Published in final edited form as:

Am J Clin Oncol. 2018 September ; 41(9): 888–893. doi:10.1097/COC.0000000000000386.

Concurrent Chemoradiotherapy in the Adjuvant Treatment of High-risk Primary Salivary Gland Malignancies

Brian J. Gebhardt, MD^{*}, James P. Ohr, DO[†], Robert L. Ferris, MD, PhD^{*,‡}, Umamaheswar Duvvuri, MD, PhD[‡], Seungwon Kim, MD[‡], Jonas T. Johnson, MD[‡], Dwight E. Heron, MD, MBA, FACRO, FACR^{*,‡}, and David A. Clump II, MD, PhD^{*}

^{*}Department of Radiation Oncology, Cancer Institute, University of Pittsburgh, Pittsburgh, PA.

[†]Department of Medicine, Division of Medical Oncology, University of Pittsburgh, Pittsburgh, PA.

[‡]Department of Otolaryngology, Head and Neck Surgery, University of Pittsburgh, Pittsburgh, PA.

Abstract

Objectives: Adjuvant radiation therapy (RT) is indicated for patients with salivary gland malignancies with risk factors for recurrence following resection. We analyzed patients treated with adjuvant RT with or without concurrent chemotherapy to determine the impact of prognostic and treatment factors.

Materials and Methods: Retrospective analysis was performed of 128 patients treated with surgical resection followed by intensity-modulated radiotherapy. In total, 31 (24.2%) patients were treated with concurrent chemoradiotherapy. The Kaplan-Meier method was used to estimate rates of progression-free survival (PFS), local-regional control, distant control, overall survival. Multivariable Cox regression was performed to evaluate factors significant on univariate analysis.

Results: The 5-year rates of PFS, local-regional control, freedom-from distant metastasis, and overall survival were 61.2%, 85.8%, 76.5%, and 73.7%, respectively. Predictors of decreased PFS on univariate analyses were age, tumor stage, nodal stage, positive surgical margins, histology, high grade, perineural invasion, lymphovascular space invasion, extranodal extension, and use of chemoradiotherapy. On multivariable analysis, elevated T-stage, positive surgical margins, and presence of extranodal extension were predictive of decreased PFS. The acute toxicity rates were 30.3% grade 1, 51.5% grade 2, 11.4% grade 3, and 0.8% grade 4. There was no difference in rates of grade 3 or higher acute toxicity with use of RT alone versus chemoradiotherapy ($P = 0.183$).

Conclusions: Use of chemoradiotherapy for adjuvant treatment of salivary gland malignancies was well-tolerated, but no improvement in survival was seen with the use of chemoradiotherapy in both the overall study population and a subset with high-risk features. Caution should be used when using this modality until randomized evidence becomes available.

Reprints: David A. Clump II, MD, PhD, 5230 Centre Ave., Pittsburgh, PA 15232. clumpda2@upmc.edu.

Presented at the ASTRO Head and Neck Symposium 2016, Scottsdale, AZ.

The authors declare no conflicts of interest.

Keywords

head and neck; salivary gland; radiotherapy; chemo-therapy; adjuvant

Primary salivary gland malignancies (SGM) are a histologically diverse group of rare tumors with an estimated incidence of 1.3 per 100,000 in the United States from 2009 to 2013.¹ Due to the rarity of these malignancies, there is a paucity of randomized evidence guiding their management. Surgical resection has been the mainstay of definitive treatment of operable tumors, and adjuvant radiation therapy (RT) is reserved for patients at significant risk for recurrence based upon the presence of adverse pathologic risk factors.²

Multiple trials have demonstrated the benefit of the addition of concurrent chemotherapy to RT for the definitive management of squamous cell carcinomas of the nasopharynx, larynx, hypopharynx, and other head and neck sites.^{3–7} Postoperative concurrent chemoradiotherapy (CRT) has also been shown to improve local-regional control (LRC) and progression-free survival (PFS) in the Radiation Therapy Oncology Group (RTOG) 9501 trial of patients with high-risk resected head and neck cancers and was associated with an overall survival (OS) benefit in the parallel European Organisation for Research and Treatment of Cancer trial.^{8,9}

