

Similar therapeutic effects of ^{125}I seed radiotherapy and γ -ray radiotherapy on lacrimal gland adenoid cystic carcinoma

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Abstract

• **AIM:** To evaluate the survival outcomes of patients with lacrimal gland adenoid cystic carcinoma who underwent eye-sparing surgery combined with ^{125}I seed implantation radiotherapy or local external γ -ray radiotherapy.

• **METHODS:** In this retrospective comparative case series, the clinical records of 27 primary and 8 recurrent patients were reviewed. Univariate and multivariate analyses were used to identify risk factors associated with distant metastasis (DM), and the overall survival (OS) after the initial surgery was analyzed.

• **RESULTS:** The median follow-up after radiotherapy was 36mo (range 6-120mo). At the last follow-up after radiotherapy, 26 (74.3%) patients had no evidence of disease, 7 (20%) patients had DM, 2 (5.9%) patients died of DM, and 1 patient with DM was lost to follow-up. Univariate analyses showed that duration of symptoms, bone destruction, T stage classification, and wide excision surgery were risk factors influencing DM ($P < 0.05$). The 5-year and 10-year OS rates after the initial surgery were 95.8% and 79.9%, respectively. The 5-year DM-free survival and disease-free survival rates after radiotherapy were 66.4% and 52.7%, respectively.

• **CONCLUSION:** ^{125}I seed radiotherapy and local external γ -ray radiotherapy may have similar therapeutic effects in preventing DM. Patients with T1/T2 stage disease have a better prognosis than those with T3/T4 stage disease.

• **KEYWORDS:** adenoid cystic carcinoma; lacrimal gland; ^{125}I seed radiotherapy; γ -ray radiotherapy; surgical excision

INTRODUCTION

Adenoid cystic carcinoma (ACC) most commonly occurs in the parotid gland, followed by the lacrimal gland, in the head and neck^[1-2]. ACC is the most common malignant epithelial tumour of the lacrimal gland and accounts for 25%-40% of lacrimal epithelial tumours and 1.6% of all orbital tumours^[3-8]. Lacrimal gland adenoid cystic carcinoma (LGACC) is slow growing with the characteristics of a high late recurrence risk, bone destruction and frequent distant metastasis (DM)^[9-10]. The common clinical manifestations include proptosis, eyelid swelling, lacrimal mass and ptosis. Pain is a unique manifestation of LGACC with bone destruction and nerve invasion^[6].

Surgical resection combined with radiotherapy is one of the mainstay options for ACC to achieve local disease control and better long-term survival. In this study, the outcomes of surgical excision combined with radiotherapy (^{125}I seed implantation radiation therapy and local external γ -ray radiation therapy) were analysed to further review the outcomes of radiotherapy for LGACC.

SUBJECTS AND METHODS

Ethical Approval The research adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Informed consent was obtained from the patient for publication of this article and any accompanying images.

The electronic medical records of 27 primary and 8 recurrent LGACC patients diagnosed by histopathology between April 2010 and April 2019 in our medical centre were reviewed. In this retrospective study, patients with detailed clinical characteristics, preoperative imaging findings, surgical procedures, local recurrence, DM, complications, and follow-up data were included. Patients without sufficient follow-up

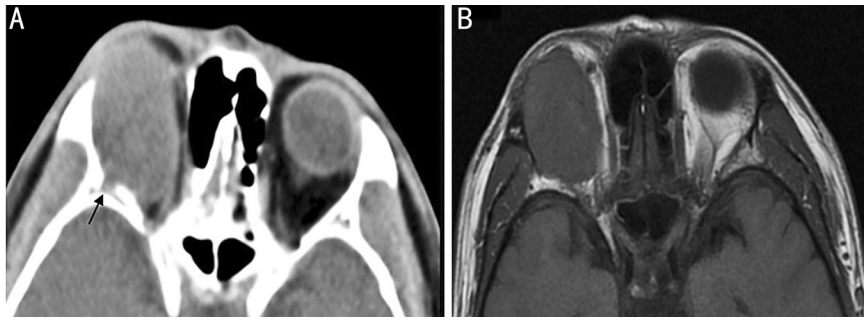


Figure 1 Imaging finding and pathological features of ACC A: CT of orbit showed that the tumour of right eye was large, almost invading the entire orbit, with unclear demarcation from the eyeball, and signs of bone destruction could be seen (arrow point); B: MRI showed large tumour and T1-weighted image was intermediate in intensity.

information were excluded. Bone invasion, tumour size, and DM were assessed with computed tomography (CT) and magnetic resonance imaging (MRI). Nerve invasion and local recurrence were confirmed *via* biopsy. DM was confirmed *via* biopsy or serial follow-up imaging. Tumours were classified according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. The timing of follow-up, local occurrence, DM, and disease-free survival (DFS) were measured from the date of tumour excision or radiotherapy in our medical centre. Overall survival (OS) was measured from the date of initial surgery to the last follow-up examination or death. Patients were followed up every 1-2mo in the first year, every 3-4mo in the second year, and every 6mo in the third-fifth years.

