Original Investigation

Efficacy of Induction Selection Chemotherapy vs Primary Surgery for Patients With Advanced Oral Cavity Carcinoma

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IMPORTANCE The University of Michigan has investigated the use of induction selection (IS) with chemoradiotherapy (CRT) for patients who respond to CRT and found this approach effective in the management of advanced laryngeal cancer. The IS approach was extended to oral cavity squamous cell carcinoma (OCSCC) to help understand whether organ preservation or survival benefit resulted.

OBJECTIVE To evaluate the efficacy of an IS protocol vs primary surgical extirpation and selective postoperative radiotherapy for advanced OCSCC.

DESIGN AND SETTING Retrospective matched cohort study at a tertiary care hospital.

PARTICIPANTS Nineteen patients with resectable stages III and IV OCSCC were enrolled into a phase 2 IS trial. Patients with a response of at least 50% underwent concurrent CRT; those with a response of less than 50% underwent surgical treatment and radiotherapy. A comparison cohort of patients treated with primary surgical extirpation during a similar time period was frequency matched for inclusion criteria and patient characteristics to those patients included from the phase 2 IS trial. No difference was noted in age, sex, pretreatment American Joint Committee on Cancer stage, T and N classifications, smoking status, alcohol consumption, or tumor subsite between the IS and surgical cohorts. Median follow-up was 9.4 years in the IS cohort and 7.1 years in the surgical cohort.

INTERVENTIONS Induction selection and CRT vs primary surgical extirpation with or without postoperative radiotherapy.

MAIN OUTCOMES AND MEASURES Overall and disease-specific survival and locoregional control.

RESULTS The Kaplan-Meier estimate for overall survival at 5 years was 32% in the IS cohort and 65% in the surgical cohort. The Kaplan-Meier estimate for disease-specific survival at 5 years was 46% in the IS cohort and 75% in the surgical cohort. The Kaplan-Meier estimate for locoregional control at 5 years was 26% in the IS cohort and 72% in the surgical cohort. Multivariable analysis demonstrated significantly better overall and disease-specific survival and locoregional control outcomes ($P = .03$, $P = .001$, and $P < .001$, respectively) in the surgical cohort.

CONCLUSIONS AND RELEVANCE Primary surgical treatment showed significantly better survival and locoregional control compared with IS in this matched patient cohort. Despite success of organ preservation IS protocols in the larynx, comparative survival analysis of an IS protocol vs primary surgical extirpation for OCSCC demonstrates significantly better outcomes in the surgical cohort. These findings support surgery as the principal treatment for OCSCC.

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Head and neck squamous cell carcinoma (SCC) is the sixth most common malignant neoplasm, affecting more than 40 000 Americans and resulting in 11 000 deaths annually.[1] Despite a historically high mortality rate, patients with nasopharyngeal, oropharyngeal, and laryngeal SCC have demonstrated improved survival during the past several decades. For patients with oral cavity SCC (OCSCC), evidence suggests that postoperative chemoradiotherapy (CRT) can improve survival for high-risk patients by approximately 6.5%, but the improved survival is associated with additional morbidity.[2-4]

During the past 2 decades, investigators have made an effort to understand the benefits and limitations of CRT in head and neck cancer. Numerous trials focused on developing definitive CRT protocols for organ preservation. The European Organization for Research and Treatment of Cancer larynx trial[5] and Veterans Affairs Laryngeal Cancer Study for induction chemotherapy (IC)[6] were the first IC trials to show survival outcomes similar to those of surgery for laryngeal or hypopharyngeal SCC. Response to IC identifies a favorable prognostic group that often responds well to definitive radiotherapy. Our institution has focused on using induction selection (IS) to "chemoselect" responders and nonresponders to chemotherapy. Definitive treatment is based on the response to IC, with the responders undergoing concomitant CRT and the nonresponders undergoing surgery with adjuvant radiotherapy. This type of approach allows personalized treatment, with selection of patients who may have a greater likelihood of organ preservation through chemoselection. Laryngeal SCC has shown the greatest improvement in survival with this approach.[7-9]

A phase 2 trial at the University of Michigan (UMCC 9921) evaluated the role of IS for patients with stages III and IV OCSCC. The trial was designed to analyze each cohort by primary tumor site with specific rules for stopping therapy for each cohort. We elected to perform a retrospective matched cohort study to compare the patients with OCSCC undergoing IS with a group of patients treated with surgery and selective postoperative radiotherapy (PORT) and chemotherapy after careful matching based on inclusion criteria for the IS trial. We performed a comprehensive evaluation of overall (OS) and disease-specific (DSS) survival and locoregional control (LRC) outcomes in 2 matched cohorts of patients with advanced-stage OCSCC: one in the IS chemotherapy trial and the other undergoing primary surgical extirpation.

