or biopsy, the permission to use my tissue will not involve any additional procedure or expense to me. The tumor tissue's cells will be examined to see if any special "markers", tests which predict how a patient with tumors like mine responds to treatment, can be identified.

Potential Risks

I have been informed of the discomforts and risk which I may reasonably expect as part of this study. The irradiation may cause temporary skin redness, difficulty swallowing, reduction in blood counts. Late effects may include dryness of the mouth, continued soreness in the mouth and throat, hoarseness, and damage to the jaw bone causing bone destruction that might produce pain or require surgery if severe.

I understand that there may be some unknown or unanticipated discomforts or risks in addition to those specified above because some of the procedures are relatively new and are attempts to advance medical knowledge.

Potential Benefits

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be useful scientifically and possibly helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

Alternatives

Alternatives which could be advantageous in my case include radiation therapy combined with surgery and/or chemotherapy. Another alternative would be no further treatment in which case my tumor would be expected to grow.

Contact Persons

In the event injury occurs as a result of this research, I will not be provided with reimbursement for medical care or other compensation. For more information concerning the research and research-related risks or injuries, I can contact Dr. _____, the investigator in charge at _____ . For information regarding patient's rights in research studies I can contact at _____.

The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand I am free to ask my physician any questions concerning this program that I may wish in the future. I have been assured that any procedures related solely to research which would not otherwise be necessary will be explained to me. Some of these procedures may result in added costs and some of these costs may not be covered by insurance. My doctor will discuss these with me.

Voluntary Participation

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to take part in this study at any time without prejudice to my future care. I am free to seek care from any physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or *Legal Representative*)

Date

revised 3/17/92, 4/14/95

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

- 100 Normal; no complaints; no evidence of disease.
- 90 Able to carry on normal activity; minor signs or symptoms of disease.
- 80 Normal activity with effort; some sign or symptoms of disease.
- 70 Cares for self, unable to carry on normal activity or do active work.
- 60 Requires occasional assistance, but is able to care for most personal needs.
- 50 Requires considerable assistance, but is able to care for most personal needs.
- 40 Disabled; requires special care and assistance.
- 30 Severely disabled; hospitalization is indicated, although death not imminent.
- 20 Very sick; hospitalization necessary; active support treatment is necessary.
- 10 Moribund; fatal processes progressing rapidly.
- 0 Dead.

APPENDIX III

Eligible Patients & 1988 American Joint Commission AJC Staging

Eligible Patients

Oral Cavity

Stage III, IV

Tongue (Anterior two-thirds)

Floor of Mouth

Buccal Mucosa

Palate (hard)

Gingiva

Retromolar Trigone

Oropharynx and Hypopharynx

Stage III, IV

Tonsil and/or pillars

Faucial Arch/Soft Palate

Pharyngeal Walls (posterior or lateral)

Stage II, III, IV

Base of Tongue

Hypopharynx

Supraglottic Larynx

Stage III, IV

Ventricular band

Arytenoid

Suprahyoid epiglottis

Infrahyoid epiglottis

Aryepiglottic fold

AJC STAGING-Primary Tumor (T)

Oral Cavity

Buccal mucosa

Lower alveolar ridge

Upper alveolar ridge

Retromolar gingiva (Retromolar trigone)

Floor of mouth

Hard palate

Anterior two-thirds of the tongue

TX Tumor that cannot be assessed

T0 No evidence of primary tumor

TIS Carcinoma in situ

T1 Greatest diameter of primary tumor \leq 2 cm

T2 Greatest diameter of primary tumor $> 2 - \leq 4$ cm

T3 Greatest diameter of primary tumor more than 4 cm

T4 Tumor invades adjacent structures (e.g. through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin).

Oropharynx

Faucial arch including soft palate, uvula and anterior tonsillar pillar

Tonsillar fossa and tonsil

Base of tongue including glossoepiglottic and pharyngoepiglottic folds

Pharyngeal wall including lateral and posterior walls and posterior tonsillar pillar

TX Tumor that cannot be assessed

T0 No evidence of primary tumor

TIS Carcinoma in situ

T1 Tumor 2 cm or less in greatest diameter

T2 Tumor greater than 2 cm, but not greater than 4 cm in greatest diameter

T3 Tumor greater than 4 cm in greatest diameter

T4 Tumor invades adjacent structures (e.g. through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin)

Hypopharynx

Pyramidal sinus

Postcricoid area

Posterior hypopharyngeal wall

TX Tumor that cannot be assessed

T0 No evidence of primary tumor

TIS Carcinoma in situ

T1 Tumor limited to one subsite of hypopharynx.

T2 Tumor invades more than one subsite of hypopharynx or an adjacent site without fixation of hemilarynx.

