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Systematic Review

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Outcomes of Patients With Nasopharyngeal Plasmacytoma: A Systematic Review

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ABSTRACT

Background: This study reviews the published literature related to nasopharyngeal plasmacytoma. Clinical presentation, demographics, treatment, and outcomes of this uncommon disease have been reported.
Methods: A systematic review of studies on nasopharyngeal plasmacytoma from 1935 to 2016 was conducted. A PubMed database search was performed for articles related to this condition along with the bibliographies of those selected articles. Articles were examined for patient data that reported the disease outcome.
Results: Fifty-eight journal articles were included in this analysis, comprising of a total of 114 studies indicative of a predilection for cases particularly in men with a mean age of 55 years (sixth decade of life) characterized with symptoms such as nasal obstruction, epistaxis and neck lymphadenopathy. Radiotherapy was the most common treatment modality, followed by a combination of surgery and radiotherapy. Most of the patients were alive with no evidence of the disease after the median follow-up of 59 months. Of the 3 most common treatment modalities, a combination of radiotherapy and surgery had the most favorable outcome for a majority of patients. The existing condition for 8 patients (7%) deteriorated leading to the development of multiple myeloma.
Conclusion: This review contains a large pool of information about nasopharyngeal plasmacytoma patients examined to date suggesting that aggressive radiotherapy is the most common treatment modality for this condition. Of the 3 most common treatment modalities, a combination of surgery and radiotherapy was shown to have the best survival outcomes.

KEY WORDS: Pharyngeal plasmacytoma; Extramedullary plasmacytoma; Nasopharyngeal tumor; plasmacytoma; Radiotherapy; Chemotherapy; Surgical management.

ABBREVIATIONS: EMP: Extramedullary plasmacytoma; MM: Microcystic Meningioma; OS Overall Survival; DSS: Disease-specific survival; DOD: Died of Disease; ANED: Alive with no evidence of disease; AWD: Alive with disease.

INTRODUCTION

Extramedullary plasmacytoma (EMP) is an uncommon tumor, constituting only 3% of all plasma cell neoplasms and less than 1% of all head and neck tumors. Nasopharyngeal plasmacytomas are very rare tumors with very few cases reported in the literature. Thus, there is little evidence regarding the epidemiology, optimal management, and long-term prognosis for these types of cancers. Because it is an uncommon tumor, it is difficult to perform a randomized controlled trial to determine the optimal management of nasopharyngeal EMPs.Therefore, in this article; we perform a systematic review of 114 cases of nasopharyngeal EMPs, representing the largest unified collection of nasopharyngeal EMPs investigated to date.

Our goal was to analyze the demographics, presentation symptoms, treatment modalities, prognosis, recurrence, and microcystic meningioma (MM) development of this rare form of tumor.

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MATERIALS AND METHODS

Search Strategy

A systematic review was conducted for all cases of nasopharyngeal plasmacytoma reported from 1935 to 2016 using the PubMed database. The search criteria were set as "nasopharyngeal plasmacytoma," "head and neck plasmacytoma," "upper airways plasmacytoma," and "sinonasalplasmacytoma". Four hundred eighty-one articles were initially analyzed. Articles were then filtered to exclude studies conducted in non-human subjects and non-English articles.

Abstracts were first reviewed to search for articles that discussed cases of plasmacytoma occurring in the nasopharynx and full-text articles were subsequently selected and reviewed for data extraction. References of the included studies were examined for additional cases (Figure 1).

Selection Criteria and Data Extraction

All studies conducted on human subjects and published in English language that reported individual data for nasopharyngeal plasmocytoma were included if they reported diagnosis, treatment, follow-up, and outcome. Non-human, radiologic, cadaveric, anatomical, and histological studies were excluded, on account of being sources with insufficient or unextractable data. Articles with unobtainable full text were also excluded from the study. Outcome measures extracted included: demographic data, presenting symptoms, primary treatment modality, recurrence, MM development and metastasis.

