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The Impact of Gender, Partner Status, and Race on Locoregional Failure and Overall Survival in Head and Neck Cancer Patients in Three Radiation Therapy Oncology Group (RTOG) Trials

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Abstract

PURPOSE—We investigated the impact of race, in conjunction with gender and partner status, on both locoregional control (LRC) and overall survival (OS) in three head and neck trials conducted by the Radiation Therapy Oncology Group (RTOG).

METHODS AND MATERIALS—Patients from RTOG 9003, 9111, and 9703 were included. Patients were stratified by treatment arms. Covariates of interest were partner status (partnered/non-partnered), race (white/non-white), and sex (female/male). Chi-square testing demonstrated homogeneity across treatment arms. Hazards ratio (HR) was used to estimate time to event outcome. Unadjusted and adjusted HRs were calculated for all covariates with associated 95% confidence intervals (CIs) and p-values.

RESULTS—1736 patients were analyzed. Unpartnered males had inferior OS to partnered females (adjusted HR=1.22, 95% CI=(1.09, 1.36)), partnered males (adjusted HR=1.20, 95% CI=(1.09, 1.28)), and unpartnered females (adjusted HR=1.20, 95% CI=(1.09, 1.32)). White females had superior OS compared with white males, non-white females, and non-white males. Non-white males had inferior OS compared to white males. Partnered whites had improved OS relative to partnered non-white, unpartnered white, and unpartnered non-white patients.

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Unpartnered males had inferior LRC than partnered males (adjusted HR=1.26, 95% CI=(1.09, 1.46)) and unpartnered females (adjusted HR=1.30, 95% CI=(1.05, 1.62)). White females had superior LRC to non-white males and females. White males had improved LRC than non-white males. Partnered whites had improved LRC than partnered and unpartnered non-white patients. Unpartnered whites had improved LRC than unpartnered non-whites.

CONCLUSIONS—Race, gender, and partner status impacted on both overall survival and locoregional failure, both singly and in combination.

Keywords

Head and Neck Cancer; Gender; Partner Status; Race

INTRODUCTION

Classically, the results of clinical trials have described physical or physiologic properties of patients (or tumors) that predict response and outcome. However, research is proving that psychosocial factors, too, can be predictive in cancer patients. Non-White (1–3), lower socioeconomic status (4, 5), unmarried (4, 6–13) or non-cohabitating (14) individuals often fare worse than others. These different effects are sometimes contradictory in different studies (15–17).

A previous analysis from an RTOG study of breast and prostate cancer patients undergoing palliative radiotherapy for bony metastases demonstrated that married men/women and single women receiving 30 Gy of radiation had significantly longer time to retreatment than single men, and, interestingly, retreatment rates were not significantly different for single men receiving 30 vs. 8 Gy of radiation, in contrast to the other groups.(6)

Spurred in part by these findings, the RTOG performed an analysis of the effect of gender and partner status on survival for head and neck (H&N) cancer patients treated on three clinical trials. The results have been published previously; the researchers found an unequivocal disadvantage for survival in unpartnered men, even when controlling for a variety of disease and demographic variables.(7)

The present analysis expands upon the previous study. In particular, we have revised the previous binary model (sex and partner status) by specifically exploring the interrelationship of race, along with partner status and gender, on outcome. We hypothesize that the interaction among gender, partner status, and race delineates a group at particular risk for poor outcomes, namely unpartnered non-white males. Furthermore, the present analysis evaluates these psychosocial characteristics not only as predictors of overall survival, but also of locoregional failure.

METHODS AND MATERIALS

Patients treated on three RTOG head and neck cancer trials are included: RTOG 9003, 9111, and 9703. RTOG 9003 was a randomized phase III clinical trial that evaluated four different radiotherapy fractionation schedules; Arm 1: Standard Fractionation (SFX), Arm 2: Hyperfractionation (HFX), Arm 3: Accelerated Hyperfractionation with Split (AHEX-S), and Arm 4: Accelerated Fractionation with Concomitant Boost (AFX-C). RTOG 9111 was a randomized phase III trial evaluating induction chemotherapy (CT) and radiation therapy (RT) versus concomitant chemotherapy and RT versus RT alone to preserve the larynx in patients with glottic or supraglottic tumors; Arm 1: Induction cisplatin/5-FU and RT (I+RT), Arm 2: Concurrent cisplatin and RT (CRT), and Arm 3: RT alone (RT alone). RTOG 9703 was a randomized phase II trial evaluating three different chemotherapy and radiotherapy

regimens; Arm 1: RT + Concurrent cisplatin/5-FU (Cispl/5-FU), Arm 2: RT + Concurrent hydroxyurea/5-FU (Hydroxy/5-FU), and Arm 3: RT + Concurrent cisplatin/paclitaxel (Cispl/Taxol).

The treatment results for each trial have been published previously.(18–20) Eligibility criteria for the three trials varied. However, none used gender, partner status, or race as eligibility criteria.

