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Outcomes of patients with oropharyngeal squamous cell carcinoma treated with induction chemotherapy followed by concurrent chemoradiation compared with those treated with concurrent chemoradiation

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Abstract

BACKGROUND—Induction chemotherapy (IC) has been associated with decreased risk of distant metastasis in locally advanced head and neck squamous cell carcinoma. However, its role in treatment of oropharyngeal squamous cell carcinoma (OPSCC) is not well established.

PATIENTS AND METHODS—Outcomes of OPSCC patients treated with IC followed by concurrent chemoradiation (CRT) were compared with those treated with CRT alone. The primary

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outcome was overall survival (OS), and the secondary endpoints were time to locoregional and distant recurrence.

RESULTS—From an existing database, 585 patients met the inclusion criteria: 137 received IC+CRT, and 448 received CRT. Most patients were HPV-positive (90.9%). Patients receiving IC were more likely to present with higher T stage, higher N stage, and low neck disease. The 3-year OS rate was significantly lower in patients receiving IC (75.7%) compared with CRT alone (92.9%). In multi-covariate analysis, receipt of IC (adjusted hazard ratio [aHR] 3.4, $p<0.001$), HPV tumor status (aHR 0.36, $p=0.005$), and receipt of concurrent cetuximab (aHR 2.7, $p=0.002$) were independently associated with OS. Risk of distant metastasis was also significantly higher in IC patients (aHR 2.8, $p=0.001$), while HPV-positive tumor status (aHR 0.44, $p=0.032$) and completion of therapy (aHR 0.51, $p=0.034$) were associated with lower risk of distant metastasis. In HPV-positive patients, IC remained associated with distant metastatic progression (aHR 2.6, $p=0.004$) but not OS.

CONCLUSIONS—In contrast to prior studies, IC was independently associated with worse OS and higher risk of distant metastasis in OPSCC patients. Future studies are needed to validate these findings.

Precis:

Use of induction chemotherapy has remained controversial in the treatment of locally advanced head and neck squamous cell carcinoma. In this retrospective analysis of 585 patients with oropharyngeal squamous cell carcinoma showed that, in contrast to prior studies, treatment with induction chemotherapy was independently associated with worse overall survival and higher risk of distant metastasis.

Keywords

Oropharyngeal cancer; Induction chemotherapy; distant metastasis

Introduction

Neoadjuvant or induction chemotherapy (IC) for treatment of locoregionally advanced head and neck squamous cell carcinoma (HNSCC) has been practiced with the goal of improving both progression-free survival (PFS) and overall survival (OS).[1] However, the evidence remains controversial, and many major trials were conducted prior to the rise of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC). Early trials evaluated regimens for treatment, with TPF (docetaxel, platinum, fluorouracil[5FU]) becoming a regimen of choice.[2–4] Additional randomized trials showed no difference in OS or PFS with the addition of induction therapy,[5–7] though some trials were underpowered due to incomplete accrual. Newer trials have demonstrated the feasibility of PCC (paclitaxel, carboplatin, cetuximab) with similar efficacy, particularly for lower risk disease such as small HPV-positive tumors.[8,9] A meta-analysis of clinical trials showed that IC for HNSCC was associated with a lower rate of distant metastasis but did not improve OS or locoregional disease control.[10] Accordingly, other clinical trials in HNSCC did associate IC with a reduction in distant metastases.[11,12]

Additional work has investigated the role of IC for specific patient sub-populations. In laryngeal cancer, response to IC was associated with laryngeal preservation with a trend toward improved disease-specific survival.[13] Within HPV-associated OPSCC, a retrospective review of 88 patients with low neck or N3 disease showed that these high-risk patients had improvement in OS and decreased distant metastasis with the addition of IC.[14] Larger retrospective reviews of OPSCC patients showed no difference in OS between those receiving IC vs chemoradiation (CRT) alone, but these studies did not evaluate control of distant disease.[15–16]

In the most recent National Comprehensive Cancer Network guidelines, IC is presented as an option for the treatment of OPSCC but remains a category 3 recommendation owing to lack of consensus among experts.[17] Furthermore, the 2017 American Society for Radiation Oncology guidelines recommended against routine use of IC for OPSCC.[18] Given the continued controversy, the purpose of this study was to elucidate the impact of IC on OS, locoregional control, and development of distant metastasis in standard-of-care practice. Therefore, we retrospectively reviewed the outcomes of a large cohort of OPSCC patients treated within a multi-specialty group head and neck oncology practice at a single institution.

Methods

Patient cohort and inclusion criteria

Patients treated for OPSCC at The University of Texas MD Anderson Cancer Center (UTMDACC) between June 2015 to March 2019 were prospectively consented and enrolled in a clinical database. All patients underwent evaluation by a multidisciplinary treatment team as well as staging with cross-sectional imaging. Of the 585 patients included, pretreatment work up included positron emission tomography (PET) imaging in 466 patients (79.7%), and the remainder with chest computed tomography. Baseline patient demographics including age, gender, diagnosis, smoking history, American Joint Committee on Cancer Staging (AJCC) 7th edition staging, HPV status, and treatment regimen were collected at the time of enrollment. Protocols for prospective enrollment of patients (Stiefel Oropharynx Cancer Program Database) and review of additional outcomes following treatment (Protocol #2019-1137) were approved by the UTMDACC institutional review board. Additionally, chemotherapeutic regimens for induction and concurrent therapy were reviewed, and baseline pretreatment imaging studies were reviewed to determine presence of low neck disease (defined as level 4 or supraclavicular level 5b nodal disease).

