CANCER DIAGNOSIS & PROGNOSIS
2: 503-511 (2022) doi: 10.21873/cdp.10134

Review

Adenoid Cystic Carcinoma (ACC) Infiltrating the Skull Base: A Systematic Review of Clinical Characteristics and Management Strategies

OTHMAN BIN-ALAMER[1,2], ALI S. HAIDER[3], ADHIRAJ CHAUDHARY[4], KISHORE BALASUBRAMANIAN[3], TESSA BREEDING[5], PAOLO PALMISCIANO[6], MARYAM HAIDER[7], AARON A. COHEN-GADOL[8], TAREK Y. EL AHMADIEH[9] and KENNY YU[9]

[1]*College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia;*
[2]*King Abdullah International Medical Research Center, Riyadh, Saudi Arabia;*
[3]*Texas A&M University College of Medicine, Houston, TX, U.S.A.;*
[4]*Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India;*
[5]*Dr. Kiran C. Patel College of Allopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, U.S.A.;*
[6]*Department of Neurosurgery, Trauma, Gamma Knife Center, Cannizzaro Hospital, Catania, Italy;*
[7]*Department of Radiology, Baylor College of Medicine, Houston, TX, U.S.A.;*
[8]*Department of Neurological Surgery, Indiana University School of Medicine, Indianapolis, IN, U.S.A.;*
[9]*Department of Neurosurgery, Memorial Sloan Kettering Cancer Center, New York, NY, U.S.A.*

Abstract. *Background/Aim: To systematically review the patient characteristics and management approaches of adenoid cystic carcinoma (ACC) infiltrating the skull base. Materials and Methods: According to PRISMA guidelines, PubMed, Scopus, and Cochrane were searched to retrieve studies reporting management protocols and survival outcomes of patients with skull base ACCs. Patient characteristics, management strategies, and outcomes were investigated. Results: The review encompassed 17 studies involving 171 patients, with a female predominance (57.9%) and a mean age of 49±7.12 years. ACCs mostly infiltrated the paranasal sinus (22.2%), cavernous sinus (8.8%), and nasopharynx (7.1%). Perineural invasion was reported in 6.4% of cases. Facial pain, nasal obstruction, and facial paresthesia were the most common symptoms. Surgical resection (45.6%) was favored over biopsy (12.2%). Employing the free flap technique (4.7%), surgical reconstruction of the bony defect after resection was performed using abdominal and anterior thigh muscle grafts in 1.8% of patients each. As adjuvant management, 22.8% of cases had radiotherapy and 14.6% received chemotherapy. Recurrence of skull base ACCs occurred in 26.9% of cases during a mean follow up-time of 30.8±1.8 months. Conclusion: Skull base ACCs pose a surgical challenge mainly due to their proximity to critical neurovascular structures and aggressive behavior. Surgical resection and radiotherapy are shown to be safe and effective treatment modalities. The dismal prognosis and limited data on non-surgical strategies highlight the need for further evaluation of the current management paradigm and upraising innovative therapies to improve patient mortality and quality of life.*

Correspondence to: Othman Bin-Alamer, MBBS, Department of Stem Cells and Regenerative Medicine, King Abdullah International Medical Research Center, Ali Al Arini, Ar Rimayah, Riyadh 11481, Kingdom of Saudi Arabia. Tel: +96 60114294444. e-mail: oabinalamer@gmail.com

Key Words: Adenoid cystic carcinoma, skull base, review.

Adenoid cystic carcinomas (ACCs) represent a primary salivary neoplasm with an estimated incidence of 3-4.5 cases per million and typically present with advanced skull base invasion (1). Because of their propensity for skull base and perineural invasion, skull base ACCs (SBACCs) are a major surgical challenge (2). Pathologically, ACCs are carcinomas of major and minor salivary glands of the upper aerodigestive tract and consist of non-luminal, basaloid, hematoxyphilic