Pretreatment and demographic information were obtained at registration for each trial. The form to collect this information was typically completed by the patient, a caregiver, or a staff member at the participating institution. From the provided demographic information, the following major covariates of interest were considered in the models: race (white vs. non-white), gender (female vs. male), and partner status (Partnered/other live-in relationship [partnered] vs. Unpartnered/divorced/separated/widowed [unpartnered]). These trials accrued 1736 patients from 1991 to 2000 across ten treatment arms.

A Chi-square test was applied to evaluate the homogeneity of the data and to establish whether one estimate could be used to represent the metadata from three different trials. To take into account the differences among the trials such as the patient population, treatment, and the period of accrual, the metadata were stratified by the treatment arms. This resulted in 10 stratification variables (STR) among the 3 included trials. Hazards ratio (HR) was used as an estimator for time to event outcome. The pooled HR estimator(21, 22) with weight of the inverse of variance of estimator was used. If there was homogeneity among the treatment arms, the pooled HRs would be used as the estimator for the combined data. The Chi-square test was applied to these data to assess heterogeneity among the individual treatment arms at the significance level of 0.1. Chi-square test statistics and t-test statistics were used to determine if there was a difference with respect to the pretreatment characteristics and outcomes of patients with and without missing data. These test statistics were also used to compare pretreatment characteristics of patients.

Overall survival (OS) was defined as a death due to any cause and time to OS was measured from randomization to date of death or the last follow-up. Locoregional failure (LRF) was measured from randomization to date of failure. The following covariates were considered in the two outcomes in the models; race (white [reference level; RL] vs. non-white), gender (female [RL] vs. male), and partner status (married/other live-in relationship (Partnered) [RL] vs. single/divorced/separated/widowed (Unpartnered). The other covariates considered for OS in addition to race, gender, and partner status were age (continuous 9003 and 9703 only), KPS (60–80 [RL] vs. 90–100), T-stage (T1–T3 [RL] vs. T4), N-stage (N0-N2a (RL) vs. N2b-N3) and primary site [oropharynx (RL) vs. others]. The additional covariates considered for LRF (only for 9003 and 9703) were hyperfractionation (yes [RL] vs. no) and chemotherapy (RT + any CT [RL] vs. RT only).

The Kaplan-Meier method(23) was used to estimate the survival rate for OS, and the cumulative incidence method(24) was used for failure rate for LRF. To analyze whether each covariate was independently associated with outcomes while adjusting for other covariates, Cox proportional hazards regression models(25) were used for OS and Fine and Gray's regression models(26) were used for LRF. Unadjusted and adjusted (HRs) were calculated for all covariates with associated 95% confidence intervals (CIs) and p-values. All statistical tests were two-sided and a p-value <0.05 was considered statistically significant. Statistical Analysis System (SAS Institute, Cary, NC) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

RESULTS

There were 87 (4.8%) patients with missing or unknown pretreatment data that were excluded from the analysis: unknown marital status (n=85), missing N-stage (n=1) and missing T-stage (n=1). Across the ten treatment arms in the three trials, the percentage of patients with missing data ranged from 1–9%, although the average was 5% missing data across each of the arms. The remaining 1736 comprise the patients in the analysis. There were no statistically significant differences between the patients with and without missing data except race and KPS (data are not shown here, $p=0.008$ and $p<0.001$, respectively). No missing data imputation was done because the percentage of missing data is less than 5% and the distribution of pretreatment characteristics is fairly balanced except for the two variables (Complete Case Analysis). Table 1 shows the distribution of patients in the three trials.

The results from heterogeneity testing for this analysis are shown in Tables 2 and 3. Note that the right-hand column demonstrates hazard ratios which were adjusted for T-stage, N-stage, KPS, primary site of disease (in two studies), and age. The ten treatment arms from the three trials were found to be homogeneous in respect to the adjusted hazard ratios (HRs) of OS and LRF for each covariate of interest (gender, partner status, and race) across each study arm (p-value >0.1). The results show that male (pooled HR=1.19; 95% C.I.=1.03, 1.38), unpartnered (pooled HR=1.31; 95% C.I.=1.16, 1.47), and non-white (pooled HR=1.24; 95% C.I.=1.09, 1.42) patients were statistically significantly more likely to have died than female, partnered, and white patients, respectively. Similar results were found with respect to LRF for both partner status and race but not gender (Table 3). However, the lower limits of the confidence intervals for the HR are close to 1, which indicates that the effect is not large.

Table 4 presents the 2-year overall survival and locoregional failure rates for each subgroup. The numbers of patients in the partnered and unpartnered non-white female groups are too few to have statistically meaningful results. Partnered white females had the highest 2-year survival rate of 72% and unpartnered non-white males had the lowest 2–year survival rate of 42.7%. Partnered males (69.2%), white females (66.6%), and married white (69.6%) had higher 2-year survival rates than other groups. The data demonstrate similar findings in terms of LRF. Non-white unpartnered males had the highest 2-year rate of LRF (61.3%) while married white females, married white males, and unpartnered white females did much better, with LRF of 36.8%, 34.5%, and 35.4%, respectively.

