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Original Research Article

Spectrum of primary salivary gland tumors with special emphasis on their management and outcome at a rural tertiary care centre

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ABSTRACT

Background: Salivary gland tumors (SGT) are uncommon tumors of diverse histopathology accounting for <2% of all neoplasms. Early diagnosis differentiates between benign and malignant SGT and less extensive surgical procedure can be performed. The objective is to study the spectrum of primary SGT with special emphasis on their distribution, treatment and outcome at a rural tertiary care centre.
Methods: A prospective observational study was conducted on 30 consecutive primary SGT patients attending the Departments of Surgery and Otorhinolaryngology of North Bengal Medical College and Hospital over a period of one and half years. All patients were clinically evaluated, investigated, treated accordingly and followed up during the period of study. Data was collected and compiled in Excel sheet and analysed using GraphPad Software and GraphPad QuickCalcs 2018 (San Diego, CA). A p value <0.05 was considered statistically significant.
Results: Maximum patients (83.3%) were in the age range of 31-60 years. The male to female ratio was 1:4 for benign tumours and 1:1 for malignant tumours. Malignant cases were 66.67%. Involvement of parotid gland was the commonest (43.3%) and mostly presented with swelling (73.3%). Pleomorphic salivary adenoma was the commonest benign tumor (33.3%) and mucoepidermoid carcinoma was the commonest malignant tumor (16.7%). Permanent facial palsy was observed in 2 (9.5%) and recurrence in 4 patients (19%).
Conclusions: SGT are rare and present in various modes. Malignant cases were singularly more in this study.

Keywords: Mucoepidermoid carcinoma, Pleomorphic salivary adenoma, Salivary gland

INTRODUCTION

Salivary gland tumors (SGT) can show a striking range of morphological diversity between different tumor types and sometimes within an individual tumor mass. Despite their relatively simple morphology the salivary glands give rise to no fewer than 30 histologically distinct tumors.[1] These neoplasms are uncommon and represent less than 2% of all tumors in humans. About 65%-80% arise within the parotid, 10% in the submandibular gland and the remainder in the minor salivary glands, including the sublingual glands. Approximately 15-30% of tumors in the parotid glands are malignant. In contrast approximately 40% of submandibular, 50% of minor salivary glands and 70% of sublingual tumors are malignant. Thus, the likelihood of a salivary gland tumor being malignant is more or less proportionately to the size of a gland. Pleomorphic adenomas constitute about 50% of all SGT and is the commonest benign tumor whilst mucoepidermoid carcinoma constitute 15% of all SGT and is the commonest malignant tumor.[1] Salivary gland cancers are an incredibly heterogeneous group of tumors that include 24 histologically distinct tumor types.[2] In addition, hybrid tumors, dedifferentiation and the propensity for some benign tumors to progress to malignancy can confound histopathological

interpretation. These features, together with the relative rarity of a number of tumors, can sometimes make diagnosis difficult, despite the abundance of named tumor entities.

These tumors usually occur in adults, with a slight female preponderance but about 5% occur in children younger than 16 years of age. Warthin tumors occur much more often in males than in females perhaps reflecting the higher prevalence of smoking, a predisposing factor in males. The benign tumors most often appear in the fifth to seventh decades of life. The malignant ones tend to appear somewhat later.[1]

The etiological agents of salivary gland malignancy remain vague. Though head and neck cancers are strongly related to smoking and drinking, these do not play a role in the salivary glands. Certain studies revealed that a diet rich in vitamin C and low in cholesterol may be important in preventing salivary gland cancer.[3] However few other studies found that possible risk factors include therapeutic radiation for other head and neck cancers, occupational exposures in rubber manufacturing and woodworking and even employment at hairdressers or beauty salons.[4,5] *Epstein-Barr* virus induced malignancies, radiation and immunosuppression were also associated with an increased risk of salivary gland cancer. In a Swedish study, the risk of salivary gland malignancy was found to be increased 4 fold in patients suffering from Hodgkin's lymphoma.[6] HIV infection was also found to increase the risk of salivary gland cancers.[7] Salivary gland cancer occurs when some cells in a salivary gland develop mutations in their DNA. The mutations allow the cells to grow and divide rapidly. The mutated cells continue living when other cells would die. The accumulating cells form a tumor that can invade nearby tissue. Cancerous cells can break off and spread (metastasize) to distant areas of the body.