Methods

Study Population and Eligibility Criteria

Nineteen patients were initially enrolled in the IS cohort from January 1, 2000, through November 30, 2002, at the University of Michigan. Eligibility criteria for the IS protocol included previously untreated, resectable stage III or IV OCSCC. Staging workup included direct laryngoscopy, tumor biopsy, and computed tomographic imaging. Patients with clinical or radiographic evidence of bone involvement or a Karnofksy performance status of less than 60% were ineligible. After accrual of 19 patients, the OCSCC patient cohort was closed to accrual because the stopping rule had been met. The rule required at least 40% of patients to achieve organ preservation after definitive CRT. We believed that if fewer than 40% of patients could not achieve organ preservation, the therapeutic approach would not be viewed as an advance in therapy. The institutional review board at the University of Michigan approved the data collection and study for this manuscript. Written informed consent was obtained for all patients in the study.

To create a valid comparison group based on inclusion criteria and patient characteristics, 299 patients were initially identified who underwent surgery and selective PORT/chemotherapy for OCSCC at the University of Michigan from April 7, 1998, through February 19, 2009. We then retrospectively identified all patients from the OCSCC database who would have met the pretreatment inclusion criteria for the IS trial, including patients with OCSCC who had received no previous treatment, who had an advanced clinical stage of disease, and who had no clinical evidence of gross bone invasion. To match pretreatment decision making between the IS and surgical treatment cohorts, postoperative pathological reporting was not used to determine eligibility. Seventy-five patients from the surgical database met the IS eligibility criteria. The surgical cohort included patients who were frequency matched and would have been eligible for the initial study. To further validate the match, an analysis was performed comparing the 2 cohorts using an optimal matching algorithm to match on sex and American Joint Committee on Cancer (AJCC) stage (III vs IV).[10,11] All patients were matched 1:1, and 15 of the 19 participants in the surgical cohort (79%) matched the IS cohort 3:1. This match resulted in 53 patients in the surgical cohort with pretreatment covariates comparable to those of the IS cohort. Clinical and demographic characteristics were evaluated for balance across the 2 cohorts by using χ^2 tests. For instances in which the χ^2 validity was questionable owing to small sample size, Monte Carlo methods of simulation were used to generate *P* values for an exact test. Covariates of interest were age at presentation (in years), sex, disease site (oral tongue, floor of the mouth, buccal space, upper alveolus, and lower alveolus), T and N classifications, smoking exposure (cumulative pack-years), smoking history (never vs past [quit >6 months ago]) vs current), and alcohol consumption (never vs past [quit >6 months ago]) vs current). We analyzed T and N classifications, smoking status, and alcohol status as ordinal data, and we found no difference between the 2 cohorts (**Table 1**). Median follow-up was 7.1 years in the surgical cohort and 9.4 years in the IS cohort.

Treatment Plan

The IS treatment schema is illustrated in **Figure 1**A. Nineteen patients were accrued into a phase 2 IS trial using 1 cycle of IC (cisplatin or carboplatin and fluorouracil) to select patients for definitive CRT. Clinical tumor response was evaluated 3 weeks after infusion by direct laryngoscopy. Patients with a response of at least 50% were classified as responders and underwent concurrent CRT (radiotherapy, 70 Gy in 35 fractions; concurrent chemotherapy with cisplatin, 100 mg/m^2, or carboplatin [area un-

Table 1. Demographics of Surgical and IS Cohorts[a]