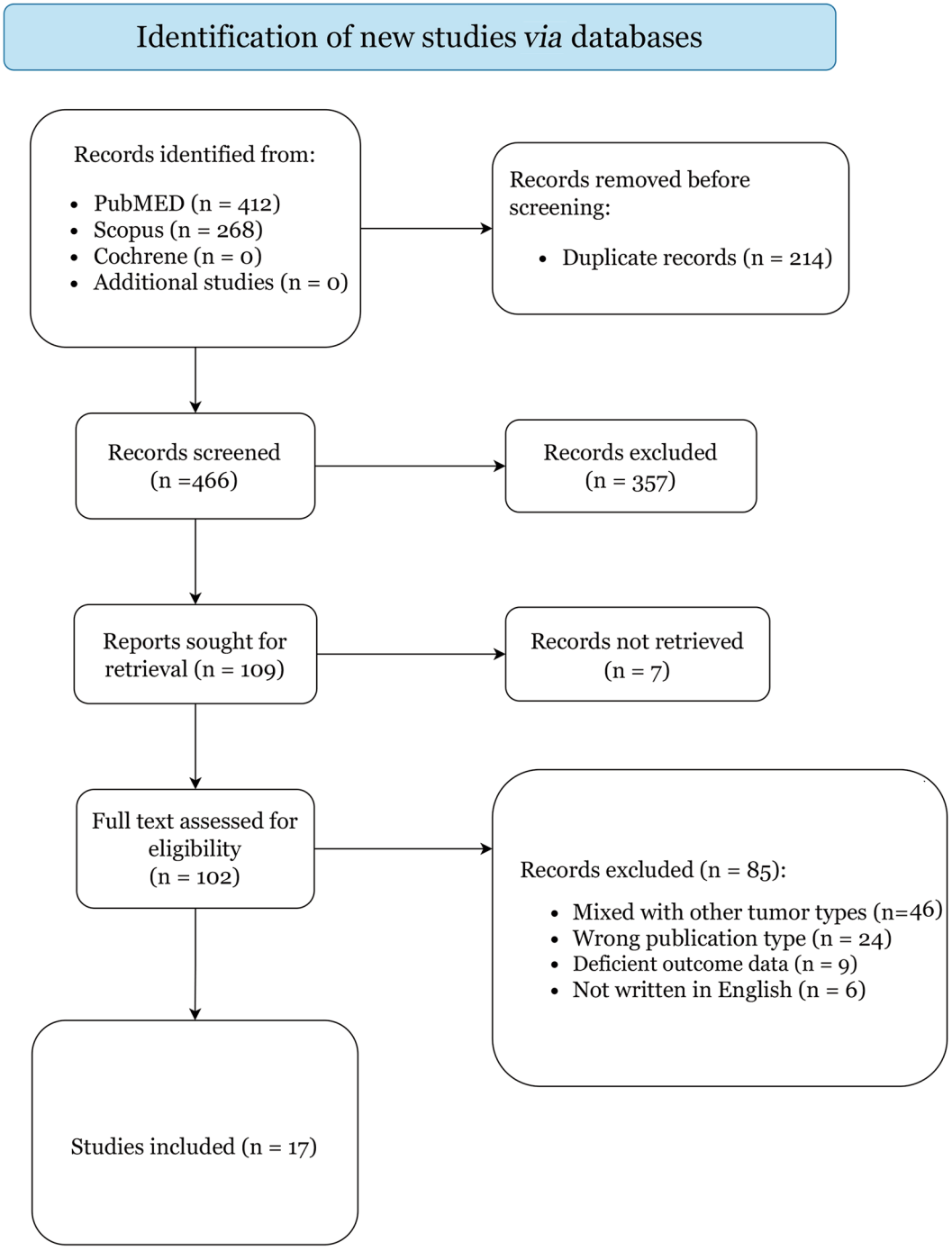

Figure 1. *PRISMA flowchart illustrating the search strategy and data selection based on the inclusion and exclusion criteria.*

cells, with minor to moderate cytoplasm, and far fewer luminal, short cuboidal, eosinophilic cells (3). Although ACCs tend to proliferate slowly, they eventually lead to bone destruction and diffuse skull base infiltration at primary sites, leading to a locoregional recurrence and seeding the leptomeninges *via* the cerebrospinal fluid (CSF) (4, 5). Therefore, developing a therapeutic strategy of maximal resection with minimal morbidity is a substantial challenge (2).

Because of SBACCs dearth in the literature, a consensual standard of care has not been established, resulting in a wide

Table I. *Overview of treatment outcomes for included studies.*

Author	Cohort	Age median (range)	Sex No. females (%)	Surgery No. (%)	Biopsy only No. (%)	Extent of surgery No. (%)	Reconstruction technique No. (%)	Reconstruction material No. (%)	Chemo-therapy No. (%)	Radio-therapy No. (%)	Recurrence No. (%)	Site of recurrence No. (%)	Mean months of follow-up (range)	Alive status at last follow-up No. (%)
Liu *et al*.-2021 (13)	4	55 (49-63)	1 (25)	4 (100)			Free flap technique, 4 (100)	Abdominis Flap, 1 (25); Anterolateral thigh Flap, 3 (75)	1 (25)		3 (75)		32 (25-67)	4 (100)
Haddad *et al*.-2006 (10)	4	45 (33-54)	1 (25)						4 (100)	4 (100)	1 (25)	Distant, 1 (25)	29 (20-43)	4 (100)
Valentini *et al*.-2006 (14)	4	42 (26-65)	4 (100)	4 (100)			Free flap technique, 4 (100)	Abdominis Flap, 2 (50); Fibula Osteomyo-cutaneous, 2 (50)						
Tarsitano *et al*.-2012 (15)	8			8 (100)							8 (100)	Local, 7 (87); distant, 3 (37)		
Morimoto *et al*.-2014 (16)	3	59 (24-64)	2 (66)							3 (100)	1 (33)	Local and distant, 1 (33)		3 (100)
A. Dautruche - *et al*.-2017 (17)	13	55	7 (62)	10 (77)					3 (23)	13 (100)				9 (69)
Gentile *et al*.-2016 (18)	14	52 (26-71)	7 (50)	3 (21)	11 (79)	PR, 3 (21)			7 (50)				69 (34-175)	
Issing *et al*.-1999 (19)	56	54 (24-77)	32 (57)											
Xu *et al*.-2019 (20)	33	50 (25-81)		30 (90)						3 (9)	24 (72)	Local, 9 (28); distant, 15 (46)		9 (72)
Schulz-Ertner *et al*.-2003 (21)	9			3 (33)	6 (66)	PR, 3 (33)				9 (100)				
Ginsberg *et al*.-1998 (22)	3	47 (35-49)	2 (66)	3 (100)					1 (33)	3 (100%)	3 (100)			
Bhattasali *et al*.-2016 (23)	5	47 (32-71)	5 (100)	1 (20)	4 (80)									
Frank *et al*.-2014 (24)	3	33 (32-47)	3 (100)						3 (100)					
Taylor *et al*.-2014 (25)	3	50 (39-55)	3 (100)	3 (100)		GTR, (100)			3 (100)	3 (100)	1 (33)		21 (7-46)	2 (66)
Mori *et al*.-2006 (26)	3	59 (55-62)	1 (33)	3 (100)									10 (4-11)	0 (0)
Serracino *et al*.-2013 (27)	4	46 (33-77)	1 (25)	4					2 (50)		4 (100)			
Gil *et al*.-2007 (28)	2	41 (30-52)	1 (50)	2 (100)					1 (50)	1 (50)	1 (50)			2 (100)

PR: Partial resection; GTR: gross total resection.