Two-year overall survival (OS), disease-specific survival (DSS), locoregional recurrence and MM development rates were calculated using the Kaplan-Meier method. Differences in the survival rates were assessed by the log-rank test. All the recorded *p*-values were two-sided, and a *p*-value <0.05 was adopted as the threshold for statistical significance.

RESULTS

The final PubMed searches using the selected keywords yielded 58 studies from a total of 114 patients which were left for statistical analysis. All 58 studies included individual patient data that was extractable and fit the minimum criteria for inclusion (Table 1).

Demographics

Patient demographics for 113 patients included in this review are summarized in Table 2.

The mean age of patients was 55 years, ranging from 3 to 85 years. Males constituted nearly 69.4% of the cases, whereas females constituted nearly 30.6% of the cases. The mean follow-up for patients was 59 months. Information about histological grade was reported in only 19 articles. The most common presenting symptom was nasal obstruction (29.8% of cases). Further demographic information is summarized in Table 2.

Treatment Modalities and Outcome

A majority of patients nearly 56% were treated with radiotherapy alone (n=63) and nearly 21% were treated in combination with surgery, or in combination with surgery and chemotherapy (n=3), or in combination with chemotherapy (n=4). The remaining patients received surgery alone (n=13) or chemotherapy alone (n=1). Further information regarding treatment modality

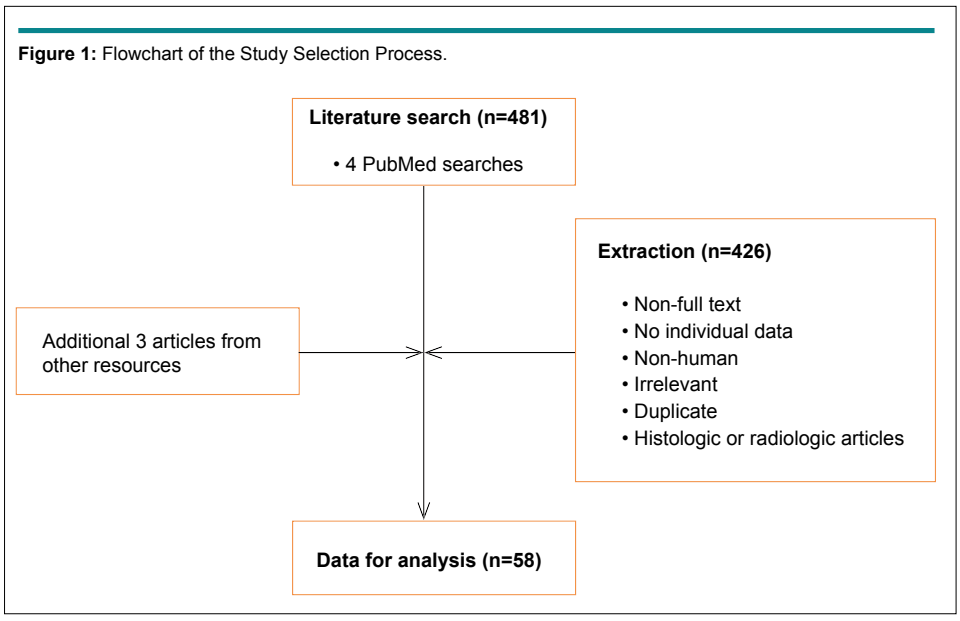

Figure 1: Flowchart of the Study Selection Process.

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Table 1: Patients Data.