Signs and symptoms of a SGT may include a lump or swelling on or near your jaw or in the neck or mouth, numbness in part of the face, muscle weakness on one side of the face, persistent pain in the area of a salivary gland and difficulty in swallowing.

In general, when they are first diagnosed both benign and malignant lesions range from 4 to 6 cm in diameter and are mobile on palpation except in the case of neglected malignant tumors.[1]

Generally, there is a lag phase of months to years before clinical detection in the case of benign SGT as they are usually slow growing tumors. However malignant SGT are generally detected earlier due to their rapid growth. Ultimately however there are no reliable clinical criteria to differentiate benign from malignant SGT. Minor salivary gland tumors present as a submucosal intraoral mass which subsequently ulcerates. Clinical features suspicious for malignancy include ipsilateral facial nerve palsy, sudden tumor growth and pain.

Ultrasound is the preferred imaging tool for the initial assessment of tumors in the superficial parotid and submandibular glands. Ultrasound imaging resolution of these superficial structures is excellent and it does not carry any risk of radiation. It can also be employed to guide the needle for carrying out fine needle aspiration cytology (FNAC) to reduce sampling error. For tumors located deep in the parotid gland or in the minor salivary glands, CT and MRI are more helpful. Between the two modalities, MRI has an edge over CT in predicting malignancy and is also more sensitive in picking up small sized SGT. Benign tumors generally show high signal on T2-weighted scans, while malignant lesions usually show intermediate to low signal. MRI is more useful in detecting deep lobe extension, marrow infiltration and perineural spread and involvement of the facial nerve. MR spectroscopy is employed to differentiate malignant and benign salivary gland tumors and also to distinguish Warthin's tumor from pleomorphic adenoma.[8] The evaluation of cortical bone involvement and the detection of concurrent presence of calculus disease is very well documented by CT scan. The role of positron emission tomography (PET) in salivary gland disease is still being evaluated. Characteristically, Warthin's tumors and oncocytomas show a strong uptake of technetium pertechnetate. FNAC in salivary gland masses is fairly reliable for correct preoperative diagnosis. It is safe, minimally invasive, inexpensive and outdoor procedure and provides diagnosis within a very short time. The diagnostic yield of FNAC is very good with large study series showing sensitivity up to 85% and specificity up to 99%.[9]

The World Health Organization (WHO) proposed the first histological classification of salivary gland tumors in 1972.[10] Due to advances in the understanding of the etiology and behavior of these tumors as well as their wide morphological diversity, the WHO published the fourth and last edition of this classification in 2017.[11]

From 2010 onwards, salivary gland cancers are staged according to the Seventh Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. The primary tumor (T) is staged according to size, extra parenchymal extension, and direct invasion. Regional lymph node (N) staging is dependent on the size and location of the draining lymph nodes.

The detection of distant metastasis is considered as M1. The overall cancer stage is obtained from the combination of these three factors. Efficacy of treatment of malignant SGT is essentially dependent upon their stage, location, presence of perineural invasion, treatment modality, histologic type and presence of regional invasion.[12]

Surgery is the mainstay of treatment for SGT. In the case of parotid gland tumors, superficial parotidectomy with facial nerve dissection and its preservation is the standard diagnostic procedure. This operation will serve as the

adequate therapeutic procedure in cases of benign or small malignant tumors limited to the superficial lobe of the parotid. If the tumor involves the deep lobe of the parotid gland, a total parotidectomy is the procedure of choice in order to achieve adequate tumor clearance. It is customary to try and preserve the facial nerve unless it appears to be involved by the cancer or there is any sign of facial nerve paresis. When dealing with submandibular gland tumors, complete excision of the gland is adequate treatment only if the lesion is small, limited to the gland parenchyma and also of benign or low-grade malignant nature. More extensive tumors will require excision of the entire gland bed and also adjacent soft tissues much like a supraomohyoid neck dissection.[13]