Table II. *Summary of clinical characteristics, management strategies and outcomes of all pooled patients.*

Characteristics (n=171)	Value (percentage among available data)
Demographics	
Age (yrs), mean±SD	49±7.1
Sex (n=121)	Female: 70 (57.9%)
Most common reported symptoms	No. (%)
Facial pain	20 (11.6%)
Facial paresthesia	9 (5.2%)
Nasal obtrusion	5 (2.9%)
Most frequently effected cranial nerves	23 (13.4%)
CN V	14(8.1%)
CN II	2 (1.1%)
CN IX	2 (1.1%)
CN VI	1 (0.5%)
Most frequently invaded structures	No. (%)
Paranasal sinus	38 (22.2%)
Cavernous sinus	15 (8.8%)
Nasopharynx	12(7.1%)
Meckel's cave	9 (5.2%)
Pterygopalatine fossa	8 (4.6%)
Oral palate	7 (4.1%)
Perineural invasion	11 (6.4%)
Surgery	No. (%)
Biopsy only	21(12.2%)
Surgical resection	78 (45.6%)
Reconstruction technique and material	
Free flap technique	8 (4.7%)
Abdominis flap	3(1.8%)
Anterolateral thigh flap	3 (1.8%)
Fibula osteomyocutaneous flap	2 (1.2%)
Chemotherapy (n=25, 14.6%)	No. (%)
Cisplatin	10 (5.8%)
Paclitaxel	7 (4.0%)
Not mentioned	8 (4.6%)
Radiotherapy (Gy) (n=39; 22.8%)	
Dose, mean±SD	64.1±9.2 Gy
External beam radiotherapy	15 (8.8%)
Brachytherapy	3 (1.7%)
Recurrence (n=46, 26.9%)	
Local recurrence	17 (9.9%)
Distal recurrence	20 (11.6%)
Follow-up time	Mean±SD
Months	30.8±1.8
Status (n=62)	No. (%)
Alive	33 (53%)
Died	29 (47%)

array of diagnostic protocols and management approaches (6). Currently, the conventional diagnostic workup consists of imaging modalities, primarily MRI, for preliminary diagnosis and determining tumor characteristics often followed by biopsy and histological examination for definitive diagnosis (7, 8). Additionally, available evidence also recommends surgical management in combination with postoperative radiation, which offers higher tumor control rates compared to radiation alone (6, 9). However, investigations into other therapeutic modalities such as chemotherapy and targeted therapy are limited (4, 10).

In addition to clinical characteristics and therapeutic strategies, the survival outcomes of skull base infiltrating ACCs are sparsely reported in the literature, leaving many questions still unanswered. This study therefore aims to review and summarize the current literature regarding the clinical management of adult SBACCs, with particular focus on patient characteristics, management strategies, and survival outcomes.

Materials and Methods

Literature search. A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, as previously described (11, 12). PubMed, Scopus, and Cochrane databases were searched from inception to June 2021. A medical subject headings (MeSH) term and keyword search of each database was conducted using the Boolean operators OR and AND. Terms used were as follows: "adenoid cystic carcinoma" AND "skull AND base".

Study selection. We included studies meeting the following criteria: 1) prospective or retrospective studies reporting more than one patient with adenoid cystic carcinoma infiltrating the skull base, 2) patients with histologically confirmed adenoid cystic carcinoma, 3) patients aged 18 years or older, and 4) sufficient data report on patient characteristics and management outcomes. Studies were excluded if they: 1) were meta-analyses, reviews, editorials, letters, or books, 2) contained insufficient clinical data (lacking both patient demographics or management details), and 3) were not written in English.

Data extraction. One author (A.C.) extracted data from the target articles, which were confirmed independently by another author (O.B.A.) to ensure accuracy. Variables extracted included: 1) author's name, 2) date of publication, 3) sample size, 4) sex, 5) presenting symptoms, 6) management strategy and treatment modalities used (radiotherapy, chemotherapy, surgical resection), 7) recurrence, and 8) survival. Missing data are either not reported by the authors or reported indistinctively from other data that could not be differentiated.

Results

Study selection. The literature search of PubMed, Scopus, and Cochrane databases yielded 680 citations. The selection process (Figure 1) yielded a total of 17 articles, categorized as level IV, that met the pre-specified inclusion criteria (Table I) (10, 13-28) The risk of bias assessment categorized the included studies as "good" quality (*i.e.* low risk of bias).

Patient demographics and clinical features. Our demographic results showed a mean age of 49±7.1 with a female predominance (57.9%) in our patient cohort (Table II). Facial pain was the most common symptom (11.6%), followed by