From the prospectively collected database, 1459 patients were available for review (Figure 1). Patients were included if they received treatment for primary OPSCC at UTMDACC with curative intent (excluding M1 disease) and had known HPV tumor status (by HPV in situ hybridization and/or p-16 immunohistochemistry) and at least one follow-up evaluation showing no evidence of disease at completion of therapy. Patients with persistent disease (n =11) were excluded. Patients with definitive CRT-based treatment with or without IC were included. Whether a patient completed intended chemotherapy without interruption was available for a subset of patients. Reasons for incomplete treatment were evaluated from medical chart abstraction, and toxicities were reviewed in the subset of patients who were

unable to complete treatment. Radiation treatment was provided by clinician preference. Of patients with available radiation treatment details (n=444), a majority of patients were treated with volumetric modulated arc therapy (VMAT, 67.1%), with remaining patients receiving intensity-modulated radiation therapy (IMRT, 14.2%), intensity-modulated proton therapy (IMPT, 16.4%) and 2.2% receiving 3D conformal radiation therapy (3D CRT). Length of radiation therapy (RT), within or beyond 8 weeks,[19] and total treatment dose were available for a subset of patients and reported accordingly.

Statistical analysis

The primary outcome was OS, and secondary outcomes were time to progression, both locoregional and distant. Data was analyzed using Stata, version 14.1 (Stata Corp, LLC, College Station, TX). Differences in means were evaluated by two-way Student *t* test, and differences in median were evaluated by Wilcoxon rank-sum test. Median follow-up was compared between groups of surviving patients. Categorical variables were compared using chi-squared or Fisher exact test. Survival was analyzed using Kaplan-Meier survival curves, with log-rank testing. Cox proportional hazards model was used for univariate and multivariate survival analyses. Additional subgroup analysis was performed for patients with high-risk disease (with at least one of the following risk factors: T4, N2c-N3, positive low nodes, or HPV-negative status) and for HPV-positive patients with similar methods as above.

Matched cohort analysis was performed on approximately half of the patient cohort. A subset of 124 patients were matched 1:1 between those who receiving IC and CRT. Matching was performed by propensity score matching using MatchIt package version 3.0.2 in R (version 3.5.2). Patients were matched by HPV tumor status, high N stage (N2c-N3), presence of positive low nodes, high T stage (T4), and current tobacco use.

Results

Patient cohort

A total of 585 patients met inclusion criteria for evaluation (Table 1). The median follow-up time for surviving patients was 26.7 months, and the mean age at diagnosis was 60.4 years. A majority of patients were HPV-positive (90.9%) and male (88.6%). About half of patients had a prior history of smoking (49.6%), with 12.3% who were active smokers at the time of diagnosis. A subset of patients had data on whether they completed therapy, and 77.4% (370 of 478) completed intended chemotherapy treatment without interruption.

When patients were compared by HPV tumor status, similar to previously published studies, patients with HPV-positive disease were more frequently male (p=0.002 and less likely to be active smokers (p<0.001). HPV-positive tumors were more likely to present at lower T stage (p=0.014) and present with tonsillar disease (p<0.001). However, nodal staging (p=0.854) and presence of positive low neck disease (p=0.195) did not differ by HPV status (Supplemental Table 1). HPV-negative patients were also more likely to have extended RT with a trend toward lower total radiation dose (p=0.09).

Treatment modality

Most patients received concurrent CRT alone (448, 76.6%). Median follow-up time, age, smoking history and completion of therapy did not differ between treatment groups (Table 1). Patients with HPV-positive disease were more likely to receive CRT (p=0.001). IC patients were more likely to initially present with base of tongue primary tumors, higher T stage, higher N stage, and significantly higher prevalence of low neck disease (46.6% vs 9.1%, p<0.001). The most common reasons cited for treatment with IC were bulky nodal disease (36.5%), bulky primary disease (29.9%), positive bilateral nodes (29.9%) and presence of low neck disease (25.5%). Notably, 10.9% of patients (n=15) were documented to have received IC to avoid treatment delays due to insurance delay or need for dental management prior to RT. As expected, the total length of treatment was longer for IC patients, with mean length of 15.9 weeks compared with 6.3 weeks for CRT patients, but length of RT was similar in both groups (6.3 weeks, p=0.995). IC patients were more likely to have extended RT of greater than 8 weeks (3.9% vs. 1.1%, p=0.048) and receive a lower mean total radiation dose (65.2 vs. 67.9 Gy, p=0.003).

