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Abstract

Objective. Due to histological heterogeneity, biological behaviour and rarity, recommendations for the treatment of malignant submandibular gland tumors (MSGT) are inconsistent. Aim of this study was to present a single center experience in the treatment of MSGT with an emphasis on surgical treatment including indication on elective neck dissection (END).

Study Design. Twenty-four MSGT were primary surgically treated (gland excision with neck dissection). Their records were retrospectively collected and analysed.

Results. The most frequent histology was adenoid cystic carcinoma (41.6%), followed by mucoepidermoid carcinoma (25%) and carcinoma ex-pleomorphic adenoma (16.7%). There were 18 elective and 6 therapeutic neck dissections. Histopathological examination confirmed 29% (7/24) of positive neck dissection specimens. The Kaplan-Meier analysis presented rates of DSS, DFS and OS of 81%, 78% and 52% at 5 years respectively. Patients undergoing post-operative radiotherapy had significantly higher overall survival rates compared with patients treated with surgery alone (p=0.0209).

Conclusion. Results of this study suggest that elective neck dissection has questionable benefit in early stage MSGT. Elective SND levels I-III is recommended in high-grade and advanced stage MSGT without evidence of multi-level lymphadenopathy.

Introduction

Salivary glands tumors are rare neoplasms accounting approximately 3% of all head and neck tumors [1-3]. Due to the diverse nature and heterogeneity of salivary glands tumors, diagnostics can be challenging and treatment usually depends on various factors. Tumors of the submandibular gland are uncommon occurring almost ten times less frequently compared to the parotid [4-6]. Additionally, appearance of malignant submandibular gland tumors (MSGT) is less common compared to benign counterparts [1-6]. Due to histological heterogeneity, rarity and challenges in diagnostics, recommendations for the treatment of MSGT are inconsistent. Generally, for patients with resectable MSGT surgery is the primary treatment and minimal procedure that should be performed is a complete excision of the gland along with a neck level I dissection.

Aim of this study is to present a single center experience in the treatment of MSGT, with emphasis on surgical treatment including indication on elective neck dissection as well as the extent of surgery performed.

Material and Methods

Due to the retrospective nature of this study, it was granted an exemption in writing by the UHD IRB. Study was conducted in compliance with the World Medical Association Declaration of Helsinki on medical research protocols and ethics. The study included patients with malignant submandibular gland tumor (MSGT) primarily surgically treated in a tertiary medical center in time period from January 1, 1985 to December 31, 2015. Their medical records were reviewed retrospectively and clinicopathologic characteristics (age, sex, histological subtype of tumor, stage according to the 8th edition of TNM classification, perineural and lymphovascular invasion), treatment (type of surgery, adjuvant therapies) and follow-up were obtained. The exclusion criteria were: 1) patients who did not undergo surgery as a first treatment modality, 2) patients with recurrence or metastatic tumor in the submandibular region, 3) non-malignant diseases of submandibular gland, 4) patients with incomplete medical documentation and follow-up information.

Pre-operative evaluation included medical history, careful physical examination, fine needle aspiration cytology (FNAC) of suspected mass (both primary tumor and cervical lymph nodes) and multislice computed tomography (MSCT) or magnetic resonance imaging (MRI). The neck was considered to be clinically negative (cN0) when there were no palpable lymph nodes (LNs) and the diameter of the LNs was < 1 cm without the area of central necrosis (central low density or inhomogeneity) determined by imaging method. Neck dissections being employed were selective neck dissection (SND) levels I-III, SND levels I-IV, radical neck dissection (RND) and its variants (modified or extended RND). All neck dissections were ispsilateral and were performed in the *en-block* fashion with an intraoperative marking of the lymph node levels. All cN0 patients were treated with neck dissection. Following surgical procedure, a neck dissection specimen was separated regarding intraoperative markings and sent to the subsequent histopathological examination. High-grade lesions, advanced T stage, positive surgical margins, presence of perineural invasion (PNI) and perivascular invasion (PVI), and positive neck dissection specimen with/without extranodal extension (ENE) were factors that indicated adjuvant therapy. Adjuvant therapy protocol was post-operative radiation therapy (RT) with daily fractions of 2 Gy, in a prophylactic dose of 50 Gy to clinically undissected neck levels, with a boost of 60 Gy to the tumor bed and metastases confined to the lymph nodes. Presence of ENE was the indication for the addition of chemotherapy to adjuvant irradiation (chemotherapy-based RT). The chemotherapy regimen was: cisplatin 100 mg/m2 on days 1, 22, and 43. The follow-up protocol consisted of a medical history and physical examination every 3, 6, 8, and 12 months, in the first, second, third, and fourth year of the follow-up, respectively. Post-treatment imaging (primary, neck and chest) was performed within 1 and 2 years after initial treatment. Chest imaging for patients with adenoid cystic carcinoma (AdCC) was performed life-long annually.