Although the role of concurrent CRT is well established for most head and neck sites, its use in primary SGM is largely based upon extrapolation from squamous cell carcinoma data, retrospective evidence, and institutional experience. A matched-pair analysis of patients with locally advanced salivary gland carcinomas appeared to demonstrate an OS benefit among patients receiving adjuvant chemoradiation compared with radiation alone, particularly among patients with adenocarcinoma or salivary ductal carcinoma histologies.¹⁰ This finding is contradicted by a later retrospective series that failed to demonstrate improved outcomes with the addition of chemotherapy.¹¹ Although the efficacy of concurrent chemotherapy for squamous cell carcinoma is demonstrable, it remains unclear whether this benefit extends to salivary gland histologies or merely increases the toxicity of an already intense treatment regimen. We report the outcomes of a series of 128 consecutively treated patients with primarily resected SGM undergoing adjuvant intensity-modulated radiation therapy (IMRT) with or without concurrent chemotherapy including a subset analysis of patients at high risk of recurrence as defined by RTOG 1008.¹²

MATERIALS AND METHODS

Patient Population

This retrospective study was approved by the University of Pittsburgh Cancer Institute Institutional Review Board. The records of all patients treated for SGM in the UPMC Cancer Center network between September 2002 and March 2015 were retrospectively analyzed. This study included only patients with primary major or minor SGM as defined by the World Health Organization classification system. Salivary gland squamous cell carcinomas were not included due to the rarity of this entity and the difficulty of distinguishing primary carcinomas from metastatic tumors from cutaneous and other head and neck sites. Individual tumors were staged using the American Joint Committee on Cancer 7th edition staging

guidelines. Toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.0.

The study included patients undergoing definitive surgical resection followed by adjuvant RT. Patients treated with definitive RT, with gross residual tumor following surgery, with recurrent disease after primary management, or with distant metastatic disease upon presentation were excluded from analysis. Decisions regarding adjuvant management were made by the treating physicians in a multidisciplinary manner based upon clinical and pathologic characteristics.

Statistical Analysis

The primary study outcome was PFS, which was defined as time from surgical resection to local-regional (LR) recurrence, distant metastasis, death, or last follow-up. Secondary measures include LRC, freedom-from distant metastasis, OS, and acute and late treatment-related toxicity. Toxicity was retrospectively graded using CTCAE version 4.0. The Kaplan-Meier method was utilized to estimate the rates of PFS, LRC, distant control, and OS. Associations of patient factors with outcomes were assessed with the log-rank test. Multivariable Cox regression analyses were performed of patients with complete pathologic data to evaluate factors associated with primary and secondary outcomes. Factors with a $P < 0.1$ were included as covariates. Factors associated with concurrent chemotherapy use were assessed using binary logistic regression. Relationships with outcomes were summarized with hazard ratio (HR) and the 95% confidence interval (CI). Statistical significance was determined at the 5% level. Statistical analyses were conducted using IBM SPSS version 23.

A subset analysis was performed of 54 patients considered at high risk of recurrence as defined by the inclusion criteria from RTOG 1008.¹² This cohort included patients with intermediate-grade to high-grade mucoepidermoid carcinoma or adenocarcinoma, high-grade salivary ductal carcinoma, acinic cell carcinoma, or adenoid cystic carcinoma (> 30% solid component) and who had one of the following risk factors: stage T3–T4, lymph node involvement, or close (< 1 mm), or positive surgical resection margins. This subset was analyzed for rates of PFS and LRC utilizing the above statistical methods.

RESULTS

Patient and Treatment Characteristics

During the study period, 328 patients with SGM were treated with RT. Three patients were excluded for insufficient data, 4 for distant metastatic disease, 79 for nonprimary salivary gland histologies, and 114 for receiving RT as primary management, for recurrent disease, or with palliative intent. A total of 128 patients were eligible for analysis.