The chemotherapeutic agents administered during the induction and concurrent treatment phases were recorded (Table 1). For patients receiving IC, 20.4% received PCC induction, 39.4% received TPF, and 40.1% received a platinum doublet with a taxane (cisplatin or carboplatin with docetaxel or paclitaxel). Burden of disease including tumor stage, nodal stage and presence of low nodes did not differ by induction regimen (Supplemental Table 2). During the concurrent phase of therapy, the majority of patients received cisplatin (55.1%). Within the IC group, 17 patients had significant response to IC and subsequently received single-modality RT. Because these patients were intended for treatment with IC+CRT, they were included in the analysis. Notably, the IC group was more likely than the CRT only group to receive carboplatin as a concurrent agent (28.8% vs 8.5%, p<0.001) and less likely to receive cisplatin (44.1% vs 57.9%, p=0.008).

For patients who did not complete planned chemotherapy regimen (n=108), reasons for incomplete treatment and toxicities were evaluated (Supplemental Table 3). Patients with incomplete therapy did not differ between IC and CRT group (21.8% vs 22.8%, p=0.82). However, within IC patients, PCC patients were more likely to have incomplete treatment (44% compared to 16.7% TPF and 12.5% platinum doublet patients, p=0.008, Supplemental Table 2). The most common cause of incomplete therapy was a switch of treatment regimen (61%). Patients also experienced treatment breaks (13.9%) and early discontinuation of therapy (27.8%). In addition, 22% of patients with incomplete treatment required hospitalization during treatment. The induction group was more likely to experience treatment breaks (30.8% vs 8.5%, p=0.004), and there was a trend towards higher rates of hospitalization in IC patients (34.6% vs 18.3%, p=0.081). Most common toxicities in patients who did not complete treatment were mucositis (41.7%), renal insufficiency (33.3%), and dysphagia (25.9%). Induction patients were more likely to experience folliculitis (19.2% vs.0%, p=0.001), neutropenia (23.1% vs 8.5%, p=0.047), and CRT patients were more likely to experience renal insufficiency (39% vs. 15.4%, p=0.026). In addition, 8 patients died during receipt of treatment with treatment related mortality with treatment related mortality rates of 1.46% (n=2) in IC and 1.34% (n=6) for the CRT cohort.

Overall survival

The patients treated with IC+CRT had significantly lower OS compared with those treated with CRT alone (Figure 2A, $p<0.001$). This was observed in both HPV-positive ($p=0.024$) and HPV-negative patients ($p<0.001$), as well as in patients with high N stage (N2c-N3, $p<0.001$). In univariate Cox survival analysis, factors associated with OS included current smoking (HR 2.13, $p=0.025$), HPV-positive tumor status (HR 0.276, $p<0.001$), presence of low neck disease (HR 2.42, $p=0.002$), receipt of IC (HR 3.10, $p<0.001$), completion of therapy (HR 0.51, $p=0.028$), and receipt of carboplatin (HR 2.13, $p=0.049$) or Cetuximab (HR 2.00, $p=0.024$) during CRT (vs. cisplatin). On multi-covariate Cox analysis, only HPV tumor status (adjusted hazard ratio [aHR] 0.36, $p=0.002$), receipt of IC (aHR 3.44, $p<0.001$) and receipt of cetuximab (aHR 2.69, $p=0.002$) were significantly associated with OS (Table 2). IC patients were also analyzed based on induction regimen in a separate multivariate Cox survival model, and receipt of PCC (aHR 4.03, $p=0.002$) and TPF (aHR 4.40, $p=<0.001$) were both independently associated with worse OS compared to CRT.

Time to locoregional and distant metastatic progression

IC was associated with shorter time to disease progression on Kaplan-Meier analysis ($p<0.001$, Figure 2B) but not time to locoregional progression ($p=0.294$, Figure 2C). In univariate analysis, only current smoking at diagnosis (HR 2.13, $p=0.048$) and HPV-positive disease (HR 0.432, $p=0.036$) were associated with time to locoregional progression.

In contrast, time to distant metastatic progression was significantly shorter in those receiving IC ($p<0.001$, Figure 2D). Univariate analysis of the full patient cohort also showed that high N stage, low neck disease, active smoking, receipt of carboplatin, and receipt of IC were associated with higher risk of distant progression, while HPV-positive disease, tonsillar primary, and completion of therapy were protective (Table 3). In the adjusted multi-covariate Cox model, only HPV-positive tumor status (aHR 0.444, 95% CI 0.21–0.93, $p=0.032$), completion of therapy (aHR 0.508, 95% CI 0.27–0.95, $p=0.034$), and receipt of IC (aHR 2.82, 95% CI 1.56–5.13, $p=0.001$) were associated with distant progression. Again, IC patients were also analyzed based on induction regimen in a separate multivariate Cox model, and receipt of PCC (aHR 3.67, $p=0.002$) and TPF (aHR 2.63, $p=0.020$) were independently associated with higher risk of distant progression compared to CRT.

