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Induction chemotherapy followed by chemoradiation for organ preservation compared to surgery with selective chemoradiation in patients with advanced oral cavity carcinoma

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Abstract

Objective—To evaluate the efficacy of an induction selection(IS) concurrent chemoradiation(CRT) protocol versus primary surgical extirpation in advanced oral cavity squamous cell carcinoma(OCSCC).

Design—Retrospective matched cohort study

Setting—Tertiary care hospital

Patients—Nineteen patients with resectable stage III/IV OCSCC were into a phase II IS trial. Patients with >50% response underwent concurrent CRT and patients with <50% underwent

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Study concept and design: All authors.
Acquisition of data: Chinn, Spector.
Analysis and interpretation of data: All authors.
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surgical treatment and radiation therapy. A comparison cohort of patients treated with primary surgical extirpation was selected from the University of Michigan during a similar time period and frequency matched for inclusion criteria and patient characteristics to those patients included from the phase II IS trial. There was no difference in age, gender, pre-treatment AJCC-stage, T-classification, N-classification, smoking status, alcohol status, or tumor subsite between the two groups. Median follow-up was 9.4-years in the IS cohort and 7.1-years in the surgical cohort.

Main Outcome Measures—Overall Survival(OS), Disease-specific survival(DSS) and . Local-regional control(LRC)

Results—OS at 5-years was 32% in the IS group and 65% in the surgical cohort. DSS at 5-years was 46% in the IS group and 75% in the surgical cohort. LRC at 5-years was 26% in the IS cohort and 72% in the surgical cohort. Multivariable analysis demonstrated significantly better OS, DSS and LRC outcomes (p=0.03,p=0.001 and p=0.0005,respectively) in the surgical cohort.

Conclusion—Primary surgical treatment showed significantly better OS, DSS and LRC compared to IS in this matched patient cohort. Despite success of organ preservation IS protocols in the larynx, comparative survival analysis of an IS protocol versus primary surgical extirpation for OCSCC demonstrates significantly better outcomes in the surgical cohort. These findings support surgery as the principal treatment for OCSCC.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common malignancy, affecting over 40,000 Americans with 11,000 dying annually.[1] Despite a historically high mortality rate, patients with nasopharyngeal, oropharyngeal and laryngeal squamous cell carcinoma (SCC) have demonstrated improved survival over the last several decades. For patients with oral cavity squamous cell carcinoma (OCSCC) there is evidence that post-operative chemoradiation (CRT) can improve survival for high risk patients by approximately 6.5% but this is associated with additional morbidity.[2-4]

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

A Phase II trial at the University of Michigan (UMCC 9921) evaluated the role of IS for patients with stage III and IV oropharyngeal or oral cavity squamous cell carcinoma. The

trial was designed to analyze each cohort by primary tumor site with specific stopping rules for each cohort. We elected to perform a retrospective matched cohort study to compare the oral cavity patients undergoing IS to a group of patients treated with surgery and selective postoperative radiation therapy (PORT)/chemotherapy after carefully matching based on inclusion criteria for the IS trial. The objective of this study was to comprehensively evaluate survival and local-regional control outcomes of advanced stage OCSCC patients in the IS chemotherapy trial compared to a matched group of advanced stage OCSCC who underwent primary surgical extirpation.

Patient Selection and Methods

Study Population and Eligibility Criteria

Nineteen patients were initially enrolled in the induction selection (IS) cohort between January 1, 2000 and November 30, 2002 at the University of Michigan. Eligibility criteria for the IS protocol included previously untreated, resectable stage III to IV squamous cell carcinoma of the oral cavity. Staging workup included direct laryngoscopy, tumor biopsy and CT imaging. Patients with clinical or radiographic evidence of bone involvement or Karnofksy performance status less than 60% were ineligible. After accrual of 19 patients, the oral cavity patient cohort was closed to accrual since the stopping rule had been met. The rule required at least 40% of patients to achieve organ preservation after definitive chemoradiation. We felt that if less than 40% of patients could not have organ preservation, the therapeutic approach would not be viewed as an advance in therapy.

