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CLINICAL INVESTIGATION **Head and Neck**

ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK TREATED BY SURGERY WITH OR WITHOUT POSTOPERATIVE RADIATION THERAPY: PROGNOSTIC FEATURES OF RECURRENCE

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Purpose: This study sought to review a single-institution experience with the management of adenoid cystic carcinoma of the head and neck.
Methods and Materials: Between 1960 and 2004, 140 patients with adenoid cystic carcinoma of the head and neck were treated with definitive surgery. Ninety patients (64%) received postoperative radiation to a median dose of 64 Gy (range, 54–71 Gy). Distribution of T stage was: 26% T1, 28% T2, 20% T3, and 26% T4. Seventy-eight patients (56%) had microscopically positive margins. Median follow-up was 66 months (range, 7–267 months).
Results: The 5- and 10-year rate estimates of local control were 88% and 77%, respectively. A Cox proportional hazards model identified T4 disease ($p = 0.0001$), perineural invasion ($p = 0.008$), omission of postoperative radiation ($p = 0.007$), and major nerve involvement ($p = 0.02$) as independent predictors of local recurrence. Radiation dose lower than 60 Gy ($p = 0.0004$), T4 disease ($p = 0.005$), and major nerve involvement ($p = 0.02$) were predictors of local recurrence among those treated with surgery and postoperative radiation. The 10-year overall survival and distant metastasis-free survival were 64% and 66%, respectively.
Conclusion: Combined-modality therapy with surgery followed by radiation to doses in excess of 60 Gy should be considered the standard of care for adenoid cystic carcinoma of the head and neck.

Adenoid cystic carcinoma, salivary gland, surgery, radiation therapy.

INTRODUCTION

Initially described by Billroth in 1856 and named cylindroma for its classic histologic appearance, adenoid cystic carcinoma comprises approximately 10% of salivary gland neoplasms and is the predominant histologic type among malignancies of the minor salivary glands and the submandibular gland (1–3). Although the histologic appearance is low grade, management of this malignancy is a distinct therapeutic challenge because of its insidious local growth pattern, propensity for perineural involvement, tendency for distant metastasis, and pronounced ability to recur over a prolonged period.

For nearly all patients, surgery represents the mainstay of treatment. Historically, salivary gland cancers were thought to be radioresistant until publications by Stewart *et al.* in 1968 and King and Fletcher in 1971 showed that surgery followed by adjuvant radiation therapy provided superior disease control compared with either modality alone (4, 5). However, the role of postoperative radiation therapy is still controversial, and indications for its use currently differ both within and between institutions. Although some physicians advocate radiation therapy for essentially all patients with adenoid cystic carcinoma of the head and neck, others reserve radiation therapy for only those with unfavorable features such as perineural invasion or positive surgical margins (6–10).

The purpose of this study is to review a long-term, single-institution experience with the management of adenoid cystic carcinoma of the head and neck focusing on patterns of recurrence after surgery with or without postoperative radiation therapy in an attempt to identify clinical and pathologic parameters correlating with outcomes.

METHODS AND MATERIALS

Patient population

This study was formally approved by the Institutional Review Board at the University of California, San Francisco (UCSF) School of Medicine before the retrospective review of patient information. Between January 1960 and June 2004, 155 consecu-

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Table 1. Patient characteristics

Characteristic	Total patients (%)	Surgery alone (%)	Surgery plus radiation therapy (%)
Primary site			
Parotid	20 (14)	11 (22)	9 (10)
Submandibular	25 (18)	15 (30)	10 (11)
Sublingual	10 (7)	2 (4)	8 (9)
Oral cavity	33 (24)	11 (22)	22 (24)
Oropharynx	12 (9)	3 (6)	9 (10)
Hypopharynx	5 (4)	1 (2)	4 (4)
Paranasal sinus	28 (20)	7 (14)	21 (23)
Trachea	4 (3)	0 (0)	4 (4)
Lacrimal	3 (2)	0 (0)	3 (3)
T stage			
1	37 (26)	23 (46)	14 (16)
2	39 (28)	10 (20)	29 (32)
3	28 (20)	7 (14)	21 (23)
4	36 (26)	10 (20)	26 (29)
Age (y)			
<40	20 (14)	6 (12)	14 (15)
40–60	62 (44)	20 (40)	42 (47)
>60	58 (41)	24 (48)	34 (38)
Margin status			
Negative	62 (44)	29 (58)	33 (37)
Positive	78 (56)	21 (42)	57 (63)
Perineural invasion			
No	58 (41)	25 (50)	33 (37)
Yes	82 (59)	25 (50)	57 (63)
Major nerve involvement			
No	128 (91)	50 (100)	78 (87)
Yes	12 (9)	0 (0)	12 (13)
Bone invasion			
No	115 (82)	49 (98)	66 (73)
Yes	25 (18)	1 (2)	24 (27)

