Literature review of 86 cases of mandibular ameloblastic carcinoma

ABSTRACT

Ameloblastic carcinoma is considered to be a rare epithelial malignant neoplasm of odontogenic origin occurring mainly in the mandible. Ameloblastic carcinoma has been a topic of controversy regarding management from past many years. We reviewed 86 cases of mandibular ameloblastic carcinoma from 1981 to 2014, on the basis of the electronic search of peer-reviewed journals in MEDLINE (PubMed) database. Age, sex, tumor size, treatment delivered, recurrence, metastasis, follow-up period, and dead/alive status are tabulated, and the data are analyzed. The mean age was 43.47 years with standard deviation ± 21.09. The age range was between 15 and 91 years, and male to female ratio was 2.18:1. Knowledge gained from the present review would help in establishing the best therapeutic options for ameloblastic carcinoma, and it also encourages the further reporting of ameloblastic carcinoma.

Keywords: Ameloblastic carcinoma, mandible, radiotherapy, surgical resection

INTRODUCTION

Odontogenic malignancies are rare lesions that comprise 1% of all cysts and tumors occurring in the jaws.^[1,2] Different terms are used to designate odontogenic carcinomas which include malignant ameloblastoma, ameloblastic carcinoma, metastatic ameloblastoma, or primary intraosseous epidermoid carcinoma.

Ameloblastic carcinoma is a rare entity that shows the histopathological signs of ameloblastoma with cytological atypia with or without distant metastasis. For past many years, ameloblastic carcinoma has been a topic of controversy regarding definition and classification due to its rarity and also due to various terminologies related to malignant or metastasizing variant of tumor.

In 1972, WHO published classification of odontogenic malignant tumors, which also included malignant ameloblastoma.^[3] In 1982, Elzay^[4] introduced term ameloblastic carcinoma and suggested a modified classification to distinguish between ameloblastic carcinoma (with histopathological features of malignancy) and malignant ameloblastoma (which retains histopathological features of a simple ameloblastoma at

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the distant metastasis site). In 1984, Slootweg and Müller^[5] proposed a modification in Elzay's classification related to the origin of the tumor. In the latest update of WHO classification of odontogenic tumors^[6] published in 2005, ameloblastic carcinoma is subdivided into primary type (developing *de novo*) and secondary type (developing by malignant transformation of ameloblastoma). The secondary type is further subdivided into intraosseous and peripheral type. Among the reported cases of ameloblastic carcinoma, the prevalence of mandibular ameloblastic carcinoma comprises around two-third with maxillary incidence of one-third.^[7]

AIM OF PRESENT LITERATURE REVIEW

The aim of the present literature review is to collate and analyze the various modalities utilized in the management

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of mandibular ameloblastic carcinoma as well as to see the recurrence and metastasis associated with the various procedures. Knowledge gained from the present review would help in establishing the best therapeutic options for ameloblastic carcinoma, and it also encourages the further reporting of ameloblastic carcinoma.

MATERIALS AND METHODS

The published cases of mandibular ameloblastic carcinoma since 1981 were presented in Table 1. Age, sex, tumor size, treatment delivered, metastasis, recurrence, follow-up period, and dead/alive status were tabulated and the data were analyzed. However, all the details for every case were not available. Search engines and medical database such as PubMed, Medline, and Pubgate were tapped for information and relevant articles related to the mandibular ameloblastic carcinoma. The search words "Ameloblastic Carcinoma," "Surgical intervention in ameloblastic carcinoma," and "Radiotherapy in ameloblastic carcinoma" were employed for retrieval of data. The analysis of various treatment modalities, reason for choice of particular modality, recurrence, and follow period was done. The search was restricted to English language articles, published from 1981 to 2014.

RESULTS

The mean age was found to be 43.47 years with standard deviation \pm 21.09. The age range for the patients was between 15 and 91 years. Male to female ratio was 2.18:1. Follow-up period ranged from 0 to 540 months. Out of 86 cases reported, 50 had received surgical management only, 14 had received additional radiotherapy, two had surgery plus radiotherapy and chemotherapy, and eight patients declined any treatment. There were single cases of isolated radiotherapy and chemotherapy. In 10 reports, the treatment was not specified. Out of 68 cases, which had the treatment mentioned specifically, only 21 report \geq 5 years follow-up. Out of these 21, 11 had disease-free state and 10 had either local recurrence or metastasis. Interestingly, only one of the eleven disease-free cases had received postoperative radiotherapy. On the other hand, 33/68 cases showed recurrence/metastasis at follow-up ranging from 6 to 540 months. These patients with recurrent disease had treatment distribution as follows: 18 had only surgical treatment, 11 had surgery and radiotherapy, two patients had surgery plus radiotherapy and chemotherapy, and another two patients had isolated radiotherapy and chemotherapy each. In variable follow-up period, 10 had lymph node spread and 13 had distant metastasis. These figures suggest aggressive nature and malignant potential of the pathology.

