Oral Oncology 50 (2014) 208–212

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Long-term survival after distant metastasis in patients with oropharyngeal cancer

Sean M. McBride [a,b], Paul M. Busse [a], John R. Clark [c], Lori J. Wirth [c], Marek Ancukiewicz [a], Annie W. Chan [a,*]

[a] Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States
[b] Harvard Radiation Oncology Program, Harvard Medical School, Boston, MA, United States
[c] Department of Medicine, Division of Medical Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

ARTICLE INFO

Article history:
Received 5 May 2013
Received in revised form 26 October 2013
Accepted 30 October 2013
Available online 31 December 2013

Presented at the 2012 Annual Meeting of the American Society of Clinical Oncology, Chicago, IL.

Keywords:
Oropharyngeal carcinoma
Distant metastasis
Human papilloma virus
Prognostic factors

SUMMARY

Objectives: For patients with oropharyngeal squamous cell carcinoma (OPSCC), especially for those with HPV-positive tumors, locoregional control is excellent. Distant metastasis, however, remains a substantial problem. The purpose of our study was to evaluate outcomes and predictors of survival after distant metastasis in OPSCC.

Materials and methods: Between June 2002 and January 2011, 25 OPSCC patients treated with curative intent subsequently developed distant metastasis. The primary end-points evaluated were time-to-distant metastasis and overall survival after development of distant metastasis. Predictors of outcome were evaluated with median regression analysis or Cox regression. Best subset models were chosen to minimize the Bayesian Information Criterion (BIC). A prognostic index for survival after distant failure was created based on the selected model.

Results: Median time-to-distant metastasis after completion of radiation was 7.9 months (range, 1.6–25.4). Median overall survival from distant metastasis was 18.3 months (95% CI, 14.3–39.8). The overall survival rates at 1- and 2-year after development of distant metastasis were 72.0% (95% confidence interval [CI], 53.4–89.6) and 40.8% (95% CI, 20.6–61.0), respectively. In multivariate analysis, Karnofsky Performance Status score (KPS) $\geqslant$ 80 ($p = 0.01$, hazard ratio [HR] 0.15, 95% CI, 0.04–0.52) and limited, single-organ disease ($p = 0.003$, HR 0.13, 95% CI 0.03–0.61) predicted for increased survival from distant metastasis. Patients with both limited disease and good KPS formed the most favorable risk group with a 2-year survival of 100%. Two patients with human papilloma virus (HPV)-positive tumors were alive without any evidence of disease at 64.6 and 60.4 months, respectively, after aggressive local treatment of solitary metastasis.

Conclusion: For OPSCC patients with limited, single-organ disease and good KPS, long-term survival can be achieved.

Introduction

The proportion of head and neck squamous cell carcinomas (HNSCC) arising in the oropharynx is increasing [1]. Due to the improvement in radiation precision, the use of concurrent chemotherapy, and the increase incidence of HPV-positive disease, loco-regional tumor control is excellent [2]. As such, continued reductions in mortality from oropharynx squamous cell carcinoma (OPSCC) will in part depend upon control of distant disease.

There is a robust literature on predictors of distant failure in HNSCC generally and to a lesser extent of distant recurrence in OPSCC, specifically [3–6]. But while identifying individuals at increased risk of distant metastasis is important, improvements in outcome for those already with distant metastasis requires that we prospectively pinpoint patients who will potentially benefit from aggressive intervention at the time of such failures.

Currently available prospective evaluations of clinical and pathologic factors prognostic in recurrent HNSCC include patients with both loco-regional and distant failure; in none of these studies did the investigators look exclusively at patients with distant metastasis [7–9]. Only the Princess Margaret group has retrospectively reported on outcomes after distant failure exclusively in OPSCC [10,21]. The remaining limited number of retrospective studies reporting on survival after metastasis were from the pre-concurrent chemotherapy, pre-IMRT era, and contained patients with all types of HNSCC primary sites [11–17]. In the modern era of HPV-related disease, oropharynx primaries may have a distinct

* Corresponding author. Address: Department of Radiation Oncology, Massachusetts General Hospital, Cox 337, 55 Fruit Street, Boston, MA 02114, United States. Tel.: +1 617 724 1159; fax: +1 617 726 3603.
E-mail address: awchan@partners.org (A.W. Chan).

1368-8375/$ - see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.oraloncology.2013.10.020

biology that separates them from other head and neck sub-sites [18]. In short, although instructive, the current literature does not give us sufficient insight into outcomes after distant metastasis in patients with OPSCC. Given this, we undertook a retrospective cohort study of OPSCC patients who failed distantly in order both to determine outcomes after distant failure, and, more importantly, to develop a model predictive of survival after metastasis in these patients.

