Original Article

Randomized Trial Comparing Surgery and Adjuvant Radiotherapy Versus Concurrent Chemoradiotherapy in Patients With Advanced, Nonmetastatic Squamous Cell Carcinoma of the Head and Neck: 10-Year Update and Subset Analysis

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BACKGROUND: The current study was performed to report the long-term results of a trial comparing concurrent chemotherapy and radiotherapy (CCRT) with surgery and adjuvant radiotherapy (RT) in patients with stage III/IV nonmetastatic head and neck squamous cell carcinoma. **METHODS:** Patients with stage III/IV resectable head and neck squamous cell carcinoma were randomized to surgery followed by RT or CCRT. The trial was halted prematurely due to poor accrual. Human papillomavirus status was tested on archival material using polymerase chain reaction sequencing. **RESULTS:** Of the total of 119 patients, 60 patients were randomized to primary surgery (S arm) and 59 patients were randomized to CCRT (C arm). Human papillomavirus status was tested in 75 patients, and only 3 were found to be positive. The median follow-up for surviving patients was 13 years. Analysis of the entire cohort demonstrated no statistically significant difference in overall survival and disease-specific survival (DSS): 5-year rates were 45% versus 35% for overall survival ($P = .262$) and 56% versus 46% for DSS ($P = .637$) for the S arm and C arm, respectively. Analysis by subsites indicated that this difference favoring the S arm was mainly driven by survival data among patients with cancers of the oral cavity and maxillary sinus. For patients with oral cavity cancer, survival was significantly better in those who underwent primary surgery compared with CCRT; the 5-year DSS rate was 68% versus 12% for the S arm and C arm, respectively ($P = .038$). For patients with cancers of the maxillary sinus, the 5-year DSS rate was 71% for patients on the S arm and 0% for patients on the C arm ($P = .05$). **CONCLUSIONS:** These long-term results demonstrate a significant advantage for primary surgery in patients with cancers of the oral cavity or maxillary sinus, providing strong support for primary surgery as the main modality of treatment for these subsites. In other subsites, CCRT and surgery with adjuvant RT were found to demonstrate similar efficacy for survival in patients with advanced resectable tumors. ***Cancer*** **2015;121:1599-607.** *© 2015 American Cancer Society.*

KEYWORDS: head and neck squamous cell carcinoma, head and neck cancer, surgical arm, oral cancer.

INTRODUCTION

The management of patients with locally advanced head and neck squamous cell carcinoma (HNSCC) has undergone several major paradigm shifts in the last 2 decades. Early interest in the combined use of chemotherapy and radiotherapy (RT) was stimulated by the landmark Veterans Affairs and European Organization for Research and Treatment of Cancer (EORTC) studies, both of which compared chemoradiotherapy (CRT) with primary surgery for patients with cancers of the larynx and hypopharynx.[1,2] At the same time, there was much interest in the use of concurrent CRT for head and neck cancers including nasopharyngeal cancers, and this study was undertaken to determine whether CRT can replace surgery in patients with head and neck cancer regardless of subsites, keeping the surgical arm as the gold standard control.[3] The slew of trials that ensued supported the belief that concurrent CRT was superior to induction CRT in a range of subsites in which organ preservation was critical, but to the best of our knowledge none of these included a surgical arm as a control.[4,5]

The discovery that a significant percentage of oropharyngeal cancers were associated with the human papillomavirus (HPV)[6,7] has led to studies demonstrating that HPV positivity confers a better prognosis compared with HPV-negative

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status.[7] As a result, there has been a call for the de-escalation of therapy and renewed interest in primary surgery as the mainstay of treatment and surgical staging of disease. This surgical strategy has been further supported by the advent of new endoscopic techniques, the introduction of transoral laser and robotic surgery, modern perforator flap techniques, and our increasing understanding of tumor biology and concepts of functional surgery; surgery as a primary modality is certainly gaining ground in many of the head and neck subsites.

Despite these changes, the fact remains that there is a paucity of evidence of either level 1 or 2 that compare with surgery on 1 arm of a prospective study. In 2005, we published the results of SHN01, which demonstrated that concurrent chemotherapy is comparable to surgery followed by adjuvant RT in patients with AJCC stage III/IV nonmetastatic HNSCC, after a median follow-up of 5.6 years.[8] The objective of this trial was to determine whether concurrent chemotherapy was superior to the prevailing conventional treatment at that time, namely surgery and adjuvant RT, with survival as the endpoint. The trial was stopped prematurely due to the difficulties in accruing patients. We now report the long-term survival update, describe patterns of failure, report results of HPV typing, and analyze outcomes by tumor subsite.