tively treated patients with a histologic diagnosis of adenoid cystic carcinoma localized to the head and neck were definitively treated at UCSF. The following patients were excluded from this analysis: 8 patients with recurrent disease, 5 patients treated with radiation therapy alone for surgically unresectable or medically inoperable disease, and 2 patients treated with radiation therapy for gross residual disease after subtotal resection. Table 1 outlines the clinical and disease characteristics of the 140 remaining patients who had gross total tumor resection and comprised the primary population of this retrospective review. Median age was 57 years (range, 11–91 years). Eighty-one patients (58%) were male. Racial distribution was as follows: 75 Caucasian (54%), 26 Asian (19%), 20 Hispanic (14%), and 19 black (14%).

Staging evaluation consisted of history and physical examination, complete blood count, liver function tests, chest X-ray, and imaging of the primary site. Sixty patients (43%) underwent magnetic resonance imaging (MRI) of the head and neck as a component of the initial workup. Axial imaging with computed tomography (CT) has generally been a routine part of patient evaluation since it became available at UCSF in 1974. Tumors of the major salivary glands were retrospectively staged in accordance with the 2003 American Joint Committee on Cancer (AJCC) staging system. Those involving the minor salivary glands were staged using the criteria for squamous cell carcinoma in similar sites. Adenoid cystic carcinoma arising in the minor salivary glands (61%) was more common than those arising in the major salivary glands (39%). The most common site of involvement was the oral cavity (33 patients), most frequently the hard palate (21 patients), followed by the paranasal sinuses (28 patients), the submandibular gland (25 patients), and parotid gland (20 patients). Less common sites of involvement were the oropharynx (12 patients), sublingual glands (10 patients), hypopharynx (5 patients), trachea (4 patients), and lacrimal glands (3 patients). Distribution of T stage was as follows: 26% T1, 28% T2, 20% T3, and 26% T4.

Treatment

All patients were treated with definitive surgery. The type of procedure was dependent on the primary site, extent of disease, cosmetic considerations, and discretion of the surgeon. In general, an attempt was made to maximize local control with preservation of cosmetic and functional outcomes. Seventy-eight patients (56%) had microscopically positive margins, and 62 (44%) had negative surgical margins. Eighty-two (59%) had perineural invasion, 12 (9%) had pathologic invasion of a major (named) nerve, and 25 (18%) had evidence of bone invasion. Because histologic grading was not routinely assessed during the time period of this study, this parameter was not analyzed.

Ninety patients, representing 64% of the study population, received postoperative radiation therapy. No definite policy existed regarding postoperative radiation therapy, but, in general, patients were referred for radiation therapy at the discretion of the treating surgeon when there was uncertainty about the completeness or adequacy of the excision based on intraoperative and pathologic findings. Radiation technique varied depending largely on the site of disease, the time period of treatment, and the discretion of the radiation oncologist. All patients were treated with megavoltage equipment using photons or mixed photons and electrons. The treatment volume was designed to cover the primary site with 2- to 3-cm margins. The base of the skull was routinely treated for all tumors with perineural invasion. None of the patients received interstitial or intraoperative radiation therapy. The interval between surgery and the start of radiation therapy ranged from 6 to 177 days (median, 29 days), with 19 patients (21%) beginning treatment in excess of 42 days after surgery. Patients were treated with conventional fractionation, most commonly 2 Gy per fraction. Median dose was 64 Gy (range, 54–71 Gy). Treatment was by continuous-course radiation with once-per-day treatment. Radiation therapy techniques included mixed photon-electron appositional fields (24 patients), wedged pair fields (21 patients), 3-field isocentric treatments (12 patients), and parallel opposed lateral fields prescribed to midplane (11 patients). Wedges or tissue compensators were used to maintain dose homogeneity within 10% of the prescribed dose. Beginning in 1997, intensity-modulated radiation therapy (IMRT) was used and 22 patients were treated with this technique. Ten patients (7%) received adjuvant chemotherapy, 8 concurrently with radiation therapy and 2 after radiation therapy. Details of radiation therapy are summarized in Table 2.