In this study, eye-sparing surgery included wide excision surgery (WES, involving bone, muscles, fat) and local excision surgery (LES, tumour only). Radiotherapy included ¹²⁵I seed implantation radiotherapy (Treatment A) and external γ -ray radiotherapy (Treatment B). ¹²⁵I seeds could be implanted at the inner and outer margins of the superior rectus muscle, the superior and lower margins of the superior temporal muscle, and the superior and lower margins of the external rectus muscle, with an interval of 1 cm and a distance of 0.8 cm from the skin. The average number of implanted seeds was 20, with an activity of 0.7-0.9 mCi per seed. The external radiation field for γ -ray therapy included the superior and inferior orbital fissures and the anterior cavernous and skull base depending on the fields of tumour invasion. The cumulative radiation dose was approximately 60-70 Gy/6-7wk, and the single radiation dose was 180-200 cGy.

Statistical Analysis Variables were compared between patients with and without DM by using Fisher's exact test ($n < 40$). Univariate and multivariate analyses were used to analyse the risk factors influencing DM. Multivariate models were obtained using a backward stepwise selection procedure with all the variables with $P < 0.1$ in univariate analysis. The test level was set at $\alpha = 0.05$. The hazard ratios and 95% confidence intervals (CIs) were estimated. The Kaplan-Meier method

was used to visualize OS, distant metastasis-free survival (DMFS), and DFS distributions, and log-rank tests were used to determine statistical significance. Statistical analyses were performed using SPSS 19.0, and Kaplan-Meier curves were generated using GraphPad Prism 8.0.1.

RESULTS

Clinical Characteristics The patient characteristics are summarized in Table 1. There were 13 males and 22 females in this retrospective study. The median age was 42y (range 17-61y). The ratio of left to right eye was 0.94:1. The median duration of symptoms was 12mo (range 1-180mo). The median tumour size (the largest length identified by pathology or imaging) was 2.6 cm (range 1.5-4.5 cm). The patients were followed up for a median of 30mo (range 6-120mo). MRI and CT clearly showed the relationship between the tumour tissues and surrounding structures as well as signs of bone destruction (Figure 1). Of these 35 patients, 12 patients (34.3%) had signs of bone destruction, 2 patients (5.7%) presented bone absorption, and 7 patients (20%) had extraocular muscle involvement.

AJCC and Histopathological Features According to the 8th edition of the AJCC guidelines, locally advanced T3-T4 tumours were observed in 8 patients (22.8%), and T1-T2 stage tumours were observed in 27 patients (77.2%). None of the patients had lymph node or DM prior to radiotherapy. After radiotherapy, 1 patient (2.9%) had lymph node metastasis, and 7 patients (20%) had DM, including bone, cranial, and lung invasions. The histological patterns were as follows: cribriform in 11 patients (31.4%), basaloid in 8 patients (22.9%), mixed in 6 patients (17.1%), and unknown in the remaining patients. Nine patients (25.7%) had histological evidence of perineural invasion, of whom 4 developed DM and 5 had local recurrence.

Treatment and Complications Eight patients (22.9%) had a past operation history without radiotherapy. WES combined with ¹²⁵I seed radiotherapy was performed in 11 patients (31.4%), of whom 7 had local recurrence, and 6 had DM. Fifteen patients (42.8%) underwent LES combined with ¹²⁵I

Table 1 Clinical characteristics of 35 cases of lacrimal gland adenoid cystic carcinoma