Systemic therapies for salivary gland cancers are reserved for advanced disease but they have only a modest response with cisplatin-based regimens the most frequently studied.[14]

Management of the clinically N0 neck in salivary gland cancer has always been and yet remains a controversial topic. Studies on the long term efficacy of various approaches in dealing with N0 neck are sparse. Mandatory neck dissection for every salivary gland cancer patient is advised by few, while others opt for selective neck dissection or irradiation of the neck for high-risk cancers only.[15-17] Because of the small size of these studies, no single approach has been shown to be superior. The overall risk of regional lymph node metastasis in salivary gland malignancy is low compared to other head and neck cancers and range from 14-20%.[18] High-risk factors are high-grade and advanced T-stage tumors, tumors with extracapsular extension and presence of preoperative facial paralysis.[19] Therefore, elective selective neck dissection may be recommended in these patients. Elective neck dissection should also be performed if resection of the primary tumor is aided by removal of the surrounding lymph nodes. An exception to this is in the case of adenoid cystic carcinoma in which the chance of occult lymph node metastasis is low and elective neck dissection is not expected to offer any additional benefit.[15] Selective neck dissection for parotid gland cancer should include levels IB, II, III, IV and VA, while that for submandibular gland cancer should include levels I, II, and III. For patients with proven nodal metastasis, a formal radical neck dissection should be carried out. Postoperative radiotherapy has documented benefit in salivary gland cancer patients at high risk of locoregional recurrence.[20]

Highest incidence of SGT is observed in Croatia.[21] In the United States, there is a rise in the incidence of salivary gland cancers; this group accounted for 6.3% of all head and neck cancers in 1974-1976 as compared to 8.1% in 1998-1999.[22]

In India, overall incidence of SGT can be ascertained from the cancers registry established by Indian Council of Medical Research.[23] However, the geographic area and population covered by these registries are small and perhaps unrepresentative of Indian population. In addition, there is a limited published literature on salivary gland tumors in Indian population.[24]

METHODS

Study settings and design

The study was conducted in the Departments of Surgery and Otorhinolaryngology of North Bengal Medical College and Hospital over a period of one and half years and is an institution based prospective descriptive study with a cross-sectional design.

Methodology

A total of 30 consecutive patients with primary SGT were studied. The cases were obtained from patients attending the OPDs or IPDs of General Surgery and Otorhinolaryngology of North Bengal Medical College and Hospital during March 2018 to August 2019. Approval from Institutional Ethics Committee was taken. Informed consent from all the patients or their guardians was taken, confidentiality of the patients was ensured, and data was utilized purely for academic purpose. A detailed clinical history was obtained from each patient using a preformed data collection form. Each patient was thoroughly examined clinically, and requisite investigations were done. Metastatic SGT were excluded from this study.

The patients were offered the standard treatment modalities which included surgical intervention and adjuvant therapy in the form of chemotherapy and radiotherapy available in the rural tertiary care hospital of ours. The patients were then followed up for the entire duration of hospital stay and then 2 weeks post-surgical resection and then at interval of 3 months for the study period.

Statistical analysis

Data was collected and compiled in Excel sheet followed by analysis using GraphPad Software and GraphPad QuickCalcs 2018 (San Diego, CA). Descriptive statistical analysis included the calculation of means, medians and Standard Deviation (SD) of the data obtained. Continuous variables were expressed as mean±SD and compared using a two tailed unpaired Student's t test. Categorical data was analysed using Fishers exact test and chi square test. A p value <0.05 was considered statistically significant.

RESULTS

In the present study, the age range of patients presenting with salivary gland masses vary from 11 to 70 years, maximum number of patients (83.3% cases) were in the age range of 31-60 years. Benign tumors (mean 31.90) appeared to be more common below 40 years of age.