Treatment of the neck was dependent on multiple factors. Six patients (4%) presented with palpable cervical lymphadenopathy (upper jugular). All of these patients underwent a neck dissection followed by postoperative radiation. Elective neck radiation was administered at the discretion of the treating radiation oncologist with consideration given to the extensiveness and lymphatic drainage of the primary tumor. No definitive policy existed regarding regional lymph node treatment in patients with a clinically negative neck during the time span of this analysis. Overall, 49 of the 90 patients (54%) treated with surgery and postoperative radiation therapy received elective neck radiation.

Table 2. Radiation therapy details

Characteristic	No. of patients (%)
RT technique	
Wedged pair	21 (23)
Mixed beam	24 (27)
2-field	11 (12)
3-field	12 (13)
IMRT	22 (24)
Radiation dose	
<60 Gy	20 (22)
≥60 Gy	70 (78)
Days from surgery to RT	
<14	9 (10)
14–42	60 (67)
42–60	9 (10)
>60	12 (13)
Elective neck irradiation	
No	41 (46)
Yes	49 (54)
Decade of treatment	
1960s	4 (4)
1970s	15 (17)
1980s	29 (32)
1990s	29 (32)
2000s	13 (14)

Abbreviations: RT = radiation therapy; IMRT = intensity-modulated radiation therapy.

Follow-up consisted of routine physical examination and appropriate imaging studies of the primary site. Patients were typically seen at 3-month intervals for 1 year and then annually thereafter. Patient follow-up was reported to the date last seen in clinic. Survival status was obtained from information provided by the UCSF Tumor Registry and from publicly accessible databases using patient Social Security numbers. In some cases, referring physicians were contacted to obtain information regarding patient health status.

Endpoints and statistical analysis

The endpoints analyzed were overall survival, local control, and distant metastasis. All events were measured from the date of histologic diagnosis of the initial biopsy specimen. Median follow-up was 66 months (range, 7–267 months). Tests of association or categorical variables were performed using a chi-square statistic. Five-year and 10-year estimates of the probability of overall survival, local control, and distant metastasis–free survival were calculated using the Kaplan-Meier method, with comparisons among groups performed with two-sided log–rank tests (11). A Cox proportional hazards model was used to identify independent predictors of local recurrence and distant metastasis (12). Selection of variables to consider as predictors was based on univariate analysis. A stepwise forward method was carried out, and the likelihood ratio test (LLR) was used to identify significant independent predictors of outcomes. Hazards ratio parameters were determined using the Wald test. All tests were two-tailed, with a probability value of <0.05 considered statistically significant.

RESULTS

Survival

Overall survival for the entire patient population at 5 and 10 years was 85% and 64%, respectively. Univariate analysis of the clinical and pathologic variables analyzed did not reveal any differences in overall survival with the following exceptions. As might be expected, survival decreased as age at diagnosis increased (age >60 years vs. age <60 years, $p = 0.01$). Furthermore, increased T stage seemed to be associated with decreased survival, with patients having Stage T1 disease surviving significantly longer than patients with Stages T2, T3, and T4 disease ($p = 0.01$). The 5- and 10-year estimates of overall survival rates were 97% and 84% for patients with T1 tumors, 83% and 52% for patients with T2 tumors, 82% and 75% for patients with T3 tumors, and 74% and 49% for those with T4 tumors, respectively ($p = 0.24$). Notably, the use of postoperative radiation therapy was not associated with a significant improvement in overall survival at 10 years (65% for surgery and postoperative radiation therapy vs. 60% for surgery alone, $p = 0.21$).