The median age was 60.5 (range, 18 to 93) years, and 56.3% of patients were male and 43.8% female. The study included 24 (18.8%) patients with mucoepidermoid carcinoma, 24 (18.8%) with salivary ductal carcinoma, 23 (18.0%) with adenoid cystic carcinoma, 17 (13.3%) with adenocarcinoma, 14 (10.9%) with acinic cell carcinoma, 13 (10.2%) with epithelial-myoepithelial carcinoma, 12 (9.4%) with carcinoma-expleomorphic adenoma, and

1 (0.8%) with lymphoepithelial carcinoma. In total, 104 (81.3%) patients had parotid malignancies. A total of 66 (51.5%) patients had stage III to IVB disease. The study population included 128 patients treated with macroscopically complete surgical resection, of which 68 (53.1%) underwent a surgical neck dissection. All patients were treated with adjuvant IMRT to a median dose to the primary tumor bed of 66 Gy (range, 45 to 70.2 Gy). In total, 106 (82.8%) patients received IMRT to at-risk nodal regions to a median dose of 50 Gy. A complete listing of patient and treatment characteristics is included in Table 1.

Concurrent Chemotherapy Utilization

In total, 28 (21.9%) patients were treated concurrently with chemotherapy regimens including 14 (10.9%) with carboplatin and paclitaxel, 6 (4.7%) with cisplatin, 5 (3.9%) with carboplatin, 1 (0.8%) with paclitaxel, 1 (0.8%) with docetaxel, 1 with (0.8%) cetuximab. The use of concurrent chemotherapy was significantly associated with male sex ($P = 0.027$), T-stage ($P = 0.05$), N-stage ($P < 0.001$), histology ($P = 0.006$), grade ($P = 0.015$), perineural invasion (PNI) ($P < 0.001$), lymphovascular space invasion (LVSI) ($P < 0.001$), extranodal extension (ENE) ($P < 0.001$). On multivariable analysis, the use of chemotherapy was only associated with salivary ductal carcinoma histology (HR, 5.63; 95% CI, 1.37–23.17; $P = 0.017$).

Toxicity

Acute toxicity data were available for 119 patients. A total of 39 (32.8%) patients experienced grade 1 symptoms as their highest graded acute toxicity, and 65 (54.6%) patients experienced a maximum of grade 2 acute toxicity. The most common acute adverse events included mucositis and xerostomia. Only 14 (11.8%) grade 3 toxicities were reported, consisting of 12 patients needing feeding tube placement and 2 patients with moist skin desquamation. The one grade 4 toxicity consisted of an intensive care hospitalization within 2 months following treatment secondary to dehydration, electrolyte abnormalities, and aspiration pneumonia. There was no statistical difference in the rates of grade 3 or higher acute toxicity with the use of IMRT alone versus concurrent chemotherapy ($P = 0.183$). Late grade 1 toxicities were reported in 66 patients, and late grade 2 toxicities were reported in 16 patients. No late grade 3 or higher toxicities were reported.

Outcomes

The median follow-up among living patients was 53.5 (range, 9 to 162) months. The overall 5-year PFS rate was 61.2%. Factors significantly associated with decreased PFS on univariate analysis included elevated T-stage, elevated N-stage, positive surgical margins (SM), adenocarcinoma, adenoid cystic and salivary ductal histologies, high grade, PNI, LVSI, ENE, and neck dissection (Table 2). Use of concurrent chemotherapy was associated with decreased PFS on univariate analysis (Fig. 1). On multivariable analysis, only T-stage, positive SM, and ENE-retained significance, (Table 3) and use of chemotherapy was no longer detrimental. The crude LR recurrence rates were for 17.4% for adenoid cystic carcinoma, 11.8% for adenocarcinoma, 12.5% for salivary ductal carcinoma, 16.7% for mucoepidermoid carcinoma, 7.1% for acinic cell carcinoma, and 7.7% for other histologies. The overall 5-year LRC rate for the entire cohort was 85.8%. Factors significantly associated with decreased LRC included T-stage, and margin status. There was a trend toward

significance for PNI ($P = 0.079$) and LVSI ($P = 0.06$). Positive SM (HR, 14.01; 95% CI, 1.85–106.22; $P = 0.011$) was the only factor associated with decreased LRC on multivariable analysis.