Pair-wise comparisons between any two subgroups were performed and the statistically significant results are shown in Table 5. Again, note that the right-hand column demonstrates hazard ratios which were adjusted for T-stage, N-stage, KPS, primary site of disease (in two studies), and age. Unpartnered males were more likely to have died than partnered females (adjusted HR=1.22, 95% CI=(1.09, 1.36)), partnered males (adjusted HR=1.20, 95% CI=(1.09, 1.28)), and unpartnered females (adjusted HR=1.20, 95% CI=(1.09, 1.32)). White females were less likely to have died than white males, non-white females, and non-white males. Non-white males were more likely to have died than white males. Also, partnered whites were less likely to have died than partnered non-white, unpartnered white, and unpartnered non-white patients. Unpartnered males were more likely to have LRF than partnered males (adjusted HR=1.26, 95% CI=(1.09, 1.46)) and unpartnered females (adjusted HR=1.30, 95% CI=(1.05, 1.62)). White females were less likely to have LRF than non-white female and non-white male. White males were less likely to have LRF than non-white males. Partnered whites were less likely to have LRF than partnered non-white and unpartnered non-white patients. Unpartnered whites were less likely to have LRF than unpartnered non-whites.

DISCUSSION

A previously-published analysis has shown that unpartnered males with head and neck cancer treated on these RTOG trials had diminished overall survival.(7) However, the present analysis extends these findings further, showing that race also impacts on overall survival, in addition to partner status and patient gender. Furthermore, not only is overall survival impacted, but also locoregional failure.

Two of the traits that we analyzed (gender and race) could imply that there are genetic differences in squamous cell carcinomas of the head and neck in men versus women, and/or whites versus non-whites. In general, little is known at this point regarding influence of gender or race on genotype/phenotype of solid malignancies.

The presence of HPV DNA in HNSCC is increasingly recognized as a marker of improved prognosis in terms of recurrence-free and overall survival.(27) In a recent study, researchers found that patients with HPV-positive tumors trend toward improved overall survival, disease-free survival, and local control when compared with HPV-negative tumors(28). In that particular analysis, HPV-positive tumors tended to occur in younger patients. However, race, sex, and alcohol or tobacco consumption did not predict for HPV-positivity. In contrast, another recently published single institution retrospective and prospective analysis of patients with oropharyngeal primary tumors has demonstrated that the racial disparity in OS between white and African American patients was due to a large difference in prevalence of HPV infection between the white and African American patients [34% in white versus 4% in black patients ($p = 0.0004$)].(29) It remains unexplained as to why race was variably-associated with HPV-positivity in these two studies. This might reflect a regional variation in HPV-positivity among African Americans, or perhaps a temporal shift in HPV-positivity over time.

In any case, the patients included in our analysis did not undergo HPV screening. However, additional analysis of these patients demonstrates no association between oropharyngeal primary and either altered local control or overall survival by unadjusted hazard ratio (Table 6). This negative finding held up after multivariate adjustment for T-stage, N-stage, KPS, age, gender, partner status, and race (Tables 6–7). In contrast, T-stage (T4 vs T1–3) was predictive of overall survival and local control, whether adjusted for the above demographic factors or not (Tables 8–9). Association between HPV-positivity and outcome will require prospective validation in future multi-institutional trials.

In this analysis, white females had better OS and a trend toward improved local control compared with white males. However, non-white females fared similarly to non-white males for both OS and LRF. While at least one study has failed to find gender to be predictive of HPV positivity(28), others have generally found HPV to be far more common in males.(28, 30) If significantly more males were HPV-positive in our cohort of patients, then our finding of improved outcome in white females remains unexplained. Perhaps some additional (or different) biological factor explains these findings. Gender differences in response to treatment are most notable in non-small cell lung cancer patients treated with tyrosine kinase inhibitors targeting the epidermal growth factor receptor (EGFR). About 10% of these patients have mutations that predict for rapid response with treatment. Such mutations are more commonly seen in women, especially of Asian origin, and in non-smokers.(31)

Other biologic factors have been implicated in tumor aggressiveness. Molecular markers such as p53 mutations(32), decreased expression of p16(33–35) and increased expression of EGFR(34) have all been found to be associated with a poor survival and worse prognosis.

Certainly, psychosocial or demographic factors might predict income, distinct from any biologic factors. In our analysis, unpartnered, non-white males fared worse than other groups. One possible explanation might be that they were more likely to be uninsured or comparatively underinsured. Studies have shown that uninsured patients, patients receiving Medicaid, and patients under the age of 65 receiving Medicare are all at increased risk of poor outcomes after treatment of head and neck cancers.(36, 37) Therefore, gender, race, and cohabitation status might simply interplay to predict a patient's insurance status. In any case, patients with less or no insurance tend to present for treatment later and with more advanced disease, suggesting that a relative lack of access to healthcare might actually be one of the factors which partially explains our findings. However, this cannot be the sole explanation, as our findings were also borne out when controlling for tumor stage.

