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Long term local control rates of patients with Adenoid Cystic Carcinoma of the Head and Neck managed by Surgery and Post-Operative Radiation

Safina Ali, MD¹, Frank L Palmer, BA¹, Nora Katabi, MD³, Nancy Lee, MD², Jatin P. Shah, MD¹, Snehal G. Patel, MD¹, and Ian Ganly, MD, PhD¹

¹Head and Neck Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065

²Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065

³Department of Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065

Abstract

Objectives—To report long term local control in patients with adenoid cystic cancer (ACC) of the head and neck managed by surgery and identify factors predictive for local failure.

Study Design—Single institution retrospective cohort study

Methods—87 patients who had surgery for ACC between 1985–2009 were identified. Patient, tumor and treatment characteristics were recorded. Local recurrence free survival (LRFS) was recorded by the Kaplan Meier method. Predictors of local control were identified.

Results—The median age was 54 years. 72(83%) had perineural invasion, 61(70%) close/positive margins, 58(67%) pT1T2. 59(68%) patients had PORT. With a median follow up of 85 months, the 10 year LRFS was 78.7%. There were 14 local recurrences. On multivariable analysis, pathological T3T4 stage and no PORT were independent predictors for local failure. Patients with no PORT had a 13 fold increased risk of local failure compared to patients treated with PORT (p=0.003) after adjusting for stage.

Conclusion—After adjusting for T stage, patients who do not get PORT are more likely to have local recurrence.

Keywords

Salivary gland; Adenoid Cystic Carcinoma; Local Recurrence; Radiotherapy

Introduction

Adenoid cystic carcinoma (ACC) is a rare tumor of the salivary glands, and accounts for only 1% of all head and neck malignancies¹. It affects people in all decades of life and has no known risk factors. Histologically, there are three main growth patterns : solid, cribriform, and tubular patterns. Solid ACC has been reported to show a more aggressive biological behaviour^{2,3,4}. Surgery with post-operative radiation therapy (PORT) forms the cornerstone of treatment. ACC has a predilection for perineural invasion which may increase the risk for local recurrence⁵. Other factors associated with local failure include advanced T stage and the presence of positive margins^{2,3,5}. These factors are considered indications for post-operative radiation, although perineural invasion as an isolated factor is controversial if no named nerves are involved⁶. The aim of our study was to report the long term local control rate of a large series of patients with ACC treated at a single institution. In particular we wanted to assess the impact of these factors on local control.

Materials and Methods

After obtaining approval from the institutional review board, we identified 87 patients with ACC of the head and neck treated with curative intent with surgery at Memorial Sloan Kettering Cancer Center (MSKCC) between 1985–2009. Only patients with ACC of the major salivary glands and ACC of minor salivary glands of the oral cavity and oropharynx were selected for study. ACC of the larynx, trachea, sinonasal complex were not included in the study. Only patients who had surgery with the intent of curative resection were included in the analysis; patients deemed to be unresectable (ie R2 resection) were excluded from this study. Surgery involved resection of the primary tumor with appropriate reconstruction. A selective approach was carried out for neck dissection. Our selection criteria are clinically positive nodes, large T stage tumors, cases where the neck had to be opened as part of an transcervical access approach such as for cancers of the base of tongue or any case where free flaps were indicated for reconstruction of the primary defect. Indications for postoperative radiation included stage III/IV cancers and adverse pathological factors such as close/positive margins and perineural invasion. In brief, the median prescription dose delivered to the post-operative bed was 63 gray (Gy). If margins were positive, this dose was 66Gy. For IMRT patients, the high-risk clinical target volume (CTV) included the pre-operative gross disease and the post-operative tumor bed at the primary site, along with any nodal regions with disease involvement. The margin for high-risk CTV was generally 0.5 cm. In patients with perineural invasion the field of radiation involved the path of nerves to the skull base. Therefore the radiation field is designed to encompass the potential spread of nerves. For tumors of the parotid gland the field covers cranial nerves V, VII and IX. For tumors of the submandibular gland and sublingual gland the radiation field covers cranial nerves V and XII. For tumors of the hard palate the radiation field covers cranial nerve V.