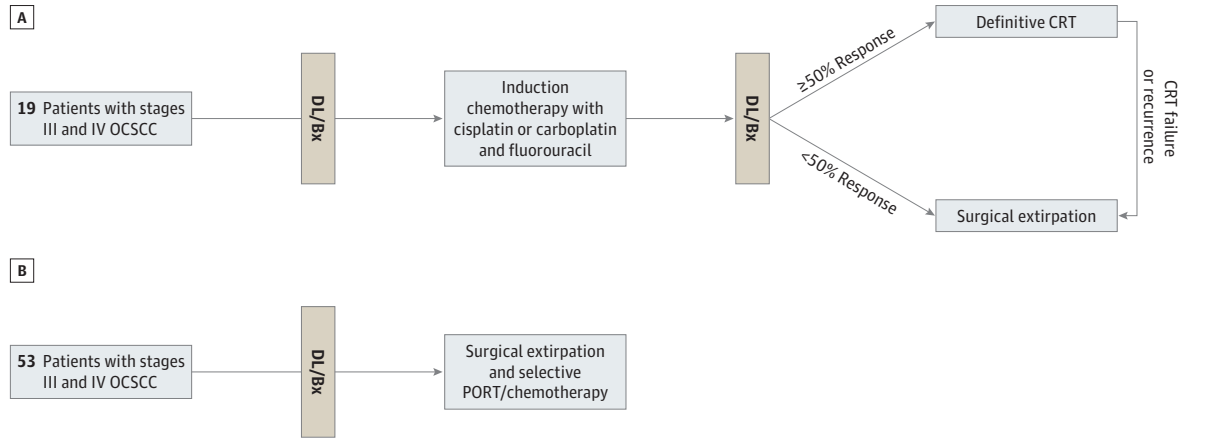
Characteristic	Surgical Cohort (n = 53)	IS Cohort (n = 19)	*P* Value
Sex			
Male	37 (70)	11 (58)	.34
Female	16 (30)	8 (42)	
Age, mean (SD) [range], y	57.9 (8.9) [43-76]	63.9 (14.5) [39-87]	.11
AJCC stage			
III	19 (36)	6 (32)	.74
IV	34 (64)	13 (68)	
Tumor classification			
T2	15 (28)	2 (11)	.12
T3/4	38 (72)	17 (89)	
Node classification			
N0	15 (28)	4 (21)	.87
N1	12 (23)	4 (21)	
N2	26 (49)	11 (58)	
Alcohol use[b]			
None	21 (40)	8 (42)	.69
Past	10 (19)	5 (26)	
Present	22 (41)	6 (32)	
Cumulative tobacco exposure, mean (SD) [range], pack-years	32.6 (19.2) [0-60]	36.1 (23.5) [0-60]	.45
Anatomic subsite			
Tongue	27 (51)	12 (63)	.12
Floor of mouth	17 (32)	3 (16)	
Buccal space	3 (6)	3 (16)	
Alveolus/palate	6 (11)	1 (5)	
Median follow-up, y	7.1	9.4	.86

Abbreviations: AJCC, American Joint Committee on Cancer; IS, induction selection.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Described in the Study Population and Eligibility Criteria subsection of the Methods section.

Figure 1. Treatment Schema



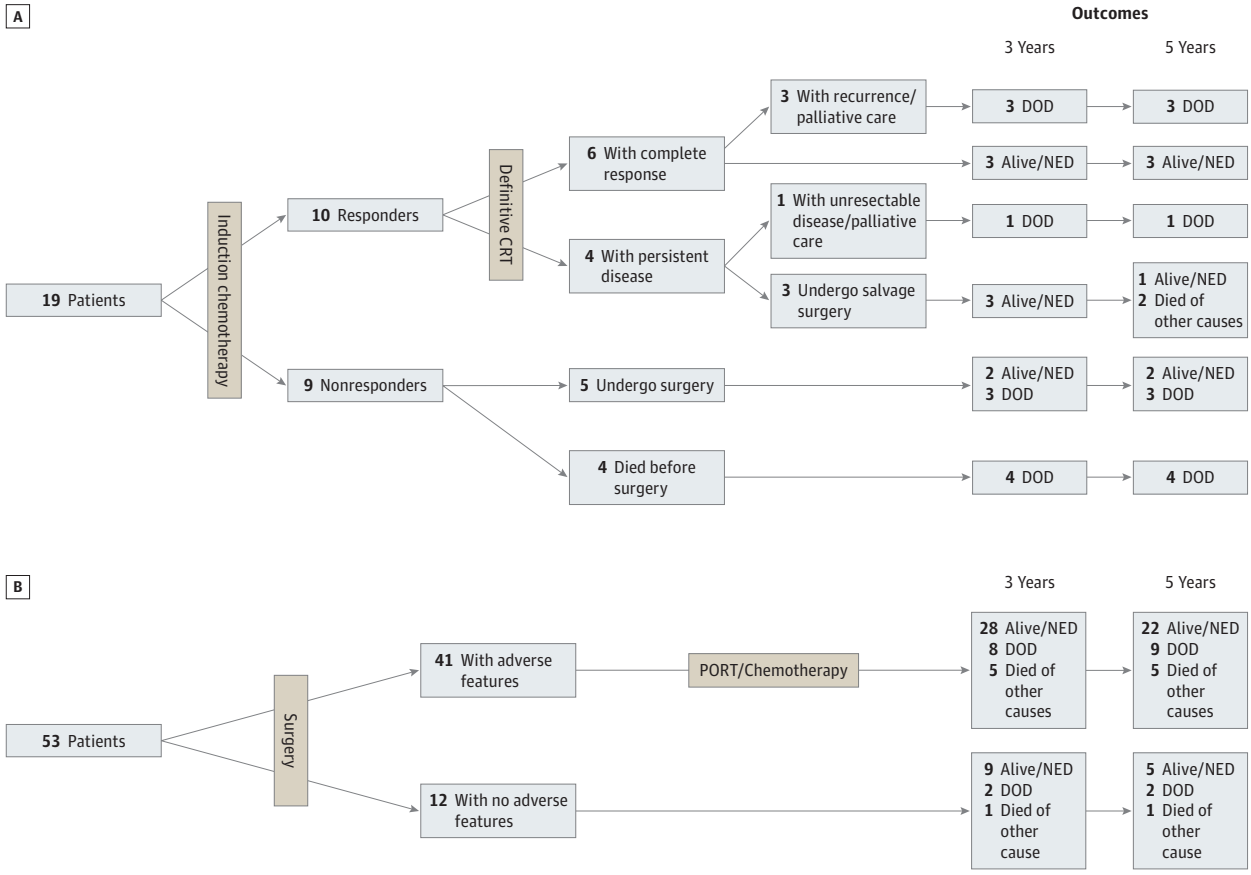
A, Induction selection cohort. B, Primary surgical cohort. CRT indicates chemoradiotherapy; DL/Bx, direct laryngoscopy and biopsy; OCSCC, oral cavity squamous cell carcinoma; and PORT, postoperative radiotherapy.