To create a valid comparison group based on inclusion criteria and patient characteristics, 299 patients were initially identified from April 1998 through February 2009 who were treated with surgery and selective PORT/chemotherapy for OCSCC at the University of Michigan. We then retrospectively identified all patients from the OCSCC database who would have met the pre-treatment inclusion criteria for the IS trial which included OCSCC patients with no previous treatment, advanced clinical stage, and no clinical evidence of gross bone invasion. To match pre-treatment decision making between the IS and surgical treatment, post-operative pathology reporting was not used to determine eligibility. Seventy-five patients from the surgical database met the IS eligibility criteria. The surgical cohort included patients that were frequency matched that would have been eligible for the initial study. To further validate the match, an analysis was performed comparing the two cohorts using an optimal matching algorithm to match on gender and AJCC stage (III vs IV).[10,11] All patients were matched 1:1 and 79% (15/19) of the surgical cohort matched the IS cohort 3:1. This resulted in 53 patients in the surgical cohort with comparable pre-treatment covariates to the IS cohort. Clinical and demographic characteristics were evaluated for balance across the two groups using chi-square tests and in instances where the chi-square validity was questionable due 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 (years), gender, disease site (oral tongue, floor of mouth, buccal space, upper alveolus and lower alveolus), T-classification, N-classification, smoking exposure (cumulative pack-years), smoking history (never v past [quit > 6 months ago]) v current) and alcohol exposure (never v past [quit > 6 months ago]) v current exposure). T-classification, N- classification,

smoking status and alcohol status were analyzed as ordinal data with no assumptions about the degree of difference between categories. There was and there were no difference between the two groups (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 1A. Nineteen patients were accrued into a phase II IS trial using one cycle of IC (cisplatin or carboplatin and 5-fluorouracil) to select patients for definitive chemoradiation (CRT). Clinical tumor response was evaluated 3-weeks post-infusion by direct laryngoscopy. Patients with >50% response were classified as responders and underwent concurrent CRT (70Gy; 35 fractions with concurrent cisplatin 100mg/m^2 or carboplatin (AUC 6) every 3-weeks for 3 cycles). Those with <50% were considered non-responders and underwent surgical extirpation and adjuvant radiation therapy.[9]

Patient responses to IS and descriptive outcomes at 3 and 5-years are summarized in Figure 2A. Nineteen patients were enrolled and treated with induction chemotherapy. 58% (10/19) had a greater than 50% response, while 42% (9/19) were considered nonresponders based on a less than 50% response to induction chemotherapy. Of the responders only 6/10 (60%) were disease free after completion of definitive chemoradiation.

The surgical cohort treatment schema is shown in Figure 1B. All patients in this cohort underwent primary surgical extirpation based on involved subsites with 1 cm margins and a neck dissection for the at-risk neck. Adjuvant treatment after surgical extirpation was determined based on standard PORT criteria.[12,13] This included extracapsular spread (ECS), positive margins, regional metastasis, and perineural invasion.

The type of primary site surgical extirpation included 36% (19/53) composite resections, 28% (15/53) hemiglossectomies, 13% (7/53) subtotal glossectomies, 13% (7/53) extended hemiglossectomies, 6% (3/53) extended floor of mouth resections, 2% (1/53) total glossectomies, and 2% (1/53) buccal resection. Microvascular free flap reconstruction was performed in 79% (42/53) of patients.

All patients in the surgical cohort underwent a therapeutic neck dissection. The type of neck dissection was performed at the discretion of the operating surgeon. There were 76 neck dissections in 53 patients. Fifty-seven percent (30/53) of patients in the surgical cohort had a unilateral lesion that did not cross the midline. A unilateral neck dissection was performed in 93% (28/30) of these cases with at least an ipsilateral level I-III neck dissection. The two patients with a unilateral lesion who underwent bilateral neck dissections had clinical evidence of lymphadenopathy bilaterally. In patients with midline tumors or tumors crossing midline, 96% (22/23) underwent a bilateral neck dissection with at least a level I-III neck dissection on the more involved side and at least a level I dissection on the less involved side.

Figure 2B describes the treatment and descriptive outcomes at 3 and 5-year in the surgical cohort. Of the patients treated with adjuvant therapy, 58% (31/53) of patients underwent

XRT alone and 18% (9/53) underwent concurrent CRT. Twenty-three percent (12/53) of patients were treated with surgery alone. High-risk features were identified in 77% (41/53) of patients. Positive margins in 4% (2/53), perineural invasion in 40% (21/53), nodal metastasis in 49% (26/53) and of the patients with nodal metastasis 50% (13/26) had ECS.

Statistical Analysis

The primary outcomes of interest were overall survival (OS), disease-specific survival (DSS) and local-regional control (LRC) between treatment groups. OS was defined as time from treatment to time of death by any cause; DSS was defined as the time of treatment to time of death from OCSCC, where the occurrence of a second primary or death from another cause was treated as a censored event. LRC was defined as 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, 3-year and 5-year survival of the two groups were compared. Secondary outcomes were evaluation of significant adverse events and treatment related morbidity.