DISCUSSION

Ameloblastic carcinoma is considered to be a rare malignant neoplasm of odontogenic origin. Clinically and radiographically, ameloblastoma and ameloblastic carcinoma both resemble each other but ameloblastic carcinoma can be suspected if there is a sudden increase in the size of the swelling, pain, paresthesia, expansion, and perforation of cortical plate with soft tissue extension or if there is any foci of calcification as these features are unusual in ameloblastoma. A preoperative $18F-\alpha$ -methyl tyrosine or 18-fluorodeoxyglucose positron emission tomography (PET) scan may help to differentiate the malignant and benign areas in the tumor mass.^[37,45]

Histopathologic evaluation shows ameloblastic differentiation, palisading of basaloid cells, and stellate reticulum pattern in the follicles and the features of malignancy such as cellular atypia, mitotic figures, and nuclear hyperchromatism. Immunohistochemical studies may help to differentiate ameloblastic carcinoma from simple ameloblastoma. Increased expression of Ki-67 and Notch1 and decreased expression of Syndecan-1 are associated with the diagnosis of ameloblastic carcinoma over that of simple ameloblastoma.^[33] In simple ameloblastoma alpha- smooth muscle actin, expression is found in only stroma close to the epithelium, whereas in ameloblastic carcinoma, this is found in both the stellate reticulum-like cells as well as in the stroma. This may signify epithelial-mesenchymal transition and may be associated with distant metastasis.^[33] Hypermethylation of p16 tumor suppressor gene is thought to be related to carcinomatous transformation of a benign ameloblastoma.[46] Likewise, proliferating cell nuclear antigen marker signifies aggressiveness of any ameloblastoma and hence its potential to develop into a secondary ameloblastoma.^[47] Raised matrix metalloproteinase-2 levels with reduced expression of RECK mRNA and upregulation of NK-1R are also associated with malignant transformation.^[48,49]

In cases of ameloblastic carcinoma, patient should be further evaluated to rule out any nodal and distant metastasis. Staged workup including computed tomography of head and neck, chest radiograph, and abdominal ultrasonography needs to be done because even in the absence of local or regional recurrence, distant metastasis can occur.^[15] PET scan is useful to monitor for recurrence and/or metastatic spread. Postoperative PET scan is also helpful to differentiate between postoperative fibrosis and tumor recurrence and for restaging local nodal or distant metastatic spread.^[50] All the necessary investigations are required to rule out local recurrence and metastasis at required interval. Some studies

Table 1: Literature review of 86 cases of mandibular ameloblastic carcinoma from 1981 to 2014