The 5-year distant control rate was 76.5%. Male sex ($P = 0.002$), nonparotid tumor site ($P = 0.021$), elevated nodal stage ($P < 0.001$), salivary ductal carcinoma, and adenocarcinoma histologies ($P < 0.001$), grade ($P = 0.010$), PNI ($P = 0.047$), LVSI ($P = 0.043$), ENE ($P < 0.001$), and use of chemotherapy ($P < 0.001$) were associated with increased rates of distant metastasis on univariate analysis. On multivariable analysis, the only factor significantly associated with distant metastasis was ENE (HR, 7.39; 95% CI, 3.05–17.88; $P < 0.001$). The 5-year rate of OS was 73.7%. Factors associated with decreased survival included age 60 and above ($P = 0.003$), high T-stage ($P = 0.015$), high N-stage ($P < 0.001$), salivary ductal carcinoma, and adenocarcinoma histologies ($P < 0.001$), high grade ($P = 0.038$), LVSI ($P = 0.008$), ENE ($P < 0.001$), and use of chemotherapy ($P = 0.038$). On multivariable analysis, only advanced age (HR, 2.93; 95% CI, 1.28–6.69; $P = 0.011$), and ENE (HR, 3.48; 95% CI, 1.53–7.87; $P = 0.003$) retained statistical significance for decreased survival. Use of chemotherapy was neither beneficial nor detrimental to any outcome on multivariable analysis.

High-risk Subset Analysis

A total of 54 patients were included in the subset analysis based upon histology, grade, and the presence of high-risk features. The 5-year rate of PFS among these patients was 45.1%. Factors associated with decreased PFS on univariate analysis included male sex ($P = 0.032$), LVSI ($P = 0.038$), ENE ($P = 0.013$), and mucoepidermoid histology. There was a trend toward significance for positive margins ($P = 0.061$) and salivary ductal histology ($P = 0.059$). Chemotherapy was received by 18 (33.3%) patients. On multivariable analysis, only ENE was associated with decreased PFS (3.1; 95% CI, 1.18–7.95; $P = 0.021$). Chemotherapy was not significantly associated with PFS (Fig. 2). The 5-year rate of LRC among this subset was 76.7%. On univariate analysis, positive SM ($P = 0.008$) and adenoid cystic histology ($P = 0.009$) were significantly associated with decreased LRC. Chemotherapy was not associated with LRC on either univariate ($P = 0.636$) or multivariable analysis ($P = 0.888$). Possibly owing to the small number of events, no variables were associated with LRF on multivariable analysis, though there was a trend toward an association with positive SM ($P = 0.147$).

DISCUSSION

Malignant salivary gland tumors are a rare and diverse entity, with 24 distinct histologies recognized by the WHO classification.¹³ Large retrospective series of patients identified the parotid as the most common site of malignancy, constituting approximately one-half of cases.^{14,15} Complete macroscopic surgical resection remains the definitive management of choice for patients with operable SGM, and surgical series have demonstrated high rates of disease-free survival with surgery alone.¹⁶ Retrospective series have shown improved outcomes with adjuvant RT in appropriately selected patients.^{2,17,18} A Dutch series found improved local control with adjuvant RT among patients with stage T3–T4 tumors, close or positive margins, bone invasion, and PNI. Elective nodal irradiation has also been shown to

reduce the nodal failure rate in patients with adenocarcinoma and mucoepidermoid histologies.¹⁹