The Kaplan-Meier method and the log-rank test were used to test for 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 were subsequently treated by CRT compared with the survival function for IS non-responders and required surgical extirpation as their primary treatment. All statistical analyses were done using SAS version 9.2 (SAS Institute, Carey, NC). A two-tailed P value of .05 or less was considered statistically significant.

The Institutional Review Board at the University of Michigan approved the data collection and study for this manuscript.

Results

Comparing primary surgical extirpation with selective PORT/chemotherapy demonstrated significantly better OS, DSS and LRC ($p=0.01$, $p=0.002$ and $p<0.0001$ respectively) when compared to IS treatment for advanced stage OCSCC (Figure 3). Kaplan-Meier estimates of 1, 3 and 5-year survival are shown in Table 2. Table 3 shows univariable and multivariable analysis of covariates of interest. Multivariable analysis demonstrated primary surgical extirpation was associated with improved OS, DSS and LRC ($p=0.03$, $p= 0.001$ and $p=0.0005$ respectively) after controlling for other factors such as age and clinical stage. In addition, multivariable analysis demonstrated AJCC stage III (versus stage IV) disease was associated with improved OS, DSS and LRC ($p=0.01$, $p= 0.02$ and $p=0.02$ respectively), while younger age was associated with improved OS and LRC ($p=0.01$ and $p=0.05$ respectively) independent of treatment modality. Tobacco exposure, alcohol exposure, pre-operative T-classification, pre-operative N-classification and gender were not significantly associated with poor outcomes when controlling for stage, age and treatment type.

The goal of IS is to chemoselect patients for appropriate therapy based on tumor response to IC. In the IS cohort 52% (10/19) of patients responded to IC. Of the responders, only 30% (3/10) were complete responders after concomitant CRT and remained disease free at 5-years. Only 14% (1/7) of the remaining responders were successfully salvaged after definitive CRT failure at 5-years. Evaluation of the nonresponders demonstrated only 22% (2/9) were alive with no evidence of disease after surgical extirpation at 5-years. Comparison of the IS responders and non-responders demonstrated that neither age, gender, stage, T-classification, N-classification, tobacco exposure or alcohol exposure were predictive for response to IC. Kaplan-Meier survival analysis of outcomes between the IS responders and non-responders demonstrated no difference in survival (Figure 4). Five-year survival estimates are shown in Table 4. These findings suggests that the IS approach for OCSCC does not optimally chemoselect patients and demonstrates that outcomes were significantly worse in both the responder and non-responder IS groups when compared to patients treated with primary surgical extirpation with selective PORT/chemotherapy for high risk features.

Serious adverse reactions to surgery and IS were evaluated. In the surgical cohort, there were no fatalities, pulmonary embolisms, deep vein thrombosis, or cerebral vascular accidents within 30 days of surgery. One patient in the surgical cohort developed ORN after adjuvant therapy. One patient developed post-operative atrial fibrillation requiring treatment and a second had a mild elevation of cardiac enzymes after surgery; neither required long term therapy. Two patients developed hematomas that warranted take back to the operating room for drainage, neither resulted in long-term sequelae. Gastrostomy tube dependence was identified in 9.4% (5/53) of patients treated surgically. None (0/53) of the patients in the surgical cohort were tracheostomy tube dependent. In the IS cohort, one patient died during induction chemotherapy due to neutropenic sepsis secondary to a dihydropyrimidine dehydrogenase deficiency. Three patients (16%) developed osteoradionecrosis (ORN). A fourth patient developed a massive myocardial infarction (MI) during IS making him a non-surgical candidate. Gastrostomy tube dependence was identified in 42% (8/19) patients. One patient (5%; 1/19) was tracheostomy tube dependent.

Discussion

Despite 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-IV) OCSCC than a combined induction and concurrent chemoradiation approach.

Surgery versus definitive CRT for OCSCC has been evaluated in two small cohort studies. These studies evaluated different treatment approaches and patient selection varied between the cohorts. Sher et al. studied 12 unresectable patients who underwent CRT for OCSCC compared to 30 who underwent primary surgical extirpation. Two year overall survival was 85% in the surgical cohort compared to 63% in the definitive CRT arm.[14] Umeda et al evaluated 9 patients undergoing definitive CRT compared to 18 undergoing primary surgical management. Three year survival was 29.6% in the IC group, compared to 81.5% in the

surgical group ($p<0.05$).[15] These findings support our results and suggest definitive CRT may be an inadequate treatment modality for advanced stage OCSCC.