Variable	n	%
Median age (range, y)	42 (17-61)	
Sex (M/F)	13/22	37.1/62.9
Eye (left/right)	17/18	48.6/51.4
Durations of symptoms (mo), median (range)	12 (1-180)	
Symptoms		
Eyelid mass	21	60
Proptosis	12	34.3
Eyelid swelling	5	14.3
Pain	9	25.7
Eye movement disorder	8	22.9
Ptosis	6	17.1
Vision loss	3	8.6
Diplopia	3	8.6
Imaging findings		
Bone destruction	12	34.3
Bone absorption	2	5.7
Involvement of extraocular muscles	7	20
Tumor size (cm), median (range)	2.6 (1.5-4.5)	
TNM stage (AJCC 8 th ed.)		
T1a/ T1c/T2a/T2b/T2c/T3c/T4a/T4b	7/2/11/2/5/2/2/4	20/5.7/31.4/5.7/14.3/5.7/5.7/11.4
N0/N1	34/1	97.1/2.9
M0/M1	28/7	80/20
Perineural invasion	9	25.7
Treatment		
Past-operation history	8	22.9
WES+particle ¹²⁵ I radiotherapy	11	31.4
LES+particle ¹²⁵ I radiotherapy	15	42.8
WES+γ-ray radiotherapy	1	2.9
LES+γ-ray radiotherapy	8	22.9
Follow-up after radiotherapy (mo), median (range)	30 (6-120)	
Local recurrence/DM	11/7	31.4/20
Local recurrence (mo), median (range)	36 (6-108)	
Distant recurrence (mo), median (range)	36 (24-72)	
Last status, NED/DODM/DM	26/2/7	74.3/5.9/20

WES: Wide excision surgery; LES: Local excision surgery; NED: No evidence of disease; DODM: Died of distant metastasis; DM: Distant metastasis. TNM stage: Pathological tumour-node-metastasis staging proposed by the American Joint Committee on Cancer (AJCC, 8th edition).

seed radiotherapy, and 1 of these patients had local recurrence. WES combined with γ-ray radiotherapy was performed in 1 patient (2.9%), and this patient had DM. Eight patients (22.9%) underwent LES combined with γ-ray radiotherapy, 3 of whom had local recurrence.

Radiation-related complications included dry eye (71.4%), poor visual acuity (60%), eyelid erythema (17.1%), radiation retinopathy and neuropathy (17.1%), ptosis (14.3%), and sunken socket syndrome (11.4%). Other complications included eye movement disorder (5.7%), exotropia (2.9%), diplopia (2.9%), cataracts (2.9%), secondary glaucoma (2.9%), and retinal haemorrhage (2.9%).

Recurrence and Survival After radiotherapy, 11 patients (31.4%) had local recurrence, and 7 patients (20%) had DM. The median times of local recurrence and DM were 36mo (range 6-108mo) and 36mo (range 24-72mo), respectively. Two patients (5.9%) died of DM, and 1 patient with DM was lost to follow-up. Twenty-six patients (74.3%) had no evidence of disease.

In total, 7 of 12 patients (58.3%) who underwent WES had local recurrence and DM. Four of 23 patients (17.4%) who underwent LES had local recurrence and no DM. ¹²⁵I seed radiotherapy was performed in 26 patients, of whom 8 (30.8%) had local recurrence and 6 (23.1%) had DM. Additionally,

Table 2 Univariate and multivariate analyses of factors influencing DM of lacrimal gland adenoid cystic carcinoma

Variable	Assignment	HR (95%CI)	P
Univariate analysis			
Age>50y	≤50=0, >50=1	0.625 (0.152-2.574)	0.608
Sex, male	Male=0, Female=1	1.618 (0.266-9.852)	0.689
Eye, left	Left=0, Right=1	0.300 (0.049-1.820)	0.228
Durations of symptoms, >12mo	≤12mo=0, >12mo=1	9.273 (0.979-87.868)	0.041 ^a
Tumour sizes, >3cm	≤3cm=0, >3cm=1	1.538 (0.289-8.181)	0.294
Bone destruction	No=0, Yes=1	2.400 (1.229-4.688)	0.00 ^a
Perineural invasion	No=0, Yes=1	6.133 (1.032-36.449)	0.055
T classification, T1-T2/T3-T4	T1-T2=0, T3-T4=1	78.00 (6.034-1008.320)	0.00 ^a
N classification	N0=0, N1=1	0.176 (0.085-0.365)	0.200
Past-operation history	No=0, Yes=1	0.417(0.130-1.339)	0.312
Surgery, WES/LES	WES=0, LES=1	0.179 (0.081-0.395)	0.00 ^a
Radiotherapy	¹²⁵ I=0, γ-ray=1	0.833 (0.568-1.222)	0.648
Local recurrence	No=0, Yes=1	0.300 (0.128-0.702)	0.021 ^a
Multivariate analysis			
Bone destruction	No=0, Yes=1	0	0.998
T classification	T1-T2=0, T3-T4=1	0.111 (0.007-1.776)	0.120

HR: Hazard ratio; CI: Confidence interval; WES: Wide excision surgery; LES: Local excision surgery; Fisher's exact test was used in the univariate analysis with $P<0.1$. The multivariate models were prepared using a backward stepwise selection procedure with $P<0.05$. ^a $P<0.05$.