Although the benefit of adjuvant RT is supported by retrospective evidence, the rationale for adjuvant concurrent CRT in SGM is extrapolated from squamous cell carcinoma trials. RTOG 9501 demonstrated a 10% LRC benefit with the use of concurrent cisplatin, whereas the European Organisation for Research and Treatment of Cancer trial also demonstrated a survival benefit.^{8,9} A subsequent pooled analysis demonstrated that ENE and positive margins predicted a survival benefit with cisplatin.²⁰ This survival advantage came at the cost of approximately doubling the rates of grade 3 or higher acute toxicity, which indicates that caution is warranted when extrapolating these results to different histologies. Although some data exist demonstrating response rates of SGM in the metastatic setting, prospective evidence for definitive or adjuvant concurrent CRT is even more limited.^{21–23}

Small retrospective series of patients with SGM treated with surgery and adjuvant RT with or without chemotherapy have demonstrated the approach to be well-tolerated and associated with high rates of LRC, though the small sample sizes have prevented analysis of the additional benefit of concurrent chemotherapy.^{24,25} A matched-pair analysis of 24 patients found that patients receiving adjuvant platinum-based CRT had a 3-year OS rate of 83% compared with 44% among those undergoing adjuvant RT alone, though a later series from the same institution was unable to replicate this benefit.^{10,11} The authors analyzed 140 patients with primary SGM treated with adjuvant RT alone (74%) or various concurrent CRT regimens (26%) and reported a 3-year PFS rate of 88%, which was not impacted by the addition of concurrent chemotherapy.¹¹ A recent analysis from the National Cancer Data Base also failed to demonstrate an OS benefit with the addition of chemotherapy to adjuvant RT, whereas an analysis from the SEER database found an increase in treatment toxicity and mortality with this approach.^{26,27}

This analysis of 128 patients with primary SGM treated with definitive surgery followed by adjuvant IMRT within a large, National Cancer Institute-designated comprehensive cancer network demonstrated an overall 5-year PFS rate of 61%. T-stage, positive SM, and ENE were associated with decreased PFS. Our data demonstrated a high rate of LRC of 86% at 5 years, whereas 23.5% of patients developed distant metastatic disease at a median of 28 (range, 4 to 84) months. Only positive SM and ENE were associated with LR recurrence and distant metastasis, respectively. The use of concurrent chemotherapy was associated with decreased rates of PFS, OS, and distant control on univariate analyses. This was not a significant factor on multivariable analyses, suggesting that the apparent detrimental effect was due to patients at high risk of failure being selected for more intensive adjuvant treatment.

We performed an exploratory subset analysis of 54 patients considered at high risk of recurrence as defined by the inclusion criteria from RTOG 1008 to further investigate the potential benefit of CRT.¹² This subgroup had 2- and 5-year PFS rates of 70% and 45%, respectively. This compares favorably with the estimated 2-year PFS rate of 65% in the RTOG trial, which is powered to detect a 12% improvement in PFS. We were not able to demonstrate a significant impact with the addition of concurrent chemotherapy even in this

group of patients with particularly high-risk features. The rate of grade 3 or higher acute toxicity was not significantly higher in the group receiving CRT, and the relatively low toxicity rate further suggests that the decreased rate of PFS among the concurrent CRT cohort was related to higher baseline risk factors rather than the additional toxicity of chemotherapy.

Treatment was well-tolerated overall in the present study. Only 13% experienced grade 3 or higher acute toxicities, which may be due to the fact that all patients were treated using IMRT. A prior series of patients treated exclusively with adjuvant IMRT found overall grade 3 mucositis, dermatitis, and esophagitis rates of 14%, 11%, and 6%, respectively.²⁴ To our knowledge, the present study is the largest available series of patients with SGM treated with adjuvant IMRT, which has been shown in other head and neck malignancies to reduce acute and late xerostomia.²⁸ Our data demonstrated late grade 2 toxicity rates of 9.0%, though this number is likely under-reported and prevents any meaningful comparison with prospectively gathered data.