Results from centers advocating IC and definitive CRT for advanced stage OCSCC have shown equal or better survival rates than the patients in our IS trial. Retrospective analysis of three small phase II studies evaluating outcomes after definitive CRT for OCSCC showed 5-year overall survival rates of 56 -76%, death as a result of CRT occurring in 7.2 - 7.6%, and ORN in 14 -18% of their patient population.[16-18] These results demonstrate better OS compared to our IS cohort, but survival appears to be equivocal or worse compared to our surgical cohort in regards to OS. Additionally, there were higher rates of treatment related deaths and post-treatment complications in both our IS cohort and these IS and CRT trials compared to our surgical cohort. Gastrostomy tube dependence was 9.4% in our surgical cohort compared to 9.3-14% in the definitive CRT literature.[15-16]

Induction selection protocols for laryngeal SCC effectively differentiate patients who will respond to definitive CRT versus those who will respond to surgery.[7] This method of chemoselection is a crude, but effective form of personalized medicine. However, this study suggests IS protocols for chemoselection in OCSCC is not effective. Of the IS responders, only 30% (3/10) experienced control of their disease at 5-years. Additionally the IS non-responders demonstrated significantly worse survival compared to those patients who receive 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, the proximity to the mandible, and the difficulty in surgically salvaging patients after CRT. Additionally, no clinical variables studied yield any power to predict a favorable outcome in the IS cohort. Prior studies of radiation alone for oral cavity carcinoma also show poor results unless external radiation is combined with neck dissection and brachytherapy techniques for the primary tumor site.[21-23]

Limitations of the current study are 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. Matching of the retrospective cohort from patients treated at the University of Michigan was utilized 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 gender and AJCC stage that best represented the trial design. The comparison cohorts were selected based on pre-treatment variables to control for bias resulting from the non-randomized nature of this study. Multivariable analysis was performed to control for any 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 radiation techniques.

One of the reasons that CRT is favored at some centers is the concern about function after surgical resection of critical structure in the oral cavity. 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 radiation technique improved function in the oropharynx, finesse of reconstructive techniques can improve oral cavity function.[19-22] Additionally, there are more treatment related deaths and treatment related morbidities in CRT protocols that are not seen in surgically managed patients. Future aims should focus on functional capacity after surgical ablation and molecular marker analysis for selecting patients who will do well with surgery versus those who might do well with definitive CRT. Overall survival rates for patients with oral cavity carcinoma remain dismal and 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.

Conclusion

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 an IS protocol. Additionally, IS does not appear to adequately chemoselect patients for organ preservation therapy in OCSCC and results in worse treatment related complications compared to surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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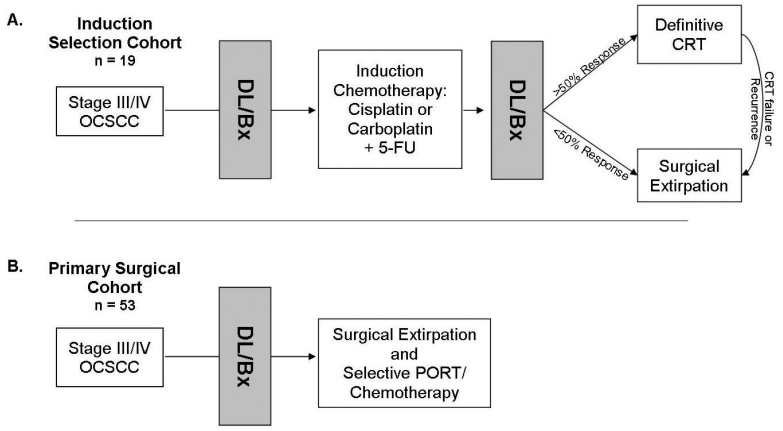


Figure 1.