Article	Age/Sex	S/M	Symptom	Path	LN	R/x	LRC	DM	Outcomes
Fu et al[1]	68/M	S	Nasal obstruction	N/A	-	S	-	-	NED 3 M
	35/M	S	Nasal obstruction	N/A	-	S	-	-	NED 1 M
Poole et al[2]	51/M	M	Nasal obstruction foreign body sensation	N/A	-	S+RT	-	-	Dead 4 Y
	41/M	M	Epistaxis	N/A	-	S+RT	-	-	Dead 5 Y
	78/M	S	Nasal obstruction epistaxis	N/A	-	S+RT	-	-	NED 7 Y
	59/F	S	Nasal obstruction epistaxis	N/A	-	RT	-	-	NED 8 Y
Lindberg et al[3]	65/M	S	Nasal obstruction epistaxis	N/A		RT	-	-	NED 10 Y
Bush et al[4]	41/M	S	N/A	N/A	-	RT	+ local	Another solitary mylonatibia 18 months	AWD On chemotherapy 7.5 year
	56/M	S	N/A	N/A	-	RT	-	-	MM 2 Y Dead 9 Y
Kapedia et al[5]	45/M	S	N/A	N/A	-	RT	-	-	N/A
	78/M	S	N/A	N/A	-	RT	-	-	N/A
	52/M	S	N/A	N/A	-	RT+ CH	-	Other back of tibia	MM 2 M Dead MM 14 M
Du et al[6]	63/M	S	Nasal obstruction epistaxis 6 cranial nerve palsy	N/A	-	RT	-	-	NED 18 M
Stout et al[7]	61/F	s	Nasal obstruction	N/A		RT	-	+ femur	Dead from metastasis 3.5 Y
	38/M	s	Post nasal discharge	N/A		S+RT	-	-	NED 2 Y
Figi et al[8]	48/M	s	N/A	N/A	-	S+RT	-	-	NED 3 Y
	47/F	s	N/A Invasive	N/V	-	S+RT	-	-	AWD 20
Scuderi et al[9]	39/M	s	N/A	N/A	-	S+RT	-	-	NED 6 M
Mattick et al[10]	61/M	M	N/A	N/A	-	S	-	-	NED 3 M
Ewing et al[11]	61/M	S	N/A	N/V	-	RT	-	-	N/A
	48/F	S	Hearing loss	N/A	-	RT	-	-	Dead of stomach cancer 3 Y
Webb et al[12]	48/M	S	Accidentally	N/A	-	S	-	-	NED 22 Y
	83/F	S	Epistaxis	N/A	-	RT	-	Another Solitary Ankle	Dead 1 Y metastasis
	49/M	S	Nasal obstruction	N/A	-	RT	Lymph node 7 year removed s+RT	-	NED 7 Y
	76/M	S	Nasal obstruction	N/A	+	RT	-	-	Dead 6 M
Waltner et al[13]	39/M	S	Nasal obstruction	N/A	-	RT	-	-	NED 2 Y
	61/F	S	N/V	N/A	-	RT	-	+	Dead 6 Y metas-tasis
Anderson et al[14]	39/M	S	Nasal obstruction	N/A	+	RT	Local 1 year	+ 1 Y	Dead 1 YEAR metastasis
	72/M	S	Nasal obstruction	N/A	-	S+RT	-	-	NED 5 Y
	77/F	S	Nasal obstruction	N/A	+	RT	-	-	Dead 7 M

