A

pproximately 14,400 new cases of squamous cell carcinoma (SCC) of the pharynx are diagnosed each year, with approximately 3400 new cases of hypopharyngeal (HP) SCC diagnosed annually. Reported 5-year survival rates for stage III and IV HP SCC are 36% and 24%, respectively. The relatively poor prognosis and frequently advanced stage at diagnosis are commonly attributed to the relative lack of symptoms from early-stage disease in this region. In addition, these tumors are locally aggressive, with a propensity for submucosal spread, invasion into adjacent structures, and metastasis due to abundant lymphatic drainage.

There is no consensus whether primary surgery followed by either adjuvant radiotherapy (RT) or adjuvant chemoradiation (CRT) or definitive CRT should be the standard primary treatment approach to advanced-stage hypopharyngeal squamous cell carcinoma (HP SCC).

OBJECTIVES To determine survival outcomes for patients with advanced-stage HP SCC treated at a single institution with either primary surgery plus RT or CRT or definitive CRT.

EVIDENCE AND DATA ACQUISITION We conducted a retrospective analysis of prospectively collected medical records in an institutional database for patients with HP SCC newly diagnosed between January 1999 and April 2013. Overall survival (OS) and recurrence-free survival (RFS) were calculated and compared between treatment groups using the Kaplan-Meier method, with multivariate Cox regression analysis used to control for demographic and clinicopathologic features.

RESULTS We identified 166 consecutively treated patients, 90 of whom did not meet study criteria. Of the 76 included patients, 48 (63%) had undergone definitive CRT, and 28 (37%) had undergone primary surgery with adjuvant RT or CRT. The groups were well balanced by age, smoking history, and alcohol use. Five-year OS and RFS for patients treated surgically were 66.3% and 53.6%, respectively; for patients treated with definitive CRT, OS and RFS were 41.3% and 34.5%, respectively. Multivariate Cox regression analysis showed that surgical management was associated with clinically improved OS (hazard ratio [HR], 4.78; 95% CI, 0.91-25.03; P = .06) and RFS (HR, 2.97; 95% CI, 0.76-11.53; P = .12), although the difference was not statistically significant.

CONCLUSIONS AND RELEVANCE Patients with advanced-stage HP SCC treated surgically with adjuvant RT or CRT showed a trend toward clinically improved OS and RFS compared with patients treated with definitive CRT. However, the difference was not statistically significant, and further investigation with larger controlled trials using modern approaches should be undertaken to optimize the initial management of advanced-stage HP SCC.

 IMPORTANCE There is no consensus whether primary surgery followed by either adjuvant radiotherapy (RT) or adjuvant chemoradiation (CRT) or definitive CRT should be the standard primary treatment approach to advanced-stage hypopharyngeal squamous cell carcinoma (HP SCC).
limited data are available for treatment results within the last decade, since integration of cisplatin-based chemotherapy and use of modern RT approaches have become more widespread. Many studies have also included early-stage disease or laryngeal cancer, which has a markedly better prognosis and should be considered a distinct clinical entity. The aim of the present study was to evaluate and compare more recent outcomes for patients with locally advanced HP SCC treated with primary surgery plus adjuvant RT or CRT (surgery group) vs definitive CRT with salvage surgery as needed (CRT group) at a single tertiary care center.

Methods
Selection of Patients
All investigations were approved by the institutional review board of the University of California, Davis (UCD), waiving written informed consent. Patient data were collected by retrospective review of prospectively collected data in the UCD database of 166 patients with advanced HP SCC cancer treated at UCD from January 1999 through April 2013. Patients undergoing surgery or CRT with curative intent for advanced-stage HP SCC were included. Tumor staging was based on the TNM classification system, American Joint Committee on Cancer.1 Exclusion criteria were a second primary lesion, early-stage disease (stage I or II), metastases at presentation, treatment with palliative intent, or loss to follow-up within 3 months. Patient demographic characteristics, including age, sex, smoking status, alcohol intake, tumor stage, Karnofsky performance status (KPS), and histopathologic results for surgical patients were recorded.

Surgery
 Patients treated with primary surgery underwent total laryngectomy and partial pharyngectomy with or without regional or free-flap tissue transfer. For patients undergoing surgical intervention or salvage surgery (when needed) with neck dissection, 37 patients underwent bilateral modified radical neck dissection (MRND), while 18 underwent unilateral MRND. Bilateral vs unilateral dissection was performed at the discretion of the primary surgeon based on clinical impression.

