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Review Article

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A CRITICAL APPRAISAL OF PROGNOSTIC FACTORS IN PAROTID GLAND MALIGNANCY: SYSTEMATIC REVIEW

Dr. Jaspreet Singh Badwal*

Consultant Oral and Maxillofacial Surgery, Phulkian Enclave, Jail Road, Patiala – 147001, Punjab.

***Corresponding Author: Dr. Jaspreet Singh Badwal**

Consultant Oral and Maxillofacial Surgery, Phulkian Enclave, Jail Road, Patiala – 147001, Punjab.

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ABSTRACT

Purpose: The aim of this present systematic review is to investigate into the evidence required in relation to prognostic factors in malignancies of the parotid gland. **materials and methods:** An electronic search was conducted across the various databases such as PUBMED, SCOPUS, EMBASE. In addition, a search over the Google search engine was conducted to find related studies. The search terms used were "parotid gland", "malignancy", "cancer", "survival". **Results:** A total of 16 prognostic factors have been identified that affect survival outcomes for parotid gland cancer. **Conclusion:** Through this paper, any reader can easily comprehend the effect of each of these prognostic factors by relating to best evidence available, thus making it easy to apply the academic knowledge towards practical decision making.

KEYWORDS: Parotid gland, malignancy, cancer, tumours, prognostic factors, survival.

INTRODUCTION

Tumours of the salivary gland constitute 3% of the tumours found to occur in the head and neck region. Of these, 75% - 85% of tumours occur in the parotid gland. 20% - 25% of parotid gland neoplasms are malignant.[1,2,3] The WHO International Histopathological Classification of parotid gland cancers has changed progressively since 1972. While the 1972 classification,[4] described seven subtypes of parotid malignancy, the 2017 classification.[5,6] has evolved to include a vast array of more than 20 subtypes of parotid cancers. Nevertheless, the incidence of various subtypes remains largely similar. The most common malignancies of parotid gland in decreasing order of incidence are mucoepidermoid carcinoma, adenocarcinoma, malignant mixed tumour, adenoid cystic carcinoma and squamous cell carcinomas.

As the incidence of parotid gland malignancies is very low as compared to other cancers of head and neck region, most of the studies describing these tumours are retrospective in nature. As such, in the absence of randomized controlled trials and prospective studies, the most appropriate way to derive any meaningful conclusions from the evidence available, is to conduct a systematic review of literature. The aim of this present systematic review is to investigate into the evidence required in relation to prognostic factors in malignancies of the parotid gland.

MATERIALS AND METHODS

An electronic search was conducted across the various databases such as PUBMED, SCOPUS, EMBASE. In addition, a search over the Google search engine was conducted to find related studies. The search terms used were "parotid gland", "malignancy", "cancer", "survival". A total of 1209 articles had been published in English language from 1966 to 15th November 2022. These included retrospective studies, SEER Database surveys, Multicenter studies and smaller descriptive studies. The inclusion criteria were –

- Studies based on greater than 30 subjects
- Studies based on primary parotid malignancies
- Studies describing long term follow-up of at least three years
- Studies containing information on prognostic factors for parotid gland malignancy
- Studies describing survival outcomes of parotid gland malignancy.
- Any of the studies was excluded if
- It was based on metastatic parotid gland malignancy
- Study describing treatment of recurrent malignancies only
- Studies with ≤ 30 number of subjects.

Out of the 1209 articles that described various aspects of parotid gland malignancies, 43 articles described the prognostic factors for parotid gland cancer and were selected for final inclusion. To reduce the level of

heterogeneity, studies were selected in accordance with the recommendations made by the working committee on PRISMA guidelines.[7]

RESULTS

The various prognostic factors for parotid gland malignancy may be enumerated as follows

1. T-stage
2. N-stage
3. Overall stage of disease
4. Histopathology of tumour
5. Grade of differentiation
6. Presence of facial nerve palsy
7. Surgical Margins
8. Lymph node ratio
9. Perineural invasion
10. Age
11. Lymphovascular invasion
12. Extraparenchymal extension
13. Skin invasion
14. Parapharyngeal space invasion
15. Presence of pain
16. Intercurrent diseases (comorbidities)

DISCUSSION

Though a myriad of papers discuss tumours of the parotid gland, a handful of them intrigue with their content for prognostic factors in cancer of the parotid gland. Yet, one who seeks answers, may be content with the quality of evidence available. In the absence of well controlled prospective studies on this malignancy, due to the low incidence of occurrence, a critical appraisal of the evidence available from studies based on large number of subjects, may help draw an inference towards the impact of prognostic factors on survival from parotid cancer.