Survival analyses were performed using the Kaplan-Meier method. Survival endpoints were defined as any-type recurrence or death from any cause, whichever occurred first, for disease-free survival (DFS), date of death from the disease for disease-specific survival (DSS) and death from any cause for overall survival (OS). All analyses were done using the MedCalc Statistical Software version 19.1.3. (MedCalc Software bvba, Ostend, Belgium).

Results

Patients' clinical and pathological characteristics

Among all major salivary gland tumors primary surgically treated in our center (n=981), there were 24 patients (2.4%) with malignant submandibular gland tumors (MSGT) (**Figure 1**). There were 15 males (63%) and 9 females (37%). The median age was 61 year (range between 13 and 81 year). In 20 patients (83%) pre-operatively fine needle aspiration cytology (FNAC) of suspected submandibular mass was conducted with the accuracy to histopathological diagnosis of 80% (16/20) (**Table I**). The most frequent histological subtype was adenoid cystic carcinoma (AdCC) (41.6%), followed by mucoepidermoid carcinoma (MEC) (25%) and carcinoma ex-pleomorphic adenoma (CEPA) (16.7%). Other cases (16.7%) included adenocarcinoma, squamous cell carcinoma (SCC) and lymphoepithelial carcinoma. Clinicopathologic characteristics are presented in **Table II**.

Treatment and survival analysis

There were 18 elective and 6 therapeutic neck dissections. All neck dissections were ipsilateral. Among lymphadenectomies there were 11 selective neck dissections (SND) levels I-III, one SND levels I-IV, two modified radical neck dissections (mRND) (both included preservation of accessory nerve), four RND and six extended RND (four were extended to the skin and included digastric muscle, external carotid and hypoglossal nerve). Histopathological examination confirmed 29% (7/24) of positive neck dissection specimens (two high grade MEC, two primary squamous cell carcinoma of SMG, one AdCC, one adenocarcinoma and one lymphoepithelial carcinoma). All therapeutic neck dissections (6/6, 100%) were associated with histopathological positive finding and 1 of 18 elective (6%) demonstrated pN+ (neck level II, without ENE). Three MSGT affected one level of the neck, while four affected two or more levels. Most frequently affected levels of neck were level I, II and III (by involvement percentage all equally represented). The average number of dissected lymph nodes was 14. Post-operative radiation therapy (RT) was administered in 18 patients, while concomitant chemoradiotherapy (CRT) was administered in one patient due presence of extranodal extension (ENE).

Median follow-up of presented cohort was 76 months (between 3 and 360 months). During follow-up period, a total of five patients (17%) relapsed (one patient had loco-regional recurrence, one distant, and three loco-regional with distant metastatic spread). Recurrences included three patients with high-grade MEC, one with AdCC and one with squamous cell carcinoma (SCC). One patient experienced metachronous second primary lung malignancy. One patient with AdCC (1/10) presented with late distant metastases (lung) 52 months after conducted surgery and post-op RT. A total of 16 patients died (all patients who relapsed died (n=5), while others (n=11) died from non-malignant diseases). Median survival was 46 months. The Kaplan-Meier analysis presented rates of DSS, DFS and OS of 81%, 78% and 52% at five years, 81%, 78% and 37% at ten years, respectively (**Figure 2**). There was a significant difference in final outcome between patients treated with surgery alone compared to those receiving post-op RT (p=0.0209). Patients undergoing adjuvant irradiation had significantly higher survival rates (**Figure 3**).