γ-ray radiotherapy was performed in 9 patients, of whom 3 (33.3%) had local recurrence and 1 (11.1%) had DM. Fisher's exact test was performed to analyse the association between surgery (WES/LES) and recurrence or DM, which revealed statistically significant association ($P=0.022$, $P=0.000$, respectively). And there were no statistically significant associations between radiotherapy and recurrence or distant recurrence ($P=1.000$, $P=0.648$, respectively).

The assignment of influencing variables was shown in Table 2. Univariate analyses showed that the duration of symptoms (>12mo), bone destruction, T stage classification (T3-T4), surgery (WES), and local recurrence were significant factors associated with DM ($P<0.05$). Multivariate analysis included bone destruction and T stage classification, but both had $P>0.05$, which may be due to the small sample size and inadequate follow-up period (Table 2). The 5- and 10-year OS rates of all patients were 95.8% and 79.9%, respectively. The 5-year DMFS and DFS rates after radiotherapy were 66.4% and 52.7%, respectively. The log-rank test was performed to compare DFS between Treatment A and Treatment B and showed no significant difference ($P=0.708$). The log-rank test was performed to compare DFS between WES and LES, and no significant difference was observed ($P=0.123$). Kaplan-Meier curves showed that the survival rate of patients with stage T1/T2 disease was higher than that of patients with stage T3/T4 disease, and the log-rank test revealed a statistically significant difference ($P=0.015$; Figure 2).

DISCUSSION

Achieving local disease control and long-term survival and preventing DM have always been the focus of clinical research. Radiotherapy is the common treatment for LGACC. In this study, we analysed two radiotherapies, and the rates of local recurrence and DM were 31.4% and 20%, respectively, which was consistent with the reported DM rate of 16%-29%^[11]. It was reported that 35% of the 20 LGACC patients who underwent surgery combined with radiotherapy had local recurrence, 80% had DM, and 65% died of the disease^[7]. And the overall tumour-related mortality of LGACC is 10%-87%^[8,12-15]. A recent study found that 6 (54.5%) LGACC patients had local recurrence and DM^[16]. We hypothesize that the reasons for the lower recurrence and metastasis rates in our study may be the inadequate follow-up period and the effect of primary surgery. The 5- and 10-year OS rates of 3026 patients with ACC in the head and neck were 90.3% and 79.9%, respectively^[17]. In a recent study, the 10- and 20-year OS rates of 125 patients with ACC in the head and neck were 71.4% and 50.6%, the 5- and 10-year DFS rates were 52.2% and 37.9%, and the 5- and 10-year DMFS rates were 65.4% and 52.4%, respectively^[18]. The 5-year and 10-year OS rates of 20 LGACC patients were 56% and 49%, respectively^[7]. Hung *et al*^[16] reported that the 5-year and 10-year OS rates of 11 LGACC patients were 81.8% and 68.2%, and the 5- and 10-year DFS rates were 54.5% and 27.3%, respectively. Yang *et al*^[12] reported the 1-, 3- and 5-year recurrence rate of 24 LGACC patients was