We have conducted a systematic review to identify and understand the prognostic factors in parotid cancers, which revealed an astonishing number of underlying causes that bring about a complex interplay of effects on the progression of disease and its survival outcomes.

1. T-stage – T-stage has been identified as the most important prognostic factor affecting long term survival outcomes. Studies reporting results from large number of subjects have confirmed the same. Bhattacharya et al[8] (2005) conducted a SEER database survey to identify prognostic factors affecting survival in parotid gland malignancy. Results were obtained from a large number of 651 subjects and showed T-stage to be an independent prognostic factor. Similar results were reported from studies by Spiro[9] (1989) and Terhaard,[10] (2005), which involved 463 and 498 subjects respectively. Other authors have tried to categorise their results based on T-stage, i.e., T3-T4 versus T1-T2.[11,12] Terhaard.[10] (2005) suggested that T3-T4 tumours should be treated by surgery followed by adjuvant RT, since they pose significant risk of locoregional recurrence.

2. N-stage – Tumours exhibiting higher T-stage and / or high grade have higher incidence of nodal positivity. Bhattacharya et al.[8] (2005) published that nodal positivity significantly influenced survival in a negative manner ($p \leq .001$), as per cox proportional hazards modelling. Similar results were reported by Harbo et al.[13] (2002), who conducted cox hazard regression analysis including 136 patients. Studies by Cederblad[14] (2009), Chakrabarti.[11] (2018), Kim[15] (2020) have confirmed that N-stage is a significant prognostic factor for survival in parotid gland malignancy. Various authors have reported the incidence of occult neck metastasis to be 22% to 48%. Paderno et al[16] have reported the incidence of cervical lymph node metastasis to be 26%.

3. Stage of disease – The overall stage of disease has been mentioned as a prognostic factor in multiple studies. However, different authors have reported different survival rates as per stage of disease. Koul et al[17] (2007) published their results in a study involving 184 patients. 5-years survival for stages I to IV was 85.35%, 76.9%, 56.1%, and 8.4% respectively ($p < .0001$). Harbo et al.[13] (2002) reported comparable results in a study involving 152 patients. 5-year survival was 65% for stage I, 50% for stage II, 21% for stage III and 9% for stage IV. In a study by Lima et al.[18] (2005), the 10-year disease specific survival was 97% for stage I, 81% for stage II, 56% for stage III and 20% for stage IV. For all stages combined, the 5-year and 10-year disease specific survival was 72% and 69% respectively.

Tullio et al.[19] (2001) reported that stage of tumour was a more important prognostic variable than tumour grade, on multivariate analysis. However, Park et al (2020) showed that T1 – T2 high grade parotid cancers generally have poor prognosis. Distant metastasis during follow-up is a major factor in treatment failure and it is significantly associated with lymphovascular invasion and lymph node metastasis.

4. Histopathology of tumour – the histological type of tumour has been confirmed as an independent prognostic factor in multiple studies, as per both univariate and multivariate analysis. Magnano et al,[20] (1999) have reported the percentage recurrence rate for different tumour histologies as follows: Mucoepidermoid carcinoma – 38.4%, Adenoid cystic carcinoma – 35.7%, Squamous cell carcinoma – 31.2 %, Acinic cell carcinoma – 28.5%, Adenocarcinoma – 25% and Undifferentiated carcinoma – 22.2%. however, in the study by Bhattacharya et al, involving a large number of 651 patients, survival was poorest for squamous cell carcinoma and best for acinar cell carcinoma. Acinic cell carcinoma and adenoid cystic carcinoma are usually associated with low risk of occult metastasis.