Discussion

During 30-year time period, 58 primary SGT were surgically treated in our center. Compared to parotid gland tumors, SGT were more than a ten times less common (**Figure 1**). While some authors reported predominance of benign submandibular gland tumors over malignant [1,6], our study presented similar incidence of both tumor types. The average age of patients with MSGT was 60 years and the ratio male versus female was approximately 2:1, which is consistent with a literature [2,4,7]. The most frequent histologic subtype was adenoid cystic carcinoma (AdCC). Together with mucoepidermoid carcinoma (MEC) and carcinoma ex-pleomorphic adenoma (CEPA), these malignant subtypes included more than 80% of all MSGT in our cohort (**Table II**). Adenoid cystic carcinoma is characterized by two major features; first is an early lung lesions at the time of the primary diagnosis and second is long term (>5 years) drop of the overall survival rate due to late distant metastases. Distribution of histological subtypes is consistent with reports published by other authors [2,5,7] Lee at al. [8] in their retrospective cohort of 2626 MSGT showed dominance of AdCC (36.0%), followed by primary SCC (18.1%) and MEC (16.9%).

Management of MSGT is challenging due the heterogeneity and diversity of their biological behaviour. For these reasons, clear recommendations do not exist and treatment of clinically negative neck is generally controversial. According to the literature, as a minimal procedure that should be employed in resectable MSGT, excision of submandibular gland along with a neck level I dissection is advised [9-11]. More extensive surgery of the neck, including selective neck dissection (SND) and variants of radical neck dissection (RND) are recommended for high-grade and advanced-stage MSGT [10-12]. For non-resectable MSGT radiation therapy (RT) should be a primary treatment modality (with or without chemotherapy) [13,14]. Other indications for primary RT with curative intent in MSGT are technically inoperable disease, patients at high risk of complications because of comorbidities and patients who have refused surgery [15]. Although chemotherapy is not often used in the treatment of MSGT, in our study one single case of primary submandibular SCC was treated with concommitant adjuvant chemoradiotherapy (CRT). Due the presence of extranodal extension in several lymph nodes and aggressiveness of the tumor, institutional multidisciplinary team made decision to treat that case with adjuvant CRT.

In our cohort 29% patients (7/24) had histopathologically positive lymph nodes of the neck (pN+). All patients treated with therapeutic neck dissection (6/6) were confirmed as a positive, while one patient whose neck was treated electively was false negative (cN0, pN+). In our series 5.6% patients had occult neck metastases in cN0 neck (1/18), making elective dissection in MSGT highly questionable. The only case of initially negative neck with histopathologically confirmed neck metastasis was patient with high-grade MEC treated with elective SND levels I-III. Mucoepidermoid carcinoma is known for its unpredictable behaviour characterized by higher propensity for neck compared to other histological subtypes, therefore occult metastasis is not a rare finding [16,17]. Vander Poorten et al. [18] suggest that MSGT without clinical evidence of neck metastases should be treated with elective SND levels I-III, as the minimal procedure to avoid the uncertainty in the extent of surgery and presumably the high risk of occult neck metastasis. Less comprehensive elective neck treatment for MSGT is advocated by Silver et al. [9], who reported that along with complete excision of submandibular gland, a neck dissection level I should be employed. Neck dissection level I do not significantly prolong the duration and morbidity of operative treatment, and represents an additional procedure in detection of occult metastases in first echelon of lymph nodes. Although many authors advocate a routine elective treatment of the neck irrespective of stage and grade of the disease [3,10,19], there are reports on omission of END in most cases, with consideration only in a group of high-grade and advanced T stage of tumors that have a high propensity for neck lymph nodes [20]. As reported for parotid gland tumors, algorithmic approach could be one potentially solution for decision making in the treatment of MSGT. However, larger studies are needed for adopting such approach [21]. The current NCCN Guidelines break the surgical algorithm of salivary gland malignancies in into 3 groups [22]. The first group includes cN0 T1-2 malignancies whose management should include complete surgical resection. The second, most debating group, includes cN0 and cN+ whose management should include complete surgical resection while ND may be considered if cN0, but should be performed if cN+. In the setting of cN0, the decision regarding whether to perform an elective ND have to be made on the context of histopathology and grade of tumor and its implications regarding risk of occult metastases. The third group includes T4b tumors in which complete surgical resection is not deemed possible or prohibitive in terms of morbidity or ability to achieve clear surgical margins. Management of these cases includes definitive RT or concurrent CRT. According to our results it seems reasonable to omit elective ND in an early stage MSGT. On the other hand, considering metastatic distribution in neck levels I – III, elective SND levels I-III is recommended in high-grade and advanced stage MSGT.