MATERIALS AND METHODS

The current study was conducted to compare concurrent chemotherapy and RT versus upfront surgery followed by adjuvant RT in patients with nonmetastatic stage III/IV HNSCC. Details regarding eligibility criteria, randomization and treatment, follow-up, and statistical considerations have previously been reported in the initial publication.[8] The more important details are briefly summarized below.

Patient Population

The trial was open to all newly diagnosed patients with histologically proven, resectable, nonmetastatic stage III/IV HNSCC (excluding that of the nasopharynx and salivary glands) who had a good Eastern Cooperative Oncology Group performance status (0 or 1) and adequate bone marrow, hepatic, and renal function.

Randomization and Treatment

After recruitment, patients were then randomized to either of the 2 treatment arms: the standard arm (S arm) consisting of radical surgery and adjuvant RT or the experimental arm consisting of combination chemotherapy with cisplatin and 5-fluorouracil and concurrent RT (CRT; C arm). Randomization was stratified according to primary tumor site (oral cavity/oropharynx, larynx/hypopharynx, others) and lymph node status (lymph node positive vs lymph node negative).

Patients on the S arm underwent radical resection of the primary tumor with comprehensive neck dissection (removing levels 1-5) for unilateral or bilateral disease as needed, followed by adjuvant RT given to primary tumor and upper neck at 2 gray (Gy) per fraction for 5 days per week to a total of 60 Gy in 30 fractions over 6 weeks. When lymph node disease was present, the lower neck was treated with a total dose of 50 Gy in 25 fractions over 5 weeks. In patients with positive surgical margins, the dose to the area at risk was brought up to 70 Gy using reduced volumes. Patients on arm C received 2 cycles of chemotherapy comprising cisplatin at a dose of 20 mg/m^2 on day 1 and 5-fluorouracil at a dose of 1000 mg/m^2 on day 1, both given as continuous intravenous infusion for 96 hours on days 1 and 28 of the RT course. The total dose of RT given to the primary tumor and upper neck was 66 Gy in 33 fractions over 6.5 weeks whereas involved lymph nodes received at least 60 Gy. Patients with lymph node disease classified as at least N2 at the onset were scheduled to undergo elective neck dissection 4 to 6 weeks after CRT regardless of response. Salvage surgery was performed for patients with persistent or recurrent disease.

Follow-Up

After completing treatment, patients were followed monthly for the first year, every 2 months for the second year, every 3 months for the third year, and every 6 months up to 5 years and yearly thereafter for life.

Ethical Considerations

This study was approved by the ethics committee of the respective local participating institutions. Written informed consent was obtained from each patient. The data safety monitoring committee reviewed the trial at 1 year and 5 years after the initiation of the study, and advised early termination of the trial at the time of the second review due to poor accrual.

HPV Genotyping

Paraffin specimens from patients were obtained from the tissue bank in the pathology department of each respective study institution. Only specimens from patients who provided written informed consent for tissue use for research and follow-up data were recovered and used. DNA was extracted from 10 μm-thick slices of formalin-fixed, paraffin-embedded HNSCC samples using the QIAamp