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	57/M	S	Foreign body sensation	N/A	-	RT	-	-	NED 2 Y
Fuerste et al[15]	M/56	M	N/A	N/A	-	none	-	+	Dead 2 Y metas-tasis
Dolin et al[16]	M/66	S	N/A	N/A	-	S+RT	Local recurrent 2 year	-	AWD 2 Y
	M/65	S	N/A	N/A	-	S+RT	Local recurrent 1 year	-	AWD 1 Y
Mann et al[17]	M/3	S	N/A	N/A	-	S	-	-	NED 4 Y
	M/3	S	N/A	N/A	-	S	-	-	NED 1 Y
Tan et al[18]	F/12	S	N/A	N/A	-	S+RT	-	-	NED 1 Y
Rutherford et al[19]	F/13	S	N/A	N/A	-	none	-	-	N/A
Strojan et al[20]	M/43	MM	N/A	N/A	-	RT	-	-	NED 19.5 Y
	M/38	S	N/A	K		S+RT	-	-	NED 14.4 Y
	M/56	S	N/A	L	-	S+RT	-	-	NED 4.2 Y
	M/43	M	N/A	K	-	S+RT	-	-	NED 3.7 Y
	M/85	S	N/A	L	-	RT			NED 2 M
Kayrouz et al[21]	M/71	S	N/A	N/V	-	RT	Recurrent 2 years treated with radiotherapy	-	NED 10 Y
Corwin et al[22]	54/M	S	N/A	N/A	-	RT	-	-	NED 320 M
	57/M	S	N/A	N/A	-	RT	-	-	NED 116 M
Wiltshaw et al[23]	F/21	S	N/A	N/A	-	RT+Ch	-	-	NED 8 Y
Ching et al[24]	F/66	S	Headache	N/A	-	RT	-	-	NED I Y
	F/43	S	Epistaxis	N/A	-	RT	Recurrent local 1 year	-	AWD 1 Y
Zou et al[25]	M/45	S	N/A	N/A	-	S	-	-	N/A
	F/66	S	N/A	N/A	-	S+RT	-	-	NED 65 M
Khademi et al[26]	F/60	S	Nasal obstruction	N/A	-	S	-	-	NED 32 M
Susnerwala et al[27]	M/72	S	N/A	k	-	RT	-	-	Dead 48 M from MI
	M/48	S	N/A	k Amyloidosis	-	RT	-	-	MM 120 M Dead 180 M
	M/73	S	N/A	k	-	RT	-	-	NED 40 M
	M/74	S	N/A	L	-	RT	-	-	NED 44 M
Wein et al[28]	M/48	S	Nasal obstruction epistaxis anosmia	k	-	RT	Recurrent 6 months retreated stereotactically	-	NED 1 Y
Manganaris et al[29]	F/41	S	Epistaxis	N/A	-	S	-	-	NED 2 Y
Chang et al[30]	M/15	S	Epistaxis nasal obstruction	N/A	+	S+RT	-	-	NED 3 M
Abdullah et al[31]	64/F	S	Epistaxis nasal obstruction	N/A	-	S+RT	-	-	NED 6 M
Lin et al[32]	42/M	S	Nasal Obstruction	N/V	-	RT	-	-	N/A
Azman et al[33]	M56	S	Epistaxis nasal obstruction	I	-	RT	-	-	NED 7 Y
Natt et al[34]	M75	S	Epistaxis	N/A	-	RT	-	-	NED 6 M
Sulzner et al[35]	M/56	S	Epistaxis	N/A	+	RT	-	-	Dead 6 Y of MI