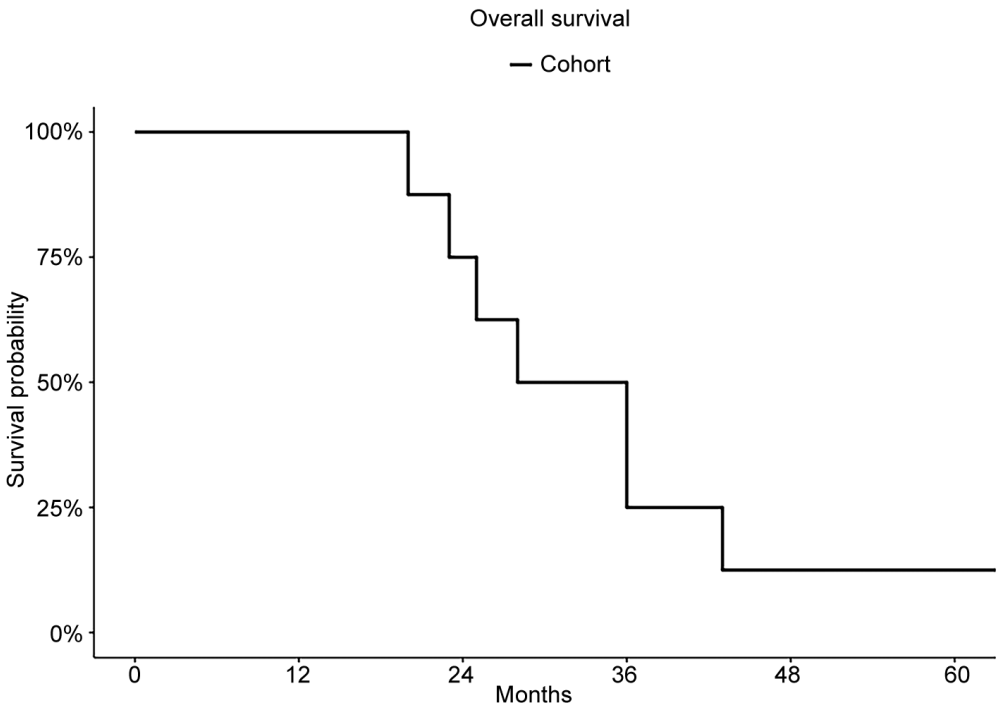

Figure 2. *Kaplan-Meier survival curves for the overall survival (OS) of the cohort.*

facial paresthesia (5.2%), and nasal obtrusion (2.9%). In our cohort, 13.4% reported cranial nerve deficits; trigeminal, optic, and glossopharyngeal nerves were the most frequently affected in 8.1%, 1.1%, and 1.1% of cases. The most commonly invaded structures were the paranasal sinus (22.2%), the cavernous sinus (8.8%), nasopharynx (7.1%), and Meckel's cave (5.2%). Perineural invasion was recorded in only 6.4%.

Management approaches and survival outcomes. At the last follow-up, 46 patients (26.9%) had recurrent tumors, and 47% of reported data (*n*=62) died due to tumor progression. Mean follow up time was 30.8±1.8 months with a 5-year survival rate of 18% (Figure 2). Surgical intervention was the primary treatment strategy, with 45.6% undergoing surgical resection; however, 12.2% had biopsy only. Of the surgical cases, only a few reported reconstruction details (*n*=8). A free flap was used in all cases, and the rectus abdominis and anterior lateral thigh were the most frequently used flap material. A total of 39 patients (22.8%) received radiotherapy, with a mean dose of 64.1±9.2 Gy. External beam radiotherapy was the most common radiotherapeutic modality employed (8.8% of patients). Chemotherapy was used in a small fraction of patients (*n*=25; 14.6%), and Cisplatin was the most frequently used agent (5.8%). No survival benefit was detected in surgical resection, radiotherapy, or chemotherapy (Figure 3).

Discussion

ACCs invading the skull base represent challenging tumors, given their anatomical proximity to critical neurovascular structures and unique perineural metastatic potential. Microsurgical resection in conjunction with radiotherapy has been the primary treatment strategy. However, large series on SBACCs are limited in the literature. The present review described the clinical characteristics and management outcomes of SBACC. We found that surgical resection, radiotherapy, or chemotherapy confer no survival benefits. Part of these data has been previously published (29).

Patients and clinical characteristics. In our review, the mean age at presentation was 49±7.1, similar to laryngeal ACCs, which were reported to generally affect patients in their fifth decade (30). Although most agree that there is no difference in prevalence between males and females in ACCs, our results found a slight female predominance in SBACC (57.9%).

Skull base tumors usually present with CSF obstruction-related symptoms or direct brainstem compression (31, 32). Likewise, nasal obstruction, facial pain, and facial parathesis were the main symptoms in our data set. The trigeminal nerve was the most affected, followed by the optic and glossopharyngeal nerves. The high rate of cranial