der the curve, 6] every 3 weeks for 3 cycles). Patients with a response of less than 50% were considered nonresponders and underwent surgical extirpation and adjuvant radiotherapy.[9]

Patient responses to IS and descriptive outcomes at 3 and 5 years are summarized in **Figure 2**A. Nineteen patients were enrolled and treated with IC. Ten of these (53%) had a response of at least 50%, whereas 9 (47%) were considered nonresponders based on a response of less than 50% to IC. Of the responders, only 6 of 10 (60%) were disease free after completion of definitive CRT.

The surgical cohort treatment schema is shown in Figure 1B. All patients in this cohort underwent primary surgical extir-

Figure 2. Descriptive Outcomes



A, Induction selection cohort. B, Surgical cohort. CRT indicates chemoradiotherapy; DOD, died of disease; NED, no evidence of disease; and PORT, postoperative radiotherapy.

pation based on involved subsites with 1-cm margins and a neck dissection for the at-risk neck. Adjuvant treatment after surgical extirpation was determined on the basis of standard PORT criteria,[12,13] including extracapsular spread, positive margins, regional metastasis, and perineural invasion.

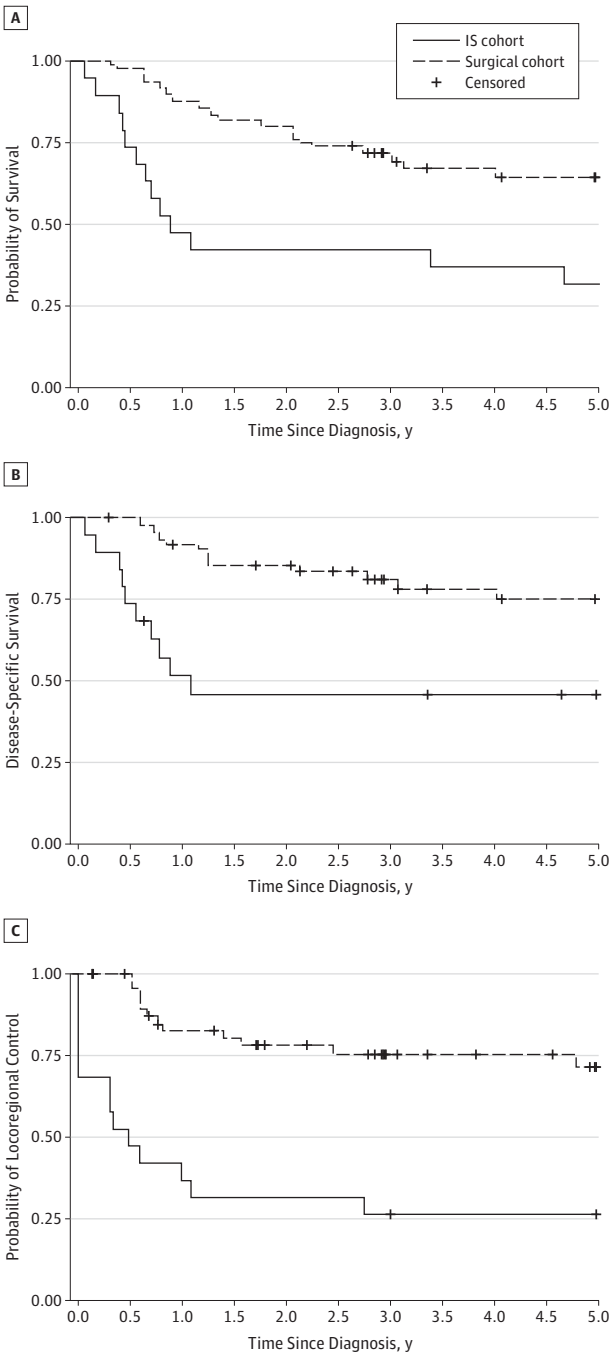
The type of primary site surgical extirpation included 19 composite resections (36%), 15 hemiglossectomies (28%), 7 subtotal glossectomies (13%), 7 extended hemiglossectomies (13%), 3 extended floor of the mouth resections (6%), 1 total glossectomy (2%), and 1 buccal resection (2%). Consistent with the intent-to-treat model, the only patients included in the composite resection portion of the surgical cohort were the patients who were booked for surgery with no intent for composite resection but for whom an intraoperative decision was made to remove bone. Microvascular free flap reconstruction was performed in 42 patients (79%). All patients in the surgical cohort underwent a therapeutic neck dissection. The type of neck dissection was selected at the discretion of the operating surgeon. Seventy-six neck dissections were performed in 53 patients. Thirty patients in the surgical cohort (57%) had a unilateral lesion that did not cross the midline. A unilateral neck dissection was performed in 28 of these cases (93%), with a neck dissection of at least ipsilateral levels I through III. The 2 patients with a unilateral lesion who underwent bilateral neck dissections had clinical evidence of lymphadenopathy bilaterally. In the 23 patients with midline tumors or tumors crossing the midline, 22 (96%) underwent a bilateral neck dissection, with a neck dissection of at least levels I to III on the more involved side and at least level I on the less involved side.