Rates of 5-year and 10-year DFS, DSS and OS in our cohort (**Figure 2**) were in accordance what other authors reported [8,10]. It is known that the regional metastases and recurrence play a major role in the outcome of patients with salivary gland malignancies [11,12]. Sixty-seven percent of patients in our cohort had advanced stage of tumor (stages III and IV) at presentation what explains the decision to treat patients more radical. However, the percentage of occult neck metastases (5.6%) suggests that elective neck dissection in the treatment of MSGT may not be mandatory. According to our results, as standard procedure based on accepted clinical criteria of the preoperative risk of occult metastases, benefit of elective neck dissection is questionable, except for high-grade MEC where elective SND levels I-III is indicated.

Considering imaging methods in the assessment of MSGT, trends in our cohort presents MRI as a more employed method in the last decade. Although CT provides important anatomic relationships of the tumor to surrounding bone, MRI is preferred for evaluation of malignant tumors because of superior ability to delineate perineural invasion. While neither CT nor MRI is accurate enough for definitive diagnosis of malignancy, several features of MRI have been demonstrated to be associated with malignancy (T2 hypointensity, irregular margins, invasion of local structures, and low signal on diffusion-weighted images) [23]. There has been some changes in the preoperative work-up including employment of the fluorodeoxyglucose (FDG)-PET/CT for advanced-stage and high-grade salivary gland cancers. However, while PET/CT may more accurately predict the extent of nodal and distant metastatic disease in high-grade tumors and identify locoregionally recurrent and metastatic disease [24,25], it does not provide the spatial resolution for anatomic details. Also, some salivary malignancies do not have high FDG uptake and many benign tumors including Warthin and benign mixed tumors are FDG-avid [26].

Despite reliability as diagnostic modality for the diagnosis and treatment of salivary gland malignancies [27], the reported accuracy of FNAC in our cohort was 80% (**Table I**). Fail to achieve diagnostic accuracy may be due cytologist not experienced in the field of salivary gland tumors which are known for their histological heterogeneity. Additionally, histological classification of salivary tumors constantly evolved during last 30 years representing additional potential reason in failing to achieve higher diagnostic rates. Ultrasound guided FNAC in the diagnostics of salivary gland malignancies and suspected cervical nodes have been routinely used in our center for the last 20 years, which is evident from the patient documentation. This method in the assessment of salivary gland malignancies is also recommended by the current and widely accepted guidelines [28]. Considering a 30-year period and retrospective design of our study, we are aware that there is a certain possibility that some patients recived FNAC solely. On the other hand, anatomical position of submandibular gland offers a solid chance to collect adequate sample for further analysis so we believe it didn't interfere results. According to our results, FNAC is not completely reliable procedure in decision making for the treatment of a neck and caution is needed. In light of this, the utilization of intra-operative frozen section may play a role in the decision of a neck treatment. It is reported that frozen section pathology for parotid tumors has high accuracy and utility in intraoperative decision making, facilitating timely complete procedures [29,30].