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33 2007 Akrish et al. ^[27] 80 Male SR 12 A 34 2007 Hall et al. ^[21] 27 Male S Recurrence 114 D 35 2007 Hall et al. ^[21] 31 Male S + RT Recurrence 492 A 36 2007 Hall et al. ^[21] 43 Female S + RT Recurrence 60 D 37 2007 Hall et al. ^[21] 43 Female S + RT Recurrence 59 D 38 2007 Hall et al. ^[21] 53 Female S Recurrence 141 D 39 2007 Hall et al. ^[21] 53 Female S Recurrence 141 D 40 2007 Hall et al. ^[21] 53 Female SR Recurrence 141 D 41 2007 Hall et al. ^[21] 17 Female SR Recurrence 18 A 42 2009 Yoon et al. ^[28] 46 Male SR + RT LN/recu	32	2006	Miyake et al.[26]	91	Female		SR		6	А
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36 2007 Hall et al. ^[2] 43 Female S + RT LN/recurrence 60 D 37 2007 Hall et al. ^[2] 50 Male 2.5×3 S Recurrence 156 D 38 2007 Hall et al. ^[2] 49 Male S + RT Recurrence 59 D 39 2007 Hall et al. ^[2] 53 Female S 369 D 40 2007 Hall et al. ^[2] 59 Male S + RT Recurrence 141 D 41 2007 Hall et al. ^[2] 59 Male S + RT Recurrence 141 D 41 2007 Hall et al. ^[2] 17 Female SR LN/recurrence 18 A 43 2009 Yoon et al. ^[28] 65 Male SR + RT LN/recurrence 18 A 44 2009 Reid-Nicholson et al. ^[28] 15 Male SR + RT Lung/brain A 45 2009 Cherry et al. ^[30] 16 Male SR + RT	35	2007	Hall et al. ^[2]	31	Male		S + RT	Recurrence	492	А
37 2007 Hall et al. ^[2] 50 Male 2.5×3 S Recurrence 156 D 38 2007 Hall et al. ^[2] 49 Male S + RT Recurrence 59 D 39 2007 Hall et al. ^[2] 53 Female S 369 D 40 2007 Hall et al. ^[2] 59 Male S + RT Recurrence 141 D 41 2007 Hall et al. ^[2] 17 Female S 122 D 41 2007 Hall et al. ^[2] 17 Female SR 122 D 42 2009 Yoon et al. ^[28] 46 Male 5 SR+RT LN/recurrence 18 A 43 2009 Yoon et al. ^[28] 15 Male SR LN - - 44 2009 Reid-Nicholson et al. ^[28] 15 Male SR + RT Lung/brain A 45 2009 Cherry et al. ^[30] 58 Male SR + RT Lung/brain - -	36	2007	Hall et al. ^[2]	43	Female		S + BT	LN/recurrence	60	D
38 2007 Hall et al. ^[2] 49 Male S + RT Recurrence 59 D 39 2007 Hall et al. ^[2] 53 Female S 369 D 40 2007 Hall et al. ^[2] 59 Male S + RT Recurrence 141 D 41 2007 Hall et al. ^[2] 17 Female SR 122 D 42 2009 Yoon et al. ^[28] 46 Male 5 SR + RT LN/recurrence 18 A 43 2009 Yoon et al. ^[28] 65 Male SR LN - - 44 2009 Reid-Nicholson et al. ^[28] 15 Male SR LN - - 45 2009 Cherry et al. ^[30] 16 Male 7×7×6 SR + RT Lung/brain - - 46 2010 Jeremic et al. ^[31] 58 Male SR - - - 48 2010 Ndukwe et al. ^[32] 16 Female SR - -	37	2007	Hall et al. ^[2]	50	Male	2.5×3	S	Recurrence	156	D
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40 2007 Hall et al. ^[2] 59 Male S + RT Recurrence 141 D 41 2007 Hall et al. ^[2] 17 Female SR 122 D 42 2009 Yoon et al. ^[28] 46 Male 5 SR + RT LN/recurrence 18 A 43 2009 Yoon et al. ^[28] 65 Male SR + RT LN 13 A 44 2009 Reid-Nicholson et al. ^[29] 15 Male SR + RT LN - - 45 2009 Cherry et al. ^[30] 16 Male 7×7×6 SR + RT Lung/brain A 46 2010 Jeremic et al. ^[31] 58 Male SR - - - 47 2010 Ndukw et al. ^[32] 16 Male SR - - - 48 2010 Ndukw et al. ^[32] 16 Female SR - - - 49 2010 Ndukw et al. ^[32] 23 Male Declined - - <td>39</td> <td>2007</td> <td>Hall et al.^[2]</td> <td>53</td> <td>Female</td> <td></td> <td>S</td> <td></td> <td>369</td> <td>D</td>	39	2007	Hall et al. ^[2]	53	Female		S		369	D