Additional limitations of this study include its retrospective design and inherent problems with selection bias. Although the majority of SGM do arise from the parotid gland, this disease site was overrepresented in our data. There were also very few minor salivary gland tumors recorded, likely due to limitations from querying our database utilizing ICD-9 coding. Although our data did not show any conclusive benefit or detriment with the use of concurrent CRT, this may be due to lack of statistical power due to the number of patients receiving concurrent chemotherapy or confounding bias from elevated baseline risk factors causing patients to be selected for more intensive treatment. Multivariable analysis was used in an attempt to control for this imbalance in risk factors, though it is not possible to fully eliminate this bias from a retrospective study. Furthermore, adjuvant CRT regimens administered were heterogeneous, which could obscure the beneficial effect of a particular agent.

Despite these limitations, the present study reports 5-year outcomes of a relatively large group of patients diagnosed with a rare malignancy undergoing adjuvant treatment utilizing IMRT technique with or without concurrent chemotherapy. This retrospective analysis of patients treated with adjuvant IMRT demonstrated high rates of LRC and PFS rates that compare favorably with previously published data. The use of concurrent chemotherapy was well-tolerated but was associated with decreased PFS in comparison with adjuvant RT alone on univariate analysis. This was not seen on multivariable analysis, suggesting that the apparent effect was due to higher rates of adverse pathologic risk factors in this group, resulting in selection of these patients for treatment intensification. Considering the potential for increasing the toxicity of an already difficult treatment regimen by adding an additional modality without proven efficacy, caution should be used with utilizing concurrent chemotherapy for treatment of SGM until randomized evidence becomes available.

REFERENCES

1. US National Institutes of Health, National Cancer Institute. "Cancer of the oral cavity and pharynx by subsite (invasive)." SEER Cancer Statistics Review 1975–2013. 2016 Available at: <http://>

seer.cancer.gov/csr/1975_2013/browse_csr.php?sectionSEL=20&pageSEL=sect_20_table.09.html. Accessed July 15, 2016.

2. Terhaard CJ, Lubsen H, Rasch CR, et al. The role of radiotherapy in the treatment of malignant salivary gland tumors. *Int J Radiat Oncol Biol Phys*. 2005;61:103–111. [PubMed: 15629600]
3. Al-sarraf BM, Leblanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup Study 0099. *J Clin Oncol*. 1998;16:1310–1317. [PubMed: 9552031]
4. Forastiere AA, Goepfert H, Maor M, et al. Concurrent Chemo-therapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003;349:2091–2098. [PubMed: 14645636]
5. Prades JM, Lallemand B, Garrel R, et al. Randomized phase III trial comparing induction chemotherapy followed by radiotherapy to concomitant chemoradiotherapy for laryngeal preservation in T3M0 pyriform sinus carcinoma. *Acta Otolaryngol*. 2010;130: 150–155. [PubMed: 19449227]
6. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. 2003;21: 92–98. [PubMed: 12506176]
7. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst*. 1999;91:2081–2086. [PubMed: 10601378]
8. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004; 350:1937–1944. [PubMed: 15128893]
9. Bernier J, Dornge C, Matuszewska K, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350: 1945–1952. [PubMed: 15128894]
10. Tanvetyanon T, Qin D, Padyha T, et al. Outcomes of postoperative chemoradiotherapy for locally advanced major salivary gland carcinoma. *Arch Otolaryngol Head Neck Surg*. 2009;135:687–692. [PubMed: 19620591]
11. Mifsud MJ, Tanvetyanon T, McCaffrey JC, et al. Adjuvant radiotherapy versus concurrent chemoradiotherapy for the management of high-risk salivary gland carcinomas. *Head Neck*. 2016;38:1628–1633. [PubMed: 27098984]
12. Radiation Therapy Oncology Group. RTOG 1008 protocol information. 2015 Available at: www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1008. Accessed July 9, 2016.
13. Barnes L, Eveson JW, Riechart P, et al. World Health Organization Classification of Tumors. Pathology and Genetics of Head and Neck Tumours. Lyon: IARC Press; 2005.
14. Ostman J, Anneroth G, Gustafsson H, et al. Malignant salivary gland tumours in Sweden 1960–1989—an epidemiological study. *Oral Oncol*. 1997;33:169–176. [PubMed: 9307725]
15. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. *Head Neck Surg*. 1986;8:177–184. [PubMed: 3744850]
16. Schroeder U, Groppe D, Mueller RP, et al. Parotid cancer: impact of changes from the 1997 to the 2002 American Joint Committee on cancer classification on outcome prediction. *Cancer*. 2008; 113:758–764. [PubMed: 18613074]
17. Garden AS, El-Naggar AK, Morrison WH, et al. Postoperative radiotherapy for malignant tumors of the parotid gland. *Int J Radiat Oncol Biol Phys*. 1997;37:79–85. [PubMed: 9054880]
18. Armstrong JG, Harrison LB, Spiro RH, et al. Malignant tumors of major salivary gland origin. A matched-pair analysis of the role of combined surgery and postoperative radiotherapy. *Arch Otolaryngol Head Neck Surg*. 1990;116:290–293. [PubMed: 2306346]
19. Chen AM, Garcia J, Lee NY, et al. Patterns of nodal relapse after surgery and postoperative radiation therapy for carcinomas of the major and minor salivary glands: what is the role of elective neck irradiation? *Int J Radiat Oncol Biol Phys*. 2007;67:988–994. [PubMed: 17234357]
20. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck*. 2005;27: 843–850. [PubMed: 16161069]