Ultrasound guided fine needle aspiration biopsy (FNAB) of suspected salivary gland mass also represents one of the possible diagnostic tools and some authors recommend it in the evaluation of parotid gland tumors [31,32]. In our institution FNAB was not utilised regularly, but according to the reported results it could potentially bring more accurate results in the assessment of MSGT [32].

Results of our study confirmed a significant difference in final outcome between patients treated with surgery alone compared to those receiving post-operative RT (p=0.0209). Patients undergoing adjuvant irradiation had significantly higher survival rates (Figure 3). On the other hand, there were insufficient data for Kaplan-Meier analysis with respect to DFS due to insufficient data (events). According to the literature, post-operative RT is indicated in salivary malignancies for patients with T(3-4) tumors, incomplete or close resection margins, bone invasion, perineural invasion, and pN(+) [33].

Limitations of present study are retrospective study design, single center experience and small numbers (n=24), especially in respect of histological subtypes and treatment. Data regarding survival should be tested and validated in a prospectively designed trial. Sample size restricted additional statistical analyses of potential prognostic factors affecting survival and recurrence. During 30-year time period standards in diagnostic protocols (imaging methods, fine-needle aspiration cytology procedure) and a treatment of MSGT changed, especially regard advances in adjuvant radiotherapy. Adjuvant therapy protocol presented in methods section was administered in 65% of our patients with confirmed neck metastases, while the rest of cohort (35%) differed or was not accurately documented. Our cohort presented inconsistency in neck dissection techniques performed in the treatment of MSGT (22 SND and 12 RND). Constantly evolving recommendations regarding MSGT treatment and preferences of involved surgeons resulted in indefinite indications on neck dissection technique during presented time period.

Necessity and indications for elective neck dissection in the treatment of MSGT are still controversial [19,20]. By giving the insight in a selection of surgical modalities and treatment outcomes, we believe that our study offers a valuable view regarding indications and extension of the neck dissection in MSGT. Selection of an appropriate treatment is a vital determinant affecting the outcome, and failure to do it consequently decreases rates of survival. Survival rates (DFS, DSS) in our cohort confirm effectiveness of presented modalities in the treatment of MSGT (**Figure 2, Figure 3**).

Conclusion

Malignant submandibular gland tumors (MSGT) are rare and heterogeneous salivary malignancies. Appropriate diagnostic procedures and imaging methods are crucial to achieve correct diagnosis and extent of disease in order to adjust surgical treatment individually. According to results of our study benefit of elective neck dissection in early stage MSGT is questionable. Elective SND levels I-III is recommended in high-grade and advanced stage MSGT without clinical evidence of multi-level lymphadenopathy.

Declarations

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Declarations of interest: none.

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Patient consent: Written patient consent has been obtained.

References

1. Bradley PJ, McGurk M. Incidence of salivary gland neoplasms in a defined UK population. Br J Oral Maxillofac Surg. 2013;51(5):399-403
2. Boukheris H, Curtis RE, Land CE, Dores GM. Incidence of carcinoma of the major salivary glands according to the WHO classification, 1992 to 2006: a population-based study in the United States. Cancer Epidemiol Biomarkers Prev. 2009;18(11):2899-906.
3. Pohar S, Venkatesan V, Stitt LW et al. Results in the management of malignant submandibular tumors and guidelines for elective neck treatment. J Otolaryngol Head Neck Surg. 2011;40(3):191-5.
4. Luksic I, Virag M, Manojlovic S, Macan D. Salivary gland tumors: 25 years of experience from a single institution in Croatia. J Craniomaxillofac Surg. 2012;40(3):e75-81.
5. Tian Z, Li L, Wang L, Hu Y, Li J. Salivary gland neoplasms in oral and maxillofacial regions: a 23-year retrospective study of 6982 cases in an eastern Chinese population. Int J Oral Maxillofac Surg. 2010;39(3):235-42.
6. Etit D, Ekinci N, Tan A, Altinel D, Dag F. An analysis of salivary gland neoplasms: a 12-year, single-institution experience in Turkey. Ear Nose Throat J. 2012 ;91(3):125-9.

