

Intermediate-grade carcinoma of the parotid and the impact of adjuvant radiation[☆]

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ABSTRACT

Purpose: To determine the influence of adjuvant radiotherapy on survival in surgically-managed early stage intermediate-grade mucoepidermoid and acinic cell carcinoma of the parotid.

Materials and methods: The National Cancer Database was reviewed between 2004 and 2015 to identify patients with intermediate-grade, early T-stage, node-negative parotid carcinoma who underwent parotidectomy ± radiotherapy.

Results: There were 744 patients identified of which 81% had mucoepidermoid carcinoma and 19% had acinic cell carcinoma. Positive surgical margins were identified in 21% and adjuvant radiotherapy was administered in 38% of cases. Of the 159 patients with positive margins, 113 (71%) received adjuvant radiotherapy. Of the 585 patients with negative margins, 173 (30%) underwent adjuvant radiotherapy. In multivariable analysis, age (over 52 years: HR 5.19, 95%CI 2.33–11.57), insurance status (private insurance: HR 0.24 95%CI 0.13–0.43), and extent of parotidectomy (total parotidectomy: HR 2.02 95%CI 1.23–3.31) were significantly associated with overall survival, while adjuvant radiotherapy was not a significant predictive factor (HR 0.81, 95%CI 0.49–1.36). In patients with positive margin resections, however, adjuvant radiation was an independent predictor of improved survival when adjusted for age, insurance status, and extent of parotidectomy (HR 0.34, 95%CI 0.13–0.88). Conversely, in patients with negative margin resections, adjuvant radiation did not influence survival outcomes when adjusted for these covariates (HR 1.02, 95%CI 0.53–1.93).

Conclusions and relevance: In patients with early stage intermediate-grade parotid carcinoma, adjuvant radiotherapy significantly and independently improves survival in those with post-operative positive margins. Adjuvant therapy, however, does not appear to improve survival outcomes in those with negative margin resections.

1. Introduction

Management of salivary gland carcinoma includes upfront surgery with or without risk-adjusted post-operative adjuvant therapy. For those with resected T1-2 tumors, current guidelines recommend consideration of post-operative radiation therapy for patients with adenoid cystic pathology, close (< 1 mm) or positive margins, perineural or lymphovascular invasion, lymph node metastasis, and intermediate- or high-grade histology [1].

While the majority of these risk factors are well-established, the independent prognostic implications of intermediate-grade disease are less certain [2]. For most histologies, low-grade parotid tumors without

high risk features have an excellent prognosis and are treated with surgery alone [3,4]. Conversely, high-grade tumors are associated with an increased risk of recurrence and are managed with adjuvant radiotherapy [5–7]. Treatment recommendations for intermediate-grade parotid carcinomas, however, remain controversial. Several reports have demonstrated excellent long-term locoregional control for surgical resection of intermediate grade parotid malignancy without adjuvant therapy [3,8]. Conversely, other studies have suggested that intermediate grade histology is independently associated decreased survival and may benefit from adjuvant radiation [9–11]. Most studies, however, group intermediate-grade tumors with either low- or high-grade disease for analysis. This complicates interpretation and leads to a

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limited understanding of the independent prognostic impact of intermediate-grade histology [3,5,12]. The objectives of this study, therefore, were to better delineate the prognostic factors associated with survival for intermediate-grade parotid carcinoma and to evaluate the impact of adjuvant radiotherapy in these patients through the analysis of a large nationwide cancer database.

2. Methods

The 2015 participant user file from the National Cancer Database (NCDB) was analyzed for this study, including patients diagnosed between 2004 and 2015. The NCDB is a joint project between the American College of Surgeons Commission on Cancer and the American Cancer Society. Established in 1989, it is a nationwide, facility-based, comprehensive clinical surveillance oncology database which includes approximately 70% of all newly diagnosed cancers in the United States.