Adenoid cystic carcinoma is known for its tendency towards perineural invasion, which makes it reach T4 status early in the course of disease. It has low incidence of cervical lymph node metastasis but higher incidence

of delayed lung metastasis.[21] This tumour thus requires long term follow-up. Kane et al.[22] (1991) and Spiro et al.[23] (1992) reported that clinical stage of adenoid cystic carcinoma is more than grade of tumour, as a prognostic factor. Some authors.[20,24,25] have proposed to classify all cases of adenoid cystic carcinoma as high grade. Spiro et al.[26] (1975) reported that mucoepidermoid carcinoma was the most common histology in parotid gland malignancies, while malignant mixed tumour was the second most common type. Carillo et al.[27] (2007) found that disease free interval was shorter for patients with adenocarcinoma and undifferentiated carcinoma, while it was longer for mucoepidermoid carcinoma and adenoid cystic carcinoma.

5. Grade of differentiation – Renehan et al,[28] classified parotid malignancies into low grade, intermediate grade and high grade, representing different levels of biological behaviour. Mucoepidermoid carcinoma and adenocarcinoma were further subclassified into low grade and high grade histologies. This classification system was similar to that reported by Ellis et al,[29] (1991), Kane et al,[22] (1991) and Spiro et al,[30] (1986).

Various salivary gland malignancies show classical high grade and low grade features, characteristic to particular type of histopathology. Thus adenocarcinoma, mucoepidermoid carcinoma high grade, malignant mixed tumours and salivary duct carcinomas are classified as high grade tumours.[18] These tumours require more aggressive treatment approach. Calearo31 (1998), Magnano,[20] (1999) and Al-Mamgani,[32] (2012) have reported that grading of parotid gland malignancy is a significant prognostic factor affecting survival outcomes. In a study involving 126 patients, Magnano et al,[20] found that 5-year survival was 52% for low grade malignancy, while it was 42% for high grade malignancy. Renehan et al,[28] (1999) have published that 10 year survival for patients with low grade, intermediate grade and high grade parotid cancers was 91%, 41% and 50% respectively.

Carillo et al,[27] (2007) published that low grade tumours had better disease free survival and fewer recurrences as compared to high grade tumours. In a study involving 57 subjects, Kim et al,[15] (2020) reported that none of the patients with low and intermediate grade developed distant failure. Armstrong et al,[33] (1992) and Ferlito et al,[34] (2001) have recommended elective neck dissection for malignancies with high grade histology. However, a practical problem encountered is the difficulty to know exact histology and grade of malignancy before and during surgery. Zbaren,[35] (2005) reported that it was difficult to determine the precise grade of tumour in 55% of cases, preoperatively and intraoperatively.

In order to create a benchmark for future reference, precise criteria should be laid down for grading of these tumours so that there can be uniformity in collection of data across different centers.

6. Presence of facial paralysis – Calearo et al,[31] (1998) and Harbo et al,[13] (2002) identified preoperative facial paralysis as a significant factor influencing prognosis. Zbaren,[36] (2003) reported that facial paralysis is a significant risk factor influencing prognosis. Gallo et al,[24] (1997) published that presence of facial paralysis is associated with high risk of distant metastasis. Lima et al,[18] (2005) reported incidence of facial nerve dysfunction to be 24.5 %. Of these, 35.5 % showed locoregional metastasis while 32.3 % had distant metastasis.

Yamamoto,[37] (2021) conducted a study to analyze the impact of surgical strategy on clinical outcomes in patients with parotid carcinoma. Patients in Group A were treated with total parotidectomy and elective neck dissection in cT3-T4 patients who were cN0, while patients in Group B underwent superficial parotidectomy without elective neck dissection, followed by adjuvant radiotherapy. In patients with preoperative facial nerve palsy, in both groups, the facial nerve was resected. In patients where preoperative facial nerve palsy was absent, if the nerve was found to be in contact with the tumour intraoperatively, the nerve was sacrificed in group A patients, while the nerve was preserved in group B patients. Incidence of postoperative facial nerve palsy in patients with preoperative facial palsy was 65.4% in group A while it was 48.6% in group B. The 5-year overall survival for Group A was 77.6 % versus 77.1% for Group B ($p = 0.709$). The 5-year disease free survival for Group A was 71.0% versus 72.4% for Group B ($p = 0.548$). Patients found to have intraoperative facial nerve invasion had lower 5-year overall survival as compared to those without invasion (50.0% versus 89.2%; $p = 0.009$). Incidence of local recurrence was (16.4%) whereas that of distant metastasis was 13.4%.