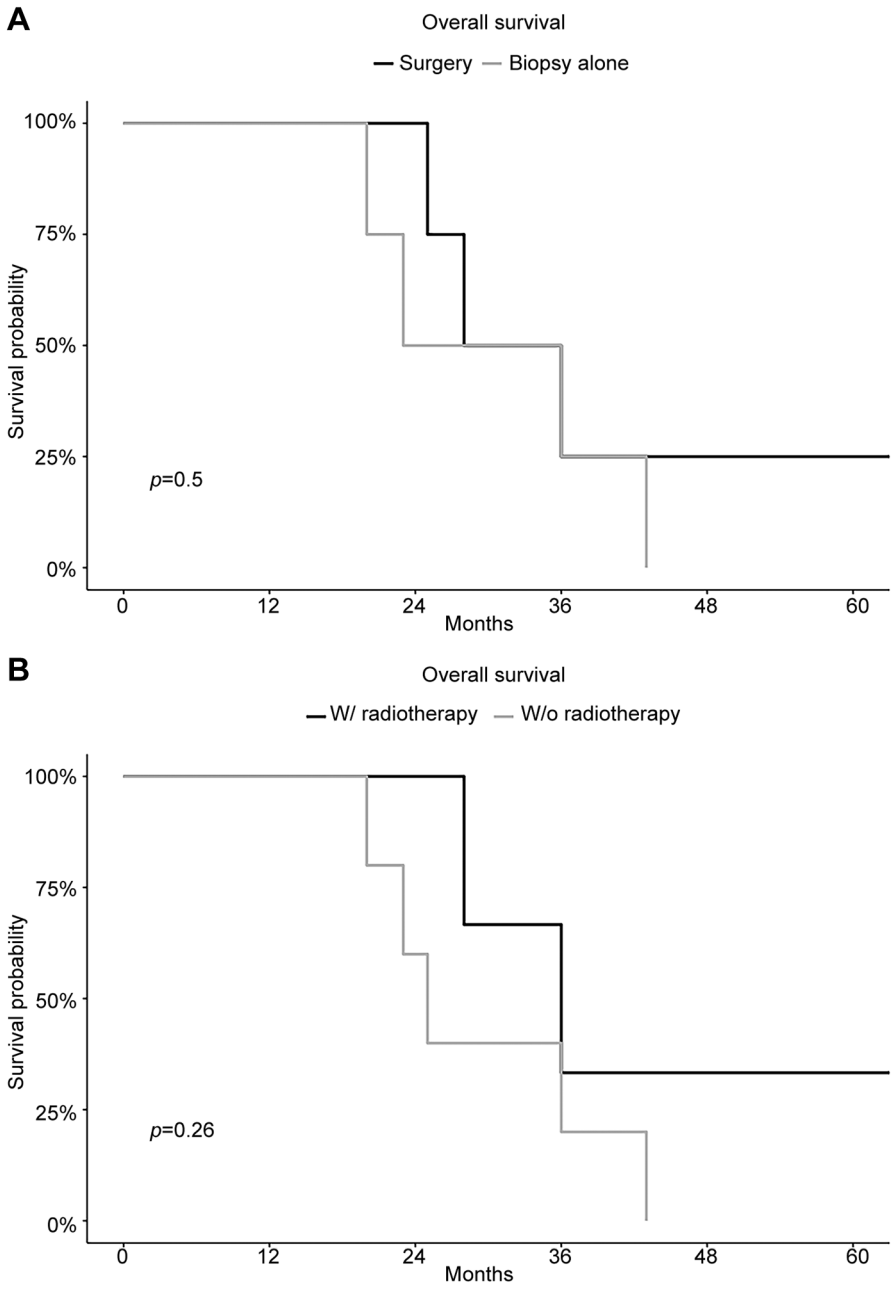

Figure 3. *Continued*

nerve deficit is attributed to either the tumor mass effect or the tumors' perineural invasion ability, although perineural invasion was reported in only 6.4% of the cases analyzed. In contrast, in a separate systematic review investigating perineural invasion on head and neck ACC (HNACC) prognosis, the perineural invasion was detected in 43% of the cohort (33). This rate difference in perineural invasion is likely ascribed to the heterogeneous reporting and the study scope of our systematic review, as most SBACC articles focus on surgical techniques and reconstruction.

Other studies on HNACC document the palate as the most common invaded structure (34). However, we found that the paranasal sinuses were the most invaded structure. This is reasonable as ACCs represent a primary salivary neoplasm putting paranasal sinuses and craniofacial structures at risk of invasion due to their proximal anatomical location.

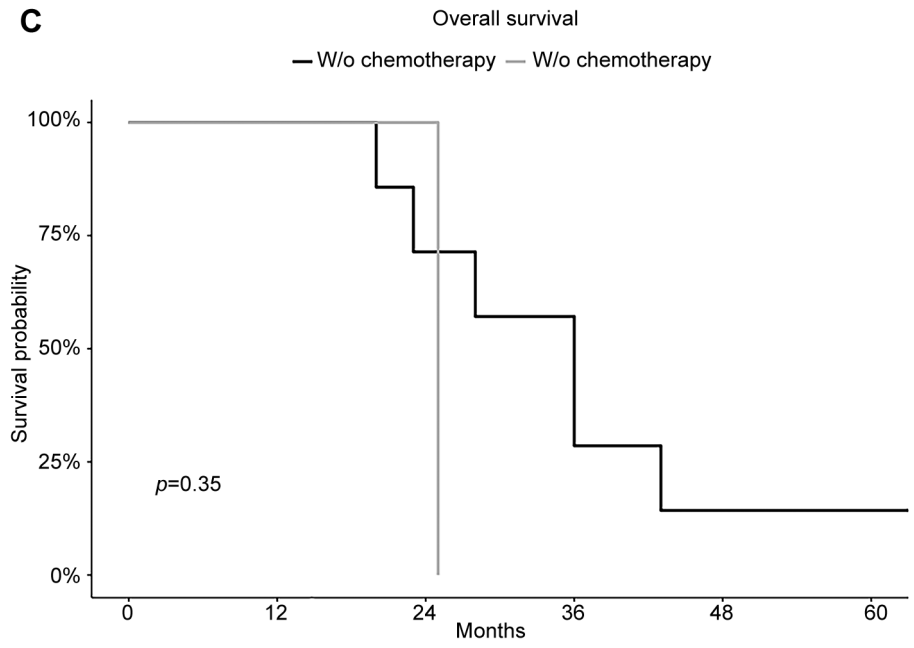

Figure 3. *Kaplan-Meier survival curves for (A) surgery vs. biopsy, (B) radiotherapy vs. no radiotherapy and (C), chemotherapy vs. no chemotherapy*

Treatment and outcomes. From the available data, 47% of patients died because of tumor progression, with a 5-year survival rate of 18%, while 26.9% had tumor recurrence. Our results agree with the HNACC recurrence rates (13.3% - 55%) but represent a more devastating survival rate (35-37).

Although surgical resection remains the cornerstone management for ACC, the extent of resection and the role of radiotherapy remain controversial (38-40). In the present study, surgical intervention was the most employed strategy, with biopsy alone being used in only 12.2% of cases. This is likely due to patients presenting with disfiguring tumors requiring surgical decompression. Historically, indications for radical surgery were limited for advanced skull base tumors as adequate reconstruction was often difficult to perform. However, advancements in reconstructive techniques have significantly improved the management of skull base tumors (14). We found that all articles that reported reconstruction performed free flap techniques, using either abdominal flap, anterior thigh flap, or fibula osteomyocutaneous flap. Our findings were consistent with the general recommendations on cranial base reconstruction materials and techniques for skull base tumor resections involving the anterior and middle cranial bases (41, 42).