7. Ellington CL, Goodman M, Kono SA et al. Adenoid cystic carcinoma of the head and neck: Incidence and survival trends based on 1973-2007 Surveillance, Epidemiology, and End Results data. Cancer. 2012;118(18):4444-51.
8. Lee RJ, Tan AP, Tong EL, Satyadev N, Christensen RE. Epidemiology, Prognostic Factors, and Treatment of Malignant Submandibular Gland Tumors: A Population-Based Cohort Analysis. JAMA Otolaryngol Head Neck Surg. 2015;141(10):905-912. doi:10.1001/jamaoto.2015.1745
9. Silver NL, Chinn SB, Bradley PJ, Weber RS. Surgery for Malignant Submandibular Gland Neoplasms. Adv Otorhinolaryngol. 2016;78:104-112. doi:10.1159/000442130
10. Lombardi D, Accorona R, Lambert A, et al. Long-term outcomes and prognosis in submandibular gland malignant tumors: A multicenter study. Laryngoscope. 2018;128(12):2745-2750. doi:10.1002/lary.27236
11. Lombardi D, McGurk M, Vander Poorten V, et al. Surgical treatment of salivary malignant tumors. Oral Oncol. 2017;65:102-113. doi:10.1016/j.oraloncology.2016.12.007
12. Spiro RH, Hajdu SI, Strong EW. Tumors of the submaxillary gland. Am J Surg. 1976 Oct;132(4):463-8. doi: 10.1016/0002-9610(76)90320-2.

13. Chen AM, Bucci MK, Quivey JM, Garcia J, Eisele DW, Fu KK. Long-term outcome of patients treated by radiation therapy alone for salivary gland carcinomas. Int J Radiat Oncol Biol Phys. 2006;66(4):1044-1050. doi:10.1016/j.ijrobp.2006.06.050
14. Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Villaret DB. Radiotherapy alone or combined with surgery for salivary gland carcinoma. Cancer. 2005;103(12):2544-2550. doi:10.1002/cncr.21083
15. Terhaard CH. Postoperative and primary radiotherapy for salivary gland carcinomas: indications, techniques, and results. Int J Radiat Oncol Biol Phys. 2007;69(2 Suppl):S52-S55. doi:10.1016/j.ijrobp.2007.04.079
16. Boahene DK, Olsen KD, Lewis JE, Pinheiro AD, Pankratz VS, Bagniewski SM. Mucoepidermoid carcinoma of the parotid gland: the Mayo clinic experience. Arch Otolaryngol Head Neck Surg. 2004;130(7):849-856. doi:10.1001/archotol.130.7.849
17. McHugh CH, Roberts DB, El-Naggar AK, et al. Prognostic factors in mucoepidermoid carcinoma of the salivary glands. Cancer. 2012;118(16):3928-3936. doi:10.1002/cncr.26697
18. Vander Poorten VL, Balm AJ, Hilgers FJ, et al. Prognostic factors for long term results of the treatment of patients with malignant submandibular gland tumors. Cancer. 1999;85(10):2255-2264.