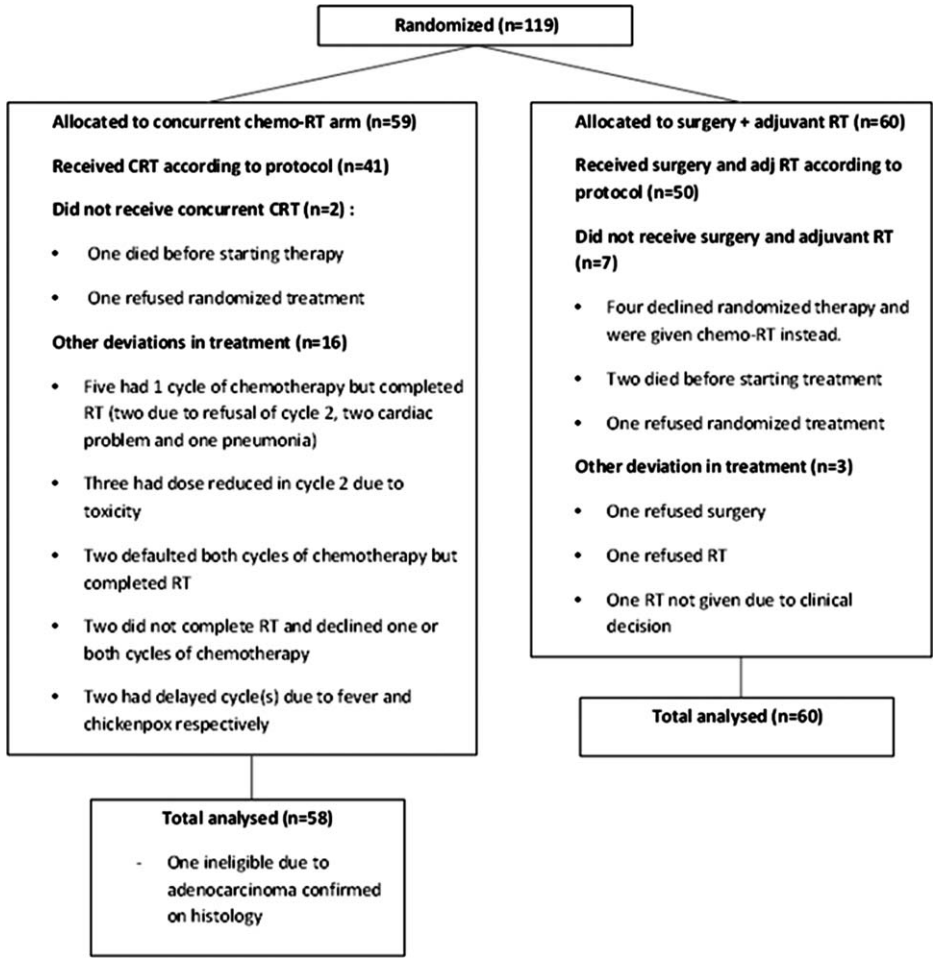

Figure 1. A CONSORT (Consolidated Standards Of Reporting Trials) diagram of the current trial is shown. Chemo-RT indicates chemotherapy and radiotherapy; CRT, chemoradiotherapy; RT, radiotherapy; adj, adjuvant.

DNA Mini Kit (Qiagen, Valencia, Calif) according to the manufacturer's protocol. The area sectioned for DNA extraction was examined and confirmed to have at least 60% tumor content by a board-certified pathologist (J.H.). Polymerase chain reaction (PCR) amplification of genomic DNA was performed as described using HPV-specific primers to amplify the L1 region.[9] Tumors deemed to be positive for HPV underwent further genotyping by direct Sanger sequencing of PCR amplicons.

Statistical Analysis

Overall survival (OS), disease-specific survival (DSS), locoregional recurrence-free survival (LRFS), and distant recurrence-free survival (DRFS) were calculated using the Kaplan-Meier method and the log-rank test was used to compare differences between treatment arms. Subgroup analyses were also performed based on different tumor subsites for the oral cavity, oropharynx, hypopharynx, and larynx. All subgroup analyses were compared based on actual treatment received rather than assigned treatment. All statistical analyses were performed using SPSS statistical software (version 21; IBM Corporation, Armonk, NY). For all statistical tests, a P value $<.05$ was deemed statistically significant.

RESULTS

Patient Cohort

From August 1996 to February 2002, a total of 119 patients were randomly assigned to the 2 treatment arms: surgery followed by adjuvant RT (S arm) or concurrent CRT (C arm). A total of 60 patients were randomized to the S arm and 59 patients were randomized to the C arm (Fig. 1). One patient on the C arm was ineligible due to confirmed adenocarcinoma histology. Six patients were lost to follow-up but were included in analyses for the period during which they were observed. The median

TABLE 1. Patient Characteristics by Treatment.