21. Cortesina G, Airoidi M, Palonta F. Current role of chemotherapy in exclusive and integrated treatment of malignant tumours of salivary glands. *Acta Otorhinolaryngol Ital.* 2005;25:179–181. [PubMed: 16450774]
22. Gilbert J, Li Y, Pinto HA, et al. Phase II trial of taxol in salivary gland malignancies (E1394): a trial of the Eastern Cooperative Oncology Group. *Head Neck.* 2006;28:197–204. [PubMed: 16470745]
23. Airoidi M, Gabriele AM, Gabriele P, et al. Concomitant chemoradiotherapy followed by adjuvant chemotherapy in parotid gland undifferentiated carcinoma. *Tumori.* 2001;87:14–17. [PubMed: 11669550]
24. Schoenfeld JD, Sher DJ, Norris CM, et al. Salivary gland tumors treated with adjuvant intensity-modulated radiotherapy with or without concurrent chemotherapy. *Int J Radiat Oncol Biol Phys.* 2012;82:308–314. [PubMed: 21075557]
25. Pederson AW, Salama JK, Haraf DJ, et al. Adjuvant chemoradiotherapy for locoregionally advanced and high-risk salivary gland malignancies. *Head Neck Oncol.* 2011;3:31. [PubMed: 21791072]
26. Amini A, Waxweiler TV, Brower JV, et al. Association of adjuvant chemoradiotherapy vs. radiotherapy alone with survival in patients with resected major salivary gland carcinoma: data from the National Cancer Data Base. *JAMA Otolaryngol Head Neck Surg.* 2016;142:1100–1110. [PubMed: 27541166]
27. Tanvetyanon T, Fisher K, Caudell J, et al. Adjuvant chemoradiotherapy versus with radiotherapy alone for locally advanced salivary gland carcinoma among older patients. *Head Neck.* 2015;38:863–870. [PubMed: 26340707]
28. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol.* 2011;12:127–136. [PubMed: 21236730]

FIGURE 1.

Kaplan-Meier estimate of progression-free survival by use of adjuvant radiation therapy versus chemoradiotherapy in the overall study population.

FIGURE 2. Kaplan-Meier estimate of progression-free survival by use of adjuvant radiation therapy versus chemoradiotherapy in the high-risk subset.