Patients were identified using the International Classification of Diseases for Oncology, Third Edition. Topographical codes were identified for the parotid gland (C07.9). Patients with a diagnosis of mucoepidermoid carcinoma (8430) and acinic cell carcinoma (8550) were included while those with less common or highly aggressive histologies which may affect management or prognosis (such as adenocarcinoma [8140], adenoid cystic carcinoma [8200], or salivary ductal carcinoma [8500]) were excluded [1,13–15].

Patients were included who underwent up-front surgery for intermediate-grade, early T-stage (T1 or T2), node-negative parotid carcinoma. Patients with prior malignancies, distant metastases, or no definitive surgery at the primary site were excluded. Those with gross residual disease after surgery were also excluded, as these patients were considered to have undergone surgical debulking or biopsy without the intent of complete surgical resection. Patients with pathologically involved lymphadenopathy, low- or high-grade histology, and those with either in-situ only or T3-4 staging (AJCC 7th edition) were excluded. To improve the transparency and stability of statistical modeling, other confounding variables which may affect prognosis were excluded, including patients receiving any chemotherapy (pre- or post-operatively) or non-traditional adjuvant radiotherapy techniques (radioisotopes, brachytherapy, pre-operative or intraoperative radiation). Finally, patients with missing data regarding survival, tumor staging, margin status, neck dissection, or adjuvant therapies were excluded.

Data were analyzed using SPSS software (SPSS v24, IBM, Chicago, IL). Descriptive analyses were used to define the study population. Univariate and multivariate hazard ratio (HR) regression modeling using Cox survival analysis were completed to identify risk factors significantly associated with overall survival. Patients were then stratified by margin status and models were adjusted for known significant covariates, to investigate the effects of adjuvant radiotherapy on patients with and without known high-risk histopathological features.

3. Results

After review of the NCDB, 27,485 parotid malignancies were identified. Patients with multiple tumors, bilateral tumors, and in situ disease were excluded (n = 20,212). Only patients with intermediate grade disease were then included, while patients were excluded with distant metastases, excisional biopsies, gross residual disease after surgery, brachytherapy or chemotherapy, and missing data regarding extent surgery, margin status, staging data, or adjuvant therapy (n = 2432). Finally, patients with advanced T- and N-stage disease were excluded and the cohort was limited to mucoepidermoid and acinic cell histologies.

Therefore, 744 patients were identified who met inclusion criteria of intermediate-grade, node-negative, early-stage (T1 or T2) carcinoma of the parotid gland. Of these patients 81% had mucoepidermoid carcinoma and 19% had acinic cell carcinoma. Demographics and treatment characteristics are shown in Table 1.

Table 1
Demographics: T1-2 intermediate grade parotid carcinoma.

	All patients (n = 744)
Gender	
• Male	311 (42%)
• Female	433 (58%)
Age (years)	
• Median	52
• Range	18 to 90
Charlson/Deyo score	
• 0	623 (84%)
• 1–3	121 (16%)
Practice type	
• Academic	254 (34%)
• Other ^a	490 (66%)
Insurance status	
• Private insurance	459 (62%)
• Other ^b	285 (38%)
Histology	
• Mucoepidermoid carcinoma	604 (81%)
• Acinic cell carcinoma	140 (19%)
Pathological staging	
• T1	477 (64%)
• T2	267 (36%)
Extent of surgery	
• Partial parotidectomy	473 (64%)
• Total parotidectomy	271 (36%)
Neck dissection	528 (71%)
Positive surgical margins	159 (21%)
Adjuvant radiotherapy ^c	286 (38%)

^a Other includes community cancer programs, integrated network cancer programs, and unknown practice type.

^b Other includes uninsured, governmental insurance including Medicare and Medicaid, and unknown insurance status.

^c 7 patients underwent concurrent adjuvant chemotherapy.

Table 2
Univariable and multivariable Cox survival analysis for survival outcomes.