ACC has been historically believed to be radioresistant (43). However, recent data have reported higher survival and lower recurrence rates following radiotherapy, supporting the radiosensitivity of ACC (44). We found that 22.8% of patients received radiotherapy, with external beam radiotherapy being the most frequently used modality, while only 14.6% received chemotherapy. A similar observation of the low rate of chemotherapy administration was also reported in the HNACC literature (33). Lastly, although surgical resection, radiotherapy, and chemotherapy showed better survival benefits, statistical significance was not reached in any modality.

Study limitations. This study had several limitations. Firstly, the reported data was heterogeneous with inconsistent definitions of variables. Similarly, the included articles suffered from selection bias in patient inclusion and the management protocols, including, but not limited to, surgical approach, radiation parameters and technique, and chemotherapy. Several variables such as histopathological type, invaded structures, tumor volume and treatment type were incompletely reported. Most articles reported SBACCs as part of craniofacial ACC, and others reported ACCs as part of other skull base tumors, limiting data extraction.

Conclusion

ACC involving the skull base is a challenging pathology, typically with indolent, relentless progression. Included articles reported various symptoms related to the invaded neurovascular structures consistent with the invasive nature of the pathology. Due to the absence of superior alternative treatments, surgical management in conjunction with radiotherapy has remained the primary treatment strategy. Free flap techniques and skull base reconstruction represent an essential element of the management after salvage resection of advanced SBACCs.

Conflicts of Interest

The Authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

Authors' Contributions

Othman Bin-Alamer: Conceptualization, Methodology, Data analysis, Writing – Original draft preparation; Adhiraj Chaudhary, Kishore Balasubramanian, Tessa Breeding: Paper screening, Resources, Writing – Reviewing and Editing; Paolo Palmisciano, Maryam Haider and Ali S. Haider: Resources, Data extraction, and Writing – Reviewing and Editing; Tarek Y. El Ahmadieh, Aaron A. Cohen-Gado, Ali S. Haider and Kenny Yu: Resources, Writing – Critically reviewing the final draft.

References

1 Bradley PJ: Adenoid cystic carcinoma evaluation and management: progress with optimism! Curr Opin Otolaryngol Head Neck Surg *25(2)*: 147-153, 2017. PMID: 28106659. DOI: 10.1097/MOO.0000000000000347

2 Coca-Pelaz A, Rodrigo JP, Bradley PJ, Vander Poorten V, Triantafyllou A, Hunt JL, Strojan P, Rinaldo A, Haigentz M Jr, Takes RP, Mondin V, Teymoortash A, Thompson LD and Ferlito A: Adenoid cystic carcinoma of the head and neck—An update. Oral Oncol *51(7)*: 652-661, 2015. PMID: 25943783. DOI: 10.1016/j.oraloncology.2015.04.005

3 Ueda K, Murase T, Nagao T, Kusafuka K, Urano M, Yamamoto H, Nakaguro M, Taguchi KI, Masaki A, Hirai H, Kawakita D, Tsukahara K, Hato N, Nagao T, Fujimoto Y, Sakurai K, Hanai N, Kano S, Onitsuka T, Okami K, Nibu KI, Tada Y, Kawata R and Inagaki H: Central pathology review of salivary gland adenoid cystic carcinoma. Head Neck *42(8)*: 1721-1727, 2020. PMID: 31970840. DOI: 10.1002/hed.26081

4 Guazzo E and Panizza B: Management of advanced adenoid cystic carcinoma infiltrating the skull base: a contemporary review. J Neurooncol *150(3)*: 419-427, 2020. PMID: 31897924. DOI: 10.1007/s11060-019-03366-x

5 Anderson JN Jr, Beenken SW, Crowe R, Soong SJ, Peters G, Maddox WA and Urist MM: Prognostic factors in minor salivary gland cancer. Head Neck *17(6)*: 480-486, 1995. PMID: 8847206. DOI: 10.1002/hed.2880170605

6 Ramakrishna R, Raza SM, Kupferman M, Hanna E and DeMonte F: Adenoid cystic carcinoma of the skull base: results with an aggressive multidisciplinary approach. J Neurosurg *124(1)*: 115-121, 2016. PMID: 26252456. DOI: 10.3171/2015.1.JNS142462

7 Baulch J, Gandhi M, Sommerville J and Panizza B: 3T MRI evaluation of large nerve perineural spread of head and neck cancers. J Med Imaging Radiat Oncol *59(5)*: 578-585, 2015. PMID: 26178307. DOI: 10.1111/1754-9485.12338

8 Gandhi M and Sommerville J: The imaging of large nerve perineural spread. J Neurol Surg B Skull Base *77(2)*: 113-123, 2016. PMID: 27123387. DOI: 10.1055/s-0036-1571836

9 Gormley WB, Sekhar LN, Wright DC, Olding M, Janecka IP, Snyderman CH and Richardson R: Management and long-term outcome of adenoid cystic carcinoma with intracranial extension: a neurosurgical perspective. Neurosurgery *38(6)*: 1105-12; discussion 1112-3, 1996. PMID: 8727139. DOI: 10.1097/00006123-199606000-00008

10 Haddad RI, Posner MR, Busse PM, Norris CM Jr, Goguen LA, Wirth LJ, Blinder R, Krane JF and Tishler RB: Chemoradiotherapy for adenoid cystic carcinoma: preliminary results of an organ sparing approach. Am J Clin Oncol *29(2)*: 153-157, 2006. PMID: 16601434. DOI: 10.1097/01.coc.0000203756.36866.17

11 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P and Moher D: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ *372*: n71, 2021. PMID: 33782057. DOI: 10.1136/bmj.n71