Radiation and Chemotherapy
For patients who underwent primary surgery, adjuvant RT was administered at a median dose of 65 Gy (range, 28-72 Gy). Twenty-one patients (25%) received chemotherapy concurrently with RT, typically for nodal extracapsular extension (n = 8) or positive surgical margins where re-resection was not achievable (n = 5). Patients treated with definitive CRT received a median dose of 70 Gy (range, 28-72 Gy) in 1.8- to 2.12-Gy fractions to the primary tumor and involved nodes. Thirty patients were treated using conventional opposed lateral fields with a shrinking-field technique. Twenty-one patients were treated with intensity-modulated radiotherapy using a simultaneous integrated boost approach. Choice of chemotherapy administered concurrently with the RT was at the discretion of the treating medical oncologist and included cisplatin (n = 17), carboplatin or paclitaxel (n = 6), and cetuximab (n = 6). Details of chemotherapy agents delivered were unavailable for 12 patients.

Results
Seventy-six patients met the inclusion criteria, with a mean age of 63.6 years (range, 27-84 years; median age, 63.3 years). Twenty-eight patients underwent primary surgery (37%) followed by CRT (n = 6) or RT (n = 22), and 48 patients (63%) were treated with definitive CRT with or without salvage surgery. Pathologic characteristics of surgically treated patients are summarized in Table 1. Seven patients (9%) with extensive tumors involving both the larynx and hypopharynx for whom epicenter could not be definitively identified were included. There was no significant difference between the 2 groups for age, sex, TNM stage, smoking status, alcohol use, or KPS (P > .05 for all comparisons; see Table 1). The mean follow-up time was 30 months (range, 6-120 months; median follow-up, 17 months).

By univariate analysis, the 5-year Kaplan-Meier estimate of OS was 66.3% in the surgical group, and 41.3% in the CRT group (P = .09) (Figure). Corresponding 5-year estimates of RFS for the surgical and CRT cohorts were 53.6% vs 34.5% (P = .18) (Figure). Multivariate analysis was performed to identify other independent predictors of OS and to assess potential confounding variables (detailed results in Table 2). Increasing KPS predicted for improved OS (P = .01) and RFS (P = .01). Age, sex, smoking status, alcohol use, and cancer stage were not predictive of any survival outcomes. On multivariate analysis, treatment with up-front surgical resection showed clinically improved RFS (P = .12) and OS (P = .06) compared with CRT, but the difference was not statistically significant.

Discussion
Despite advancements in surgical intervention and CRT for head and neck cancer, the prognosis for advanced-stage HP SCC remains poor. While HP SCC represents only 3% to 7% of head and neck cancers,15,16 approximately 75% to 80% are advanced (stage III or IV) at diagnosis,8,17 leading to significant therapeutic challenges. Many authors endorse organ preservation, with salvage surgery reserved for local relapse, while other studies suggest that primary surgery may provide superior results.16,18 There remains no firm consensus on optimal initial management of these patients.

Age, sex, tumor stage, and KPS have all been established as prognostic factors affecting survival in patients with HP SCC.3-5,7-9,10,19,20 The patient demographics identified in the present study are similar to those in other published reports.3,9,15
Table 1. Characteristics of Patients With Advanced-Stage Hypopharyngeal SCC Included in This Study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n = 76)</th>
<th>Primary Surgery Plus CRT or RT (n = 28)</th>
<th>CRT With or Without SS (n = 48)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>63.6 (8.7)</td>
<td>65.3 (8.3)</td>
<td>62.9 (8.9)</td>
<td>.24</td>
</tr>
<tr>
<td>Male sex</td>
<td>59 (77)</td>
<td>21 (76)</td>
<td>37 (78)</td>
<td>.55</td>
</tr>
<tr>
<td>TNM Stage, III vs IV</td>
<td>14 (18)</td>
<td>5 (18)</td>
<td>9 (19)</td>
<td>.38</td>
</tr>
<tr>
<td>T classification</td>
<td></td>
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<tr>
<td>T1</td>
<td>2 (3)</td>
<td>1 (4)</td>
<td>1 (2)</td>
<td></td>
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<tr>
<td>T2</td>
<td>16 (21)</td>
<td>8 (29)</td>
<td>8 (17)</td>
<td>.53</td>
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<tr>
<td>T3</td>
<td>22 (29)</td>
<td>6 (21)</td>
<td>16 (33)</td>
<td></td>
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<td>T4</td>
<td>36 (47)</td>
<td>13 (46)</td>
<td>23 (48)</td>
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<td>N classification</td>
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<tr>
<td>N0</td>
<td>15 (20)</td>
<td>6 (21)</td>
<td>9 (19)</td>
<td>.78</td>
</tr>
<tr>
<td>N1</td>
<td>15 (20)</td>
<td>5 (18)</td>
<td>10 (21)</td>
<td></td>
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<tr>
<td>N2</td>
<td>36 (47)</td>
<td>12 (43)</td>
<td>24 (50)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>10 (13)</td>
<td>5 (18)</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>Tobacco smokersc</td>
<td>68 (90)</td>
<td>24 (85)</td>
<td>45 (94)</td>
<td>.24</td>
</tr>
<tr>
<td>Pack-years, mean (SD)</td>
<td>41.2 (25.2)</td>
<td>38.1 (24.5)</td>
<td>44.1 (25.9)</td>
<td>.37</td>
</tr>
<tr>
<td>Alcohol usec</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Occasional or nondrinker</td>
<td>17 (22)</td>
<td>6 (21)</td>
<td>10 (22)</td>
<td></td>
</tr>
<tr>
<td>Moderate use</td>
<td>27 (35)</td>
<td>11 (38)</td>
<td>15 (31)</td>
<td>.78</td>
</tr>
<tr>
<td>Heavy use</td>
<td>33 (43)</td>
<td>11 (38)</td>
<td>23 (47)</td>
<td></td>
</tr>
<tr>
<td>KPS, mean (SD)</td>
<td>79.4 (16.0)</td>
<td>78.9 (19.1)</td>
<td>79.5 (12.7)</td>
<td>.91</td>
</tr>
</tbody>
</table>