Similarly, level of insurance might merely be predictive of educational attainment (and, also, of income). Higher educational attainment predicted for improved survival in RTOG 9003.(38) Multivariate analysis revealed education level was significant for predicting both OS and locoregional control when comparing those who attended college/technical school to all other education levels. Education level correlates directly with income level.(39, 40) Therefore, the findings in this analysis could be explained, in part, by differences in income level. A previous paper did show that income level was predictive of outcome in these three RTOG trials.(7) Therefore, race, gender, and partner status might simply be proxies for educational level and income (or vice versa).

Partner status, in and of itself, has been implicated as a positive factor in patient survival. In patients with heart failure, for instance, those with a spouse had longer event-free survival than non-married patients did, even after stratification for the presence or absence of depressive symptoms.(41) However, another study of patients with heart failure has demonstrated that the quality of the relationship impacts upon the patients' survival; problematic relationships were deleterious to overall survival.(42) However, the quality of the patient's relationships with their significant others was not captured in these three RTOG studies.

It can certainly be hypothesized that partnered patients received more support from their partners, both emotional and physical, throughout the treatment process, which might have enabled them to tolerate treatment better, leading to less treatment breaks and, therefore, better outcomes. We have found that unpartnered non-white males were at higher risk of adverse outcome in these studies. This is consistent with previous research that non-partnered male patients in another RTOG head and neck cancer study had poorer outcomes.(6) This finding suggests that targeted psychosocial interventions in these high-risk sub-groups might also prove beneficial.

CONCLUSION

In this analysis of three RTOG head and neck cancer trials, race, gender, and partner status each impacted on both overall survival and locoregional failure, both singly and in combination. It remains to be seen whether these demographic factors might simply be proxies for HPV-positivity or some other biologic factor, or whether these sociodemographic factors themselves might impact directly on overall survival and locoregional failure, independent of any other biologic characteristics, or perhaps via some unknown, complex interaction of these epiphenomena.

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Table 1

Pretreatment Characteristics by Study (n=1736)

Characteristic	9003 n (%)	9111 n (%)	9703 n (%)	Total n (%)
Eligible	1021	483	232	1736
Age (years)				
Mean	60.5	59.0	57.5	59.7
Range	30–90	29–79	21–83	21–90
Median	61	59	56	60
Age < 60	463 (45%)	246 (51%)	139 (60%)	848 (49%)
Age ≥ 60	558 (55%)	237 (49%)	93 (40%)	888 (51%)
Gender				
Female	214 (21%)	104 (22%)	46 (20%)	364 (21%)
Male	807 (79%)	379 (78%)	186 (80%)	1372 (79%)
Race				
White	742 (73%)	369 (76%)	172 (74%)	1283 (74%)
Non-White	279 (27%)	114 (24%)	60 (26%)	453 (26%)
Marital Status				
Partnered/other live-in relationship	505 (49%)	282 (58%)	134 (58%)	921 (53%)
Unpartnered/divorced/separated/widowed	516 (51%)	201 (42%)	98 (42%)	815 (47%)
T-Stage				
T1–T3	724 (71%)	436 (90%)	136 (59%)	1296 (75%)
T4	297 (29%)	47 (10%)	96 (41%)	440 (25%)
N –Stage				
N0-N1-N2a	535 (52%)	354 (73%)	84 (36%)	973 (56%)
N2b-N2c-N3	486 (48%)	129 (27%)	148 (64%)	763 (44%)
Primary Site				
Orpharynx	615 (60%)	0 (0%)	153 (66%)	768 (44%)
Others	406 (40%)	483 (100%)	79 (34%)	968 (56%)
KPS				
60–80	640 (63%)	357 (74%)	151 (65%)	1148 (66%)
90–100	381 (37%)	126 (26%)	81 (35%)	588 (34%)
Chemotherapy (CT) Usage				
RT + any CT	0 (0%)	321 (66%)	232 (100%)	553 (32%)
RT alone	1021 (100%)	162 (34%)	0 (0%)	1183 (68%)
Altered RT Fraction (HFX)				
Yes	516 (51%)	0 (0%)	0 (0%)	516 (30%)
No	505 (49%)	483 (100%)	232 (100%)	1220 (70%)