Local control

Twenty-three patients experienced a local recurrence, 14 of which were isolated first events. For the entire patient population, the 5-year and 10-year estimates of local control were 88% and 77%, respectively. The median time to local recurrence had not yet been reached at the time of this analysis, with 10 of the local recurrences occurring after 5

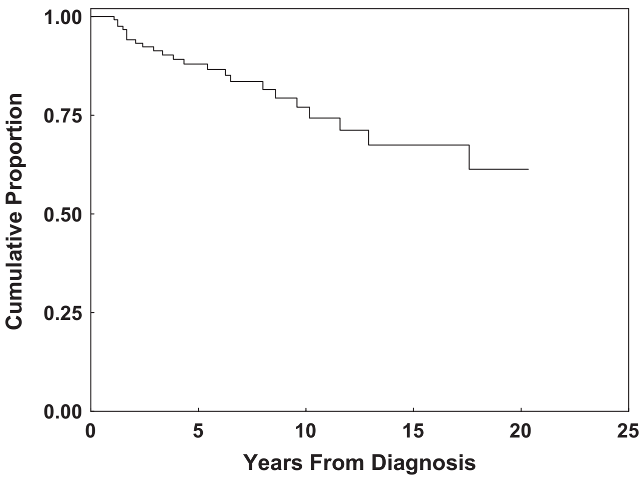

Fig. 1. Local control for all patients treated by surgery with or without postoperative radiation therapy.

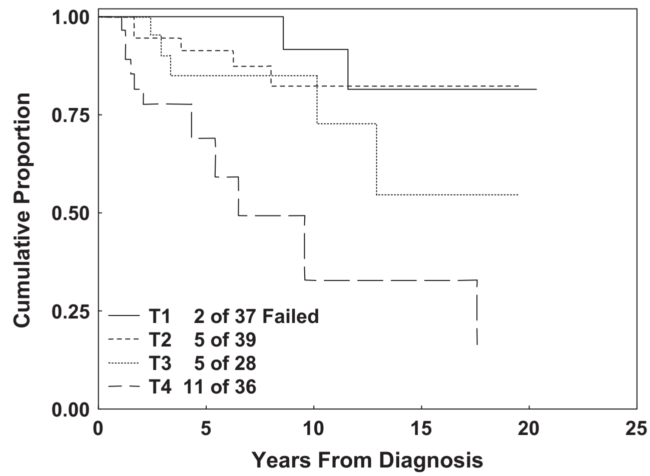

Fig. 2. Local control for patients treated by surgery with or without postoperative radiation therapy according to T stage.

years from the time of diagnosis. Figure 1 illustrates local control for the entire patient population.

Table 3 summarizes local control rates according to clinical and disease characteristics for the entire patient population. On univariate analysis, parameters predictive of local recurrence were Stage T4 disease, positive surgical margins, perineural invasion, major (named) nerve involvement, and omission of postoperative radiation therapy ($p < 0.05$ for all). As illustrated in Fig. 2, the 10-year rates of local control for patients with Stages T1, T2, T3, and T4 tumors were 92%, 82%, 85%, and 33%, respectively ($p = 0.001$). Notably, there was no statistical difference in local control among patients with Stages T1, T2, and T3 tumors ($p = 0.19$). However, when patients with Stage T4 tumors were compared with those with Stages T1–T3 tumors, statistically significantly poorer local control was observed in Stage T4 patients (83% vs. 33%, $p = 0.0003$). With respect to surgical margins, the 10-year local control rates were 92% and 68% for patients with microscopically negative and positive margins, respectively ($p = 0.01$). For patients without and with perineural invasion, the 10-year local control rates were 87% and 69%, respectively ($p = 0.04$). Additionally, the small subset of patients with major nerve involvement experienced a high rate of local recurrence (5 of 12 patients), which yielded a 10-year local control of 18%, compared with 82% for patients without major nerve involvement ($p = 0.01$). Although the presence of major nerve involvement seemed to predict strongly for local recurrence on univariate analysis, this feature was highly associated with patients with Stage T4 disease (8 of 12 patients, $p = 0.002$) and positive surgical margins (10 of 12 patients, $p = 0.004$). The primary tumor site ($p = 0.11$), age at diagnosis ($p = 0.12$), and bone invasion ($p = 0.10$) did not indicate a difference in local control.