Patient, tumor and treatment characteristics were recorded from patient charts. All pathology details including histological subtype, margin status, and perineural invasion were re-reviewed by a single pathologist with a special interest in salivary gland pathology (NK). Margin status was categorised as negative, close (<1mm) or positive. Histological subtypes were classified as cribriform, tubular or solid. Perineural invasion was classified as either

none, focal (< 4 foci) or extensive (> 4 foci). Overall survival (OS), disease specific survival (DSS) and local recurrence free survival (LRFS) were recorded by the Kaplan Meier method. Local recurrence was defined as recurrence at the primary site. Patients with regional recurrence were not included in the analysis. The impact of age, gender, primary tumor site, T stage, N stage, M stage, perineural invasion, margin status, histological subtype, post-operative radiation on local control were determined by univariable analysis. Unadjusted and adjusted hazard ratios for variables important for local control were determined using Cox proportional hazards model. Statistical analysis was carried out using the SPSS Statistics package (IBM Corporation, Armonk, NY).

Results

Patient characteristics are shown in Table 1. Of the 87 patients, there were 25(29%) males and 62 (71%) females with a median age of 54 years (range 22–88 years). Forty seven (54%) were smokers and the same number consumed alcohol. The site of primary tumor was major salivary glands (ie. parotid, submandibular and sublingual) in 28 patients (32%) and minor salivary gland in 59 patients (68%) [45(52%) oral cavity and 14 (16%) oropharynx]. Fifty four (63%) of the patients were clinically staged T1/T2 and 3 had clinical nodal disease. Table 1 shows the tumor characteristics. Perineural invasion (PNI) was present in 74 (85%) patients, 61(70%) patients had close/positive margins and 58 (67%) were pT1T2. Histological subtypes were solid 5(6%), tubular 16(18%) and cribriform 58(67%). Table 2 shows the treatment characteristics for our group. 30 (33%) patients were selected to have a neck dissection and 58(67%) underwent post-operative radiation (PORT). Post-operative radiation was delivered by conventional RT technique in 42 patients (72%), by IMRT in 13(22%) patients, and 3 (5%) patients received proton therapy.

With a median follow up of 85 months, the 10 year overall survival (OS) and disease specific survival (DSS) were 50.8% and 59.2% respectively. Of 87 patients there were 4 regional lymph node recurrences none of whom had local failure. The 10 year local recurrence free survival (LRFS) was 78.7%. Fourteen patients had local recurrence. Clinical, tumor and treatment characteristics of these 14 patients are shown in Supplementary Table 1. Factors predictive of local control are shown in Table 3. Age over 55 years of age and no PORT were predictive of poorer local control on univariate analysis. Patients who did not receive PORT had a poorer LRFS compared to those who did receive PORT (41.6% vs 90.1%, $p=0.002$) (Figure 1). Table 4 shows the unadjusted and adjusted hazard ratios for variables important for local control. The unadjusted hazard ratio for age >55, pT3T4 stage and no PORT were 3.2, 2.8 and 4.8 respectively. After adjusting for other variables, the adjusted hazard ratio for no PORT was 12.7, $p=0.003$. ie. patients who did not get PORT had a 13 fold increased risk of local failure. The adjusted hazard ratio for pT3T4 stage was 9.5, $p=0.003$.

Discussion

Adenoid cystic carcinoma (ACC) is a rare tumor of the salivary glands and accounts for 1% of all head and neck malignancies¹. Recognised characteristics of ACC are the predilection for perineural invasion (PNI), local recurrence and for late distant metastases which are

usually pulmonary^{5,6,7,8}. The objectives of our study were to report the long term local control rate and report on factors predictive of local failure. In our study we report a local control rate of 89% at 5 years and 79% at 10 years and show that pathological T3/T4 status and no PORT to be independent predictors of local failure.