Table 2

Proportional Hazards Regression Models for Overall Survival

	Gender (Male vs. Female[RL[1]])		Marital Status (Unpartnered vs. Partnered[RL[1]])		Race (Non-White vs. White[RL[1]])	
Treatment Arm	**Adjusted Hazard Ratio[2] (95% CI[*])**	**p-value**	**Adjusted Hazard Ratio[2] (95% CI[*])**	**p-value**	**Adjusted Hazard Ratio[2] (95% CI[*])**	**p-value**
9003: Arm 1 – SFX	1.14 (0.83, 1.57)	0.42	1.63 (1.21, 2.19)	0.001	1.55 (1.13, 2.13)	0.007
9003: Arm 2 – HFX	0.90 (0.63, 1.28)	0.55	1.31 (0.97, 1.77)	0.08	1.09 (0.78, 1.53)	0.61
9003: Arm 3 – AHFX-S	1.47 (1.03, 2.08)	0.03	1.19 (0.90, 1.57)	0.23	1.01 (0.73, 1.40)	0.93
9003: Arm 4 – AFX-C	1.24 (0.85, 1.83)	0.26	1.49 (1.11, 2.00)	0.008	1.31 (0.94, 1.83)	0.11
9111: Arm 1 – I+RT	0.97 (0.56, 1.67)	0.90	1.79 (1.12, 2.87)	0.02	1.52 (0.92, 2.50)	0.10
9111: Arm 2 – CRT	1.76 (1.02, 3.03)	0.04	1.01 (0.67, 1.52)	0.96	1.46 (0.93, 2.29)	0.10
9111: Arm 3 – RT Alone	1.09 (0.65, 1.83)	0.75	1.15 (0.75, 1.75)	0.53	1.37 (0.84, 2.24)	0.20
9703: Arm 1 – Cispl/5-FU	1.22 (0.60, 2.45)	0.58	0.96 (0.53, 1.74)	0.89	1.01 (0.50, 2.02)	0.99
9703: Arm 2 – Hydroxy/5-FU	1.85 (0.69, 4.92)	0.22	0.94 (0.46, 1.89)	0.85	0.90 (0.41, 1.94)	0.78
9703: Arm 3 – Cispl/Taxol	1.17 (0.51, 2.71)	0.71	1.12 (0.56, 2.26)	0.74	0.92 (0.45, 1.90)	0.82
	Chi Square T.S. (Q) = 7.359 **p-value** = 0.31		**Chi Square T.S. (Q)** = 9.000 **p-value** = 0.47		**Chi Square T.S. (Q)** = 6.979 **p-value** = 0.27	
Pooled HR[3]	1.19 (1.03, 1.38)	--	1.31 (1.16, 1.47)	--	1.24 (1.09, 1.42)	--

[1] CI = Confidence Interval; RL = Reference Level

[2] Adjusted for: T-stage (RL: T1-T3), N-stage (RL: N0-N1-N2a), KPS (RL: 60–80), primary site (RL: oropharynx; 9003 and 9703 only), and age (continuous).

[3] This is a pooled estimate.

Table 3

Proportional Hazards Regression Models for Local Regional Failure

	Gender (Male vs. Female[RL[1]])		Marital Status (Unpartnered vs. Partnered[RL[1]])		Race (Non-White vs. White[RL[1]])	
Treatment Arm	**Adjusted Hazard Ratio[2] (95% CI[1])**	**p-value**	**Adjusted Hazard Ratio[2] (95% CI[1])**	**p-value**	**Adjusted Hazard Ratio[2] (95% CI[1])**	**p-value**
9003: Arm 1 – SFX	0.97 (0.68, 1.36)	0.84	1.22 (0.89, 1.67)	0.21	1.51 (1.10, 2.09)	0.01
9003: Arm 2 – HFX	0.97 (0.62, 1.51)	0.88	1.28 (0.90, 1.82)	0.17	0.98 (0.67, 1.42)	0.90
9003: Arm 3 – AHFX-S	1.28 (0.83, 1.97)	0.27	1.09 (0.79, 1.50)	0.60	1.20 (0.85, 1.68)	0.30
9003: Arm 4 – AFX-C	1.21 (0.76, 1.93)	0.41	1.17 (0.83, 1.64)	0.37	1.59 (0.76, 1.59)	0.63
9111: Arm 1 – I+RT	0.79 (0.48, 1.31)	0.36	1.34 (0.86, 2.09)	0.20	1.40 (0.87, 2.25)	0.16
9111: Arm 2 – CRT	2.56 (0.998, 6.59)	0.052	1.31 (0.76, 2.27)	0.34	1.51 (0.85, 2.69)	0.16
9111: Arm 3 – RT Alone	1.57 (0.87, 2.82)	0.13	0.93 (0.61, 1.44)	0.75	1.18 (0.75, 1.87)	0.48
9703: Arm 1 – Cispl/5-FU	0.94 (0.45, 1.97)	0.86	1.84 (0.95, 3.55)	0.07	1.25 (0.59, 2.67)	0.57
9703: Arm 2 – Hydroxy/5-FU	4.25 (0.995, 18.17)	0.052	0.89 (0.48, 1.63)	0.70	1.03 (0.52, 2.07)	0.93
9703: Arm 3 – Cispl/Taxol	0.74 (0.32, 1.70)	0.48	1.24 (0.60, 2.58)	0.56	0.98 (0.44, 2.17)	0.96
	Chi Square T.S. (Q) = 11.931 **p-value** = 0.96		**Chi Square T.S. (Q)** = 4.662 **p-value** = 0.54		**Chi Square T.S. (Q)** = 4.772 **p-value** = 0.56	
Pooled HR[3]	1.10 (0.93, 1.30)	--	1.19 (1.04, 1.35)	--	1.22 (1.06, 1.41)	--

[1] CI = Confidence Interval; RL = Reference Level

[2] Adjusted for: T-stage (RL: T1-T3), N-stage (RL: N0-N1-N2a), KPS (RL: 60–80), primary site (RL: oropharynx; 9003 and 9703 only), and age (continuous).

[3] This is a pooled estimate.