Figure 2B describes the treatment and descriptive outcomes at 3 and 5 years in the surgical cohort. Of the 53 patients treated with adjuvant therapy, 31 (58%) underwent radiotherapy alone and 10 (19%) underwent concurrent CRT. Twelve patients (23%) were treated with surgery alone. High-risk features were identified in 41 patients (77%); positive margins, in 2 (4%); perineural invasion, in 21 (40%); and nodal metastasis, in 26 (49%). Among the patients with nodal metastasis, 13 (50%) had extracapsular spread.

Statistical Analysis

The primary outcomes of interest were OS, DSS, and LRC between treatment cohorts. Overall survival was defined as the time from treatment to the time of death from any cause; DSS, the time from treatment to the time of death from OCSCC, for which the occurrence of a second primary tumor

Figure 3. Kaplan-Meier Survival Curves for the Surgical Cohort and Induction Selection (IS) Cohort



A, Overall survival (P = .01). B, Disease-specific survival (P = .001). C, Locoregional control (P < .001). Analyses include 19 patients in the IS cohort and 53 in the surgery cohort.

or death from another cause was treated as a censored event. Locoregional control was defined as the time from treatment to local and/or regional recurrence; persistent disease and treatment failure were treated as events with an LRC time of 1 day. Time to event and 3- and 5-year survivals of the 2 cohorts were compared. Secondary outcomes included evaluation of significant adverse events and treatment-related morbidity.

The Kaplan-Meier method and the log-rank test were used to assess differences in the survival functions between strata defined by clinical variables. Univariable and multivariable Cox models were used to explore the associations of clinical variables with time-to-event outcomes. For parsimony, a backward selection algorithm was implemented to highlight final multivariable models containing the strongest independent predictor variables. For descriptive purposes, we show the survival function for IS responders who subsequently received CRT compared with the survival function for IS nonresponders and those who required surgical extirpation as their primary treatment. All statistical analyses were performed using commercially available software (SAS, version 9.2; SAS Institute Inc). A 2-tailed $P \leq .05$ was considered statistically significant.

Results

Comparing primary surgical extirpation with selective PORT/chemotherapy demonstrated significantly better OS, DSS, and LRC (P = .01, P = .001, and P < .001, respectively) when compared with IS treatment for advanced-stage OCSCC (**Figure 3** and **Table 2**). Kaplan-Meier estimates of 1-, 3-, and 5-year survival are shown in **Table 3**. **Table 4** shows univariable and multivariable analysis of covariates of interest. Multivariable analysis demonstrated that primary surgical extirpation was associated with improved OS, DSS, and LRC (P = .03, P = .001, and P < .001, respectively) after controlling for other factors, such as age and clinical stage. In addition, multivariable analysis demonstrated that AJCC stage III (vs stage IV) disease was associated with improved OS, DSS, and LRC (P = .01, P = .02, and P = .02, respectively), whereas being younger was associated with improved OS and LRC (P = .01 and P = .05, respectively) independent of treatment modality. Tobacco exposure, alcohol consumption, preoperative T and N classifications, and sex were not significantly associated with poor outcomes when controlling for AJCC stage, age, and treatment type.