Malignant tumors (mean 49.50) were common in higher age group above 40 years (p value of 0.002) (Table 1).

Table 1: Mean age distribution among the groups.

Type	N	Mean age (yrs)±SD	t	P
Malignant	20	49.5±10.40	4.33	0.0002
Benign	10	31.90±10.69		

In this study the male to female ratio was 2:3. Considering the male verses female incidence in benign and malignant SGT, a ratio of 1:4 was recorded for the benign tumors whereas a 1:1 ratio was recorded for malignant tumors (Table 2). Overall malignant cases were twice as common as benign in this study.

Table 2: Gender distribution among the groups.

Sex	Type		Statistical value
	Malignant	**Benign**	γ2=1.406
Male	10	2	df= 1
Female	10	8	p=0.2387

Moreover, when analysing age and sex wise distribution of SGT, majority of male patients in this study were between age of 31-60 years and all had malignant tumors while the females in the age group of 31-40 years mostly had benign cases and those in 51-60 years were having malignant cases.

As far as occurrence of types of salivary gland tumors is concerned, out of 30 cases observed, involvement of parotid gland was the most common, occurring in 43.3% cases, followed by submandibular gland in 30% cases (Figure 1).

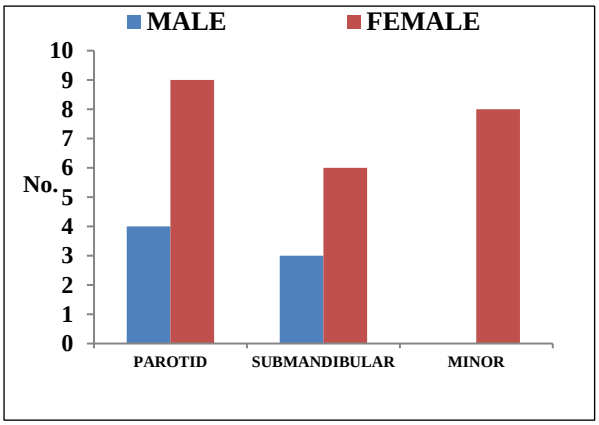

Figure 1: Site distribution among males and females.

SGT have varied modes of presentation. Most common symptom of salivary gland tumors in the present study was swelling, found in 73.3% patients. Other symptoms were pain (63.3%), ulcer (30%), recurrent tumor (33.3%), sensory impairment (60%) in the area of distribution of the greater auricular nerve and motor impairment (53.3%) of the facial nerve.

Histopathological investigations identified that out of 30 patients, 10 cases were benign, and 20 cases were malignant (Figure 2).

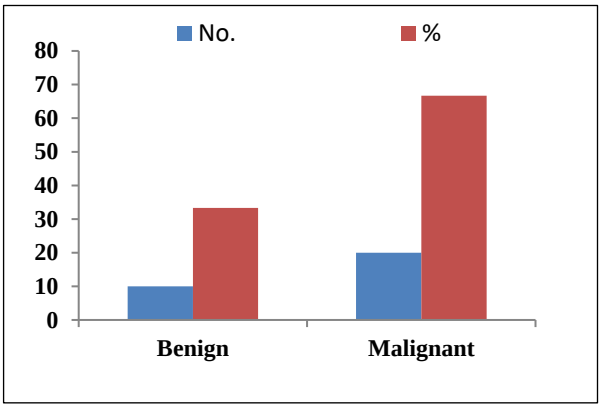

Figure 2: Distribution of benign and malignant cases.

After histopathological examination of the resected specimens, all malignant tumors (diagnosed clinico-radiologically and by FNAC) turned out to be malignant while few cases of benign disease (diagnosed clinico-radiologically and by FNAC) later turned out to be malignant. Histopathological correlation for benign and malignant tumors with clinical findings and FNAC was found only in 24 (80%) cases (Table 3).