Characteristic	C Arm (%) n=59	S Arm (%) n=60	All Patients n=119
Age, y			
Median	60	58	59
Range	35-73	27-75	27-75
Sex			
Male	51 (86)	53 (88)	104 (87)
Female	8 (14)	7 (12)	15 (13)
Site of disease			
Oral cavity	19 (32)	13 (22)	32 (27)
Oropharynx	12 (20)	13 (22)	25 (21)
Hypopharynx	7 (12)	7 (12)	14 (12)
Larynx	18 (31)	20 (32)	38 (32)
Maxillary sinus	3 (5)	7 (12)	10 (8)
Tumor classification			
T1	0 (0)	5 (8)	5 (4)
T2	9 (15)	8 (13)	17 (14)
T3	16 (27)	15 (25)	31 (26)
T4	34 (58)	32 (54)	66 (56)
Lymph node classification			
N0	19 (32)	17 (28)	36 (30)
N1	15 (25)	7 (12)	22 (19)
N2	24 (41)	31 (52)	55 (46)
N3	1 (2)	5 (8)	6 (5)
Overall disease stage (AJCC)			
III	12 (20)	12 (20)	24 (20)
IVA	46 (78)	43 (72)	89 (75)
IVB	1 (2)	5 (8)	6 (5)
HPV status			
Positive	2 (3)	1 (2)	3 (3)
Negative	35 (59)	37 (62)	72 (60)
Untested	22 (38)	22 (37)	44 (37)

Abbreviations: C, concurrent chemotherapy and radiotherapy; HPV, human papillomavirus; S, primary surgery.

follow-up was 13 years (range, 0.5-14 years). Baseline patient characteristics were comparable between both groups and are summarized in Table 1. Based on PCR genotyping, tumor tissue was obtained from 75 patients in this cohort, only 3 of whom were positive for HPV. All 3 patients had tumors arising from the tonsils (2 patients on the C arm and 1 patient on the S arm), and were confirmed to be positive for the HPV-18 subtype (data not shown). Approximately 16.7% of the patients on arm S (10 of 60 patients) and 31% of the patients on arm C (18 of 59 patients) failed to adhere to trial protocol, the details of which are summarized in Figure 1.

Survival Analysis

At the time of last follow-up, 92 patients (45 patients on arm S and 47 patients on arm C) had died. There were 29 patients with locoregional disease recurrence (13 patients on arm S and 16 patients on arm C) and 27 patients with distant metastasis (17 patients on arm S and 10 patients on arm C). Analysis of the entire cohort demonstrated that there was a difference in outcome between both treatment arms, but this was not statistically significant. The 5-year OS rates were 45% versus 35% ($P = .262$) and the DSS rates were 56% versus 46% ($P = .637$) when comparing the S and C arms, respectively (Figs. 2a and 2b). LRFS and DRFS rates demonstrated similar trends but the difference was not statistically significant between the 2 treatment arms ($P = .462$ and .134, respectively) (Figs. 2c and 2d).

Subset analyses demonstrated that the main subsites that accounted for this difference in survival favoring primary surgery were in tumors arising from the oral cavity and maxillary sinus. There were significant differences in outcome noted between the 2 treatment arms for both subsites. For the oral cavity, survival was significantly better in patients who underwent surgery and RT compared with the CRT group. The 5-year DSS rates were 68% for the S arm versus 12% for the C arm ($P = .038$) (Fig. 3a). Similarly, rates of distant metastasis were higher among patients on the C arm, with 5-year DRFS rates of 50% compared with 92% for patients on the S arm ($P = .05$) (Fig. 3b). However, no statistically significant difference was observed in locoregional disease recurrence rates between the treatment arms ($P = .355$) (Fig. 3c), although there may have been a trend favoring the S arm. In the subgroup of patients with tumors in the maxillary sinus, the DSS and LRFS rates were also found to be significantly different between both treatment arms (Figs. 4a and 4b, respectively) ($P = .05$). The 5-year DSS and LRFS rates were 0% and 0% among patients on the C arm and 71% and 86% among patients on the S arm, respectively. Only 1 patient from each arm among those in the maxillary sinus subgroup developed distant disease recurrence. No significant difference was observed between the treatment arms ($P = .306$).

There were no differences noted between the treatment arms with regard to cancers of the oropharynx, larynx, and hypopharynx (see online supporting information).

Second primary malignancies (3 lung cancers, 3 colorectal cancers, 1 esophageal cancer, and 1 pancreatic cancer) developed among a total of 8 patients (6.7%) (4 patients [6.7%] from arm S and 4 patients [6.8%] from arm C). No statistically significant difference was detected between the treatment arms ($P = .645$).