The goal of IS is to chemoselect patients for appropriate therapy based on the tumor response to IC. In the IS cohort, 10 of 19 patients (53%) responded to IC. Of the responders, only 3 (30%) had a complete response after concomitant CRT and remained disease free at 5 years. Only 1 of the 7 remaining responders (14%) underwent successful salvage after failure of definitive CRT and was alive at 5 years. Evaluation of the 9 nonresponders demonstrated that only 2 (22%) were alive with no evidence of disease after surgical extirpation at 5 years. Comparison of the IS responders and nonresponders demonstrated that age, sex, stage, T and N classifications, tobacco exposure, and alcohol consumption were not predictive of the response to IC. Kaplan-Meier survival analysis of outcomes between the IS responders and nonresponders demonstrated no difference in survival (**Figure 4** and **Table 5**). Five-year survival estimates are shown in **Table 6**. These findings suggest that the IS approach for OCSCC does not provide optimum che-

moselection of patients and demonstrates that outcomes were significantly worse in the responder and nonresponder IS groups when compared with patients treated with primary surgical extirpation and with selective PORT/chemotherapy for high-risk features.

We evaluated serious adverse reactions to surgery and IS. In the surgical cohort, no fatalities, pulmonary embolisms, deep vein thrombosis, or cerebral vascular accidents occurred within 30 days of surgery. One patient in the surgical cohort developed osteoradionecrosis after adjuvant therapy. One patient developed postoperative atrial fibrillation requiring treatment, and a second had a mild elevation of cardiac enzyme levels after surgery; neither required long-term therapy. Two patients developed hematomas that warranted return to the operating room for drainage; neither patient experienced any long-term sequelae. Gastrostomy tube dependence was identified in 5 of 53 patients (9%) treated surgically. None of the patients in the surgical cohort were dependent on tracheostomy tubes.

In the IS cohort, 1 patient died during IC because of neutropenic sepsis secondary to a dihydropyrimidine dehydrogenase deficiency. Three of the 19 IS patients (16%) developed osteoradionecrosis. A fourth patient developed a massive myocardial infarction during IS, eliminating him as a candidate for surgery. Gastrostomy tube dependence was identified in 8 of these patients (42%). One patient (5%) was dependent on a tracheostomy tube.

Table 2. Pairwise Analysis of Main Outcomes for Surgical vs IS Cohort

Outcome	Results	
	P Value	HR (95% CI)
Overall survival	.01	2.51 (1.24-5.06)
Disease-specific survival	.001	3.59 (1.52-8.51)
Locoregional control	<.001	4.98 (2.29-10.85)

Abbreviations: HR, hazard ratio; IS, induction selection.

Table 3. Kaplan-Meier 1-, 3-, and 5-Year Survival Estimates

Outcome	Mean Survival (95% CI), %	
	Surgical Cohort (n = 53)	Overall IS Cohort (n = 19)
Overall survival, y		
1	88 (75-94)	47 (24-67)
3	69 (55-80)	42 (20-62)
5	65 (49-76)	32 (13-52)
Disease-specific survival, y		
1	92 (80-97)	51 (27-71)
3	81 (67-90)	46 (23-66)
5	75 (59-86)	46 (23-66)
Locoregional control, y		
1	82 (69-90)	42 (20-62)
3	80 (66-88)	26 (10-47)
5	72 (57-84)	26 (10-47)

Abbreviation: IS, induction selection.

Discussion

Despite the success of IS protocols in other subsites, such as laryngeal SCC, comparative analysis using a matched retrospective cohort treated at the University of Michigan during the same period suggests that surgery with selective PORT/chemotherapy for high-risk features results in better OS, DSS, and LRC for patients with advanced-stage (III and IV) OCSCC than a combined induction and concurrent CRT approach.

Surgery vs definitive CRT for OCSCC has been evaluated in 2 small cohort studies. These studies evaluated different treatment approaches, and patient selection varied between the cohorts. Sher et al[14] studied 12 patients with unresectable disease who underwent CRT for OCSCC compared with 30 who underwent primary surgical extirpation. Two-year overall survival was 85% in the surgical cohort compared with 63% in the definitive CRT arm. Umeda et al[15] evaluated outcomes in 9 patients undergoing definitive CRT compared with 18 undergoing primary surgical management. Three-year survival was 29.6% in the IC cohort compared with 81.5% in the surgical cohort ($P < .05$). These findings support our results and suggest that definitive CRT may be an inadequate treatment modality for advanced-stage OCSCC.