Table 4

Summary Statistics of Subgroups

		Overall Survival		Local Regional Failure	
	n	# of failures by 2 years	2-year estimates (95% C.I.)[1]	# of failures by 2 years	2-year estimates (95% C.I.) [1]
Marital Status* Race*Gender					
Partnered white female	136	38	72.0 (63.7, 78.8)	52	36.8 (28.6, 44.9)
Partnered white male	601	185	69.1 (65.2, 72.6)	229	34.5 (30.7, 38.3)
Unpartnered white female	150	57	61.6 (53.2, 68.9)	66	35.4 (27.7, 43.2)
Unpartnered white male	396	198	49.9 (44.8, 54.7)	229	47.3 (42.4, 52.2)
Partnered non-white female	20	10	50.0 (27.1, 69.2)	12	50.0 (27.3, 72.7)
Partnered non-white male	164	66	58.6 (50.6, 65.8)	83	47.3 (39.5, 55.0)
Unpartnered non-white female	58	30	47.6 (34.2, 59.8)	36	50.2 (37.1, 63.3)
Unpartnered non-white male	211	119	42.7 (35.9, 49.3)	138	61.3 (54.6, 67.9)
Marital Status* Gender					
Partnered female	156	48	69.2 (61.3, 75.8)	64	38.5 (30.8, 46.1)
Partnered male	765	251	66.9 (63.4, 70.1)	312	37.2 (33.7, 40.6)
Unpartnered female	208	87	57.7 (50.6, 64.1)	102	39.6 (32.9, 46.2)
Unpartnered male	607	317	47.4 (43.4, 51.3)	367	52.1 (48.2, 56.1)
Race*Gender					
White female	286	95	66.6 (60.7, 71.7)	118	36.1 (30.5, 41.6)
White male	997	383	61.5 (58.4, 64.4)	458	39.6 (36.5, 42.6)
Non-white female	78	40	48.2 (36.7, 58.8)	48	50.1 (38.9, 61.4)
Non-white male	375	185	49.6 (44.4, 54.6)	221	55.2 (50.1, 60.2)

		Overall Survival		Local Regional Failure	
	n	# of failures by 2 years	2-year estimates (95% C.I.)[1]	# of failures by 2 years	2-year estimates (95% C.I.)[1]
Marital Status* Race					
Partnered white	737	223	69.6 (66.2, 72.8)	281	34.9 (31.5, 38.4)
Partnered non-white	184	76	57.6 (50.1, 64.5)	95	47.5 (40.2, 54.8)
Unpartnered white	546	255	53.1 (48.8, 57.2)	295	44.0 (39.9, 48.2)
Unpartnered non-White	269	149	43.8 (37.7, 49.6)	174	58.9 (53.0, 64.8)

[1] CI: Confidence Interval

Table 5

Comparison of Subgroups[1]

	Overall Survival		Local Regional Failure	
Pair-wise Comparison[2]	**Adjusted HR[3,4]**	**95% C.I.**	**Adjusted HR[3,4]**	**95% C.I.**
Marital Status* Race*Gender				
Partnered white female (RL) vs. Unpartnered white male	1.25	(1.11, 1.41)	--	--
Partnered white female (RL) vs. Partnered non-white female	1.35	(1.01, 1.80)	--	--
Partnered white female (RL) vs. Unpartnered non-white female	1.27	(1.06, 1.53)	--	--
Partnered white female (RL) vs. Unpartnered non-white male	1.29	(1.12, 1.49)	1.41	(1.03, 1.94)
Partnered white male (RL) vs. Unpartnered white male	1.22	(1.33, 1.32)	1.26	(1.05, 1.50)
Partnered white male (RL) vs. Partnered non-white female	1.35	(1.04, 1.76)	--	--
Partnered white male (RL) vs. Unpartnered non-white female	1.19	(1.02, 1.40)	--	--
Partnered white male (RL) vs. Unpartnered non-white male	1.25	(1.13, 1.38)	1.52	(1.23, 1.89)
Unpartnered white female (RL) vs. Unpartnered white male	1.28	(1.14, 1.44)	1.42	(1.08, 1.88)
Unpartnered white female (RL) vs. Partnered non-white female	1.45	(1.08, 1.95)	--	--
Unpartnered white female (RL) vs. Partnered non-white male	1.17	(1.02, 1.35)	1.40	(1.00, 1.95)
Unpartnered white female (RL) vs. Unpartnered non-white female	1.27	(1.06, 1.52)	1.57	(1.05, 2.36)
Unpartnered white female (RL) vs. Unpartnered non-white male	1.30	(1.13, 1.48)	1.63	(1.21, 2.21)
Marital Status *Gender				
Partnered female (RL) vs. Unpartnered male	1.22	(1.09, 1.36)	--	--
Partnered male (RL) vs. Unpartnered male	1.20	(1.12, 1.28)	1.26	(1.09, 1.46)
Unpartnered female (RL) vs. Unpartnered male	1.20	(1.09, 1.32)	1.30	(1.05, 1.62)
Race * Gender				
White female (RL) vs. White male	1.13	(1.04, 1.22)	--	--
White female (RL) vs. Non-white female	1.29	(1.11, 1.49)	1.48	(1.06, 2.08)
White female (RL) vs. Non-white male	1.22	(1.10, 1.34)	1.41	(1.13, 1.77)
White male (RL) vs. Non-white male	1.08	(1.00, 1.16)	1.22	(1.04, 1.42)
Marital Status * Race				
Partnered white (RL) vs. Partnered non-white	1.14	(1.03, 1.26)	1.27	(1.01, 1.59)