DISCUSSION

Despite changing paradigms, there is still much debate regarding the optimal treatment strategies for patients with HNSCC. Primary surgery has undergone a recent revival with the advent of newer surgical techniques and a better understanding of tumor biology. In contrast, CRT

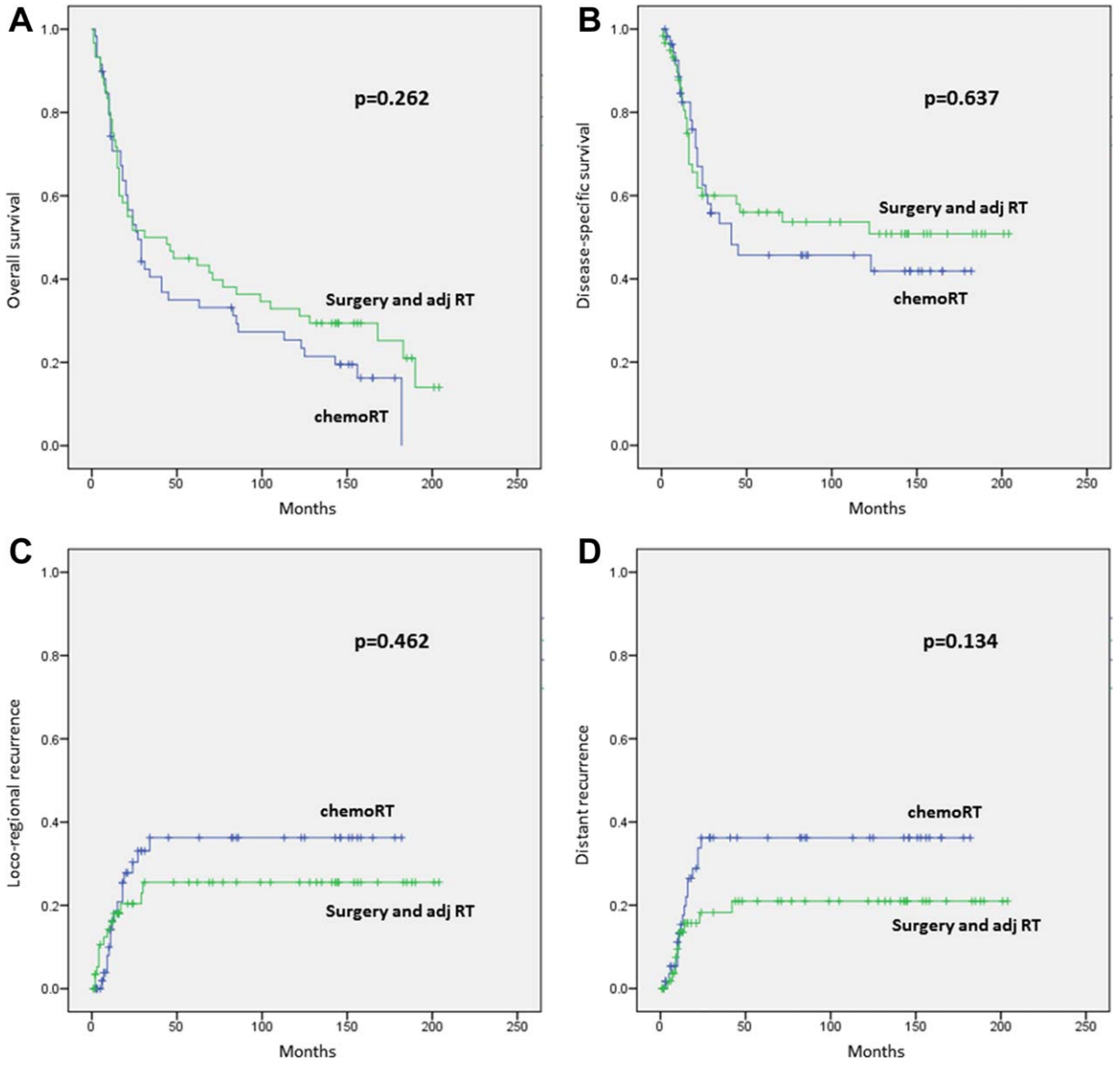

Figure 2. Kaplan-Meier plots for the entire cohort of patients in the primary surgery and concurrent chemotherapy and radiotherapy (chemoRT) arms are shown demonstrating limited but not statistically significant differences in (a) overall survival, (b) disease-specific survival, (c) locoregional recurrence-free survival, and (d) distant recurrence-free survival. adj RT indicates adjuvant radiotherapy.

provides an attractive organ-preserving alternative if survival outcomes are similar. Although survival remains the gold standard of treatment outcomes, several other considerations have to be made for the population of patients with HNSCC, among whom smoking and alcohol consumption are pervasive: the likelihood of developing a second primary malignancy with limited treatment options, late toxicities associated with radical RT, and quality-of-life issues.[10-13]