Abbreviations: CRT, chemoradiotherapy; KPS, Karnofsky performance scale (0-100); RT, radiation therapy; SCC, squamous cell carcinoma; SS, salvage surgery.

a Unless otherwise indicated, data are number (percentage) of patients.

b P value comparing patients who received primary surgery followed by RT or CRT vs patients who were treated with definitive CRT with or without SS.

c Alcohol use and smoking history was not available for 18 patients.

The substantial potential for patient selection bias for surgical and nonsurgical therapy mandates rigorous control for these and other potential confounding factors with multivariate analysis, although the potential for uncontrolled confounding remains.

In the present study, multivariate analysis identified clinically improved RFS and OS with surgical management over CRS alone, but the difference did not reach statistical significance.

Data from prospective trials evaluating HP SCC show conflicting results. Beauvillain et al report long-term outcomes from a prospective trial randomizing patients with advanced-stage HP SCC to induction cisplatin or fluorouracil followed by either surgical resection with adjuvant RT or definitive RT. The authors identified improved 5-year OS with surgery (37% vs 19%; P = .04), with dramatic differences in 5-year local control (63% vs 39%; P < .01). A large European cooperative group trial randomized 194 patients with stage II to IV HP SCC to either surgery with postoperative RT or induction chemotherapy followed by definitive RT for complete responders and surgery for non–complete responders. No concurrent chemotherapy was used with the RT regimens. Local control was simi-
lar between the approaches, and distant control was improved in the induction chemotherapy arm. Survival at 3 years favored the induction chemotherapy, with no difference identified at 5 years. For both trials, the use of induction rather than concurrent chemotheraphy may have influenced outcomes compared with current practice.

Other institutional and population-based studies have similarly reported conflicting outcomes. Hall et al conducted a population-based comparison between surgery with adjuvant RT and definitive RT for 595 patients with advanced HP SCC and identified no OS difference between the 2 groups. Notably, the last year of treatment for included patients was 1999, which was prior to the era in which concurrent chemotherapy was routinely added to definitive RT. Lajtman and Maneater11 and Zelefsky et al similarly report no difference in OS or RFS for patients with advanced HP SCC treated with surgery and adjuvant RT or definitive CRT. Similarly, Lee et al evaluated 74 patients with locally advanced HP SCC and found no significant differences in OS or disease-free survival between surgical and nonsurgical therapy. They did, however, determine that the patients who underwent surgery followed by RT had improved local control compared with those treated with CRT.

By contrast, Axon et al report a statistically significant difference in 5-year OS between surgery (45%) and RT (23%). More recently, Tsou and colleagues evaluated 202 patients with HP SCC and similarly identified a significant OS benefit to primary surgery. They also identified improved local control with surgical management. Both studies, however, included patients with stage I and II disease, which may have biased the results in favor of surgical management.

In the aggregate, both the present study and other published series suggest that surgical management may clinically improve OS and RFS compared with definitive CRT. The 5-year OS for both approaches in the present study compares quite favorably to historical controls, at 66.3% and 41.3%, respectively. Overall survival includes the burden of uncontrolled cancer in addition to comorbid disease related to older age, heavier tobacco and alcohol use, the effects of poor nutrition secondary to dysphagia, and other adverse and toxic events associated with both surgery and CRT. The toxic effects of head and neck cancer treatment have also been associated with decreased survival. Individual patient preferences and quality-of-life determinants remain critical components of selecting a treatment approach. The potential psychosocial and functional morbidity of total laryngectomy is extensively documented, but organ-preservation protocols may also lead to severe long-term functional decrements and decreased quality of life.