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42 2009 Yoon et al. ^[28] 46 Male 5 SR+RT LN/recurrence 18 A 43 2009 Yoon et al. ^[28] 65 Male SR+RT LN 13 A 44 2009 Reid-Nicholson et al. ^[29] 15 Male SR LN - - 45 2009 Cherry et al. ^[30] 16 Male 7×7×6 SR+RT Lung/brain A 46 2010 Jeremic et al. ^[31] 58 Male SR SR Lung 21 D 47 2010 Ndukwe et al. ^[32] 16 Male SR SR - - - 48 2010 Ndukwe et al. ^[32] 16 Female SR - - - 49 2010 Ndukwe et al. ^[32] 23 Male Declined - - - 51 2010 Ndukwe et al. ^[32] 25 Female Declined - - - 52 2010 Ndukwe et al. ^[32] 27 Male	41	2007	Hall et al. ^[2]	17	Female		SR		122	D
43 2009 Yoon et al. ^[28] 65 Male SR + RT LN 13 A 44 2009 Reid-Nicholson et al. ^[29] 15 Male SR LN - - 45 2009 Cherry et al. ^[30] 16 Male $7 \times 7 \times 6$ SR + RT Lung/brain A 46 2010 Jeremic et al. ^[31] 58 Male SR + RT Lung/brain A 47 2010 Ndukwe et al. ^[32] 16 Male SR SR - - 48 2010 Ndukwe et al. ^[32] 16 Female SR - - - 49 2010 Ndukwe et al. ^[32] 16 Female SR - - - 49 2010 Ndukwe et al. ^[32] 23 Male Declined - - 51 2010 Ndukwe et al. ^[32] 24 Male Declined - - 52 2010 Ndukwe et al. ^[32] 25 Female Declined - - 53	42	2009	Yoon et al.[28]	46	Male	5	SR+RT	LN/recurrence	18	А
44 2009 Reid-Nicholson et al. ^[29] 15 Male SR LN - - 45 2009 Cherry et al. ^[30] 16 Male $7 \times 7 \times 6$ SR+RT Lung/brain A 46 2010 Jeremic et al. ^[31] 58 Male SR+RT Lung 21 D 47 2010 Ndukwe et al. ^[32] 16 Male SR SR - - 48 2010 Ndukwe et al. ^[32] 16 Female SR - - - 49 2010 Ndukwe et al. ^[32] 23 Male SR - - - 50 2010 Ndukwe et al. ^[32] 24 Male Declined - - 51 2010 Ndukwe et al. ^[32] 25 Female Declined - - 52 2010 Ndukwe et al. ^[32] 27 Male Declined - - 53 2010 Ndukwe et al. ^[32] 31 Female SR - - 53 2010	43	2009	Yoon et al. ^[28]	65	Male	·	SR+RT	IN	13	A
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47 2010 Ndukwe et al. ^[32] 16 Male SR - - 48 2010 Ndukwe et al. ^[32] 16 Female SR - - 49 2010 Ndukwe et al. ^[32] 16 Female SR 6 A 50 2010 Ndukwe et al. ^[32] 23 Male Declined - - 51 2010 Ndukwe et al. ^[32] 25 Female Declined - - 52 2010 Ndukwe et al. ^[32] 27 Male Declined - - 53 2010 Ndukwe et al. ^[32] 31 Female SR - -	46	2010	Jeremic <i>et al</i> . ^[31]	58	Male		SR+RT	Luna	21	D
48 2010 Ndukwe et al. ^[32] 16 Female SR - - 49 2010 Ndukwe et al. ^[32] 23 Male SR 6 A 50 2010 Ndukwe et al. ^[32] 24 Male Declined - - 51 2010 Ndukwe et al. ^[32] 25 Female Declined - - 52 2010 Ndukwe et al. ^[32] 27 Male Declined - - 53 2010 Ndukwe et al. ^[32] 31 Female SR - -	47	2010	Ndukwe et al.[32]	16	Male		SR	9	-	-
49 2010 Ndukwe et al. ^[32] 23 Male SR 6 A 50 2010 Ndukwe et al. ^[32] 24 Male Declined	48	2010	Ndukwe et al. ^[32]	16	Female		SR		-	-
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52 2010 Ndukwe et al. ^[32] 27 Male Declined 53 2010 Ndukwe et al. ^[32] 31 Female SR	51	2010	Ndukwe et al. ^[32]	25	Female		Declined			
53 2010 Ndukwe <i>et al.</i> ^[32] 31 Female SR	52	2010	Ndukwe et al.[32]	27	Male		Declined			
	53	2010	Ndukwe et al.[32]	31	Female		SR			