	Overall Survival		Local Regional Failure	
Pair-wise Comparison[2]	**Adjusted HR[3,4]**	**95% C.I.**	**Adjusted HR[3,4]**	**95% C.I.**
Partnered white (RL) vs. Unpartnered white	1.15	(1.07, 1.23)	--	--
Partnered white (RL) vs. Unpartnered non-white	1.26	(1.15, 1.37)	1.50	(1.24, 1.82)
Unpartnered white (RL) vs. Unpartnered non-white	--	--	1.24	(1.04, 1.48)

[1] Only those models which were significant are shown.

[2] Each row represents an individual model.

[3] HR = Hazard Ratio; CI = Confidence Interval; RL = Reference Level

[4] Adjusted for: T-stage (RL: T1–T3), N-stage (RL: N0-N1-N2a), KPS (RL: 60–80), primary site (RL: oropharynx), RT method (RL: HFX), chemotherapy usage (RL: used chemotherapy), and age (continuous).

Table 6

Unadjusted Proportional Hazards Regression Models for Overall Survival

	Primary Site (Others vs. Oropharynx [RL[1]])		T-Stage (T4 vs. T1-3 [RL[1]])	
Treatment Arm	**Unadjusted Hazard Ratio (95% CI[1])**	**p-value**	**Unadjusted Hazard Ratio (95% CI[1])**	**p-value**
9003: Arm 1 – SFX	1.18 (0.89, 1.55)	0.25	2.03 (1.50, 2.74)	<0.0001
9003: Arm 2 – HFX	1.13 (0.85, 1.50)	0.41	1.50 (1.11, 2.02)	0.009
9003: Arm 3 – AHFX-S	1.13 (0.87, 1.49)	0.36	1.78 (1.33, 2.39)	<0.0001
9003: Arm 4 – AFX-C	1.11 (0.83, 1.48)	0.47	1.80 (1.34, 2.42)	<0.0001
9111: Arm 1 – I+RT	--	--	0.95 (0.44, 2.06)	0.89
9111: Arm 2 – CRT	--	--	1.60 (0.85, 2.99)	0.15
9111: Arm 3 – RT Alone	--	--	1.51 (0.76, 3.02)	0.24
9703: Arm 1 – Cispl/5-FU	1.93 (1.11, 3.35)	0.02	1.31 (0.76, 2.26)	0.33
9703: Arm 2 – Hydroxy/5-FU	1.72 (0.90, 3.29)	0.10	2.49 (1.30, 4.77)	0.006
9703: Arm 3 – Cispl/Taxol	2.15 (1.17, 3.97)	0.01	1.98 (1.09, 3.61)	0.03
	Chi Square T.S. (Q) = 8.106 **p-value** = 0.38		**Chi Square T.S. (Q)** = 4.393 **p-value** = 0.07	
Pooled HR[2]	1.22 (1.08, 1.39)	--	1.72 (1.52, 1.96)	--

[1] CI = Confidence Interval; RL = Reference Level

[2] This is a pooled estimate

Table 7

Unadjusted Proportional Hazards Regression Models for Local-Regional Failure

	Primary Site (Others vs. Oropharynx [RL[1]])		T-Stage (T4 vs. T1-3 [RL[1]])	
Treatment Arm	**Unadjusted Hazard Ratio (95% CI[1])**	**p-value**	**Unadjusted Hazard Ratio (95% CI[1])**	**p-value**
9003: Arm 1 – SFX	1.27 (0.94, 1.72)	0.11	2.04 (1.50, 2.78)	<0.0001
9003: Arm 2 – HFX	1.00 (0.71, 1.40)	0.99	2.46 (1.76, 3.44)	<0.0001
9003: Arm 3 – AHFX-S	1.09 (0.80, 1.49)	0.59	1.88 (1.37, 2.59)	0.0001
9003: Arm 4 – AFX-C	1.14 (0.81, 1.59)	0.45	2.12 (1.52, 2.95)	<0.0001
9111: Arm 1 – I+RT	--	--	0.35 (0.11, 1.16)	0.09
9111: Arm 2 – CRT	--	--	1.26 (0.52, 3.02)	0.61
9111: Arm 3 – RT Alone	--	--	1.51 (0.70, 3.25)	0.29
9703: Arm 1 – Cispl/5-FU	1.40 (0.75, 2.60)	0.29	1.97 (1.06, 3.68)	0.03
9703: Arm 2 – Hydroxy/5-FU	0.96 (0.51, 1.78)	0.89	2.16 (1.17, 3.97)	0.01
9703: Arm 3 – Cispl/Taxol	1.43 (0.72, 2.87)	0.31	2.59 (1.31, 5.12)	0.007
	Chi Square T.S. (Q) = 2.325 **p-value** = 0.20		**Chi Square T.S. (Q)** = 11.944 **p-value** = 0.96	
Pooled HR[2]	1.14 (0.99, 1.33)	--	2.02 (1.75, 2.33)	--

[1] CI = Confidence Interval; RL = Reference Level

[2] This is a pooled estimate.