12 Alamer OB, Palmisciano P, Rowe SE, Gupta AD, Haider M, Alduhaymi M, Cohen-Gadol AA, Yu K, El-Ahmadieh TY and Haider AS: Pineal region gliomas: a systematic review of clinical features and treatment outcomes. Anticancer Res *42(3)*: 1189-1198, 2022. PMID: 35220208. DOI: 10.21873/anticanres.15585

13 Liu HJ, Li DZ, Li XJ, Qian HP, An CM and Wan JH: Free flap transfer, a safe and efficient method for reconstruction of composite skull base defects after salvage resection of advanced intracranial and extracranial communicating tumors. World Neurosurg *152*: e62-e70, 2021. PMID: 33940259. DOI: 10.1016/j.wneu.2021.04.084

14 Valentini V, Fabiani F, Nicolai G, Torroni A, Gennaro P, Marianetti TM and Iannetti G: Use of microvascular free flaps in the reconstruction of the anterior and middle skull base. J Craniofac Surg *17(4)*: 790-796, 2006. PMID: 16877936. DOI: 10.1097/00001665-200607000-00035

15 Tarsitano A, Pizzigallo A, Gessaroli M, Sturiale C and Marchetti C: Intraoperative biopsy of the major cranial nerves in the surgical strategy for adenoid cystic carcinoma close to the skull base. Oral Surg Oral Med Oral Pathol Oral Radiol *113(2)*: 214-221, 2012. PMID: 22677739. DOI: 10.1016/j.tripleo.2011.02.014

16 Morimoto K, Demizu Y, Hashimoto N, Mima M, Terashima K, Fujii O, Otsuki N, Murakami M, Fuwa N and Nibu K: Particle radiotherapy using protons or carbon ions for unresectable locally advanced head and neck cancers with skull base invasion. Jpn J Clin Oncol *44(5)*: 428-434, 2014. PMID: 24620027. DOI: 10.1093/jjco/hyu010

17 Dautruche A, Bolle S, Feuvret L, Le Tourneau C, Jouffroy T, Goudjil F, Zefkili S, Nauraye C, Rodriguez J, Herman P and Calugaru V: Three-year results after radiotherapy for locally advanced sinonasal adenoid cystic carcinoma, using highly conformational radiotherapy techniques proton therapy and/or Tomotherapy. Cancer Radiother *22(5)*: 411-416, 2018. PMID: 30064829. DOI: 10.1016/j.canrad.2017.11.015

18 Gentile MS, Yip D, Liebsch NJ, Adams JA, Busse PM and Chan AW: Definitive proton beam therapy for adenoid cystic carcinoma of the nasopharynx involving the base of skull. Oral Oncol *65*: 38-44, 2017. PMID: 28109466. DOI: 10.1016/j.oraloncology.2016.11.016

19 Issing PR, Hemmanouil I, Stöver T, Kempf HG, Wilkens L, Heermann R and Lenarz T: Adenoid cystic carcinoma of the skull base. Skull Base Surg *9(4)*: 271-275, 1999. PMID: 17171116. DOI: 10.1055/s-2008-1058137

20 Xu N, Zheng L, Wu WJ, Huang MW, Zhang J and Zhang JG: Definitive ^{125}I brachytherapy of locally advanced adenoid cystic carcinoma involving the skull base with satisfying efficacy and safety. J Oral Maxillofac Surg *77(10)*: 2143-2153, 2019. PMID: 31028735. DOI: 10.1016/j.joms.2019.03.031

21 Schulz-Ertner D, Didinger B, Nikoghosyan A, Jäkel O, Zuna I, Wannenmacher M and Debus J: Optimization of radiation therapy for locally advanced adenoid cystic carcinomas with infiltration of the skull base using photon intensity-modulated radiation therapy (IMRT) and a carbon ion boost. Strahlenther Onkol *179(5)*: 345-351, 2003. PMID: 12740662. DOI: 10.1007/s00066-003-1071-7

22 Ginsberg LE and Demonte F: Palatal adenoid cystic carcinoma presenting as perineural spread to the cavernous sinus. Skull Base Surg *8(1)*: 39-43, 1998. PMID: 17171041. DOI: 10.1055/s-2008-1058589

23 Bhattasali O, Holliday E, Kies MS, Hanna EY, Garden AS, Rosenthal DI, Morrison WH, Gunn GB, Fuller CD, Zhu XR and Frank SJ: Definitive proton radiation therapy and concurrent cisplatin for unresectable head and neck adenoid cystic carcinoma: A series of 9 cases and a critical review of the literature. Head Neck *38 Suppl 1*: E1472-E1480, 2016. PMID: 26561041. DOI: 10.1002/hed.24262

24 Frank SJ, Cox JD, Gillin M, Mohan R, Garden AS, Rosenthal DI, Gunn GB, Weber RS, Kies MS, Lewin JS, Munsell MF, Palmer MB, Sahoo N, Zhang X, Liu W and Zhu XR: Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation to practice. Int J Radiat Oncol Biol Phys *89(4)*: 846-853, 2014. PMID: 24867532. DOI: 10.1016/j.ijrobp.2014.04.019

25 Taylor RJ, Patel MR, Wheless SA, McKinney KA, Stadler ME, Sasaki-Adams D, Ewend MG, Germanwala AV and Zanation AM: Endoscopic endonasal approaches to infratemporal fossa tumors: a classification system and case series. Laryngoscope *124(11)*: 2443-2450, 2014. PMID: 25513678. DOI: 10.1002/lary.24638

26 Mori Y, Kobayashi T, Kida Y, Oda K, Shibamoto Y and Yoshida J: Stereotactic radiosurgery as a salvage treatment for recurrent skull base adenoid cystic carcinoma. Stereotact Funct Neurosurg *83(5-6)*: 202-207, 2005. PMID: 16424685. DOI: 10.1159/000091084