T3 Tumor invades more than one subsite of hypopharynx or an adjacent site with fixation of hemilarynx.

T4 Tumor invades adjacent structures (e.g. cartilage or soft tissues of neck).

Supraglottic Larynx

Ventricular bands (false cords)

Arytenoids

Epiglottis (both lingual and laryngeal aspects)

Suprahyoid epiglottis

Infrahyoid epiglottis

Aryepiglottic folds

TIS Carcinoma in situ

T1 Tumor limited to one subsite of supraglottis with normal mobility.

T2 Tumor invades more than one subsite of supraglottic or glottis with normal vocal cord mobility.

T3 Tumor limited to larynx with vocal cord fixation and/or extension to involve postcricoid area, medial wall of pyramidal sinus, or pre-epiglottic tissues.

T4 Massive tumor extending beyond the larynx to involve oropharynx, soft tissue of neck, or destruction of thyroid cartilage.

Nodal Involvement (N)

NX Nodes cannot be assessed

N0 No clinically positive node

N1 Single clinically positive ipsilateral node 3 cm or less in diameter.

N2 Single clinically positive ipsilateral node more than 3 cm, but not more than 6 cm in diameter or multiple clinically positive ipsilateral or bilateral or contralateral nodes, none more than 6 cm in diameter.

N2a Single clinically positive ipsilateral node more than 3 cm, but not more than 6 cm in diameter.

N2b Multiple clinically positive ipsilateral nodes, none more than 6 cm in diameter.

N2c Bilateral or contralateral lymph node none more than 6 cm in greatest dimension.

N3 Metastases in a lymph node more than 6 cm in greatest dimension.

Stage Groupings

- Stage I - T1, N0, M0
- Stage II - T2, N0, M0
- Stage III - T3, N0, M0
T1-3, N1, M0
- Stage IV - T4, N0-1, M0
T1-4, N2-3, M0
Any T, or any N, M1

Revised 12/20/91

APPENDIX VI

ADVERSE REACTION REPORTING GUIDELINES

A. General Guidelines

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires special handling, study specific reporting procedures supercede the general guidelines.**

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reaction. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3214). When telephone reporting is required, the Principal Investigator should have all relevant material available. See the specific protocol for criteria to grade the severity of the reaction.
2. The Principal Investigator will also report to the Study Chairman by telephone the details of the significant reaction.
3. When directed, a written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol.
(FAX #215/928-0153)
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG sponsored intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator when participating in RTOG coordinated Intergroup studies is obligated to comply with all additional reporting specifications required by the individual study.
7. Institutions must also meet their individual Institutional Review Board (IRB) policy with regard to their toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of participation.

B. Modality Toxicity Guideline

1. All fatal toxicities resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the Study Chairman within 24 hours of discovery.
2. All life-threatening or grade 4 toxicities from protocol therapy must be reported by telephone to the Group Chairman, RTOG Headquarters' Data Management Staff and to the Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters with 10 working days of the reported incident.

APPENDIX V

Response Criteria For Measurable Lesions

- | | |
|-------------------|--|
| Complete Response | - Complete disappearance of measurable and palpable disease. |
| Partial Response | - Tumor shrinkage greater than 50% of the product of the perpendicular diameters of the two largest dimensions without increase in size of any other area of known malignant disease (excluding regional nodes) or without appearance of new areas of malignant disease within the treated volume. |
| Minor Response | - Tumor shrinkage greater than 25% but less than 50% of the product of the perpendicular diameters of the two largest dimensions without increase in size of any other area of known malignant disease (excluding regional nodes) or without appearance of new areas of malignant disease within the treated volume. |
| No Change | - Up to 25% growth or 25% shrinkage of the product of perpendicular diameters of the two largest dimensions without increase in size of any other area of known malignant disease (excluding regional nodes) or without appearance of new areas of malignant disease within the treated volume. |
| Progression | - Growth of tumor greater than 25% of the product of the perpendicular diameters of the two largest dimensions. |

Response Criteria for Evaluable, Non-Measurable Lesions

- | | |
|-------------------|--|
| Complete Response | - Complete disappearance of known disease |
| Partial Response | - A definite decrease in size of diseased areas amounting to an estimated 80% regression (close to complete regression) or better. This should be confirmed by at least two investigators evaluating independently, or photographs or x-rays should be submitted to the study chairman for confirmation. |
| Minor Response | - Not applicable |
| No Change | - Insufficient regression of lesion to meet criteria above and no new areas of malignant disease. |
| Progression - | An estimated increase in the size of the tumor of greater than 25% or appearance of new areas of malignant disease. |

RTOG 9003 CONSORT flow diagram