Subgroup analysis

When analysis was limited only to HPV-positive patients (n=532), IC was not associated with OS in the multi-covariate Cox model. Significant predictors of OS were low neck disease (aHR 3.62, $p=0.001$), completion of therapy (aHR 0.433, $p=0.026$) and receipt of cetuximab for CRT (aHR 3.92, $p<0.001$). However, analysis of time to distant disease progression showed that IC (aHR 2.64, $p=0.004$) and completion of therapy (aHR 0.470, $p=0.034$) were significant predictors of increased risk of distant progression in HPV-positive patients. No other risk factors remained significant.

Additional subgroup analysis was performed based on risk of distant metastasis. Patients were categorized as either low risk (T0-T3, N0-N2b, without low node disease, and HPV positive) or high risk (with at least one high-risk feature: T4 stage, N2c-N3 nodal stage,

low neck disease, or HPV-negative tumor status). Within the low-risk group (Supplemental Figure 1), receipt of IC was not associated with OS (p=0.774), locoregional recurrence (p=0.823), or distant metastasis (p=0.949). In contrast, within the high-risk group, IC was associated with shorter OS (p<0.001) and higher risk of distant metastasis (p<0.001) but not associated with locoregional progression (p=0.125). Among patients who received IC, reasons for IC, including bulky primary disease or bulky nodal disease, were not associated with differences in OS or distant progression.

Matched analysis

To further control for variations in the IC and CRT patient groups, a matched analysis was performed on approximately half of the original cohort. A subset of 124 patients receiving IC and 124 receiving only CDT were matched 1:1 by smoking history, HPV tumor status, T stage, N stage, and presence of low nodal disease (Supplemental Table 2). Within the matched cohort, OS was associated with presence of low neck disease (aHR 2.28, p=0.037), receipt of IC (aHR 4.41, p=0.003) and HPV-positive tumor status (aHR 0.158, p<0.001). High tumor stage (T4) showed a trend toward association with worse OS (aHR 2.07, p=0.061). Time to distant metastatic progression was independently associated with receipt of IC (aHR 3.54, p=0.007) and HPV-positive tumor status (aHR 0.321, p=0.010), with high N stage (N2c-N3) showing a trend toward significance (aHR 2.01, p=0.084).

Discussion

In contrast to previous studies,[4,10,11] OPSCC patients in this study who received IC had worse overall outcomes, with shorter OS and greater risk of distant metastatic progression. Given the non-randomized nature of this cohort, there are clear limitations and potential for selection bias. Patients with high-risk disease (i.e., HPV-negative disease, higher T stage, higher N stage, or with low neck disease) at diagnosis were appropriately more likely to receive treatment with IC.

However, after adjusting for these risk factors, IC remained a significant independent negative prognostic risk factor for both overall survival and development of distant metastasis. Even when patients were stratified by high-risk categories and in matched analysis, receipt of IC remained independently associated with worse OS and PFS in multi-covariate models. This is in contrast to prior studies, such as a matched retrospective review of 88 p-16 positive patients by Bhattasali et al. showing that IC was associated with decreased distant metastases,[14] or other studies showing no differences in OS.[16]

Treatment with IC was associated with use of non-cisplatin concurrent chemotherapy such as carboplatin, which could contribute to poorer outcomes in the IC group. These practices may be reflective of adoption of the TAX 324 regimen, in which IC was followed by concurrent therapy with carboplatin[2,3] to reduce overall toxicity.[20] Within this study, while patients receiving IC were more likely to receive carboplatin, in multi-covariate analysis only receipt of cetuximab was associated with shorter OS, consistent with prior literature.[21,22] IC patients were in actuality less likely to receive cetuximab (11.0% vs 30.6%). In this cohort, various induction regimens (TPF, PCC, and platinum doublets) were used, while most previously reported trials that demonstrated benefit from IC primarily

studied TPF induction regimens.[6,7,11] PCC regimens have mainly been studied in OPSCC populations,[8] but intermediate- and high-risk groups may fare worse with PCC compared with TPF (2-year PFS 67% vs 89%).[9] When IC patients were evaluated by induction regimen, the negative prognosis of induction was primarily driven by patients receiving PCC or TPF rather than platinum doublets. Notably, patients receiving PCC were more likely to experience toxicity resulting in incomplete treatment (Supplemental Table 2). However, patient tumor or nodal stage did not differ by induction regimen, but factors not captured by clinical stage may contribute to selection of higher risk patients to more aggressive induction regimens.

Inability to complete intended chemotherapy is another potential contributor to poorer outcomes of IC patients.[23] In a phase II randomized trial, Huang et al. found that IC patients had worse PFS and higher rates of distant metastases, similar to our study results.[24] Further analysis showed that IC patients were less likely to complete intended concurrent cisplatin dosing (<150 mg/m^2; 46.8% vs. 16.2%), and the negative impact of IC was no longer significant when controlled for cisplatin dosing. Similarly, Hitt et al. found that IC was only associated with improved PFS in a secondary analysis limited to patients who completed treatment.[7] Indeed, within that study, completion of therapy was associated with lower risk of distant metastasis. However, in our cohort, there were no differences between rates of treatment completion between the IC+CRT and CRT groups (78.2% vs. 77.2%). IC patients experiences higher rates of treatment breaks and a trend towards higher rates of hospitalization that may contribute to a greater impact on incomplete treatment. However, when controlling for completion of therapy, receipt of IC remained a significant independent negative risk factor.