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Knowlin et al[36]	M/79	S	N/A	N/A	-	RT	-	-	Dead 100 M of COPD
Sadek et al[37]	M/48	S	Epistaxis nasal obstruction	K	-	RT+ S+ Ch	-	+	NED 12 Y
Woodruff et al[38]	M/20	S	N/A Invasive	N/A	-	RT+CH	RE 3 M	-	DEAD 6 Y of disease
	M/77	S	N/A	N/A	-	RT	-	-	DEAD 3 M MI
	M/56	S	N/A Invasive	N/A	+	RT	-	-	DEAD 16 Y
Chao et al[39]	M/69	S	E	N/A	-	RT	-	-	MM 9 M DEAD 11M
	M/74	S	Nasal obstruction	N/A	-	RT	-	-	NED 68 M
Nikolidakis et al[40]	F/72	S	Hearing loss nasal obstruction	K	-	RT+S	-	-	NED 2 Y
Hotz et al[41]	63	M	N/A	N/A	-	RT+S	-	-	NED 108 M
	77	M	N/A	N/A	-	RT+S	-	-	AWD 18 M
	59	S	N/A	N/A	-	RT+S	-	-	NED 157 M
	44	S	N/A	N/A	-	S	-	-	N/A
	45	M	N/A	N/A	-	RT+S	-	-	AWD 108 M
	63	S	N/A	N/A	-	RT+S	-	-	AWD MM 116 M
Kotner et al[42]	59	S	N/A	N/A	-	RT	Recurrent 1 year then RT	-	NED 8 Y
	49	S	N/A	N/A	-	RT	Recurrent then RT	-	NED 9 Y
	60	S	N/A	N/A	-	RT	-	-	NED 1 M
	64	S	N/A Invasive	N/A	-	RT	-	-	MM 6 M Dead 6 M
	78	S	N/A	N/A	-	S	-	-	Dead 6 M MI
	72	S	Nasal obstruction invasive	N/A	-	none	-	-	Dead 6 M
Miller et al[43]	M/76	S	Nasal obstruction	k	-	RT 56	-	-	NED 26 M
	M/64	S	Nasal obstruction	I	-	RT 64	-	-	NED 36 M
	M/49	S	Nasal obstruction headache	N/V	-	RT 48 GY	-	-	NED 131 M
	F/20	S	Nasal obstruction	N/A	-	RT 46 Gy	-	-	NED 120 M
	M/47	S	Hearing Loss	K	-	RT 60 Gy	Local recurrence 1 year Treated with surgery	-	NED 28 M
	M/63	S	Nasal obstruction	K	-	RT 25	-	-	NED 27 M
Isri et al[44]	F/49	M	Nasal obstruction	N/A	-	RT+ch+ S	-	-	NED 2 Y
Widziszowska et al[45]	M/63	S	Nasal obstruction epistaxis invasive	N/A	-	RT+ch+ S	Recurrent 6 month	-	AWD 6 M
Satomi et al[46]	M/72	S	Epistaxis	L	-	RT+ch+ S	-	-	NED 2 Y
Lorusso et al[47]	M/71	S	Hearing loss epistaxis	K	-	S	-	-	NED 4 M
Shih et al[48]	M/49	S	N/V	N/A	-	RT	Recurrent 9 years	-	AWD 131 M
	M/28	S	Mass	N/A	+	RT+CH	Recurrent 1 year then RT+ CH	-	NED 2 Y
	M/62	S	Mass	N/V	+	RT	-	-	NED 95 M
	M/64	S	Mass	N/V	+	CH	CH	-	MM 64 M AWD 97 M

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Yavas et al[49]	F/43	M	N O	k	-	RT	-	-	N/A
Mayar et al[50]	M/73	S	N/A	N/A	-	RT	-	-	Dead 69 M Pancreas cancer
	M/47	S	N/V Invasive	N/A	-	RT	-	-	MM 12 M Dead 33 M
	M/36	S	N/A	N/A	-	RT	9 month lymph	18 month metastasis	Dead 23 M metastasis
Petrovich et al[51]	M/52	S	Epistaxis	N/A	-	RT	Recurrent 16 month Re RT 33 Gy	-	NED 13 Y
	M/68	S	Nasal obstruction	N/A	-	RT 52	-	-	NED 13 Y
	M/63	S	Nasal obstruction	N/A	-	S+RT	-	-	NED 13 Y
	M/68	S	Nasal obstruction invasive	N/A	-	RT	Local recurrent 1 year, Re radiation Lymph node metastasis 4 year	+	Dead 9 Y metastasis
	M/50	S	Hearing loss nasal obstruction	N/A	+	CH	Recurrent 1 year Treated RT+ CH	-	NED 5 Y
Abemayor et al[52]	M/34	S	N/A	N/A	-	RT	-	-	NED 2 M
Wax et al[53]	M/65	S	N/A Invasive	N/A	-	RT	-	-	NED 2 Y
Michalaki et al[54]	F/75	S	N/A	N/A	-	RT	-	-	NED 29 M
	F/72	S	N/A	N/A	-	RT	-	-	NED 33 M
Todd et al[55]	M/59	S	Nasal obstruction	N/A	-	RT	-	-	NED 5 Y
Novikc et al[56]	F/58	S	Foreign body sensation epistaxis dysphagia	N/A	-	RT+ S	-	-	NED 3 Y
Gromer et al[57]	M/50	M	Foreign body sensation	N/A	-	S	Recurrent 1 year surgery	-	Dead 28 year from colon cancer

Y: Year; M: Month; NED: No Evidence of Disease; RT: Radiotherapy; LRC: Locoregional control; DM: Distant metastases.

is summarized in Table 3.