Treatment schema for (A) Induction Selection Cohort and (B) Primary Surgical Cohort.5-FU = 5-Fluorouracil; DL/Bx = Direct Laryngoscopy and Biopsy; CRT = Chemoradiation Therapy; PORT = Post-operative radiation therapy

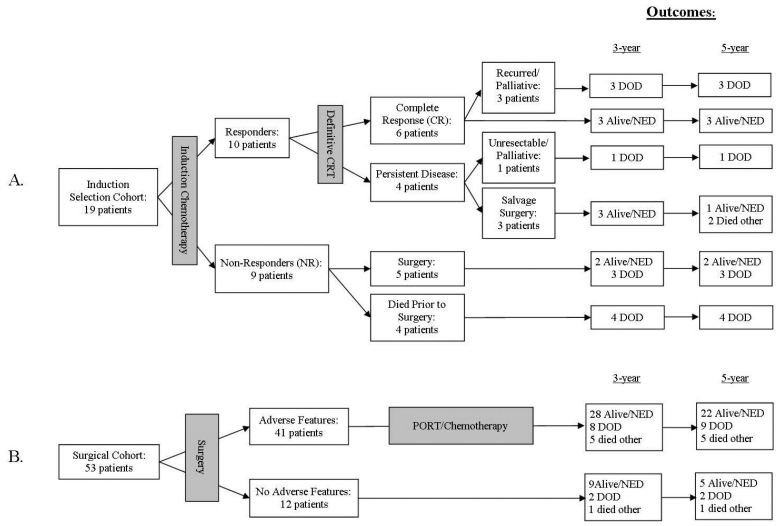


Figure 2.

Descriptive outcomes in the (A) Induction Selection Cohort (IS) and (B) Surgical Cohort. RT = Radiation Therapy; CRT = Chemo-radiation Therapy; PORT = Post-operative radiation therapy; NED = No evidence of Disease; DOD = Died of Disease.

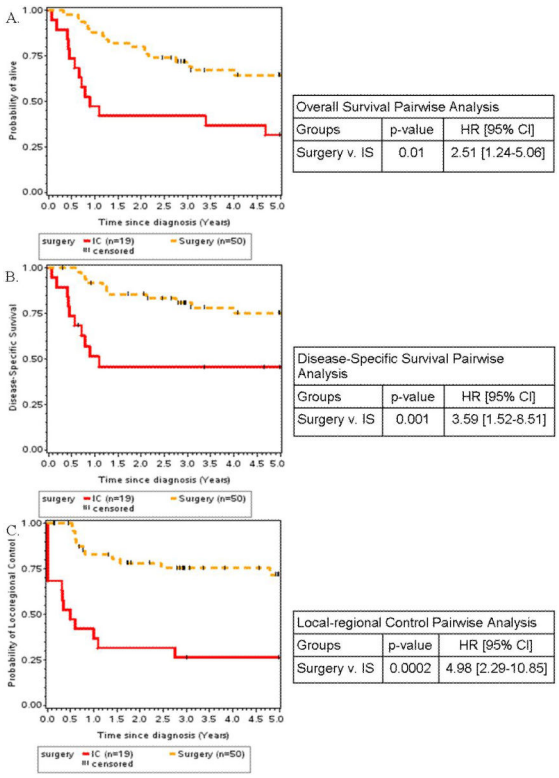
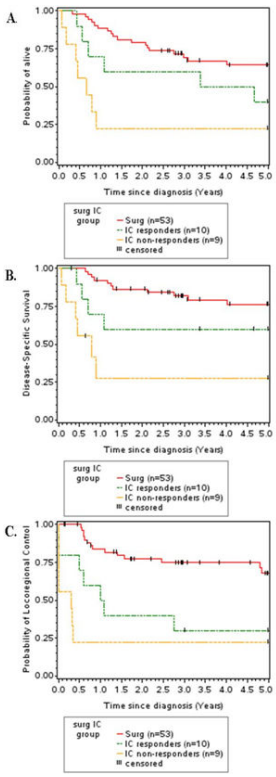


Figure 3.

Kaplan-Meier Survival Curves for the Surgical Cohort and IS Cohort. (A) Overall Survival (B) Disease Specific Survival C) Local-regional Control



Overall Survival Pairwise Analysis		
Groups	p-value	HR [95% CI]
Surgery v. ISR	0.049	2.07 [0.82-5.22]
Surgery v. ISNR	0.0002	5.23 [2.16-12.69]
ISR v. ISNR	0.37	0.40 [0.13-1.18]

Disease-Specific Survival Pairwise Analysis		
Groups	p-value	HR [95% CI]
Surgery v. ISR	0.072	2.29 [0.73-7.21]
Surgery v. ISNR	0.0006	6.99 [2.54-19.20]
ISR v. ISNR	0.2	0.33 [0.09-1.17]

Local-regional Control Pairwise Analysis		
Groups	p-value	HR [95% CI]
Surgery v. ISR	0.0003	3.51 [1.41-8.71]
Surgery v. ISNR	<0.0001	6.82 [2.69-17.30]
ISR v. ISNR	0.76	0.51 [0.18-1.45]

Figure 4.