We acknowledge that the survival percentages reported here are higher than those reported in most cases in the literature. Although many studies report a 30% to 40% survival rate for advanced-stage HP cancer, there have been reports of survival as high as 56% to 60% for patients receiving concurrent chemotheraphy with RT or multimodality treatment (surgery plus RT or CRT). The studies showing higher survival rates tend to be larger. The present study is among the largest published to evaluate only advanced-stage HP SCC, and the inclusion of patients treated recently with concurrent chemotherapy and RT regimens provides valuable data on modern treatment outcomes. Recent data reviewing concurrent CRT for cancer of the pyriform sinus have indicated survival rates as high as 56%, while patients receiving multimodality treatment may have local control as high as 97%.

The present study also has a number of limitations. Both the retrospective nature and modest number of patients included are major limitations. Without randomization between treatment strategies, selection bias is also likely for each treatment strategy despite efforts at controlling for confounding factors via multivariable analysis. Survival rates may be inflated owing to selection bias because only those patients who were doing well continued to follow up. With a short median follow-up time, the data may be skewed in favor of longer survival.

In addition, as patients underwent treatment over a period of more than a decade, a variety of surgical approaches, RT planning techniques, and chemotheraphy regimens were included. In fact, most patients treated in this study tended to have more aggressive or radical surgery and underwent multimodality treatment. There have been reports in the literature of local control rates as high as 97% for those treated with more radical surgery in addition to RT, consistent with the data reported herein. Finally, date of death was recorded either from that documented in the electronic medical record or cross-referenced with the US Social Security Index. It is possible that these data capture patients who were dead of disease but not recorded, which would inflate the survival rates. Nonetheless, the data presented herein add to the existing literature comparing surgical and organ-preserving treatment for HP SCC in the modern era.

### Table 2. Multivariate Cox Proportional Hazard Model of Survival in 76 Patients With Advanced Hypopharyngeal SCC

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Overall Survival</th>
<th>P Value</th>
<th>Recurrence-Free Survival</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (0.95-1.12)</td>
<td>.30</td>
<td>1.02 (0.94-1.10)</td>
<td>.66</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.47 (0.25-8.57)</td>
<td>.66</td>
<td>1.28 (0.23-7.21)</td>
<td>.78</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.01 (0.98-1.04)</td>
<td>.57</td>
<td>0.99 (0.96-1.02)</td>
<td>.12</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>2.10 (0.19-23.03)</td>
<td>.54</td>
<td>2.50 (0.26-24.40)</td>
<td>.43</td>
</tr>
<tr>
<td>KPS, higher vs lower score</td>
<td>7.98 (1.68-37.99)</td>
<td>.01</td>
<td>6.70 (1.72-26.10)</td>
<td>.01</td>
</tr>
<tr>
<td>TNM stage, III vs IV</td>
<td>4.69 (0.81-27.06)</td>
<td>.08</td>
<td>4.11 (0.73-23.29)</td>
<td>.11</td>
</tr>
<tr>
<td>Primary treatment, CRT vs surgery + CRT or RT</td>
<td>4.78 (0.91-25.03)</td>
<td>.06</td>
<td>2.97 (0.76-11.52)</td>
<td>.12</td>
</tr>
</tbody>
</table>

**Table 2. Multivariate Cox Proportional Hazard Model of Survival in 76 Patients With Advanced Hypopharyngeal SCC**

**Value**: HR (95% CI)  
**Abbreviations:** CRT, chemoradiation therapy; HR, hazard ratio; RT, radiation therapy; SCC, squamous cell carcinoma; SS, salvage surgery.
Conclusions

In a single-institution analysis of survival, patients with advanced-stage HPSCC treated surgically showed improved RFS and OS over those treated with CRT, and both cohorts had excellent outcomes compared with historical controls. Although institutional studies are limited in scope and power, they remain a realistic approach and potentially account for real-world differences better than randomized clinical trials (RCTs), which in this population remain difficult to execute owing to the greater financial costs associated with RCTs and the additional support and follow-up needed. Both treatment strategies compare favorably with historical controls. Further prospective investigations using modern concurrent CRT and modern surgical techniques remain necessary.

ARTICLE INFORMATION

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Author Contributions: Dr Daly had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Harris, Biron, Chen.

Critical revision of the manuscript for important intellectual content: Harris, Donald, Farwell, Luu, Bewley, Chen, Daly.

Statistical analysis: Harris, Biron, Donald, Bewley.

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Study supervision: Biron, Donald, Bewley, Chen, Daly.

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REFERENCES