7. Surgical Margins – Chakrabarti et al.[11] (2018) conducted a study involving 165 patients of parotid malignancy. The objective of the study was to identify prognostic factors in salivary gland malignancy and their impact on survival outcomes. The histopathological margin status was subclassified into three categories – (a) Tumour at resection margin or < 2 mm (b) 2mm to $\leq$ 5 mm from any resection margin (c) ≥ 5 mm from all margins. Univariate analysis was performed for resection margin status as a variable affecting survival outcomes. Patients with resection margin of < 5 mm had worse survival outcomes as compared to those with a resection margin ≥ 5 mm ($p = 0.03$ for overall survival and 0.004 for disease free survival). For cases with margins ≥ 2 mm as compared to those with margins < 2 mm, there was no difference in overall survival but a worse disease free survival was noted when margin was < 2 mm. Parikh et al,[38] (2019) presented their results from a study involving 200 patients of parotid gland malignancy. Positive margins were independent predictor of overall

and disease free survival on univariate and multivariate analysis. Tullio et al,[19] (2001) and Nakano et al[39] (2019) reported similar results.

It is pertinent to mention the study published by Huang et al.[40] (2016) with regards to pathological positive margins. The study included 85 patients of parotid gland cancer who were treated by surgery and adjuvant radiotherapy. Histopathological examination showed that margins were positive in 55 (64.7%) patients and close (< 5 mm) in 23 subjects (27.1%). All patients with positive or close margins were administered conventional radiotherapy with a total dose of 60 – 66 Gy using 6 MV photon linear accelerator. Adjuvant concurrent chemoradiotherapy (CCRT) was administered for patients with either positive margin or extranodal extension, using weekly Cisplatin at 40 mg / m^2 in 38 patients (44.7%). Elective nodal irradiation was administered in 66 patients (77.6%). The authors found that with adjuvant treatment positive and close margin status was not significant predictor of worse survival outcomes. Hence, close or positive margin was associated with poor disease free survival and overall survival.

8. Lymph Node Ratio – Jiang et al,[41] (2022) published a study involving 3259 patients from a SEER database survey, along with 99 patients from another Cancer center. Cox proportional hazard regression analysis showed that cancer specific survival was better for patients with lymph node ratio (LNR) ≤ 0.32 ($p < 0.001$), as compared with patients with LNR > 0.32. This finding was consistent for patients in N2 and N3 stage group but absent in N1 stage group. Lymph node ratio was defined as the number of positive lymph nodes divided by the number of neck lymph nodes dissected. Similarly, Elhusseiny et al,[42] (2019) reported that LNR > 0.33 was a prognostic risk factor in patients with major salivary gland cancer, such that 4608 cases involved parotid gland malignancy.

9. Perineural Invasion – Paderno et al.[16] (2019) published a retrospective review of 200 patients treated surgically for parotid gland malignancy. While the incidence of perineural invasion (PNI) was 25.5 %, the incidence of adenoid cystic carcinoma was 12.5%, thus confirming the fact that adenoid cystic carcinoma has the highest propensity for perineural invasion. The presence of perineural invasion was found to be a significant prognostic factor for overall survival and disease free survival on univariate analysis (HR [OS] = 4.7, $p <$ .ooo1, HR [DFS] = 3.8, $p < .0001$). Frankenthaler,[43] (1991) and Kim,[15] (2020) reported similar results.

10. Age – Parikh et al,[38] (2019) conducted a study on prognostic factors in parotid gland malignancy. Univariate analysis was performed using Cox proportional hazards model (n=200). Age greater than 60 years was identified as significant factor affecting overall survival (OS) and disease free survival (DFS) (hazard ratio, HR [OS] = 4.1, $p = .0001$; HR [DFS] = 3.5, $p < .0001$). The 5-year and 10-year OS were 81% and 73% respectively while the 5-year and 10-year DFS were 80% and 73% respectively. Kim,[15] (2020) and Stodulski.[44] (2012) also reported age greater than 60 years as a prognostic factor for worse survival while Lima,[18] (2005) reported age > 50 years to affect survival. Bhattacharyya,[8] (2005), Renehan.[28] (1999) and Frankenthaler,[43] (1991) also reported age to be a significant prognostic factor impacting survival outcomes.