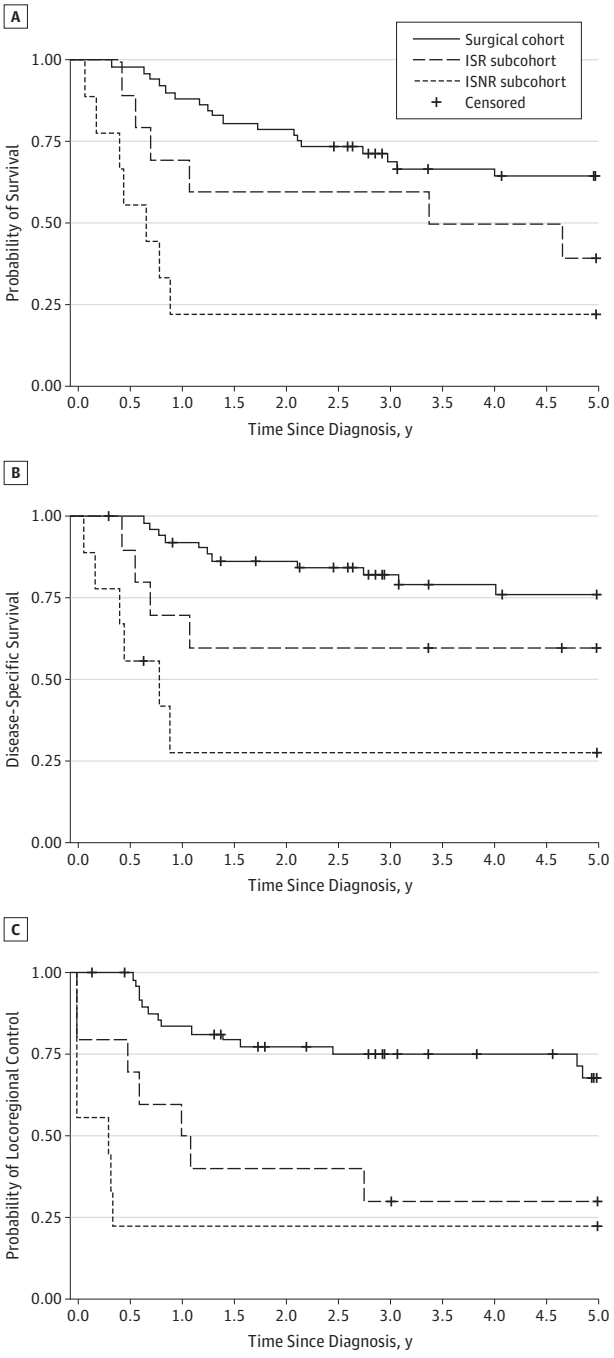
Results from centers advocating IC and definitive CRT for advanced-stage OCSCC[16-18] have shown survival rates equal to or better than those of the patients in our IS trial. Retrospective analysis of 3 small phase 2 studies evaluating outcomes after definitive CRT for OCSCC showed 5-year overall survival rates of 56% to 76%, death due to CRT in 7.2% to 7.6%, and osteoradionecrosis in 14% to 18% of their patient

Table 4. Univariable and Multivariable Analysis of Significant Clinical Variables That Predict Survival

Comparison Cohort	Outcome, HR (95% CI)					
	Overall Survival		Disease-Specific Survival		Locoregional Control	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Surgery vs IS	2.51 (1.20-4.78)	2.32 (1.07-5.02)	3.81 (1.61-9.02)	4.20 (1.76-10.05)	4.60 (2.18-9.71)	4.17 (1.86-9.36)
P value	.01	.03	.002	.001	<.001	<.001
AJCC stage III vs IV	0.47 (0.22-1.0)	0.34 (0.15-0.78)	0.26 (0.08-0.88)	0.23 (0.07-0.79)	0.42 (0.17-1.03)	0.33 (0.13-0.83)
P value	.05	.01	.03	.02	.06	.02
Age	1.04 (1.01-1.07)	1.04 (1.01-1.08)			1.04 (1.00-1.07)	1.04 (1.00-1.07)
P value	.004	.01	.28	.29	.03	.05

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; IS, induction selection.

Figure 4. Kaplan-Meier Survival Curves for Subcohort Analysis of Induction Selection Responders (ISR) and Nonresponders (ISNR) Compared With Surgical Cohort



A, Overall survival. B, Disease-specific survival. C, Locoregional control. Analyses include 10 patients in the ISR subcohort, 9 in the ISNR subcohort, and 53 in the surgery cohort. *P* values for pairwise comparisons are given in Table 5.