Table 3: Accuracy of clinical examination and FNAC in differentiating benign from malignant tumors.

Diagnosis	Clinical Examinatic	Histopathology	Statistical value
Benign	16	10	γ2=1.697
Malignant	14	20	df= 1
			p=0.1927

It was found that patients with parotid gland tumor had equal incidence for both benign and malignant disease, while patients with submandibular gland tumor had mostly malignant disease. All patients with minor salivary gland tumors had shown malignancy. Involvement of sublingual salivary gland was not found in the present study.

In the present study, cases of salivary gland lesions were grouped as per the World Health Organization's histological classification of salivary gland tumors. It was found that pleomorphic salivary adenoma was the most common benign tumor (33.3%) and mucoepidermoid carcinoma was the commonest malignant histopathological type (16.7%) followed by adenocarcinoma (13.3%) (Figure 3 and 6). Facial nerve paralysis was seen in four cases of malignant tumors on presentation.

Patients with SGT were evaluated first by USG and if needed by CT scan or MRI in setup (Figure 4). Those presenting with PSA were treated by superficial parotidectomy (23.8%) (Figure 5). Malignant parotid lesions were treated by total parotidectomy (4.8%) or revision (4.8%) or total parotidectomy with modified radical neck dissection (MRND type2) with adjuvant radiotherapy and chemotherapy (14.3%). 2 (9.5%) patients of squamous cell carcinoma required hemi mandibulectomy with MRND type 2 followed by adjuvant radiotherapy. Submandibular glands were excised in cases of benign tumors whilst malignant ones were treated by a MRND type 2 followed by adjuvant therapy. Chemoradiation as a first line of treatment was reserved for patients presenting late with advanced disease. Such patients were a considerable number in this study accounting for 30%, reflecting the delayed presentation of such malignancies at rural centre.

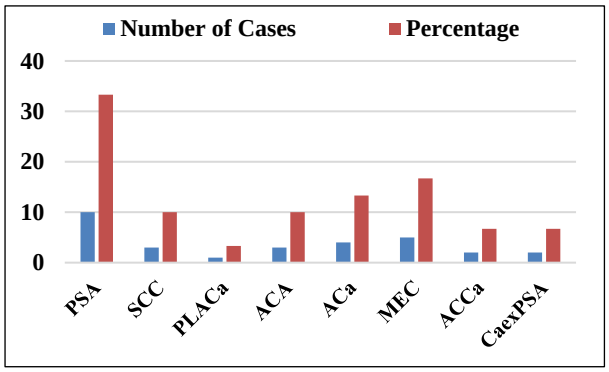

Figure 3: Distribution among benign and malignant salivary gland tumors.

PSA- pleomorphic salivary adenoma, SCC- squamous cell carcinoma, PLACa- polymorphous low-grade adeno carcinoma, ACA- adenoid cystic carcinoma, ACa- adenocarcinoma, MEC- mucoepidermoid carcinoma, ACCa- acinic cell carcinoma, CaexPSA- carcinoma ex pleomorphic salivary adenoma.

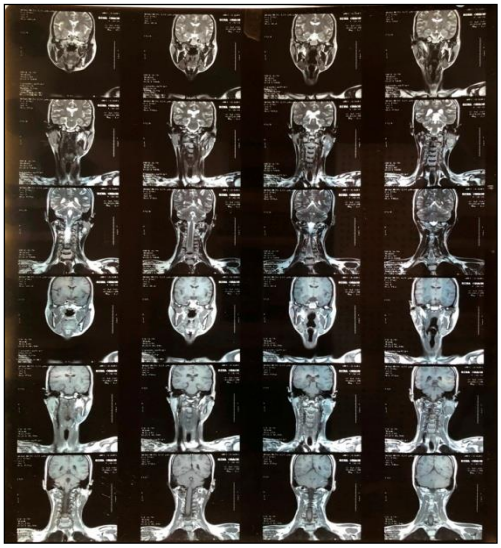

Figure 4: CT scan revealing left parotid gland tumor.