Figure 3 shows local control according to the use or omission of postoperative radiation therapy. Eleven of 90 patients who received postoperative radiation therapy experienced a local recurrence, compared with 12 of 50 patients who did not receive postoperative radiation therapy. The 5- and 10-year rates of local control were 92% and 84%, respectively, for the patients treated with postoperative radiation compared with 80% and 61%, respectively, for those treated with surgery alone ($p = 0.03$). The median follow-up time for those treated with surgery and postoperative radiation therapy was 60 months compared with 72 months

Table 3. Local control by clinical and pathological factors

Factor	No. of failures	5-yr LC (%)	10-yr LC (%)	*p*
T stage				0.001
T1	2 of 37	100	92	
T2	5 of 39	91	82	
T3	5 of 28	85	85	
T4	11 of 36	69	33	
Primary site				0.11
Major gland	7 of 55	90	80	
Minor gland	16 of 85	85	75	
Age (y)				0.12
<40	4 of 20	87	80	
40–60	7 of 62	93	83	
>60	12 of 58	83	69	
Margin status				0.01
Negative	4 of 62	95	92	
Positive	19 of 78	83	68	
Perineural invasion				0.04
No	6 of 58	96	87	
Yes	17 of 82	82	69	
Major nerve involvement				0.01
No	18 of 128	90	82	
Yes	5 of 12	55	18	
Bone invasion				0.10
No	17 of 115	90	82	
Yes	6 of 25	77	50	
Postoperative RT				0.03
No	12 of 50	80	61	
Yes	11 of 90	92	84	

Abbreviations: RT = radiation therapy; LC = local control.

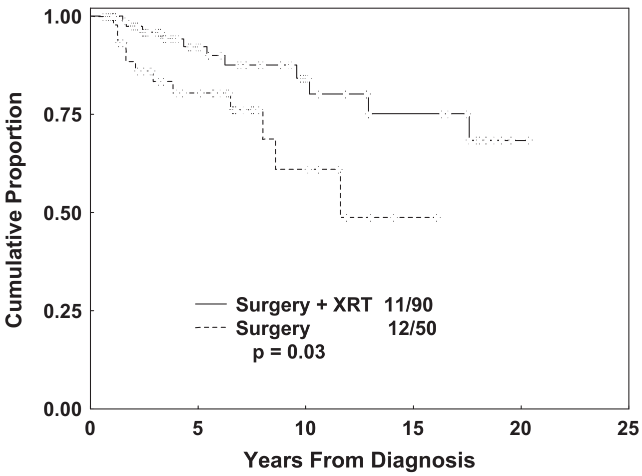

Fig. 3. Local control for patients according to omission or inclusion of postoperative radiation therapy.

for those treated with surgery alone ($p = 0.14$). As is evident in Table 4, strong associations existed between the use of postoperative radiation therapy and other disease characteristics. Patients who received postoperative radiation therapy had a smaller proportion with Stage T1 disease ($p < 0.001$) and were more likely to have positive margins ($p = 0.02$). Furthermore, no patients with major nerve involvement and only one with bone involvement were treated with surgery alone.

Among the 50 patients treated with surgery alone, Stage T4 disease, positive margins, and perineural invasion predicted for local recurrence on univariate analysis ($p < 0.05$ for all). Patients with Stage T4 disease had the poorest local control, with 5 of 10 patients experiencing local recurrence compared with 7 of 40 with Stages T1–T3 tumors ($p = 0.01$). Two of 29 patients with negative margins had local failure compared with 10 of 21 with positive margins, leading to 10-year local control rates of 90% and 30% ($p = 0.001$), respectively. Two of 25 patients without perineural invasion had local failure compared with 10 of 25 patients with perineural invasion, yielding 10-year local control rates of 76% and 46% ($p = 0.01$), respectively. Notably, none of the 13 patients treated with surgery alone for T1 tumors, negative margins, and no perineural invasion experienced a local recurrence with a median follow-up of 76 months.