Treatment with IC may also impact tolerance of definitive RT, potentially resulting in poorer outcomes.[19,24,25] Delays in total RT time of greater than 8 weeks are associated with decreased survival.[19] In our cohort, IC patients were more likely to experience such a delay. However, only 1.7% of the patient cohort experienced RT delay, consistent with prior literature showing that patients with oropharyngeal tumors, compared with other subsites, are more likely to complete intended treatment after IC;[26] and extended RT was not independently associated with survival or distant progression in this study. Patients receiving IC did show a lower mean total dose of definitive radiation, possibly due to inability of some patients to complete RT. However, patients in this study cohort had very high locoregional control rates that were comparable to other studies[27] (91.9% and 88.1% at 3 years for CRT and IC patients, respectively; Figure 2) demonstrating adequate local therapy.

In contrast to many of the trials with IC that include all non-nasopharynx head and neck cancer subsites, this study focused specifically on outcomes in OPSCC, where a majority (90%) were HPV-positive. In the TAX 324 trial, there was significant treatment benefit of TPF vs PF in patients with cancer of the oropharynx,[3] though the study was not powered to evaluate this effect by HPV tumor status.[28] When comparing IC+CRT to CRT, Ghi et al. found that IC was only associated with improved OS and PFS in patients with non-oropharyngeal disease.[11] Other retrospective studies of OPSCC have found either no difference in OS between IC+CRT[15] vs CRT or a trend toward improved survival for patients receiving CRT.[16]

These data in the context of the current study suggest that IC may not provide benefit for OPSCC patients, contributing to worse outcomes in these patients. Due to the retrospective nature of this study, we did not take the further step to recommend against use of IC for OPSCC. However, given our study findings, alternative methods of induction therapy warrant investigation. Though outside the scope of this current study, the role of IC prior to surgical therapy in OPSCC may warrant further study as high rates of pathologic response have been demonstrated.[29] Furthermore, we would encourage design and implementation of clinical trials that incorporate novel therapeutics including checkpoint inhibitors in the neoadjuvant setting that have shown efficacy in oropharyngeal cancer.[30]

Given the non-randomized nature of this study with inherent selection biases, there are significant limitations to the interpretation of the presented results. Appropriately, in clinical practice, clinicians are likely to select patients perceived to be at higher risk of distant metastasis for IC. While several patient factors were controlled for in this study, these factors still incompletely capture the full clinical picture that may push clinicians to select IC prior to CRT and may also contribute to poor prognosis. However, specific reasons for IC, including bulky disease, were not associated with worse outcomes. Additional details on response to IC, details of radiation dosing (such as bilateral vs unilateral fields and adaptive planning) or reasons for selecting heterogeneous chemotherapy regimens were not available to be included in this analysis and could not be fully controlled for outside the context of a prospective randomized clinical trial.

Conclusions

This study represents one of the largest cohorts of OPSCC patients comparing those treated with IC+CRT and CRT alone. In this OPSCC patient cohort, treatment with IC+CRT compared to CRT was independently associated with shorter OS and higher risk of distant metastatic progression, particularly in high-risk patients. Further randomized studies are needed to validate the inferior outcomes associated with IC in OPSCC patients observed in this study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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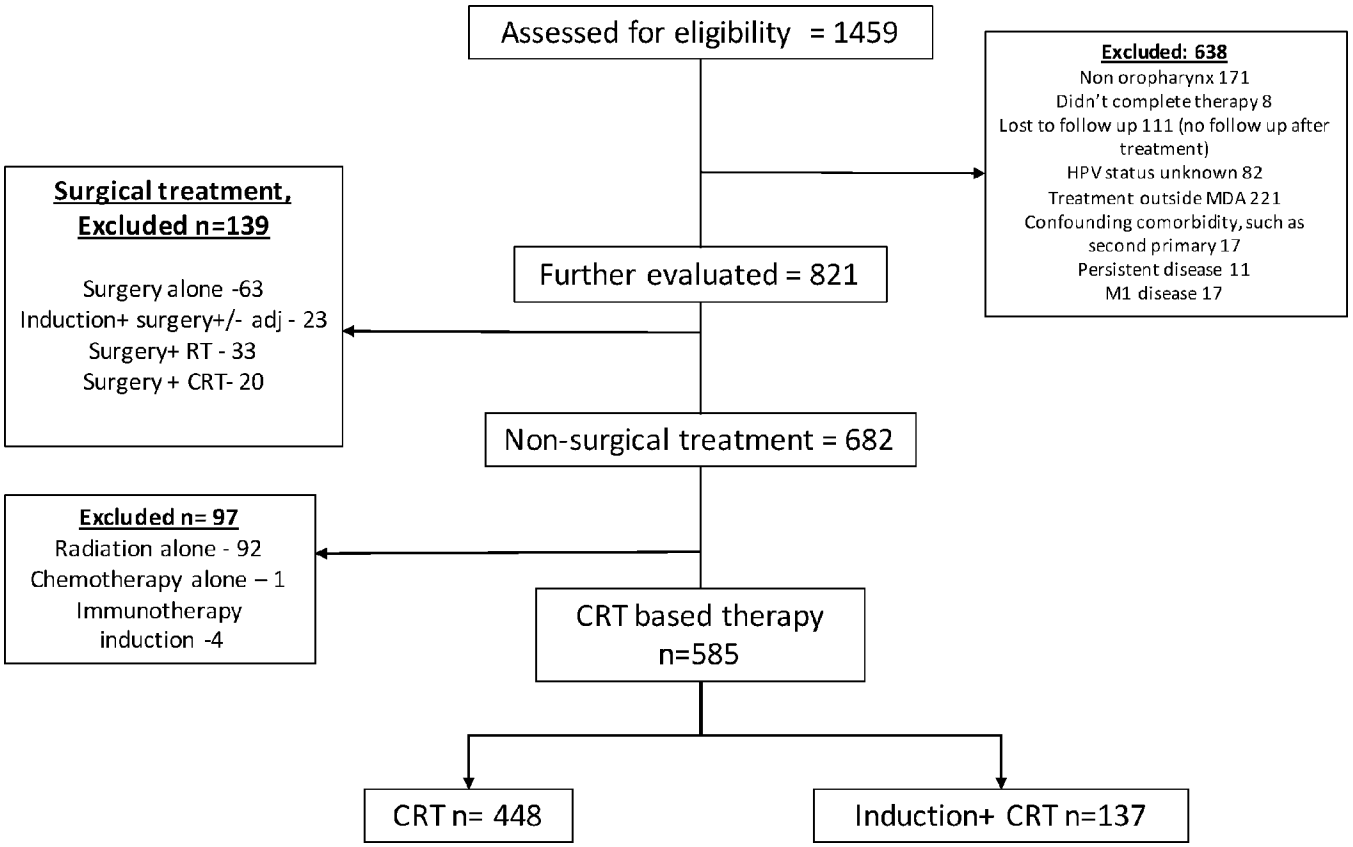