TABLE 1.**Patient and Treatment Characteristics**

Baseline Characteristics	Number	Percentage
Sociodemographic factors		
Age (y)	60.5 (median)	18–93 (range)
Sex		
Male	72	56.3
Female	56	43.8
Race		
White	119	93.0
African American	8	6.3
Asian	1	0.8
Pathologic factors		
Site		
Parotid	104	81.3
Submandibular	16	12.5
Oral cavity	5	3.9
Other	3	2.3
Side		
Right	56	43.8
Left	71	55.5
Midline	1	0.8
T-stage		
1	40	31.3
2	40	31.3
3	20	15.6
4a	26	20.3
4b	2	1.6
N-stage		
0	90	70.3
1	6	4.7
2a	2	1.6
2b	29	22.7
2c	1	0.8
Overall stage		
I	33	25.8
II	29	22.7
III	18	14.1
IVA	46	35.9
IVB	2	1.6
Primary tumor size (cm)	2.5 (median)	0.3–7.7 (range)
Surgical margin status		

Baseline Characteristics	Number	Percentage
Negative	30	23.4
Close	25	19.5
Positive	68	53.1
Unavailable	5	3.9
Histology		
Adenoid cystic carcinoma	23	18.0
Acinic cell carcinoma	14	10.9
Adenocarcinoma	17	13.3
CXPA	12	9.4
EMC	13	10.2
Lymphoepithelial carcinoma	1	0.8
Mucoepidermoid carcinoma	24	18.8
Salivary ductal carcinoma	24	18.8
Grade		
1	31	24.2
2	29	22.7
3	58	45.3
Bone invasion		
Negative	116	90.6
Positive	12	9.4
Perineural invasion		
Negative		
Positive	68	53.1
Not reported		
Lymphovascular space invasion		
Negative		
Positive	47	36.7
Not reported		
No. involved nodes	0 (median)	0–55 (range)
Extranodal extension		
Negative	104	81.3
Positive	24	18.8
Treatment-related factors		
Neck dissection		
No	60	46.9
Yes	68	53.1
Dose to primary (Gy)	66 (median)	45.0–70.2 (range)
Dose to at-risk lymph nodes (Gy)	50 (median)	0–66.0 (range)
Concurrent chemotherapy		
None	100	78.1
Cisplatin	6	4.7
Carboplatin-paclitaxel	14	10.9

Baseline Characteristics	Number	Percentage
Carboplatin	5	3.9
Paclitaxel	1	0.8
Docetaxol	1	0.8
Cetuximab	1	0.8

* CXPA indicates carcinoma-expleomorphic adenoma; EMC, epithelialmyoepithelial carcinoma.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

TABLE 2.

Factors Associated With Progression-free Survival on Univariate Analysis

Baseline Characteristics	5-Year PFS (%)	P
Sociodemographic factors		
Age		0.042
60	71.6	
> 60	50.2	
Pathologic factors		
T-stage		< 0.001
1	78.1	
2	69.1	
3	51.7	
4	33.4	
N-stage		0.002
0	70.8	
1	50.0	
2	28.8	
Surgical margin status		0.003
Negative	73.8	
Positive	52.8	
Histology		0.005
Adenoid cystic carcinoma	44.2	
Acinic cell carcinoma	83.3	
Adenocarcinoma	57.6	
Mucoepidermoid carcinoma	75.5	
Salivary ductal carcinoma	42.3	
Other histologies	78.3	
Grade		0.006
1	87.4	
2–3	48.7	
Perineural invasion		0.047
Negative	85.9	
Positive	68.6	
Lymphovascular space invasion		0.043
Negative	79.5	
Positive	65.7	
Extranodal extension		< 0.001
Negative	87.0	
Positive	24.9	
Treatment-related factors		
Concurrent chemotherapy		< 0.001
None	84.0	

Baseline Characteristics	5-Year PFS (%)	<i>P</i>
Any	44.6	0.004
Neck dissection		
Yes	73.0	
No	43.9	

PFS indicates progression-free survival.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

TABLE 3.

Multivariable Cox Regression Analysis of Progressionfree Survival

Variables	Hazard Ratio	95% Confidence Interval	P
Extranodal extension			< 0.001
Negative	1	Reference	
Positive	3.09	1.48–6.42	
Surgical margin status			0.016
Negative	1	Reference	
Positive	2.38	1.18–4.82	
T-stage			0.045
T1	1	Reference	
T2	1.07	0.42–2.75	
T3	1.37	0.51–3.69	
T4	2.75	1.15–6.58	