Among the 90 patients who were treated with surgery and postoperative radiation therapy, increased T stage (T1–T3 vs. T4), major nerve involvement, and bone invasion predicted for local recurrence on univariate analysis ($p < 0.05$ for all). In contrast to patients treated with surgery alone, neither positive surgical margins ($p = 0.20$) nor perineural invasion ($p = 0.54$) was significantly associated with local recurrence in this cohort. When radiation dose was analyzed as a categorical variable using the median dose of 64 Gy as a cutpoint, a statistical difference in local control was observed (<64 vs. ≥64 Gy, $p = 0.01$). Similarly, a statistically significant advantage in local control was also observed among patients treated with doses greater than 60 Gy ($p = 0.004$). The time interval between surgery and beginning of radiation therapy (<42 days vs. ≥42 days, $p = 0.02$) also indicated a difference in local control. Last, the decade of treatment did not predict for local control ($p = 0.22$).

A multivariate analysis of the entire patient sample was performed using a Cox proportional hazards model considering T stage (T1–T3 vs. T4), margin status, perineural invasion, major nerve involvement, bone invasion, use of postoperative radiation therapy, and age at diagnosis as possible predictors of local recurrence. Stage T4 disease, per-

Table 4. Local control rate with or without postoperative RT

Factor	Surgery alone		Surgery plus RT	
	No. of failures	10-yr LC (%)	No. of failures	10-yr LC (%)
T stage				
T1	2 of 23	83	0 of 14	100
T2	4 of 10	44	1 of 29	94
T3	1 of 7	67	4 of 21	88
T4	5 of 10	0	6 of 26	37
Margin status				
Negative	2 of 29	90	2 of 33	92
Positive	10 of 21	30	9 of 57	80
Perineural invasion				
No	2 of 25	76	4 of 33	90
Yes	10 of 25	46	7 of 57	80
Major nerve involvement				
No	12 of 50	61	6 of 78	93
Yes	0 of 0	–	5 of 12	18
Bone invasion				
No	11 of 49	62	6 of 66	93
Yes	1 of 1	–	5 of 24	53

Abbreviations as in Table 3.

ineural invasion, the omission of postoperative radiation therapy, and major nerve involvement were significant independent predictors of local recurrence (LLR test: p = 0.0001, 0.008, 0.007, and 0.02, respectively) and were identified in that order of importance in developing the predictive model as outlined in Table 5. Further exploratory analyses indicated that treatment with doses lower than 60 Gy (LLR test: p = 0.0004), Stage T4 disease (p = 0.005), and major nerve involvement (p = 0.02) were independent predictors of local recurrence among those treated with surgery and postoperative radiation therapy. If bone invasion status and time interval between surgery and radiation were also considered as possible predictors, the final predictive model did not change. Among those treated with surgery alone, positive surgical margins (p = 0.001) and Stage T4 disease (p = 0.05) were independent predictors of local recurrence. In this subset, bone invasion (1 patient) and major nerve involvement (no patients) was not evaluable. The consistent impact of T stage within each treatment group indicated that it was the most significant predictor of local recurrence overall.

Distant metastasis

The most common pattern of tumor relapse was distant metastasis, which developed in 35 patients. Three patients had a simultaneous local recurrence, and 3 others had a previous local recurrence. Median time to the development of distant metastasis had not yet been reached (range of time to distant metastasis, 4–166 months) with 9% of distant metastasis occurring more than 5 years from the time of original diagnosis. As illustrated in Fig. 4, rates of distant metastases–free survival for the entire patient population were 77% and 66% at 5 and 10 years, respectively. The presence of bone involvement was associated with a significantly greater occurrence of distant metastases (p = 0.03), with only 36% of these patients remaining free of distant disease at 10 years compared with 71% among those without bone involvement. In addition, younger patients, those under 40, had a prolonged distant metastases–free duration (p = 0.01). When a model predictive of distant metastases was developed using the Cox proportional hazards model, age >40 (LLR test: p = 0.005) and the presence of major nerve involvement (p = 0.02) were identified as independent predictors of distant disease. Last, the use of postoperative radiation therapy was not associated with distant metastasis–free survival (p = 0.58).