When this trial was initiated in the late 1990s, it was meant to be an important adjunct to other similar trials that were planned and was designed to demonstrate the superiority of non-surgical treatment at a time when concurrent CRT was popular. However, the study was prematurely terminated for poor accrual mainly due to the study design. Designing a study with such contrasting arms as radical surgery and nonsurgical therapy led to the majority of eligible patients opting for a nonsurgical approach outside of the study. This notwithstanding, our 10-year update is timely because no similar trial has since been conducted, and in the current era of minimally invasive transoral resections with microscopy, lasers, and

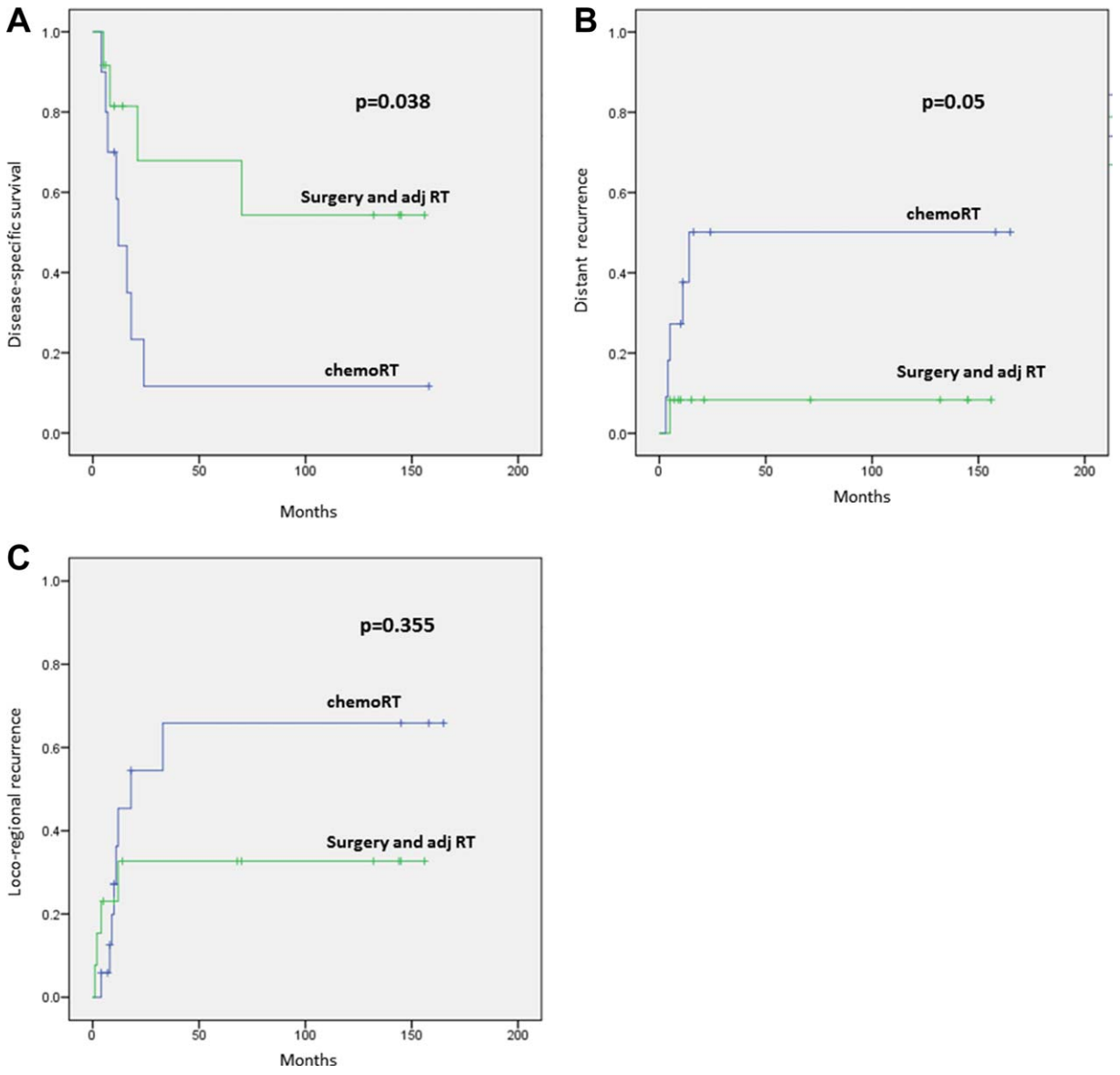

Figure 3. Kaplan-Meier plots of patients with oral squamous cell carcinoma in the primary surgery and concurrent chemotherapy and radiotherapy (chemoRT) arms are shown demonstrating statistically significant differences in (a) disease-specific survival and (b) distant recurrence-free survival but not (c) locoregional recurrence-free survival. adj RT indicates adjuvant radiotherapy.