Patient outcomes in this study were classified as either alive with no evidence of disease (ANED), alive with disease (AWD), died of disease (DOD), and died not of disease (D). The Overall outcome was favorable, as 67 patients (57.5%) were alive with no evidence of the disease and 11 patients (14.3%) were alive with the disease after a median follow-up of 59 months. A total of 26 patients (27.4%) died, such that 15 of these patients (13.8%) were dying due to the disease. Table 2 details patient outcomes by treatment modality.

Considering the entire cohort, the 2-year and 5-year rates of overall survival were 87.5% and 82.6%, respectively; the rates of DSS were 92.6% and 90 %, respectively; the rates of locoregional recurrence were 79.3% and 78.1%, respectively; and the rates of MM or distant metastasis development were 88.4% and 85.8%, respectively.

Using Kaplan- Meir log rank test; a combination of radiotherapy and surgery had the most favorable overall survival outcomes.

DISCUSSION

The overall annual incidence of plasma cell tumors is 3:100,000. Plasma cell tumors are classified into three subtypes. Multiple myeloma is the most common type, bone solitary plasmacytoma, and soft tissue EMP being considerably less common (Table 4).[30]

Genetic factors, smoking, chronic antigenic stimulation such as osteomyelitis, radiation exposure, and occupational exposures have also been reported as possible etiologic agents in the literature.[32]

Wiltshaw et al[23] reported that 80% of extramedullary plasmacytomas occur in the head and neck region, and 40% of them occur in the nasal cavity and paranasal sinus, 20% in the nasopharynx, and 18% in the oropharynx. Cervical lymph node

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Table 2: Characteristics.

Cases, n	114
Demographics	
Age, years, mean (range)	55 (3-85)
Gender	
Male	79 (69%)
Female	23 (20%)
Unknown	12 (11%)
Presenting symptoms in only 56 article	
Obstruction	36 (64%)
Epistaxis	19 (33%)
Hearing loss	4 (7%)
Nasal discharge	1 (2%)
CN VI palsy	1 (2%)
Headache	2 (3%)
Foreign body sensation	4 (6%)
neck mass	10 (18%)
Dysphagia, anosmia	3 (5%)
Associated with other solitary myeloma Multiple	11 (9%)
Pathology 19 article	
Kappa	13/19
Lambda	6/19
Follow-up, months, mean; median (range) only 106 article	59.6 (1-336)
Outcome	
NED	67 (59%)
AWD	11 (10%)
DOD	15 (13%)
D	13 (11%)
N/A	8 (7%)
Follow-up measures	
Loco-regional recurrence	20 (17%)
Multiple myeloma	8 (7%)
Metastasis	109%

NED: No evidence of disease; AWD: Alive with disease; DOD: Dead of the disease; D: Dead of other causes; N/A: Non-Available.

Table 3: Treatment Modalities.

Treatment	Cases (n)%
Radiotherapy alone	64 (56%)
Surgery alone	13 (11%)
Chemotherapy alone	1 (1%)
Surgery and radiotherapy	25 (21%)
Radiotherapy and chemotherapy	5 (3%)
Radiotherapy, surgery, and chemotherapy	3 (2%)
None	3 (2%)

metastasis is reported as initial presentation in 12-26% of the cases, and about 20% of the EMP cases have multiple lesions. The EMP stages can be identified according to the spread of the disease (Table 5).[24]