Table 8

Adjusted Proportional Hazards Regression Models for Overall Survival

	Primary Site (Others vs. Oropharynx [RL[1]])		T-Stage (T4 vs. T1-3 [RL[1]])	
Treatment Arm	**Unadjusted Hazard Ratio[2] (95% CI[1])**	**p-value**	**Unadjusted Hazard Ratio[2] (95% CI[1])**	**p-value**
9003: Arm 1 – SFX	1.07 (0.81, 1.43)	0.63	1.56 (1.13, 2.16)	0.007
9003: Arm 2 – HFX	0.98 (0.73, 1.33)	0.91	1.38 (1.00, 1.90)	0.049
9003: Arm 3 – AHFX-S	1.01 (0.76, 1.34)	0.96	1.57 (1.15, 2.13)	0.004
9003: Arm 4 – AFX-C	1.05 (0.78, 1.40)	0.77	1.48 (1.09, 2.01)	0.01
9111: Arm 1 – I+RT	--	--	0.78 (0.35, 1.76)	0.55
9111: Arm 2 – CRT	--	--	1.63 (0.84, 3.16)	0.15
9111: Arm 3 – RT Alone	--	--	1.34 (0.65, 2.74)	0.43
9703: Arm 1 – Cispl/5-FU	2.02 (1.12, 3.67)	0.02	1.14 (0.62, 2.08)	0.67
9703: Arm 2 – Hydroxy/5-FU	2.11 (1.02, 4.33)	0.04	2.38 (1.13, 5.03)	0.02
9703: Arm 3 – Cispl/Taxol	1.87 (0.95, 3.68)	0.07	2.03 (1.06, 3.89)	0.03
	Chi Square T.S. (Q) = 10.462 **p-value** = 0.60		**Chi Square T.S. (Q)** = 6.136 **p-value** = 0.20	
Pooled HR[3]	1.12 (0.98, 1.28)	--	1.49 (1.30, 1.71)	--

[1] CI = Confidence Interval; RL = Reference Level

[2] Adjusted for: T-stage (RL: T1–T3), N-stage (RL: N0-N1-N2a), KPS (RL: 60–80), primary site (RL: oropharynx; 9003 and 9703 only), and age (continuous), gender (RL: Female), marital status (RL: partnered), race (RL: white).

[3] This is a pooled estimate.

Table 9

Adjusted Proportional Hazards Regression Models for Local-Regional Failure

	Primary Site (Others vs. Oropharynx [RL[1]])		T-Stage (T4 vs. T1-3 [RL[1]])	
Treatment Arm	**Unadjusted Hazard Ratio[2] (95% CI[1])**	**p-value**	**Unadjusted Hazard Ratio[2] (95% CI[1])**	**p-value**
9003: Arm 1 – SFX	1.24 (0.92, 1.67)	0.16	1.80 (1.29, 2.51)	0.0006
9003: Arm 2 – HFX	0.86 (0.61, 1.23)	0.41	2.30 (1.62, 3.27)	<0.0001
9003: Arm 3 – AHFX-S	1.02 (0.73, 1.42)	0.93	1.70 (1.22, 2.37)	0.002
9003: Arm 4 – AFX-C	1.15 (0.81, 1.63)	0.43	1.79 (1.25, 2.55)	0.002
9111: Arm 1 – I+RT	--	--	0.35 (0.10, 1.19)	0.10
9111: Arm 2 – CRT	--	--	1.20 (0.43, 3.32)	0.73
9111: Arm 3 – RT Alone	--	--	1.55 (0.70, 3.44)	0.28
9703: Arm 1 – Cispl/5-FU	1.73 (0.84, 3.58)	0.14	2.14 (1.03, 4.43)	0.04
9703: Arm 2 – Hydroxy/5-FU	1.08 (0.56, 2.06)	0.82	1.91 (0.97, 3.74)	0.06
9703: Arm 3 – Cispl/Taxol	1.62 (0.75, 3.50)	0.23	2.52 (1.21, 5.23)	0.01
	Chi Square T.S. (Q) = 5.134 **p-value** = 0.60		**Chi Square T.S. (Q)** = 10.522 **p-value** = 0.94	
Pooled HR[3]	1.11 (0.95, 1.30)	--	1.83 (1.57, 2.13)	--

[1] CI = Confidence Interval; RL = Reference Level

[2] Adjusted for: T-stage (RL: T1-T3), N-stage (RL: N0-N1-N2a), KPS (RL: 60–80), primary site (RL: oropharynx; 9003 and 9703 only), and age (continuous), gender (RL: Female), marital status (RL: partnered), race (RL: white).