the surgical robot, it is imperative to establish the role of surgery in the primary treatment of patients with HNSCC.

The first important conclusion to be drawn from the current update is that there appears to be either no difference in outcome or a slight advantage favoring primary surgery plus RT compared with concurrent CRT. The 5-year OS rate was 45% in the S arm compared with 35% in the C arm ($P = .262$). This result has important implications in several settings. First, in patients in whom chemotherapy is contraindicated, including the elderly or patients with renal impairment, the inability to treat these individuals with concurrent CRT can be circumvented using the alternative of surgery plus adjuvant RT. This is particularly relevant in patients with locally advanced tumors of the oropharynx, hypopharynx, and larynx, in whom organ preservation strategies have traditionally been used. Second, and perhaps more controversially, surgery plus RT may provide a reasonable alternative to de-escalating therapy in patients with locally advanced HNSCC with a good prognosis. This is particularly true for those with HPV-associated oropharyngeal cancers,

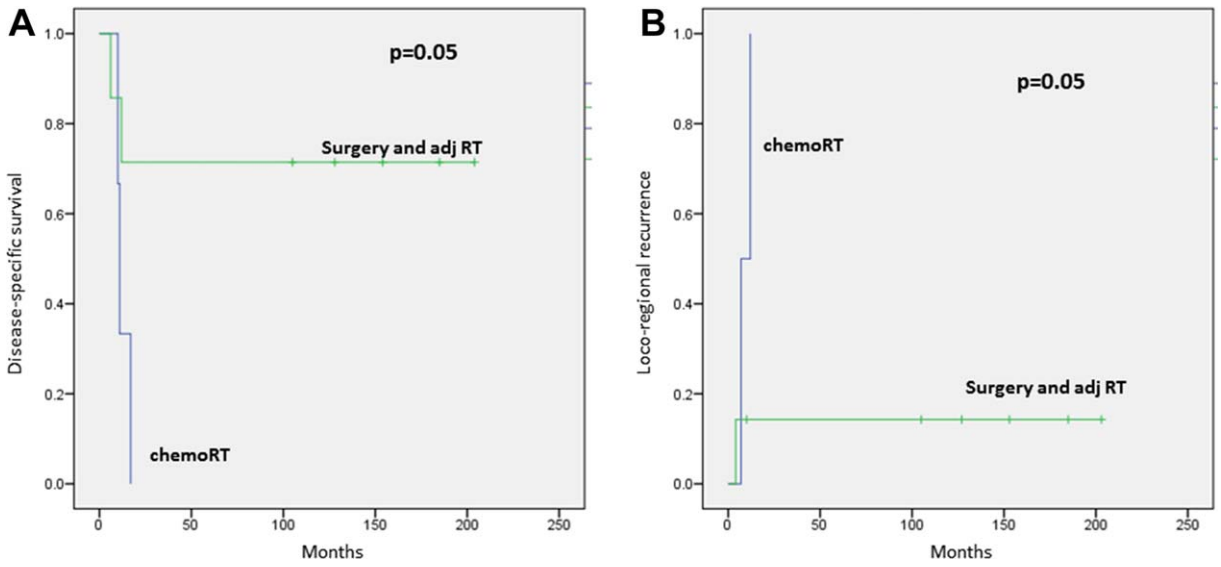

Figure 4. Kaplan-Meier plots of patients with maxillary sinus squamous cell carcinoma in the primary surgery and concurrent chemotherapy and radiotherapy (chemoRT) arms are shown demonstrating statistically significant differences in (a) disease-specific survival and (b) locoregional recurrence-free survival. adj RT indicates adjuvant radiotherapy.

although data from this trial cannot be used to draw this conclusion because there were only 3 patients who were classified into this subgroup.