Head and neck plasmacytoma tend to occur more frequently in males (male: female ratio, 3:1) during the 5th and 7th decades of life, however, it is rarely diagnosed in younger patients.[60]

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Table 4: The EMP Diagnostic Criteria of EMP.
(a) Pathological monoclonal plasma cells neoplasm involving a single extramedullary site
(b) No bone marrow involvement
(c) Negative skeletal survey results
d) No anemia, hypercalcemia or renal impairment caused by plasma cell dyscrasia
(e) Low serum or urinary levels of monoclonal immunoglobulin

Table 5: EMP Stage.
Stage I is disease confined to one site
Stage II includes tumors with local extension of lymph node involvement.
Stage III has metastatic spread.

Nasopharyngeal EMP was first reported by Kusunoki in 1915, of which about 20% of the head and neck plasmacytomas occur in the nasopharynx. (Table 4). Patel et al[58] identified 778 patients with EMP in the head and neck region, 137 of them reportedly have plasmacytoma in the nasopharynx. D'Aguillo et al[59] reported 176 cases of sinonasal extramedullary plasmacytoma, of which 36 cases were associated with the nasopharynx (Table 6).

The common symptoms of nasopharyngeal EMP include nasal obstruction, epistaxis, and conductive hearing loss. On performing nasal endoscopic examination, the lesions usually grow sub-mucosally as soft gray sessile or pedunculated masses, which can rarely be ulcerated. The diagnosis of EMP is done by tissue biopsy. Deep biopsies must be performed since the tumor is located in the submucosal layer and the mucosa may be thickened due to an inflammatory reaction. Once the diagnosis has been confirmed, further investigations are required to exclude multiple myeloma. Three histological subtypes of plasmacytoma have been reported including plasmacytic, plasmablastic and anaplastic subtypes. However, these subtypes are not indicative of prognosis or increased risk of recurrence. Local amyloid deposits may be found in 11-38% of the cases reported but systemic amyloidosis is a rare occurrence. Immunohistochemical techniques may indicate a monoclonal staining pattern for heavy chain class, light chain class tumor or both, CD 138 has been reported as a gold marker for plasma cell tumor.[30,32]

Complete surgical resection (if possible) with postoperative radiotherapy is the treatment of choice for solitary EMP. In general, EMPs are considered radiosensitive, with a local control rate of 90-100%. A radiation dose of 4050 Gy delivered to the primary site of the EMP in the nasopharynx is usually recommended. Since EMP is highly radio-sensitive with a local control rate of 90%, there is no evidence as to whether radiotherapy should also be targeted against cervical lymph nodes, in order to decrease the risk of local and regional recurrence. Chemotherapy is generally recommended for recurrent, advanced, or disseminated disease.[30]

Nasopharyngeal extramedullary plasmacytoma has a good prognosis but also requires a long-term follow-up to detect any local recurrence or progression towards multiple myeloma.[58,59]

Table 6: Nasopharyngeal Plasmacytoma.

Series	Number of head and neck plasmacytoma Patients	Number of nasopharynx plasmacytoma patients number
Liebross et al[60]	22	2
Tsang et al[61]	76	3
Tournier et al[62]	17	7
Creach et al[63]	18	2
Alexiou et al[64]	713	131
Saski et al[65]	67	7
Stout et al[7]	104	20
Ewing et al[11]	21	2

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CONCLUSION

This review contains the largest pool of data collected from nasopharyngeal EMP patients examined till date. Our data suggests that radiotherapy alone is the most common type of treatment used, followed by a combination of radiotherapy and surgery, then surgery alone. A combination of radiotherapy and surgery showed the best outcomes in patients in terms of survival and eradication of the disease; however, this subgroup consisted of only 25 patients. MM developments occurred in 7% of the patients.

Most of the data included in this study was collected from case reports and case series. Further research on the optimal treatment modality, should be done using randomized controlled clinical trials to ensure less bias and better accuracy of results.

CONFLICTS OF INTEREST

The author declared no conflict of interest.

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