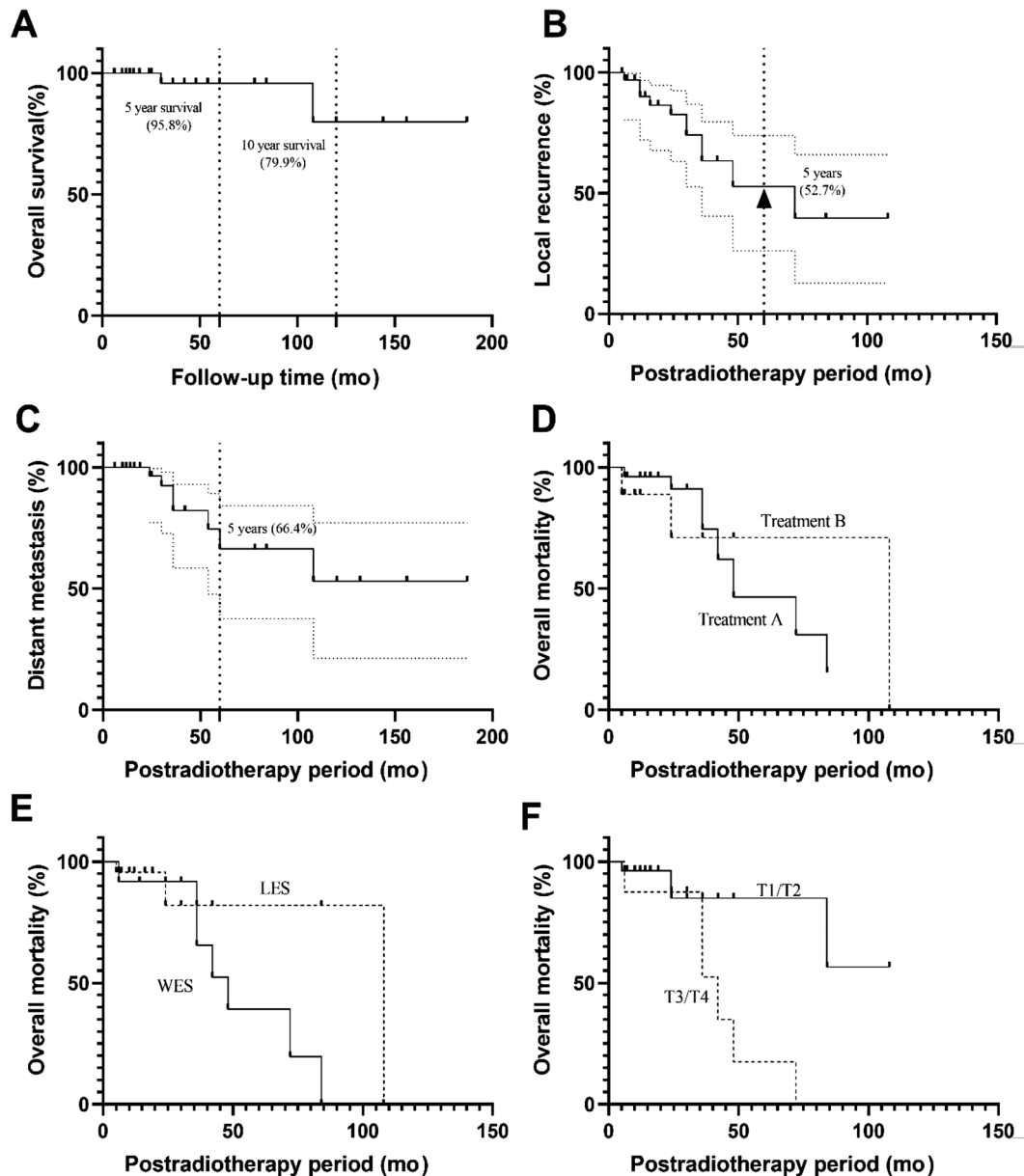


Figure 2 Survival analysis of patients with LGACC and the effect of different treatment and stages on the survival of LGACC A: Kaplan-Meier OS curve of 35 cases of LGACC after initial surgery. The 5-year survival rate was 95.8% and 10-year survival rate was 79.9%. B: Kaplan-Meier the DFS curve of 35 patients after radiotherapy. C: Kaplan-Meier DM curve of 35 patients after radiotherapy. D: Kaplan-Meier survival curve between Treatment A and Treatment B. $P=0.708$ (log-rank test). E: Kaplan-Meier survival curve between WES and LES. $P=0.123$ (log-rank test). F: Kaplan-Meier survival curve between T1/T2 and T3/T4. $P=0.015$ (log-rank test).

27.9%, 60.0%, and 80.0%, and the DM rate was 4.5%, 28.1%, and 58.0%, respectively. In our study, the 5- and 10-year OS rates of all patients were 95.8% and 79.9%, respectively. The 5-year DMFS and DFS rates after radiotherapy were 66.4% and 52.7%, respectively. LGACC patients still achieve a long survival period after treatment, even if recurrence and metastasis occur.