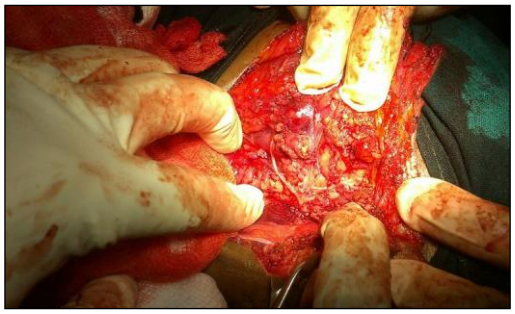

Figure 5: Facial nerve branches at superficial parotidectomy.

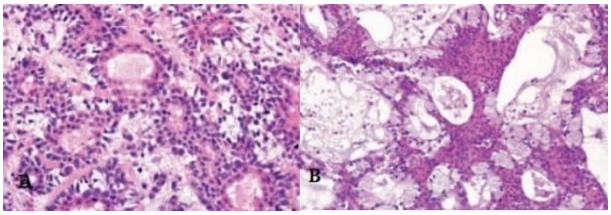

Figure 6: Histopathology. A- PSA, B- MEC.

Post-operatively temporary facial nerve palsy was observed in 5 patients (23.8%). Permanent facial palsy was observed in 2 patients with malignant tumors (9.5%). Wound infection was found in 5 patients (23.8%). Hematoma was observed in 3 patients (14.3%). Recurrence was observed in 4 patients (19%) amongst those who came for follow up.

Authors did not find any patients with complications of salivary fistula and Frey's syndrome amongst those patients who came for follow up. There was no case of salivary gland tumor with distant metastasis in this study. Paresis of the marginal mandibular branch of the facial nerve was the commonest temporary facial nerve palsy succeeded by the zygomatic branch of the facial nerve. The patients who had lid lag were given carboxymethylcellulose eye drops. Proper oral hygiene maintenance was advocated in all cases.

DISCUSSION

Age

SGT were found in patients between the ages of 16 to 65 years (mean 43.63). In the current study, patients with benign tumors generally were younger (mean 31.90 years) than patients with malignant tumors (mean 49.50 years). These data were very similar to those in other studies in Brazil.

Ito et al, documented a mean age of 43.7 (±16.9) years and peak age in the fifth decade of life.[25] Studies from Africa reported lower mean ages of impairment (less than 40 years), suggesting that factors such as low life expectancy and lack of prevention measures may contribute to this index.[26]

Sex

Overall a ratio for female to male was 3:2 in this study. However, the distribution of malignant tumors was similar between women and men. Most studies have shown that SGT are more common in women than men. Saghravanian et al, found a slightly increased incidence in women (55.4%).[27] In contrast, some studies have reported a predominance of SGT in men. Kara et al, found a ratio for female-to-male of 1:1.15.[28] Wang XD et al, in a retrospective study of 2508 patients and Gao et al, in a retrospective study of 7190 patients in north eastern China has shown that benign tumors are more common in women, while malignant tumors are more common in men.[29,30]

Gland distribution

The majority of SGT occurred in major salivary glands (73.3%), especially in the parotid gland similar to average found in the literature. Several large series, especially in Asian countries, have shown similar distribution. Gao et al, in their study found that the percentage of tumours located in the parotid, submandibular, sublingual, and minor salivary glands was 62.66%, 9.92%, 2.57%, and 24.85%, respectively; 22.26%, 35.76%, 92.97%, and 61.89% of the tumours, respectively, were malignant.[30]

Types of tumors

PSA was the most common tumor (33.3%) of all salivary tumors, accounting for 100% of benign tumors in the present study. The frequency of PSA among all SGT in the literature ranged from 32.6 to 78.6%.[31] Considering only malignant lesions, various studies reported MEC to be most common. Fonseca et al, in a study of 493 patients in southern Brazil found that PSA and MEC were the commonest benign and malignant tumors respectively, while others reported ACC to be the most prevalent.[32,33] In this study MEC was the commonest malignant tumor (16.7% of all the SGT) followed by adenocarcinoma (13.3%).