Our 5 and 10 year local control rates of 89% and 79% compare very favourably with the literature. A recent international collaborative study of over 180 patients with ACC treated over 40 years, reported a 5 year and 10 year local recurrence free survival rate of 68% and 41%⁹. This study also showed that at 10 years, local recurrence free survival was significantly worse following radiotherapy alone compared with surgery alone or surgery combined with post-operative radiotherapy⁹. The authors also reported advanced tumor stage, PNI, solid growth pattern or close/positive margins predicted local recurrence. Another series reported that local control was predicted by clinical T-stage, bone invasion, site, resection margin, and treatment¹⁰. Other studies have also reported the tumor subsite to be an important predictor of local recurrence. The local failure rate is higher in ACC arising from the minor salivary glands, at sites such as the pharynx and sino-nasal complex^{11,12}. Sino-nasal ACC in particular has a local recurrence rate as high as 37%¹¹. Unlike these previous studies, our data did not show PNI or margin status to be predictive of local control. A recent study by Van Weert et al also reported PNI was not prognostic¹³. In addition, tumor subsite was also not predictive although it must be pointed out that our series did not include any sinonasal ACC which have been reported to have the poorest local control rates. In our series, it was advanced T stage and the lack of PORT which were the main predictors of local failure.

The association between local failure and PORT requires a detailed discussion as this remains a controversial subject. A recent study from the SEER database on 3026 patients reported by Ellington et al¹² suggested PORT conferred no survival benefit. Another population based study reported by Lloyd et al¹⁴ also suggested the same. In contrast, other studies have suggested PORT to be beneficial¹⁵⁻¹⁹. However, others report better local control with PORT in only those with advanced tumors or positive margins^{20,21}. In an earlier series at our institution, Spiro et al recommended that patients with high grade tumors and/or high stage tumors benefited from PORT. Patients with T1/T2 tumors, negative margins and negative neck disease did not appear to benefit²². Therefore, at our institution, patients with T1/T2 tumors without adverse features such as positive margins, PNI and negative neck nodes do not normally receive PORT. Notably, in the current series, our analysis shows that patients who did not receive PORT had a significantly poorer local control rate. Indeed, multivariable analysis, controlling for other factors which may impact on local control (margin status, PNI, pT status) showed that patients who did not receive PORT were 13 times more likely to fail locally. When we compare the characteristics of the patients who did not receive PORT with those who did, we found that patients not treated with PORT were more likely to have smaller tumors (<2cm 59% vs. 39%, p=0.04), have negative margins (52% vs. 17%, p=0.001) and have negative PNI (30% vs. 7.7%, p=0.04) (Supplementary Table 2). Despite this, local control was poorer. Our findings therefore suggest that patients with ACC benefit from PORT regardless of T stage.

It is important to note that our study is not without its limitations. It is retrospective and therefore susceptible to all the biases associated with such studies. There is considerable heterogeneity in the patient group. We have attempted to control for multiple variables by using multivariable analyses. However, despite this one can never fully account for the selection bias associated with the decision strategy on the use of PORT. Therefore extrapolation of the data to the use of PORT in patients with early T stage tumors without adverse features needs to be done with caution. Although we suggest that PORT may benefit all patients with ACC, our data requires to be substantiated with data from other large series. A randomised control trial is the obvious gold standard to decide if PORT is efficacious in all patients, but due to the rarity of this tumor it is extremely unlikely that such a study could be successfully carried out. With the improvement of conformal RT with intensity modulated radiation therapy (IMRT), toxicity from treatment can now be more effectively minimised. The introduction of intensity modulated proton beam therapy may further enhance tumor control and limit toxicity. Since our study suggests patients who do not receive PORT have poorer local control, we recommend that consideration should be given to treat all patients with PORT with possibly the exception of small T1 tumors without adverse pathological features.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Locoregional recurrence free survival stratified by postoperative radiation.

Table 1

Patient and tumor characteristics

Characteristic	No. of patients (%)
Age	
<55	42(48)
55	45(52)
Gender	
Male	25(29)
Female	62(71)
Tobacco	
No	31(36)
Yes	47(54)
Not Recorded	9(10)
Alcohol	
No	28(32)
Yes	47(54)
Not Recorded	12(14)
Tumor Site	
Major Salivary	28(32)
Minor Salivary	59(68)
Clinical T Stage	
T1	21(24)
T2	33(38)
T3	5(6)
T4	20(23)
Tx	8(9)
Clinical N Stage	
N0	84(97)
N1	2(2)
N2	1(1)
Pathology subtype	
Cribriform	58(67)
Tubular	16(18)
Solid	5(6)
Not known	8(9)
Pathological T Stage	
T1	29(33)
T2	29(33)
T3	8(9)
T4	21(24)
Pathological N Stage	
N0/Nx	77(88)