27 Serracino HS and Kleinschmidt-Demasters BK: Skull invaders: when surgical pathology and neuropathology worlds collide. J Neuropathol Exp Neurol *72(7)*: 600-613, 2013. PMID: 23771219. DOI: 10.1097/NEN.0b013e318299c40f

28 Gil Z, Orr-Urtreger A, Voskoboinik N, Trejo-Leider L, Shomrat R and Fliss DM: Cytogenetic analysis of 101 skull base tumors. Head Neck *30(5)*: 567-581, 2008. PMID: 18098307. DOI: 10.1002/hed.20741

29 Bin Alamer O, Haider AS, Chaudhary A, Balasubramanian K, Breeding T, Palmisciano P, Haider M, Cohen-Gadol AA, El Ahmadieh TY and Yu K: Adenoid cystic carcinoma infiltrating the skull base: a systematic review. J Neurol Surg B Skull Base *83(S 01)*: A131, 2022. DOI: 10.1055/s-0042-1743723

30 Marchiano E, Chin OY, Fang CH, Park RC, Baredes S and Eloy JA: Laryngeal adenoid cystic carcinoma: a systematic review. Otolaryngol Head Neck Surg *154(3)*: 433-439, 2016. PMID: 26701176. DOI: 10.1177/0194599815621884

31 Muskens IS, Briceno V, Ouwehand TL, Castlen JP, Gormley WB, Aglio LS, Zamanipoor Najafabadi AH, van Furth WR, Smith TR, Mekary RA and Broekman MLD: The endoscopic endonasal approach is not superior to the microscopic transcranial approach for anterior skull base meningiomas-a meta-analysis. Acta Neurochir (Wien) *160(1)*: 59-75, 2018. PMID: 29127655. DOI: 10.1007/s00701-017-3390-y

32 Bin Alamer O, Haider AS, Haider M, Sagoo NS, Robertson FC, Arrey EN, Aoun SG, Yu K, Cohen-Gadol AA and El Ahmadieh TY: Primary and radiation induced skull base osteosarcoma: a systematic review of clinical features and treatment outcomes. J Neurooncol *153(2)*: 183-202, 2021. PMID: 33999382. DOI: 10.1007/s11060-021-03757-z

33 Ju J, Li Y, Chai J, Ma C, Ni Q, Shen Z, Wei J and Sun M: The role of perineural invasion on head and neck adenoid cystic carcinoma prognosis: a systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol *122(6)*: 691-701, 2016. PMID: 27727107. DOI: 10.1016/j.oooo.2016.08.008

34 Dantas AN, Morais EF, Macedo RA, Tinôco JM and Morais Mde L: Clinicopathological characteristics and perineural invasion in adenoid cystic carcinoma: a systematic review. Braz J Otorhinolaryngol *81(3)*: 329-335, 2015. PMID: 25962319. DOI: 10.1016/j.bjorl.2014.07.016

35 Yarbrough WG, Panaccione A, Chang MT and Ivanov SV: Clinical and molecular insights into adenoid cystic carcinoma: Neural crest-like stemness as a target. Laryngoscope Investig Otolaryngol *1(4)*: 60-77, 2016. PMID: 28894804. DOI: 10.1002/lio2.22

36 Nobis CP, Rohleder NH, Wolff KD, Wagenpfeil S, Scherer EQ and Kesting MR: Head and neck salivary gland carcinomas—elective neck dissection, yes or no? J Oral Maxillofac Surg *72(1)*: 205-210, 2014. PMID: 23891016. DOI: 10.1016/j.joms.2013.05.024

37 Spiro RH: Salivary neoplasms: overview of a 35-year experience with 2,807 patients. Head Neck Surg *8(3)*: 177-184, 1986. PMID: 3744850. DOI: 10.1002/hed.2890080309

38 Liu W and Chen X: Adenoid cystic carcinoma of the larynx: a report of six cases with review of the literature. Acta Otolaryngol *135(5)*: 489-493, 2015. PMID: 25743246. DOI: 10.3109/00016489.2014.990583

39 Spiers AS, Esseltine DL, Ruckdeschel JC, Davies JN and Horton J: Metastatic adenoid cystic carcinoma of salivary glands: case reports and review of the literature. Cancer Control *3(4)*: 336-342, 1996. PMID: 10765225. DOI: 10.1177/107327489600300405

40 Laurie SA, Ho AL, Fury MG, Sherman E and Pfister DG: Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: a systematic review. Lancet Oncol *12(8)*: 815-824, 2011. PMID: 21147032. DOI: 10.1016/S1470-2045(10)70245-X

41 Noguchi M, Iwasawa M, Hirose T, Kyoshima K and Yokoo A: [Reconstruction of anterior cranial base and face with free musculocutaneous flap; report of two cases]. No Shinkei Geka *20(7)*: 819-823, 1992. PMID: 1321351.

42 Bizeau A, Guelfucci B, Giovanni A, Gras R, Casanova D and Zanaret M: [15 years experience with microvascular free tissue transfert for repair of head and neck cancer defects]. Ann Otolaryngol Chir Cervicofac *119(1)*: 31-38, 2002. PMID: 11965104.

43 Saraydaroglu O, Coskun H and Kasap M: Unique presentation of adenoid cystic carcinoma in postcricoid region: a case report and review of the literature. Head Neck Pathol *5(4)*: 413-415, 2011. PMID: 21559806. DOI: 10.1007/s12105-011-0266-y

44 Testa D, Guerra G, Conzo G, Nunziata M, D'Errico G, Siano M, Ilardi G, Vitale M, Riccitiello F and Motta G: Glottic-Subglottic adenoid cystic carcinoma. A case report and review of the literature. BMC Surg *13 Suppl 2*: S48, 2013. PMID: 24427787. DOI: 10.1186/1471-2482-13-s2-s48

Received April 3, 2022
Revised June 17, 2022
Accepted June 29, 2022