Modes of presentation

The most significant sign of benign SGT is a painless swelling. Pain, rapid growth, and an ulcerative surface are noted in malignant cases and especially high-grade tumor.[34] Comoglu et al, 2018, showed that all patients with SGT with preoperative facial paralysis were diagnosed with malignant tumors, suggesting that this sign is indicative of malignancy.[35] In this study 73.3% presented with swelling whilst 63.3% presented with pain. However, authors had more malignant cases.

Nature of tumor

In this study malignant cases were twice that of benign cases. This is a singular finding as most studies from China, India and elsewhere suggest that benign tumors are predominant in SGT worldwide.[12,30]

However, in a study from Puducherry, India, Kumaran et al, over a period of 12 years showed a similar increased incidence of malignant cases. They reported malignancy in 46.2% of their cases.[36]

Also Fomete et al, in a study of 135 patients at Ahmadu Bello University Teaching Hospital, Zaria, Nigeria found a predominance (71.1%) of malignant SGTs although major salivary glands were involved in 60.7% of all SGTs in their study.[37]

Treatment

Surgical excision represents the standard option in the treatment of respectable tumors of both major and minor salivary glands. Neutron, heavy ions or proton radiotherapy may be a treatment option for inoperable locoregional disease. Surgery was possible in 70% of patients whilst only radiotherapy and/or chemotherapy was instituted in 30% of the cases. Surgery, irradiation or re-irradiation are treatment options for local relapse, whereas radical neck dissection is indicated for regional relapses. Metastatic disease may be either treated with radiotherapy or palliative chemotherapy, depending on the site of metastases. For highly selected patients the employment of anti-androgen therapy is indicated.[38] Adjuvant radiotherapy or chemotherapy had to be instituted in 52.4% of patients because most of patients had malignant salivary gland tumors.

Complications

Post-operative facial nerve dysfunction involving some or all of the branches of the nerve is the most frequent early complication of parotid gland surgery. Temporary facial nerve paresis, involving all or just one or two branches of the facial nerve, and permanent total paralysis have occurred, respectively, in 9.3% to 64.6% and in 0% to 8% of parotidectomies, reported in the literature. The cases of transient facial nerve paresis generally resolved within 6 months, with 90% within 1 month. Temporary paresis usually resolves, according to Laccourreye, within the 18th post-operative month.[39] The incidence of facial nerve paralysis is higher with total, than with superficial parotidectomy, which may be related to stretch injury or as result of surgical interference with the vasa nervorum. Authors had transient facial nerve palsy in 23.8% and permanent palsy in 9.5%.

Intra-operative opening of the pseudo capsule of pleomorphic adenomas is traditionally held to increase the risk of recurrence. Nevertheless Laskawi et al, reviewing personal experience on parotidectomy for pleomorphic adenoma found no evidence of recurrence in any of the 18 out of 475 patients in whom the tumour capsule had to be opened intra-operatively on account of difficult conditions.[40] The main reason for pleomorphic

adenoma recurrence is incomplete surgical resection. In these cases, it is suggested to perform post-operative radiotherapy.[39] Authors had recurrence in 19% of patients partly a fallout of larger group of malignant cases.

CONCLUSION

The present study was a single-institutional experience where analysis of 30 SGTs was carried out. The findings of age, sex, site distribution, and pathologic features encountered in the study were in agreement with those studies reported from India and other parts of the world. But malignant cases came out to be singularly more in this study. A large number of patients came with delayed presentation of locally advanced disease where no surgery could be offered. So early diagnosis and treatment is necessary to adequately treat these rare tumors. Although the number of SGTs discussed in this study is small, the findings should contribute in better understanding of the disease. Only a few studies based on significantly large number of cases are published from India. As very little information is available on the tumors of the head and neck over the last two to three decades, prospective multicentric studies need to be carried out to better discriminate the influencing factors.

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