Materials and methods

Patient population

Between April 2002 and December 2010, 25 of 353 patients who received treatment at the Massachusetts General Hospital for non-metastatic OPSCC subsequently developed distant metastasis. Amongst the metastatic group, the median age at initial diagnosis was 58 years (range, 43–80). Eighty-six percent of patients were male; the median KPS at diagnosis was 80 (range, 50–90). Of the 14 patients on whom HPV status was available, 13 (93%) were HPV/p16-positive. For the 11 patients in whom HPV status was not available, 2 patients had moderately-differentiated carcinoma; the remaining patients all had poorly- or non-differentiated carcinoma. The primary sites of disease were tonsil (38%), base of tongue (54%) and other (8%). Tumors were staged using the American Joint Committee on Cancer Staging, 7th Edition (2009), with 4% of patients with stage II disease, 4% stage III, 72% stage IVA, and 20% stage IVB at diagnosis. The T-category distribution was as follows: 75% T1–T3 and 25% T4. The N-category distribution was as follows: 50% N0-2b and 50% N2c-3 (Table 1).

All patients were treated with curative intent at initial diagnosis with either definitive radiation ± chemotherapy ($n = 24$) or post-operative radiation therapy ($n = 1$). For those who received definitive radiation, median dose to the gross tumor volume was 72 Gy (range, 69.96–73.4). Twenty-three patients received concurrent chemotherapy alone (17 platinum-based, 5 cetuximab alone, and 1 platinum and cetuximab); four received induction chemotherapy (docetaxel, cisplatin, and 5-fluorouracil) followed by concurrent chemotherapy; one patient with poor performance status at diagnosis did not receive any chemotherapy.

Table 1
Patient characteristics.

Age	
Median (years)	58
Range (years)	(43–80)
KPS at failure	
Median	80
Range	(50–90)
Pack-years	
Median	20
Range	(0–150)
Alcohol History	
Yes	11 (44%)
No	14 (56%)
HPV Status	
Positive	13 (50%)
Negative	1 (4%)
Unknown	11 (46%)
Residual disease at neck dissection	
Yes	20 (80%)
No	5 (20%)
LRF prior to or at time of DM	
Yes	5 (20%)
No	20 (80%)
Marital Status	
Married	12 (52%)
Single/Divorced	13 (48%)
T4 Disease	
Yes	7 (28%)
No	18 (72%)
N2b-3	
Yes	13 (52%)
No	12 (48%)
Limited disease	
Yes	7 (28%)
No	18 (72%)
Salvage Chemotherapy at DM	
Yes	16 (64%)
No	9 (36%)
Active Smoking at Distant Failure	
Yes	5 (20%)
No	20 (80%)
Time to Distant Failure > 12 months	
Yes	14 (56%)
No	11 (44%)

DM = distant metastasis.

Study end points and assessment

The two primary end-points evaluated were time-to-distant metastasis and overall survival from distant metastasis. Time-to-distant metastasis was defined as the time from completion of radiation to the first radiographic evidence of distant metastatic disease. Overall survival from distant metastasis was defined as the time from first radiographic evidence of distant failure to death or last follow-up. Patients underwent re-staging imaging approximately every 2–3 months during the first year and every 6 months thereafter using CT or PET/CT. All images demonstrating evidence of distant metastatic disease were re-reviewed for the purposes of this study. Eighty-three percent of patients had pathologic confirmation of their distant failure; pathologic confirmation consisted of either similar histology to the primary or p16/HPV positivity. Amongst the 13 patients with confirmed HPV + disease, ten had biopsy-confirmed distant failures that were either p16/HPV ($n = 2$) positive or histologically similar ($n = 8$) to the initial primary.

Statistical analyses

We evaluated the following candidate variables for their relationship to time-to-distant metastasis: Age, Gender, T4 (versus T1–T3) disease, N2b-3 (versus N0–N2a) disease, cumulative tobacco smoking history in pack-years, alcohol history, presence of residual disease on planned neck dissection, loco-regional recurrence prior to or at the time of distant failure, and marital status. A positive alcohol history was considered to be $\geqslant 14$ drinks per week. Due to the risk of overfitting, we performed a best subset selection process to identify the 1 or 2-variable median regression model (including the null model, with no parameters) that minimized the Bayesian Information Criterion (BIC); in effect, the minimization of BIC allows for the selection of the most probable and parsimonious model from amongst those examined. We considered only subsets of at most two variables due to small sample size. We chose to use median regression models because of the non-normal distribution of times to distant failure.

Overall survival from distant metastasis for the entire population was calculated using the Kaplan–Meier method. We evaluated the same candidate variables listed above, but included time-to-distant metastasis >12 months, KPS $\geqslant 80$ at the time of distant failure, limited (1 or 2 adjacent lesions) single-organ disease at distant recurrence, salvage with chemotherapy, and active tobacco smoking at the time of distant failure as additional potential predictors. Due to the risk of overfitting, we selected the 1–2 variable