Figure 1.
Consort diagram summarizing patient cohort

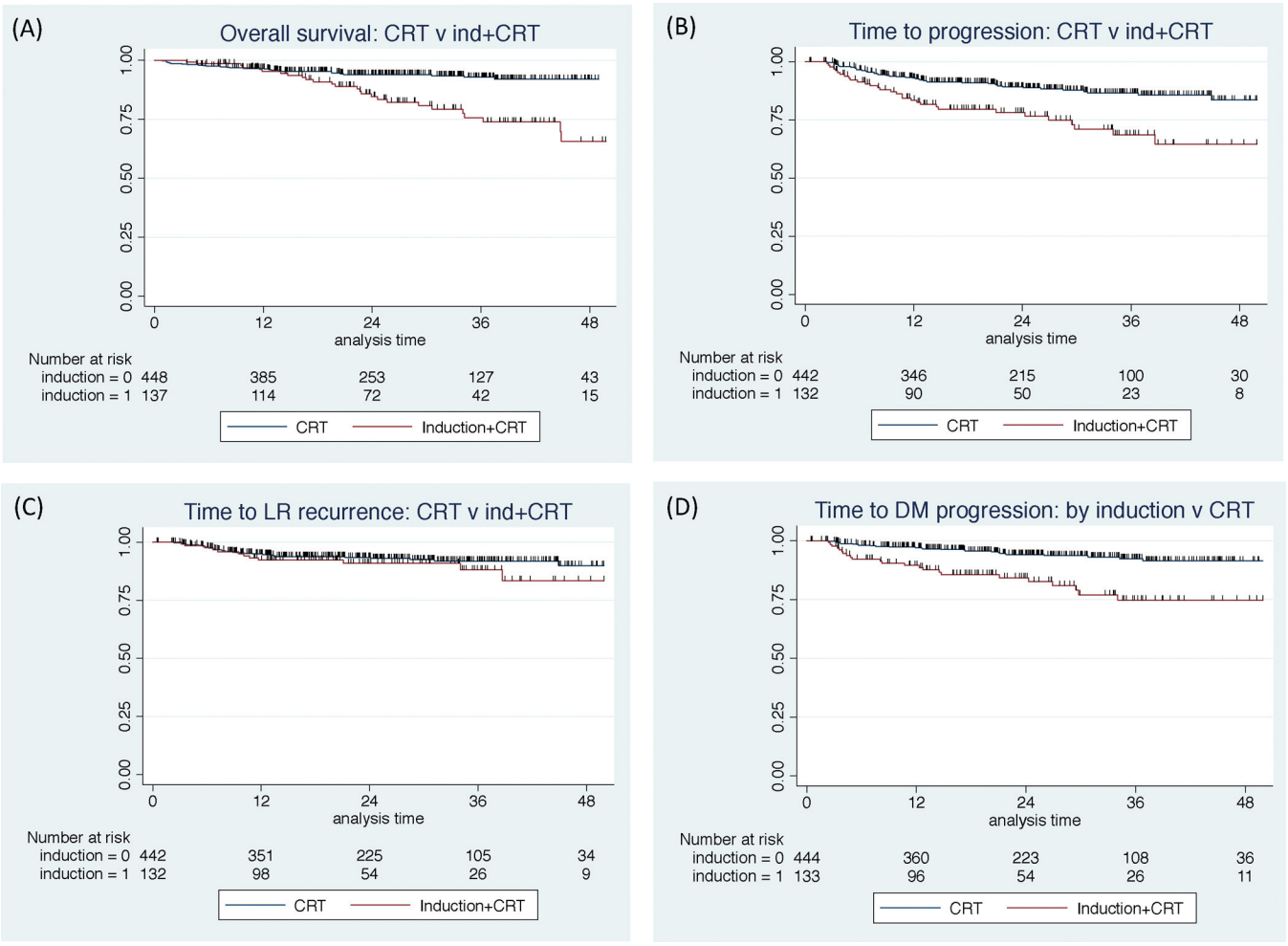

Figure 2.

A) Overall survival (OS; $p<0.001$): 2-year OS chemoradiation (CRT) 94.0% (95% CI: 91.2–96.0), induction 84.5% (76.4–90.2); 3-year OS CRT 92.9% (89.4–95.2), induction 75.7% (65.0–83.5)

B) Time to progression (TTP; $p<0.001$): 2-year TTP CRT 89.2% (85.6–92.0), induction 78.2% (69.3–84.8); 3-year TTP CRT 86.6% (82.2–90.0), induction 68.7% (56.9–77.8)

C) Time to locoregional (LRP progression (p=0.294): 2-year TTP, LR CRT 93.4% (90.5–95.5), induction 90.9% (83.4–95.1); 3-year TTP, LR CRT 91.9% (88.3–94.4), induction 88.1% (77.9–93.8)

D) Time to distant metastatic (DM) progression ($p<0.001$): 2-year TTP, DM CRT 94.2% (91.2–96.2), induction 84.3% (76.0–89.9); 3-year TTP, DM CRT 92.4% (88.5–95.0), induction 74.7% (63.0–83.2)

Table 1.

Patient characteristics by treatment modality

Characteristic	All patients (n=585)	IC + CRT (n=137)	CRT (n=448)	*p*
Median follow-up of surviving patients, mo.	26.7	26.9	26.6	0.858
Age (mean), y	60.4	60.3	60.4	0.909
Sex (male)	518 (88.6%)	126 (92.0%)	392 (87.5%)	0.15
Smoking history				0.429
Current	72 (12.3%)	22 (16.1%)	50 (11.2%)	
Former	290 (49.6%)	67 (48.9%)	223 (49.8%)	
Never	222 (37.9%)	48 (35.0%)	174 (38.8%)	
HPV status (positive)	532 (90.9%)	115 (83.9%)	417 (93.1%)	**0.001**