11. Lymphovascular invasion – Kim et al.[15] (2020) published a retrospective study involving 57 patients treated for parotid gland malignancy. Lymphovascular invasion (LVI) was found to be associated with worse survival outcomes on univariate analysis, such that 5-year OS was 37.5 in LVI positive patients versus 84.6% in LVI negative patients. On multivariate analysis, LVI was associated with high risk of distant metastasis ($p = 0.023$). Frankenthaler.[43] (1991) found lymphovascular invasion to impact survival on univariate and multivariate analysis. Park et al.[45] (2020) reported LVI to affect distant metastasis.

12. Extraparenchymal extension – the presence of extraparenchymal extension in parotid gland malignancy was found to predict worse survival outcomes by various authors, such as Frankenthaler,[43] (1991), Bhattacharyya.[8] (2005) and Chang.[46] (2015). In the study by Bhattacharyya et al,[8] 8 38.0% patients exhibited extraparenchymal extension. The 5-year and 10-year actuarial survival were 66.6 and 49.7% respectively.

13. Skin invasion – Paderno et al[16] (2018) reported their results from a study involving 104 patients. Presence of skin infiltration was identified as a critical prognostic variable affecting worse outcomes of OS and DFS. The 5-year and 10-year OS were 74.7% and 69.4% respectively. Takahama,[47] (2009) reported similar findings.

14. Parapharyngeal space invasion – Stodulski et al[44] (2012) reported that presence of parapharyngeal space invasion was a significant prognostic factor associated with worse survival outcomes. The authors concluded that presence of parapharyngeal space invasion decreased the chance of recovery by 9.8 times while the prognosis became worse 5.4 times. In this study the 5-year OS and DFS were 57% and 50% respectively.

15. Presence of pain – Colevas,[48] (2021) conducted a study involving 154 patients to understand the significance of pain as a predictor of disease severity in parotid gland malignancy. The subjects were stratified into low stage (I and II) disease and high stage (III and IV) disease groups, so as to analyze the independent effect of pain at initial presentation on disease recurrence rate and disease free survival. The results showed that

high stage patients with pain were significantly more likely to develop disease recurrence, as compared to high stage patients without pain (58.5 % versus 33.3 %, p = 0.022). Also high stage patients with pain had significantly decreased survival time compared to high stage patients without pain (p = 0.027).

16. Intercurrent diseases (comorbidities) – Cederblad,[14] (2009) conducted a study involving 144 patients with parotid cancer treated between 1948 and 2004. Presence of comorbidity was found to be a prognostic factor associated with poor survival. Among these 144 patients, 36% died of parotid cancer, 15% died from other cancers, while 30% died from other causes such as heart disease, pneumonia and other infectious diseases.

CONCLUSION

A thorough analysis of various factors associated with prognosis of parotid gland cancers revealed 16 underlying regulatory influences which compose a network of pivot points around which prognosis lies in equilibrium. Through this paper, any reader can easily comprehend the effect of each of these prognostic factors by relating to best evidence available, thus making it easy to apply the academic knowledge towards practical decision making.

Conflict of interests

The author declares that there is no conflict of interests that could influence this work.

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Ethical approval

This article does not contain any studies with human participants or animals performed by the author.