Table 5. Cox regression analysis: independent predictors of local recurrence

Variable: increased risk	Hazards ratio	95% CI	Wald test probability
T4	6.37	2.48–16.36	0.0001
Omission of RT	5.82	1.96–17.26	0.002
Major nerve involvement	5.39	1.42–20.50	0.01
Perineural invasion	3.05	1.13–8.24	0.03

Abbreviations: CI = confidence interval; RT = radiation therapy.

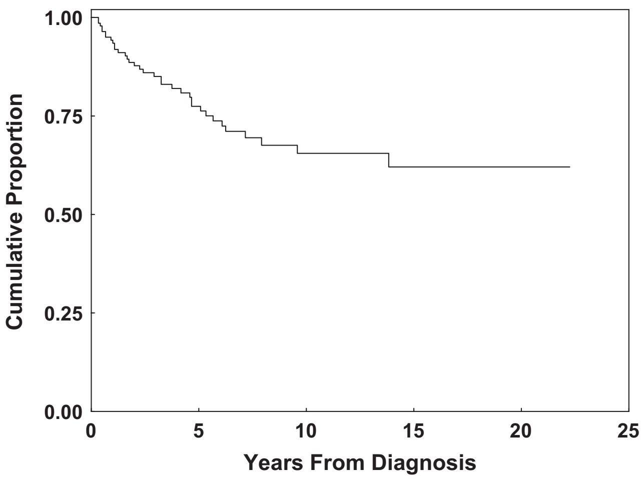

Fig. 4. Distant metastases–free survival for the entire patient population.

Sites of failure

Two patients experienced a base of skull recurrence, both of whom were treated with surgery alone and had evidence of perineural invasion. All other local recurrences were localized to the original operative site. There were no cervical nodal failures. Sites of distant failure were as follows: 25 lung (71%), 5 bone (14%), 3 liver (9%), and 2 brain (6%).

DISCUSSION

In our previous analysis of 22 patients with adenoid cystic carcinoma of the head and neck treated at UCSF between 1960 and 1978, 13 of 22 patients (59%) achieved initial control of the primary tumor, including only 3 of 10 patients (30%) treated with surgery alone (13). This update of all patients treated to the present continues to provide convincing evidence to support the routine use of combined-modality therapy with surgery and postoperative radiation therapy in the definitive treatment of patients with adenoid cystic carcinoma of the head and neck. In addition, Stage T4 disease, major nerve involvement, and the use of radiation doses less than 60 Gy were identified as independent predictors of local recurrence after this approach. However, even in the presence of adverse risk factors such as these, the use of postoperative radiation seemed to result in dramatic improvements in local control compared with surgery alone.

The present series represents the largest series to date comparing the outcomes of patients with adenoid cystic carcinoma of the head and neck treated with surgery alone to those treated with postoperative radiation therapy. Our finding that the addition of postoperative radiation therapy leads to enhanced local control is in accordance with the results of other retrospective series. Miglianico *et al.* from the Institut Gustave Roussy showed 5-year local control rates of 78% with surgery and postoperative radiation therapy compared with 44% with surgery alone (14). Simpson *et al.* from the Mallinckrodt Institute of Radiology showed that 10-year local control was 83% for patients treated with surgery and postoperative radiation therapy compared with only 25% for those treated with surgery alone (15). Most recently, Cohen *et al.* from the UCLA reported local control rates of 82% and 70%, respectively, for patients treated with and without postoperative radiation therapy for adenoid cystic carcinoma of the submandibular gland with median follow-up of 67 months (16). It is interesting to note that the improvement in local control was observed in all of these studies despite the selection bias toward more adverse prognostic features in the combined modality group.