19. Nobis CP, Rohleder NH, Wolff KD, Wagenpfeil S, Scherer EQ, Kesting MR. Head and neck salivary gland carcinomas--elective neck dissection, yes or no?. J Oral Maxillofac Surg. 2014;72(1):205-210. doi:10.1016/j.joms.2013.05.024
20. Armstrong JG, Harrison LB, Thaler HT, et al. The indications for elective treatment of the neck in cancer of the major salivary glands. Cancer. 1992;69(3):615-619.
21. Thielker J, Grosheva M, Ihrler S, Wittig A, Guntinas-Lichius O. Contemporary Management of Benign and Malignant Parotid Tumors. Front Surg. 2018;5:39. Published 2018 May 11. doi:10.3389/fsurg.2018.00039
22. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1437, December 22, 2021
23. Liu Y, Li J, Tan YR, Xiong P, Zhong LP. Accuracy of diagnosis of salivary gland tumors with the use of ultrasonography, computed tomography, and magnetic resonance imaging: a meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(2):238-245.e2. doi:10.1016/j.oooo.2014.10.020
24. Kim MJ, Kim JS, Roh JL, et al. Utility of 18F-FDG PET/CT for detecting neck metastasis in patients with salivary gland carcinomas: preoperative planning for necessity and extent of neck dissection. Ann Surg Oncol. 2013;20(3):899-905. doi:10.1245/s10434-012-2716-5

25. Cermik TF, Mavi A, Acikgoz G, Houseni M, Dadparvar S, Alavi A. FDG PET in detecting primary and recurrent malignant salivary gland tumors. Clin Nucl Med. 2007;32(4):286-291. doi:10.1097/01.rlu.0000257336.69537.cb
26. Kendi AT, Magliocca KR, Corey A, et al. Is There a Role for PET/CT Parameters to Characterize Benign, Malignant, and Metastatic Parotid Tumors?. AJR Am J Roentgenol. 2016;207(3):635-640. doi:10.2214/AJR.15.15590
27. Rossi ED, Wong LQ, Bizzarro T, et al. The impact of FNAC in the management of salivary gland lesions: Institutional experiences leading to a risk-based classification scheme. Cancer Cytopathol. 2016;124(6):388-396. doi:10.1002/cncy.21710
28. Mantravadi AV, Moore MG, Rassekh CH. AHNS series: Do you know your guidelines? Diagnosis and management of salivary gland tumors. Head Neck. 2019;41(2):269-280. doi:10.1002/hed.25499
29. Olsen KD, Moore EJ, Lewis JE. Frozen section pathology for decision making in parotid surgery. JAMA Otolaryngol Head Neck Surg. 2013 Dec;139(12):1275-8. doi: 10.1001/jamaoto.2013.5217.
30. Schmidt RL, Hunt JP, Hall BJ, Wilson AR, Layfield LJ. A systematic review and meta-analysis of the diagnostic accuracy of frozen section for parotid gland

lesions. Am J Clin Pathol. 2011 Nov;136(5):729-38. doi: 10.1309/AJCP2SD8RFQEUZJW.

31. Dostalova L, Kalfert D, Jechova A, et al. The role of fine-needle aspiration biopsy (FNAB) in the diagnostic management of parotid gland masses with emphasis on potential pitfalls. Eur Arch Otorhinolaryngol. 2020;277(6):1763-1769. doi:10.1007/s00405-020-05868-1

32. Seyhun N, Doğan U, Çalış ZAB, Kaya MF, Hasçiçek SÖ, Turgut S. The role of fine needle aspiration biopsy in deep lobe parotid tumors: Comparison of preoperative cytology and postoperative histopathologic results. Am J Otolaryngol. 2021;42(1):102590. doi:10.1016/j.amjoto.2020.102590

33. Terhaard CH, Lubsen H, Rasch CR, et al. The role of radiotherapy in the treatment of malignant salivary gland tumors. Int J Radiat Oncol Biol Phys. 2005;61(1):103-111. doi:10.1016/j.ijrobp.2004.03.018

Figures and Table Captions

Figure 1. Diagram of primary surgically treated major salivary gland tumors during 30-year time period.

Figure 2. Kaplan – Meier survival curves of patients with MSGT: a) overall survival (OS), b) disease-free survival (DFS) and c) disease-specific survival (DSS).

Figure 3. Kaplan – Meier overall survival (OS) curves between patients treated with surgery alone and surgery with post-operative radiotherapy.

Table I. Results of fine needle aspiration cytology (FNAC) in MSGT cohort.

Table II. Clinicopathologic characteristics of MSGT cohort.