REFERENCES

1. Horn-Ross PL, West DW, Brown SR. Recent trends in the incidence of salivary gland cancer. Int J Epidemiol. 1991; 20: 628–33.
2. Woods JE, Chong GC, Beahrs OH. Experience with 1,360 primary parotid tumors. Am J Surg. 1975; 130: 460–2.
3. Spiro RH. Diagnosis and pitfalls in the treatment of parotid tumors. Semin Surg Oncol. 1991; **7**: 20–4.
4. Thackray AC and Sobin LH. Histological typing of salivary gland tumours. Geneva: World Health Organization, 1972.
5. Ihrler S, Guntinas-Lichius O, Haas C, Mollenhauer M. Neues zu Tumoren der Speicheldrüsen : WHO-Klassifikation 2017 [Updates on tumours of the salivary glands : 2017 WHO classification]. Pathologe, 2018 Feb; 39(1): 11-17. German. doi: 10.1007/s00292-017-0407-5. PMID: 29372306.
6. Seethala RR, Stenman G. Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Tumors of the Salivary Gland. Head Neck Pathol, 2017 Mar; 11(1): 55-67. doi: 10.1007/s12105-017-0795-0. Epub, 2017 Feb 28. PMID: 28247227; PMCID: PMC5340736.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ., 2021 Mar 29; 372: n71. doi: 10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.
8. Bhattacharyya N, Fried MP. Determinants of survival in parotid gland carcinoma: a population based study. Am J Otolaryngol, 2005; 26(1): 39-44.
9. Spiro RH, Armstrong J, Harrison L, Geller NL, Lin SY, Strong EW. Carcinoma of major salivary glands. Recent trends. Arch Otolaryngol Head Neck Surg, 1989; 115(3): 316–21.
10. Terhaard CH, Lubsen H, Rasch CR, et al. Dutch Head and Neck Oncology Cooperative Group. The role of radiotherapy in the treatment of malignant salivary gland tumors. Int J Radiat Oncol Biol Phys, 2005; 61(1): 103–11.
11. Chakrabarti S, Nair D, Malik A, Qayyumi B, Nair S, Agrawal JP, Chaturvedi P. Prognostic factors in parotid cancers: Clinicopathological and treatment factors influencing outcomes. Indian J Cancer. 2018; 55(1): 98-104. doi:10.4103/ijc.ijc_503_17. PMID: 30147103.
12. Chen AM, Garcia J, Lee NY, Bucci MK, Eisele DW. Patterns of nodal relapse after surgery and postoperative radiation therapy for carcinomas of the major and minor salivary glands: what is the role of elective neck irradiation? Int J Radiat Oncol Biol Phys, 2007; 67: 988–94.
13. Harbo G, Bundgaard T, Pedersen D, Sogaard H, Overgaard J. Prognostic indicators for malignant tumours of salivary glands. Clinical Otolaryngology and Allied Sciences, 2002; 27(6): 512-516.
14. Cederblad L, Johansson S, Enblad G, Engström M, Blomquist E. Cancer of the parotid gland; long-term follow-up. A single centre experience on recurrence and survival. Acta Oncologica, 2009; 48:4, 549-555.
15. Kim YH, Chung WK, Jeong JU, Cho IJ, Yoon MS, Song JY, Nam TK, Ahn SJ, Lee DH, Yoon TM, Lee JK, Lim SC. Evaluation of Prognostic Factors for the Parotid Cancer Treated With Surgery and Postoperative Radiotherapy. Clin Exp Otorhinolaryngol. 2020 Feb; 13(1): 69-76. doi: 10.21053/ceo.2019.00388. Epub 2019 Sep 5. PMID: 31480828; PMCID: PMC7010496.
16. Paderno A, Tomasoni M, Mattavelli D, Battocchio S, Lombardi D, Nicolai P. Primary parotid