Primary site (n=580)				**0.003**
Tonsil	260 (44.8%)	43 (32.1%)	217 (48.7%)	
BOT	282 (48.6%)	81 (60.5%)	201 (45.1%)	
Other	28 (6.6%)	10 (7.5%)	28 (6.3%)	
T Stage (AJCC 7)				**<0.001**
T0	25 (4.3%)	9 (6.6%)	16 (3.6%)	
T1	148 (25.3%)	15 (10.9%)	133 (29.7%)	
T2	212 (36.2%)	38 (27.7%)	174 (38.8%)	
T3	106 (18.1%)	26 (19.0%)	80 (17.9%)	
T4a	78 (13.3%)	38 (27.7%)	40 (8.9%)	
T4b	16 (2.7%)	11 (8.0%)	5 (1.1%)	
N Stage (AJCC 7)				**<0.001**
N0	47 (8.0%)	3 (2.2%)	44 (9.8%)	
N1	37 (6.3%)	4 (2.9%)	33 (7.4%)	
N2a	27 (4.6%)	1 (0.7%)	26 (5.8%)	
N2b	338 (57.8%)	57 (41.6%)	281 (62.7%)	
N2c	122 (20.8%)	60 (43.8%)	62 (13.8%)	
N3	14 (2.4%)	12 (8.8%)	2 (0.5%)	
Low neck disease (level 4 or supraclavicular 5b)				**<0.001**
Absent	478 (82.0%)	73 (53.3%)	405 (90.8%)	
Present	105 (18.0%)	64 (46.7%)	41 (9.2%)	
Completed therapy (n=478)	370 (77.4%)	93 (78.2%)	277 (77.2%)	0.822
IC regimen		PCC 28 (20.4%) TPF 54 (39.4%) Plat doublet 55 (40.1%)		
Concurrent regimen				**<0.001**
Carboplatin	78 (13.4%)	38 (27.9%)	40 (8.9%)	
Cetuximab	152 (26.0%)	15 (11.0%)	137 (30.6%)	
Cisplatin	322 (55.1%)	62 (45.6%)	260 (58.0%)	
Other	15 (2.6%)	4 (2.9%)	11 (2.5%)	
None	17 (2.9%)	17 (12.5%)		
Length of treatment Mean (range)	8.52 (2.3–36.3) weeks	15.9 (7.7–36.3) weeks	6.3 (2.3–10.6) weeks	**<0.001**