The second major conclusion comes from the subsite analysis performed herein. This is the likely explanation for why the outcome data for the entire cohort favored primary surgery, and in which the role of primary surgery in SCC of the oral cavity (and, to a lesser extent, the paranasal sinus) can be defined. In our subgroup analysis of the former group, improved outcomes were starkly observed in those patients treated with surgery compared with those treated with CRT. The 5-year DSS rate was 68% among patients on the S arm compared with a mere 12% among patients on the C arm. Head and neck oncologists have traditionally been reluctant to use CRT as primary therapy for patients with tumors of the oral cavity, citing reasons such as the higher risk of early and late RT complications due to the anatomic limitations of the oral cavity and the ineffectiveness of RT if bone invasion is present. Nonetheless, National Comprehensive Cancer Network guidelines rank surgery and multimodality treatment such as CRT as equal options in the primary management of patients with locally advanced oral SCC. To the best of our knowledge, the current study is the only level 2 evidence supporting the superiority of surgery (with postoperative RT) compared with CRT as the primary modality of treatment in patients with oral SCC. There have been several retrospective studies that have suggested improved outcomes from primary surgery with adjuvant RT compared with CRT. For example, Gore et al recently reported data from 2 institutions with differing practices, in which improved survival was found in the group of patients with oral cancer who had undergone surgery and adjuvant RT.[14] In other retrospective studies examining the efficacy of primary CRT in patients with T4 oral cancer compared with historic controls, similar outcomes were achieved but with significantly higher rates of late toxicities, especially osteoradionecrosis, noted among patients on the CRT arm.[15,16]

Proponents of CRT have always cited the promise of providing better systemic tumor control, although this has not been demonstrated, even in an extensive meta-analysis.[17] Surprisingly, the results of the current study suggest that DRFS was better in patients treated on the surgical arm than those treated on the CRT arm ($P = .05$), in which the 5-year distant metastasis rates were 50% for the C arm compared with only 8% for the S arm. Although this may appear to be counterintuitive, it is possible that surgery mitigates the emergence of aggressive radioresistant clones that may account for the metastatic phenotype.

In the current study, patients with SCC of the maxillary sinus treated on the S arm were found to have improved DSS compared with those treated on the C arm. Better locoregional control was also observed in

surgically treated patients. It is important to note that the number of patients in this subgroup was small (10 patients in total: 3 on the C arm and 7 on the S arm) and care has to be taken when interpreting these results. To our knowledge, due to the lower incidence of SCC of the maxillary sinus, few studies that address the role of CRT have been performed to date and the results were mixed.[18,19] The development of second primary malignancies is a significant cause of mortality in patients with HNSCC. The rate of second primary malignancies in the current study cohort was 6.7% (8 patients), of which one-half were from the upper aerodigestive tract. This is relatively low compared with the rates of 9% to 23.1% reported in previous studies.[13,20,21]

There are several major issues with the current study. First is the finding that the study was terminated prematurely due to poor accrual, which is a common problem faced by many randomized studies of patients with head and neck cancer. This results in a trial that is underpowered to conclusively state that the 2 modalities are equivalent. Second, the subgroup analyses were not planned and, not surprisingly, numbers were small. However, the differences noted in the outcome favoring surgery and adjuvant RT in patients with tumors of the oral cavity and maxillary sinus do make us cautious in recommending concurrent CRT as a viable alternative to our patients in routine practice. It is important to note that the observation that no differences were observed in the traditional organ conservation sites such as the larynx, hypopharynx, and oropharynx despite the small sample size does lend some level of credibility to the results observed in patients with tumors in the oral and maxillary subsites. Third, in the current study, postoperative adjuvant therapy was only focused on RT and not concurrent CRT because this trial was conducted before the landmark studies by Bernier et al and Cooper et al, which each were published in 2004.[22,23]

Although treatment outcomes are comparable between patients treated with CRT and those treated with surgery followed by adjuvant RT, there are risks and benefits to each treatment modality. CRT is an acceptable option in selected groups of patients with oropharyngeal, laryngeal, and hypopharyngeal disease sites with the view of organ preservation without compromising survival. This option should not be recommended for patients with tumors in other sites except within the context of unresectability. Although often disfiguring with resultant compromise of upper aerodigestive tract function, surgery and adjuvant RT with the addition of concurrent cisplatin in the presence of high-risk pathological features (positive surgical resection margins and/or extranodal extension) remains the standard of care in these other sites.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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