Table 5. Pairwise Analyses for Main Outcomes in the Surgery Cohort and the ISR and ISNR Subcohorts

Cohort/Subcohort Comparison	Results	
	P Value	HR (95% CI)
Overall Survival		
Surgical vs ISR	.049	2.07 (0.82-5.22)
Surgical vs ISNR	<.001	5.23 (2.16-12.69)
ISR vs ISNR	.37	0.40 (0.13-1.18)
Disease-Specific Survival		
Surgical vs ISR	.07	2.29 (0.73-7.21)
Surgical vs ISNR	<.001	6.99 (2.54-19.20)
ISR vs ISNR	.20	0.33 (0.09-1.17)
Locoregional Control		
Surgical vs ISR	<.001	3.51 (1.41-8.71)
Surgical vs ISNR	<.001	6.82 (2.69-17.30)
ISR vs ISNR	.76	0.51 (0.18-1.45)

Abbreviations: HR, hazard ratio; ISNR, induction selection nonresponder; ISR, induction selection responder.

population. These results demonstrate better OS compared with our IS cohort, but OS appears to be equivocal or worse compared with that in our surgical cohort. In addition, higher rates of treatment-related deaths and posttreatment complications occurred in our IS cohort and these IS and CRT trials compared with our surgical cohort. Gastrostomy tube dependence was 9% in our surgical cohort compared with 9.3% to 14% in the definitive CRT literature.[15,16]

Induction selection protocols for laryngeal SCC effectively differentiate patients who will respond to definitive CRT vs those who will respond to surgery.[7] This method of chemoselection is a crude but effective form of personalized medicine. However, this study suggests that IS protocols for chemoselection in OCSCC are not effective. Of the 10 IS responders, only 3 (30%) experienced control of their disease at 5 years. In addition, the nonresponders in the IS cohort demonstrated significantly worse survival compared with patients who received surgery as their primary therapy. The difficulty with CRT for definitive treatment of OCSCC is multifactorial and likely includes differences in subsite tumor biology, mobility of the structures in the oral cavity, proximity to the mandible, and difficulty in surgically salvaging patients after CRT. In addition, no clinical variables studied yield any power to predict a favorable outcome in the IS cohort. Prior studies of radiotherapy alone for oral cavity carcinoma also show poor results unless external radiotherapy is combined with neck dissection and brachytherapy techniques for the primary tumor site.[19-21]

Limitations of the current study include the small IS cohort and the retrospective nature of the study. The IS cohort was small because of the inadequate response to IC and residual disease after completion of CRT, thus triggering the protocol's early stopping rules. Retrospective analyses also have limitations. We used matching of the 2 retrospective cohorts in an attempt to control for biases that may distort the true relationship between treatment and outcome. An a priori approach was used to design a matching cohort with at least a 1:1 match for sex and AJCC stage that best represented the trial design. Selection of the comparison cohorts was based on pretreatment variables to control for bias resulting from the nonrandomized nature of this study. Multivariable analysis was performed to control for any

Table 6. Kaplan-Meier 5-Year Survival Estimates

	Mean Survival (95% CI), %		
	Surgical Cohort (n = 53)	ISR Subcohort (n = 10)	ISNR Subcohort (n = 9)
Overall survival	65 (49-76)	40 (12-67)	22 (3-51)
Disease-specific survival	75 (59-86)	60 (25-83)	28 (4-60)
Locoregional control	72 (57-84)	30 (7-58)	22 (3-51)

Abbreviations: ISNR, induction selection nonresponder; ISR, induction selection responder.

potentially confounding variables. These cohorts were well balanced and matched, allowing for a sufficiently comparable patient population. Historical bias was controlled by selecting patients in the surgical cohort treated several years before and after the IS cohort was accrued. By flanking the IS cohort with the surgical cohort, we attempted to minimize the effect of historical bias and changes in surgical or radiotherapy techniques.

The concern about function after surgical resection of critical structure in the oral cavity is one reason that CRT is favored at some centers. Focus on reconstructive techniques to preserve vital functions of the oral cavity is linked to decision making to treat patients with surgery for OCSCC. Just as finesse of the radiotherapy technique improved function in the oropharynx, finesse of reconstructive techniques can improve oral cavity function.[22-25] In addition, more treatment-related deaths and morbidities occur in CRT protocols that are not seen in patients undergoing surgical management. Future studies should focus on functional capacity after surgical ablation and molecular marker analysis for selecting patients who will respond well to surgery vs those who might respond well to definitive CRT. Overall survival rates for patients with OCSCC demand improvements in patient selection, better identification of patients at high risk of distant failure, and development of improved immunologic and drug therapies that could be effective in properly selected patients. Until better regimens are available, standard therapy should remain comprehensive surgical resection combined with selective PORT/chemotherapy.

Conclusions

This matched retrospective cohort study of patients treated at the University of Michigan strongly suggests that primary surgical extirpation with selective PORT/chemotherapy for adverse features results in better OS, DSS, and LRC than does an IS protocol. In addition, IS does not appear to chemoselect patients for organ preservation therapy in OCSCC and results in worse treatment-related complications compared with surgery.

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Acquisition of data: Chinn, Spector, Teknos, Prince, Bradford, Urba, Carey, Eisbruch, Wolf, Chepeha.
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