	Overall survival HR (95% CI)	p-Value
Univariable		
Gender (male vs female)	1.36 (0.84–2.23)	0.215
Age (52 years or greater vs < 52 years)	7.76 (3.54–17.01)	0.001
Charlson/Deyo score (1 or more vs 0)	1.93 (1.08–3.44)	0.027
Practice type (academic vs other)	0.79 (0.46–1.34)	0.376
Insurance status (private vs other)	0.16 (0.09–0.29)	0.001
Histology (mucoepidermoid carcinoma vs acinic cell carcinoma)	1.42 (0.70–2.88)	0.327
Pathological staging (T2 vs T1)	1.49 (0.91–2.45)	0.116
Extent of surgery (total parotidectomy vs partial parotidectomy)	1.81 (1.11–2.96)	0.018
Neck dissection (any vs none)	1.21 (0.69–2.10)	0.507
Margin status (positive vs negative)	1.39 (0.81–2.40)	0.234
Adjuvant radiation (any vs none)	0.81 (0.49–1.36)	0.434
Multivariable		
Age (52 years or greater vs < 52 years)	5.19 (2.33–11.57)	0.001
Charlson/Deyo score (1 or more vs 0)	1.13 (0.63–2.02)	0.687
Insurance status (private vs other)	0.24 (0.13–0.43)	0.001
Extent of surgery (total parotidectomy vs partial parotidectomy)	2.02 (1.23–3.31)	0.005

Bold signifies statistical significance with p < 0.05

Uni- and multivariable Cox survival analyses are shown in Table 2. These identified age (over 52 years: HR 5.19, 95%CI 2.33–11.57), insurance status (private insurance: HR 0.24 95%CI 0.13–0.43), and extent of parotidectomy (total parotidectomy: HR 2.02 95%CI 1.23–3.31) as significantly associated with overall survival in a multivariable model. In patients with positive margin resections, adjuvant radiation was an independent predictor of improved survival when adjusted for age, insurance status, and extent of parotidectomy (HR 0.34, 95%CI 0.13–0.88). However, in patients with negative margin resections,

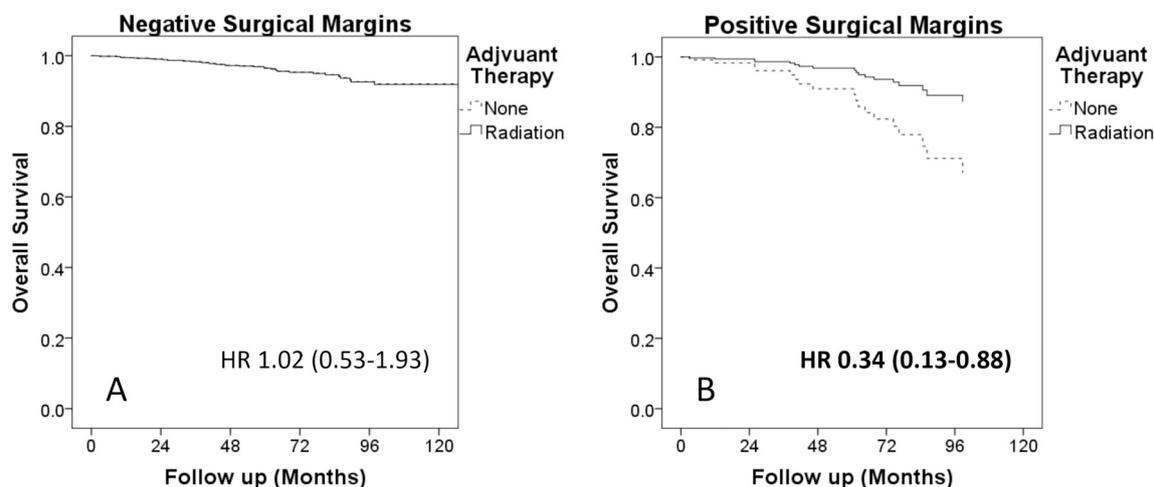


Fig. 1. The influence of adjuvant radiation on overall survival of patients with (A) negative margin resections and (B) positive margin resections when adjusted for age, insurance status, and extent of parotidectomy.

adjuvant radiation did not influence survival outcomes when adjusted for these covariates (HR 1.02, 95%CI 0.53–1.93) (Fig. 1).