Table 1: Contd...

Case	Year	Authors	Age (year)	Sex	Tumor size (cm)	Treatment delivered	Metastasis/recurrence	Follow-up (months)	Dead/alive status
54	2010	Ndukwe et al.[32]	32	Male		SR	LN	12	А
55	2010	Ndukwe et al.[32]	33	Female		Declined			
56	2010	Ndukwe et al.[32]	34	Male		SR	Recurrence	18	D
57	2010	Ndukwe et al.[32]	34	Female		Declined			
58	2010	Ndukwe et al.[32]	36	Female		-			D
59	2010	Ndukwe et al.[32]	39	Male		Declined			
60	2010	Ndukwe et al.[32]	49	Male		SR			
61	2010	Ndukwe et al.[32]	65	Male		SR	Recurrence	96	D
62	2010	Ndukwe et al.[32]	65	Male		Declined			
63	2010	Ndukwe et al.[32]	85	Female		Declined			
64	2010	Kamath et al.[33]	64	Male	6×5	SR		0	
65	2010	Karakida <i>et al</i> . ^[34]	43	Male	5.5×4.5	SR		46	А
66	2010	Roy Chowdhury et al.[35]	67	Female	4×3	SR		6	А
67	2010	Ram <i>et al</i> .[36]	21	Male	$2.4 \times 5.5 \times 6$	SR		24	А
68	2010	Devenney-Cakir et al.[37]	16	Male	8×6×5	SR	Recurrence/lung + brain	48	А
69	2011	Maheshwari et al.[38]	35	Male	5×5	SR + RT		14	А
70	2012	Pirklbauer et al.[39]	86	Male		RT	Brain	8	D
71	2012	Horváth et al.[40]	17	Male		СН	Lung + bone marrow	8	D
72	2013	Yoshioka et al.[41]	17	Male		S	Lung/recurrence	39	D
73	2014	Jayaraj <i>et al</i> . ^[42]	22	Male			LN		
74	2013	Augustine et al.[43]	44	Female		SR			
75	2014	Srikanth et al.[44]	60	Male	23×11.5	SR			
76	2014	Li et al. ^[45]	36	Male		SR	Recurrence	120	
77	2014	Li et al. ^[45]	40	Female		SR		120	А
78	2014	Li et al. ^[45]	61	Male		SR		108	А
79	2014	Li et al. ^[45]	40	Male		SR		96	А
80	2014	Li et al. ^[45]	39	Female		SR		84	А
81	2014	Li et al. ^[45]	42	Male		SR		72	А
82	2014	Li et al. ^[45]	46	Male		SR		60	А
83	2014	Li et al. ^[45]	32	Male		SR		60	А
84	2014	Li et al. ^[45]	30	Male		SR		48	А
85	2014	Li et al. ^[45]	35	Male		SR		36	А
86	2014	Li et al. ^[45]	75	Male		SR	Lung	36	

SR: Surgical resection, S: Surgery, RT: Radiotherapy, CH: Chemotherapy, LN: Lymphadenopathy, A: Alive, D: Dead

have shown metastasis to the lung,^[9,10,30,31,40,41] brain,^[22,30,39] and bone.^[8,18,40] The route of spread of malignant ameloblastoma is not clearly defined; however, the most common routes of spread are lymphatic, hematogenous, and by aspiration. Due to repeated recurrences, long-term follow-up is necessary.

There are controversies regarding management of ameloblastic carcinoma, but the most recommended treatment is jaw resection with wide surgical margins (1-2 cm) in which recurrence rate is found to be less than 15%.^[18]

Besides surgery, management of ameloblastic carcinoma has included radiotherapy, chemotherapy, cryotherapy^[51] as well as Gamma Knife stereotactic radiosurgery^[44,45] with variable success. In cases with significant lymphadenopathy, cervical lymph node dissection should be considered. Due to less number of the reported cases and high cure rates even without lymph-node dissection and possibility of a hematogenous spread, elective neck dissection is not routinely recommended.^[45] Among recent advances, carbon ion therapy can spare the adjacent normal tissues while destroying the tumor effectively.^[45] It is suggested that radiotherapy should especially be given in cases with positive resection margins, positive lymph nodes, extracapsular spread, and cases with perineural invasion.^[38] Gandy *et al.*^[12] suggested that pre- and post-operative radiotherapy might be helpful in reducing the tumor size. However, more studies are needed to ascertain usefulness of radiotherapy.

From the available literature over the last 34 years, it is clear that ameloblastic carcinoma of the mandible is a highly malignant neoplasm with very less chances of survival. Five-year survival rate was reported to be <40%.^[7] Distant metastasis is usually fatal and may appear from 4 months to 12 years postoperatively.^[52]

A longer period of close and meticulous follow-up of the patients is essential to pick up any recurrence or metastasis. Because of rarity of these lesions, it is a challenge to diagnose these malignancies and to give a prompt treatment, which can improve the prognosis. The possibility of malignant transformation should always be taken into consideration whenever ameloblastoma is diagnosed. This review paper is essential to compare the reporting and treatment of mandibular ameloblastic carcinoma to decide the most appropriate management strategies.

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Conflicts of interest

There are no conflicts of interest.

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