Characteristic	All patients (n=585)	IC + CRT (n=137)	CRT (n=448)	*p*
Length of radiation treatment (n=576)	6.30 (2–11.6) weeks	6.3 (2–11.6) weeks	6.3 (1.9–10.6) weeks	**0.995**
Extended RT (> 8 weeks (n=576)	10 (1.7%)	5 (3.9%)	5 (1.1%)	**0.048**
Total radiation dose (n=433)	67.4 (20.4–84) Gy	65.2 (20.4–77.9) Gy	67.9 (20.9–84) Gy	**0.003**

Abbreviations: CRT, concurrent chemoradiation; IC, induction chemotherapy.

Table 2.

Overall survival, univariate and multi-covariate Cox proportional hazards model

Variable	Univariate			Multi-covariate		
	HR	***p***	**95% CI**	**HR**	***p***	**95% CI**
Age	1.025	0.111	0.994–1.06	-		
Male	1.902	0.216	0.686–5.27	-		
Current smoker	2.130	**0.025**	1.10–4.13	-		
HPV positive	0.266	**<0.001**	0.147–0.482	0.357	**0.002**	0.188–0.678
Tonsil v BOT/other	0.796	0.413	0.462–1.37	-		
T4 v T0-T3	1.738	0.075	0.946–3.19	-		
N2c-N3 v N0-N2b	1.697	0.063	0.972–2.96	-		
Low neck disease	2.416	**0.002**	1.37–4.26	-		
Completed chemotherapy	0.509	**0.028**	0.279–0.931	-		
Extended RT (>8 w)	1.944	0.358	0.471–8.02	-		
Concurrent w cisplatin	*Ref*			*Ref*		
Carboplatin	2.129	**0.049**	1.002–4.52	1.454	0.342	0.672–3.14
Cetuximab	2.004	**0.024**	1.09–3.67	2.690	**0.002**	1.44–5.01
Other/none	0.403	0.375	0.054–2.99	0.269	0.201	0.036–2.02
Induction *	3.098	**<0.001**	1.83–5.26	3.44 *	**<0.001**	1.91–6.21
Induction regimen: *						
CRT	*Ref*			*Ref* *		
Induction: PCC	3.306	**0.005**	1.44–7.59	4.037	**0.002**	1.66–9.79
Induction: TPF	3.722	**<0.001**	1.95–7.10	4.403	**<0.001**	2.19–8.85
Induction: plat doublet	2.123	0.095	0.877–5.14	1.815	0.275	0.622–5.29

* Induction and induction regimen are not able to be included in the same multivariate model; adjusted hazard ratios are shown from separate models

Abbreviations: BOT: base of tongue; RT: radiation therapy; PCC: paclitaxel, carboplatin, cetuximab; TPF: docetaxel, platinum, fluorouracil; plat doublet: platinum doublet

Table 3.

Time to distant metastatic progression, univariate and multi-covariate Cox proportional hazards model

Variable	Univariate model			Multi-covariate model		
	HR	***p***	**95% conf**	**HR**	***p***	**95% CI**
Age	0.999	0.932	0.967–1.031	-		
Male	1.216	0.680	0.481–3.07	-		
Current smoker	2.301	**0.019**	1.144–4.63	-		
HPV positive	0.298	**<0.001**	0.152–0.584	0.444	**0.032**	0.212–0.931
Tonsil v BOT/other	0.451	**0.014**	0.238–0.852	-		
T4 v T1-T3	0.937	0.874	0.420–2.09	-		
N2c-N3 v N0-N2b	2.213	**0.007**	1.241–3.95	-		
Low neck	2.612	**0.002**	1.432–4.76	-		
Completed chemotherapy	0.489	**0.024**	0.262–0.912	0.508	**0.034**	0.272–0.949
Extended RT (>8wks)	1.035	0.973	0.142–7.52	-		
Concurrent w cisplatin	*Ref*			-		
Carboplatin	2.123	**0.039**	1.04–4.34			
Cetuximab	0.868	0.706	0.415–1.81			
Other	0.752	0.699	0.178–3.18			
Induction *	3.445	**<0.001**	1.955–6.07	2.82 *	**0.001**	1.56–5.13
Induction regimen: *						
CRT	*Ref*			*Ref**		
Induction: PCC	4.985	**<0.001**	2.25–11.06	3.673	**0.002**	1.58–8.53
Induction: TPF	3.621	**0.001**	1.74–7.54	2.626	**0.020**	1.17–5.91
Induction: plat doublet	2.157	0.118	0.823–5.65	2.299	0.094	0.867–6.10

* Induction and induction regimen are not able to be included in the same multivariate model; adjusted hazard ratios are shown from separate models

Abbreviations: BOT: base of tongue; RT: radiation therapy, tx: treatment; PCC: paclitaxel, carboplatin, cetuximab; TPF: docetaxel, platinum, fluorouracil; plat doublet: platinum doublet