4. Discussion

In a multivariable analysis of prognostic factors for early T-stage, node-negative, intermediate grade parotid acinic cell and mucoepidermoid carcinoma, younger age, private insurance, and surgery less than a total parotidectomy were associated with improved overall survival. While the prognostic value of younger age and private insurance are likely related to global health status and overall quality of healthcare, tumors requiring total parotidectomy may represent more invasive disease and a more aggressive pathobiology [16,17].

To delineate which sub-groups of early stage intermediate-grade parotid carcinoma may benefit from adjuvant radiotherapy, patients were stratified by surgical margin status, a known significant negative prognosticator for survival in parotid malignancy [18]. When adjusted for significant covariates (age, insurance status, and extent of parotidectomy), patients with negative surgical margins did not appear to benefit from the addition of adjuvant radiation. For those patients with positive surgical margins, however, adjuvant radiation demonstrated an association with improved overall survival. These findings suggest that intermediate-grade histology itself may not be an independent risk factor for recurrence or survival, but instead, prognosis and the addition of adjuvant therapy in these patients should depend on margin status. This conclusion is supported by several recent studies which found that intermediate-grade disease is not an adverse prognostic factor and demonstrates survival outcomes similar to low-grade histology [7,19]. Conversely, Aro et al. [11], reported high recurrence and poor survival for patients with intermediate-grade mucoepidermoid carcinoma of the parotid. These authors included patients with advanced T- and N-stage disease in their analysis, however, and margin status was not reported. Similarly, Rajasekaran et al. [9], demonstrated a negative survival impact only for intermediate grade tumors with advanced T- or N-staging. Taken together, these results suggest that for patients with a negative margin resection of early T-stage, node-negative, intermediate-grade parotid carcinoma, adjuvant radiotherapy is not required.

Another consideration in this group, however, is the need for elective neck dissection. While neck dissection was not associated with overall survival in this study, up to 10% of patients with intermediate-grade parotid carcinoma will have occult nodal metastases, although this depends greatly on tumor staging and histologic sub-type [12,15,20,21]. While the oncologic benefit of elective neck dissection in this group remains uncertain, pathological staging of the neck in these

patients may help guide decision-making for post-operative adjuvant therapy.

There are several limitations to these conclusions. These data are retrospective and subject to the omissions and inaccuracies of the medical record. Importantly, the NCDB does not include recurrence or disease-free survival. Additionally, information regarding several other important prognostic factors, including perineural invasion and margin distance are not recorded. In particular, although a close margin may not be an independent risk-factor for recurrence or survival for low-grade tumors, its prognostic implications for intermediate-grade disease are less certain [2,3,22]. Another important limitation is the inconsistency in the pathologic definition of intermediate-grade in the literature as well as absence of detailed grading information available in the NCDB. Several different grading systems have been described for salivary gland cancer which are often inconsistently employed [23–27]. There is generally good consensus when classifying low- and high-grade malignancy, but variability often exists in defining intermediate-grade tumors [28].

5. Conclusion

In patients with early stage intermediate-grade mucoepidermoid or acinic cell carcinoma, young age, private insurance, and less than total parotidectomy are associated with improved overall survival. Those with negative margin resections may be considered for omission of adjuvant therapy, while involved surgical margins should be managed with post-operative radiation. Future prospective trials should include intermediate-grade disease to better define those patient subgroups which benefit from the addition of adjuvant therapy.

Declaration of competing interest

There are no conflicts of interest.

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The data used in this study are derived from a de-identified NCDB file. The American College of Surgeons and The Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

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