carcinoma: analysis of risk factors and validation of a prognostic index. Eur Arch Otorhinolaryngol. 2018 Nov;275(11):2829-2841. doi: 10.1007/s00405-018-5122-1. Epub 2018 Sep 12. PMID: 30209560.
17. Koul R, Dubey A, Butler J, Cooke AL, Abdoh A, Nason R. Prognostic factors depicting disease-specific survival in parotid-gland tumors. Int J Radiat Oncol Biol Phys, 2007 Jul 1; 68(3): 714-8. doi: 10.1016/j.ijrobp.2007.01.009. Epub, 2007 Mar 29. PMID: 17398019.
18. Lima RA, Tavares MR, Dias FL, Kligerman J, Nascimento MF, Barbosa MM, Cernea CR, Soares JR, Santos IC, Salviano S. Clinical prognostic factors in malignant parotid gland tumors. Otolaryngol Head Neck Surg, 2005 Nov; 133(5): 702-8. doi: 10.1016/j.otohns.2005.08.001. PMID: 16274796.
19. Tullio A, Marchetti C, Sesenna E, Brusati R, Cocchi R, Eusebi V. Treatment of carcinoma of the parotid gland: the results of a multicenter study. J Oral Maxillofac Surg, 2001 Mar; 59(3): 263-70. doi: 10.1053/joms.2001.20986. PMID: 11243607.
20. Magnano M, gervasio CF, Cravero L, Machetta G, Lerda W, Beltramo G, Orecchia R, Ragona R, Bussi M. Treatment of malignant neoplasms of the parotid gland. Otolaryngol Head Neck Surg, 1999 Nov; 121(5): 627-32. doi: 10.1016/S0194-5998(99)70070-7. PMID: 10547484.
21. Cantù G. Adenoid cystic carcinoma. An indolent but aggressive tumour. Part A: from aetiopathogenesis to diagnosis. Acta Otorhinolaryngol Ital., 2021 Jun; 41(3): 206-214. doi: 10.14639/0392-100X-N1379. PMID: 34264913; PMCID: PMC8283400.
22. Kane WJ, McCaffrey TV, Olsen KD, et al. Primary parotid malignancies. A clinical and pathologic review. Arch Otolaryngol Head Neck Surg, 1991; 117: 307–15.
23. Spiro RH, Huvos AG. Stage means more than grade in adenoid cystic carcinoma. Am J Surg, 1992; 164: 623– 8.
24. Gallo O, Franchi A, Bottai GV, et al. Risk factors for distant metastases from carcinoma of the parotid gland. Cancer, 1997; 80: 844 –51.
25. Vander Poorten V, Balm AJ, Hilgers FJ, et al. The development of a prognostic score for patients with parotid carcinoma. Cancer, 1999; 85: 2057–67.
26. Spiro RH, Huvos AG, Strong EW. Cancer of the parotid gland. A clinicopathologic study of 288 primary cases. Am J Surg, 1975; 130: 452–9.
27. Carrillo JF, Vázquez R, Ramírez-Ortega MC, Cano A, Ochoa-Carrillo FJ, Oñate-Ocaña LF. Multivariate prediction of the probability of recurrence in patients with carcinoma of the parotid gland. Cancer, 2007 May 15; 109(10): 2043-51. doi: 10.1002/cncr.22647. PMID: 17410532.
28. Renehan AG, Gleave EN, Slevin NJ, McGurk M. Clinico-pathological and treatment-related factors influencing survival in parotid cancer. Br J Cancer, 1999 Jun; 80(8): 1296-300. doi: 10.1038/sj.bjc.6990501. PMID: 10376987; PMCID: PMC2362357.
29. Ellis G, Auclair P and Gnepp D Surgical Pathology of the Salivary Glands. WB Saunders Co: Philadelphia
30. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. Head Neck Surg, 1986 Jan-Feb; 8(3): 177-84. doi: 10.1002/hed.2890080309. PMID: 3744850.
31. Calearo C, Pastore A, Storchi OF, Polli G. Parotid gland carcinoma: analysis of prognostic factors. Ann Otol Rhinol Laryngol, 1998 Nov; 107(11 Pt 1): 969-73. doi: 10.1177/000348949810701112. PMID: 9823848.
32. Al-Mamgani A, van Rooij P, Verduijn GM, Meeuwis CA, Levendag PC. Long-term outcomes and quality of life of 186 patients with primary parotid carcinoma treated with surgery and radiotherapy at the Daniel den Hoed Cancer Center. Int J Radiat Oncol Biol Phys, 2012 Sep; 84(1): 189-95.
33. 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): 615–9.
34. Ferlito A, Shaha AR, Rinaldo A, et al. Management of clinically negative cervical lymph nodes in patients with malignant neoplasms of the parotid gland. ORL J Otorhinolaryngol Relat Spec, 2001; 63(3): 123–6.
35. Zbaren P, Schupbach J, Nuyens M. Stauffer E Elective neck dissection versus observation in primary parotid carcinoma. Otolaryngol Head Neck Surg, 2005; 132(3): 387–91.
36. Zbaren P, Schupbach J, Nuyens M, et al. Carcinoma of the parotid gland. Am J Surg, 2003; 186: 57– 62.
37. Yamamoto H, Kojima T, Okanoue Y, Otsuki S, Hasebe K, Yuki R, Hori R. Impact of Changing Surgical Strategies on Clinical Outcomes in Patients with Parotid Carcinoma: A 53-Year Single-Institution Experience. Medicina (Kaunas), 2021 Jul 23; 57(8): 745. doi: 10.3390/medicina57080745. PMID: 34440951; PMCID: PMC8399018.
38. Parikh AS, Khawaja A, Puram SV, Srikanth P, Tjoa T, Lee H, Sethi RKV, Bulbul M, Varvares MA, Rocco JW, Emerick KS, Deschler DG, Lin DT. Outcomes and prognostic factors in parotid gland malignancies: A 10-year single center experience. Laryngoscope Investig Otolaryngol, 2019 Nov 13; 4(6): 632-639. doi: 10.1002/lio2.326. PMID: 31890881; PMCID: PMC6929571.
39. Nakano T, Yasumatsu R, Kogo R, Hashimoto K, Asai K, Ohga S, Yamamoto H, Nakashima T, Nakagawa T. Parotid gland carcinoma: 32 years' experience from a single institute. J Laryngol Otol, 2019 Jul; 133(7): 604-609. doi: 10.1017/S0022215119001130. Epub 2019 Jun 6. PMID: 31169091.
40. Huang BS, Chen WY, Hsieh CE, Lin CY, Lee LY, Fang KH, Tsang NM, Kang CJ, Wang HM, Chang