Overall, the most favorable results from the literature seem to be from patients treated with a combined modality approach. The 5- and 10-year local control rates of 92% and 84%, respectively, observed in the present study for patients treated with surgery and postoperative radiation therapy compare closely to those from other single-institution series. Garden *et al.* reported 5-year and 10-year local control rates of 95% and 86%, respectively, for 198 patients treated at The University of Texas M.D. Anderson Cancer Center with surgery and postoperative radiation therapy (17). Similar to the results of this present study, they concluded that positive surgical margins and major nerve involvement were associated with risk of local recurrence. More recently, Mendenhall *et al.* reported 5-year and 10-year local control rates of 94% and 91% for 56 patients treated at the University of Florida with combined-modality therapy and identified increased T stage as a predictor of local failure (18). In aggregate, these large retrospective series suggest that combined-modality therapy with surgery and postoperative radiation therapy be considered the standard of care for patients with adenoid cystic carcinoma of the head and neck.

Other groups, however, have shown no local control advantage with the addition of postoperative radiation therapy. In an analysis from Yale University, Khan *et al.* were unable to identify any differences in local control among 69 patients treated with a variety of approaches for adenoid cystic carcinoma of the head and neck (19). Similarly, Kokemueller *et al.* reported a 5-year local control rate of 56% in 74 patients treated at the Hanover Medical School in Germany and could not show a benefit with postoperative radiation therapy (20). Most recently, Silverman *et al.* from the Cleveland Clinic observed a local control benefit for postoperative radiation therapy only among patients with Stage T4 tumors and/or positive margins (21). Differences in selection criteria and therapeutic approach across institutions probably account for the discrepancy between observed outcomes. For instance, studies showing no advantage to postoperative radiation therapy often included patients with gross residual disease and/or locally recurrent tumors, and it is unknown whether radiation treatment volumes included the skull base. At UCSF, we regard perineural invasion as a marker for subclinical extension of disease that may not be adequately addressed by surgery alone, even in the setting of an apparently complete surgical resection. The base of the skull is routinely included in the postoperative treatment volume when there is perineural invasion. The fact that perineural invasion was associated with local recurrence for patients treated with surgery alone, but not for those treated with surgery and postoperative radiation therapy, strongly supports the idea that radiation delivered through carefully designed portals may be effective in eradicating subclinical deposits.

Given that the incidence of occult lymph node involvement for adenoid cystic carcinoma of the head and neck is generally thought to be quite low, with Armstrong *et al.* reporting a rate of 4% among those with major salivary gland cancers, it is noteworthy that more than half of the patients in the present series received elective neck irradiation (22). Although the role of elective neck irradiation has recently become more clearly defined for this disease, our data span a period of 5 decades and include patients irradiated at a time when treatment recommendations were largely unknown. Although our current policy is to not recommend elective neck irradiation routinely, treatment of the neck is made on an individualized, case-by-case basis, with careful consideration given to the extensiveness and lymphatic drainage pattern of the primary tumor, as well as the potential for morbidity.

Our findings suggest that a dose–response relationship might exist for adenoid cystic carcinoma of the head and neck. Other studies examining the impact of dose on local control in this setting have reported similar results. Vikram *et al.* from Memorial Sloan-Kettering Cancer Center showed a significant overall survival advantage in patients who received >45 Gy (23). Garden *et al.* also detected a trend toward improved local control with doses ≥56 Gy, with statistical significance attained for patients with positive margins (17). Last, Simpson *et al.* showed statistically improved local control for patients receiving doses ≥60 Gy (15).

Finally, the distant metastasis rate observed is consistent with that in other reports and most likely suggests that improvements in systemic therapy are needed before a significant overall survival benefit of postoperative radiation therapy may be detected (24–26). Nonetheless, patients with distant metastases from adenoid cystic carcinoma can survive for long periods of time, which attests to the importance of local control to minimize morbidity and maintain quality of life. Although the present report does not examine complications secondary to treatment, results from other groups have shown that combined modality therapy for salivary gland malignancies is in general well tolerated (26–28). Although subject to the inherent limitations of any retrospective study, our results show that surgery and postoperative radiation therapy are an effective treatment strategy for patients with adenoid cystic carcinoma of the head and neck and support our policy of recommending postoperative radiation therapy to all patients except possibly for the minority who present with completely excised, small lesions without perineural invasion. In light of the relatively short follow-up duration, continued monitoring of the patients in this series is imperative to better delineate the natural history of this disease in the future.

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