Kaplan-Meier Survival Curves for Subgroup analysis of IS Responders (ISR) and Non-responders (ISNR) compared to Surgical Cohort. A) Overall Survival B) Disease Specific Survival C) Local-regional Control

Table 1

Demographics of Surgical and Induction Selection Cohort.

	Surgical Cohort	Induction Selection Cohort	p-value
Total	53	19	—
Sex			
Male (%)	37 (70)	11 (58)	NS
Female (%)	16 (30)	8 (42)	
Age (years)			
Mean (SD)	57.9 (8.9)	63.9 (14.5)	NS
Range	43-76	39-87	
AJCC Stage			
III (%)	19 (36)	6 (32)	NS
IV (%)	34 (64)	13 (68)	
TNM Classification			
T			
T2 (%)	15 (28)	2 (11)	NS
T3/4 (%)	38 (72)	17 (89)	
N			
N0 (%)	15 (28)	4 (21)	NS
N1 (%)	12 (23)	5 (26)	
N2 (%)	26 (49)	8 (42)	
Alcohol Use			
No use (%)	21 (40)	8 (42)	NS
Past use (%)	10 (19)	5 (26)	
Present use (%)	22 (41)	6 (32)	
Cumulative Tobacco (mean pack-years(SD) [Range])	32.6 (19.2) [0-60]	36.1 (23.5) [0-60]	NS
Anatomic Subsite			
Tongue	27 (51)	12 (63)	NS
Floor of Mouth	17 (32)	3 (16)	
Buccal Space	3 (6)	3 (16)	
Alveolus/Palate	6 (11)	1 (5)	
Median Follow-up (years)	7.1	9.4	NS

Table 2

Kaplan-Meier 1,3 and 5-year Survival Estimates.

		Surgical Cohort (n=53)	Overall IS Cohort (n=19)
Overall Survival	1-year	88% [75, 94]	47% [24, 67]
	3-year	69% [55,80]	42% [20, 62]
	5-year	65% [49, 76]	32% [13,52]
Disease Specific Survival	1-year	92% [80, 97]	51% [27, 71]
	3-year	81% [67,90]	46% [23, 66]
	5-year	75% [59, 86]	46% [23, 66]
Local-Regional Control	1 -year	82% [69, 90]	42% [20, 62]
	3-year	80% [66, 88]	26% [10, 47]
	5-year	72% [57, 84]	26% [10, 47]

IS = Induction Selection; [95% Confidence Interval]

Table 3

Univariate and multivariate analysis of significant clinical variables that predict survival.

	Overall Survival		Disease Specific Survival		Local Regional Control	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Treatment Groups (Surgery v. IS)	p= 0.01 HR 2.51 [1.20-4.78]	p=0.03 HR 2.32 [1.07-5.02]	p=0.002 HR 3.81 [1.61-9.02]	p=0.001 HR 4.20 [1.76-10.05]	p<0.0001 HR 4.60 [2.18-9.71]	p=0.0005 HR 4.17 [1.86-9.36]
AJCC Stage (III v IV)	p=0.05 HR 0.47 [0.22-1.0]	p=0.01 HR 0.34 [0.15-0.78]	p=0.03 HR 0.26 [0.08-0.88]	p=0.02 HR 0.23 [0.07-0.79]	p=0.057 HR 0.42 [0.17-1.03]	p=0.02 HR 0.33 [0.13-0.83]
Age	p=0.004 HR 1.043 [1.01-1.07]	p=0.01 HR 1.04 [1.01-1.08]	NS	—	p=0.03 HR 1.04 [1.00-1.07]	p=0.05 HR 1.04 [1.00-1.07]

IS = Induction selection; HR = Hazard Ratio; NS = Not significant (p>0.05); [95% Confidence IS HR = Hazard Ratio; [95% Confidence Interval]

Table 4

Kaplan-Meier 5-year Survival Estimates. Subgroup analysis of Induction Selection (IS) Responders and Non-Responders.

		Surgical Cohort (n=53)	IS Responders (n=10)	IS Non-Responders (n=9)
Overall Survival	5-year	65% [49, 76]	40% [12, 67]	22% [3, 51]
Disease Specific Survival	5-year	75% [59, 86]	60% [25, 83]	28% [4, 60]
Local-Regional Control	5-year	72% [57, 84]	30% [7, 58]	22% [3, 51]

[95% Confidence Interval]