Characteristic	No. of patients (%)
N+	10(12)
Perineural Invasion	
No	11(13)
Yes	74(85)
Not Recorded	2(2)
Perineural Invasion	
No	11(13)
Focal	52(60)
Extensive	19(22)
Not recorded	4(5)
Margin Status	
Negative	24(28)
Close/Positive	58(67)
Not Recorded	2(2)

Table 2

Treatment Characteristics (n=87)

Characteristic		No of patients(%)
Surgery	Superficial Parotidectomy	6(7)
	Deep Lobe Parotidectomy	1(1)
	Total Parotidectomy	4(5)
	Extended Parotidectomy	3(3)
	Excision Submandibular Gland	7(8)
	Excision Submandibular Triangle	5(6)
	Sublingual Excision	1(1)
	Floor of Mouth Resection	2(2)
	Soft Palate Resection	4(5)
	Resection of Tongue Base	7(8)
	Hemiglossectomy	1(1)
	Partial Glossectomy	5(6)
	Total Glossectomy	1(1)
	Partial Maxillectomy	16(18)
	Subtotal Maxillectomy	4(5)
	Total Maxillectomy	1(1)
	Wide Local Excision(Multi-site)	19(22)
Neck Dissection	No	57(66)
	Yes	30(34)
Post Operative Radiation	No	28(32)
	Yes	59(68)

Table 3

Factors predictive of local failure on univariable analysis

Characteristic	n	10 year LRFS	p value
Age			
< 55	42	87.80%	0.037
> 55	45	68.30%	
Gender			
Female	56	82.90%	0.863
Male	31	72.20%	
Smoker			
No	31	88.10%	0.14
Yes	47	65.10%	
Alcohol			
No	28	83.20%	0.307
Yes	47	69.10%	
Site			
Oral ACC	45	81.00%	0.676
Oropharynx ACC	14	69.60%	
Major Salivary ACC	28	78.70%	0.396
Minor Salivary	59	79.80%	
Major Salivary	28	78.70%	
Clinical T stage			
cT1	22	76.20%	0.073
cT2	32	82.60%	
cT3	5	100.00%	
cT4	20	65.50%	
Perineural Invasion			
No	11	87.50%	0.796
Yes	74	77.00%	
Perineural Invasion			
No	11	78.00%	0.92
Focal	52	78.00%	
Extensive	19	66.00%	
Pathology subtype			
Cribiform	58	72.70%	0.33
Tubular	16	93.80%	
Solid	5	75.60%	
Margins			
Negative	24	78.30%	0.899
Close/Positive	61	78.80%	
Pathological Stage			
pT1	30	88.40%	0.295

Characteristic	n	10 year LRFS	p value
pT2	28	77.90%	
pT3	7	68.60%	
pT4	22	72.60%	
Tumor Size			
< 2 cm	33	89.60%	0.409
2–4 cm	41	76.40%	
> 4 cm	9	66.70%	
PORT			
No	28	41.60%	0.002
Yes	58	90.10%	

Table 4

Unadjusted and adjusted hazard ratios for local failure on Cox proportional hazards model

Variable	unadjusted HR	95% CI	p value	adjusted HR	95% CI	p value
Age						
<55	reference			reference		
55	3.22	1.02,10.163	0.046	2.532	0.59,10.88	0.212
Perineural invasion						
Negative	reference			reference		
Focal	0.729	0.154,3.449	0.691	0.926	0.163,5.255	0.931
Extensive	0.809	0.131,5.001	0.82	0.242	0.029,2.036	0.192
Margins						
Negative	reference			reference		
Close/positive	1.086	0.301,3.918	0.899	1.429	0.332,6.151	0.631
pT Stage						
T1/T2	reference			reference		
T3/T4	2.781	0.923,8.377	0.069	9.49	2.107,42.744	0.003
PORT						
Yes	reference			reference		
No	4.8464	1.659, 14.975	0.004	12.716	2.367,68.313	0.003