The Kaplan-Meier survival curve showed no significant difference between Treatment A and Treatment B, and the univariate analysis results for treatment method showed no significant associations. Therefore, ^{125}I seed radiotherapy and γ -ray radiotherapy have no significant effect in preventing

DM. However, the scope of surgical resection may have a certain influence on DM, especially that of the initial surgical resection. Some lesions were initially treated with WES, which could prevent local recurrence and DM to some extent. In this study, univariate analyses showed that patients treated with WES were more likely to have DM. This was because the patients receiving WES had signs of bone destruction and extraocular muscle or fat involvement. It was difficult to completely remove the aggressive tumour by WES, which increased the risk of local recurrence and DM.

Many factors affect the prognosis of ACC, including tumour size, perineural invasion, solid histological pattern, lymph node

metastasis, and advanced stage. According to the 8th edition of the AJCC guidelines, staging is determined by tumour diameter, bone destruction, lymph node, and DM. It was reported that advanced tumour classification and extranodal extension were independent risk factors affecting prognosis^[18]. Seok *et al*^[19] reported that tumour size (≥ 2.5 cm), perineural invasion, and local recurrence were risk factors for DM. In a recent study, Atallah *et al*^[20] reported that age, BMI and N stage were the main clinical prognostic factors determining event-free survival in 470 ACC patients. T stage also affected the prognosis of patients. The log-rank test was performed to compare OS and DFS between patients with T1/T2 disease and patients with T3/T4 disease, revealing statistically significant differences ($P=0.001$ and $P=0.006$, respectively)^[16]. In this study, age, tumour size, perineural invasion and lymph node metastasis were not independent risk factors for DM. Kaplan-Meier curves showed that the DFS rate of patients with stage T1/T2 disease was higher than that of patients with stage T3/T4 disease, revealing a statistically significant difference. Bone destruction and T stage classification are likely to be risk factors influencing DM, but this still needs further study with an increased number of samples.

The basaloid pattern was considered an important risk factor. Lee *et al*^[21] found that the survival time of non-basaloid patients was significantly longer than that of basaloid patients. Gamel and Font^[22] reported that patients with a predominantly basaloid subtype had poorer outcomes than those with a predominantly cribriform subtype. In this study, the common subtypes were cribriform in 11 patients (31.4%) and basaloid in 8 patients (22.9%). Due to the absence of pathological data, no statistical analysis was carried out.

Both internal ¹²⁵I seed implantation radiotherapy and external γ -ray radiotherapy had some side effects. Dry eye and vision loss were the most common radiation-related complications, followed by eyelid erythema, radiation retinopathy and neuropathy, ptosis, and sunken socket syndrome. A few patients had symptoms of diplopia, cataracts, eye movement disorders, exotropia, secondary glaucoma and retinal haemorrhage. However, ¹²⁵I seed radiotherapy also had a risk of particle shedding. To prevent the side effects of radiotherapy, symptomatic treatment was carried out in the early stage to improve circulation and nourish nerves and most side effects could be mitigated.

This study has limitations owing to the inadequate number of patients and missing data. Alternative therapies, such as proton therapy and chemotherapy, were also considered. Wolkow *et al*^[23] reported that 18 LGACC cases received globe-preserving surgery with proton beam radiation, the 3y OS rate of 80% and 75% for 5y progression free survival. Pelak *et al*^[24] reported 35 patients with ACC of the head and neck who underwent

pencil beam-scanning proton therapy; the 2-year local control, distant control and OS rates were 92.2%, 77.8%, and 88.8%, respectively. Lesueur *et al*^[25] reported that 15 LGACC patients received high dose adjuvant proton therapy, and the 3-year OS, local progression free survival, and progression free survival rates were 78%, 70%, and 58%, respectively. Le Tourneau *et al*^[26] considered that intra-arterial neoadjuvant chemotherapy had certain effect, but its side effects should not be ignored. Liao *et al*^[27] found that delivering chemotherapy through the internal carotid artery may result in visually significant thrombotic vascular events. These findings suggest that there is no significant difference between proton therapy and radiation therapy, while no studies have shown that chemotherapy has a better therapeutic effect but carries more side effects. Other treatments, such as the cyclin-dependent kinase inhibitor dinaciclib, and the Notch inhibitor crenigacestat, might be promising strategies in the treatment of ACC and should be further studied.

In conclusion, this study describes the outcomes of LGACC patients treated with radiotherapy and finds that ¹²⁵I seed implantation radiotherapy and local external γ -ray radiotherapy may have similar therapeutic effects in achieving local disease control. Patients with T1/T2 stage disease have a better prognosis than those with T3/T4 stage disease.

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