JT. Outcomes and prognostic factors for surgery followed by modern radiation therapy in parotid gland carcinomas. Jpn J Clin Oncol, 2016 Sep; 46(9): 832-8. doi: 10.1093/jjco/hyw067. Epub 2016 Jun 17. PMID: 27317738.

41. Jiang WM, Xu JF, Chen J, Li GL, Gao YF, Zhang Q, Chen YF. Prediction of Long-Term Survival Outcome by Lymph Node Ratio in Patients of Parotid Gland Cancer: A Retrospective study. Front Surg, 2022 May 11; 9: 903576. doi: 10.3389/fsurg.2022.903576. PMID: 35647020; PMCID: PMC9130709.
42. Elhusseiny KM, Abd-Elhay FA, Kamel MG, Abd El Hamid Hassan HH, El Tanany HHM, Hieu TH, Tieu TM, Low SK, Hou V, Dibas M, Huy NT. Examined and positive lymph nodes counts and lymph nodes ratio are associated with survival in major salivary gland cancer. Head Neck, 2019 Aug; 41(8): 2625-2635. doi: 10.1002/hed.25742. Epub 2019 Mar 23. PMID: 30905082.
43. Frankenthaler RA, Luna MA, Lee SS, Ang KK, Byers RM, Guillamondegui OM, Wolf P, Goepfert H. Prognostic variables in parotid gland cancer. Arch Otolaryngol Head Neck Surg, 1991 Nov; 117(11): 1251-6. doi: 10.1001/archotol.1991.01870230067009. PMID: 1747227.
44. Stodulski D, Mikaszewski B, Stankiewicz C. Are all prognostic factors in parotid gland carcinoma well recognized? Eur Arch Otorhinolaryngol, 2012 Mar; 269(3): 1019-25. doi: 10.1007/s00405-011-1716-6. Epub 2011 Aug 6. PMID: 21822857; PMCID: PMC3275734.
45. Park YM, Yoon SO, Koh YW, Kim SH, Lim JY, Choi EC. Clinical-pathological prognostic factors and treatment failure patterns in T1-2 high-grade parotid gland cancer. Oral Oncol. 2020 Nov;110:104884. doi: 10.1016/j.oraloncology.2020.104884. Epub, 2020 Jul 3. PMID: 32629407.
46. Chang JW, Hong HJ, Ban MJ, Shin YS, Kim WS, Koh YW, Choi EC. Prognostic Factors and Treatment Outcomes of Parotid Gland Cancer: A 10-Year Single-Center Experience. Otolaryngol Head Neck Surg, 2015 Dec; 153(6): 981-9. doi: 10.1177/0194599815594789. Epub, 2015 Jul 22. PMID: 26203086.
47. Takahama A Jr, Sanabria A, Benevides GM, de Almeida OP, Kowalski LP. Comparison of two prognostic scores for patients with parotid carcinoma. Head Neck, 2009 Sep; 31(9): 1188-95. doi: 10.1002/hed.21086. PMID: 19408288.
48. Colevas S, Thompson J, Glazer T, Hartig G. Prognostic Significance of Pain in Parotid Gland Malignancy. Laryngoscope, 2021 Jul; 131(7): 1503-1508. doi: 10.1002/lary.29273. Epub 2020 Dec 12. PMID: 33314225.