WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Treatment Approaches for Salivary Gland Tumours: A Systematic Review of Surgical and Non-Surgical Option

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ABSTRACT

Salivary gland tumors represent a diverse group of neoplasms arising from the major and minor salivary glands. Management of these tumors requires a multidisciplinary approach, and treatment decisions should be based on tumor histology, location, grade, and patient-specific factors. Surgical interventions have traditionally been the cornerstone of treatment for salivary gland tumors. Non-surgical options are increasingly recognized as valuable alternatives or adjuncts to surgery, particularly in cases where surgical resection may be challenging or pose significant morbidity. This systematic review comprehensively evaluates surgical and non-surgical treatment options for salivary gland tumours, emphasizing personalized treatment strategies and the latest evidence.

Keywords: Salivary gland tumours; Surgical resection; Non-surgical options; Treatment approaches; Systematic review

INTRODUCTION

Salivary gland tumours encompass a diverse and intricate spectrum of neoplasms that arise within the salivary glands, presenting a formidable challenge to clinicians and oncologists. These tumours exhibit substantial histological variability, clinical behavior, and treatment responses, necessitating a multidisciplinary approach to their management.[1,2] The rarity of these neoplasms further complicates the development of evidence-based treatment strategies, making the synthesis of available knowledge crucial for informed clinical decision-making. Salivary gland tumours are categorized based on their histological characteristics, with numerous subtypes identified. This diversity underscores the need for a nuanced understanding of each tumour's behavior and response to treatment. Furthermore, the intricate anatomy of the salivary glands, situated in close proximity to critical structures, adds complexity to surgical interventions and radiation therapy planning.[3] Over the years, advances in surgical techniques, radiation therapy modalities, and the emergence of targeted therapies and immunotherapy have broadened the spectrum of treatment options available for salivary gland tumours. However, the relative efficacy of these various approaches and their optimal sequencing remain subjects of ongoing research and clinical debate.[4] This systematic review aims to consolidate the existing body of knowledge regarding the treatment of salivary gland tumours, with a specific focus on both surgical and non-surgical modalities

SALIVARY GLAND TUMOURS: CLASSIFICATION AND EPIDEMIOLOGY

Salivary gland tumors are relatively rare compared to other cancers, accounting for approximately 3-6% of all head and neck neoplasms. The incidence of salivary gland tumors varies by geographic region and population, with some subtypes showing distinct epidemiological patterns. Factors such as age, gender, and exposure to environmental carcinogens may influence the development of these tumors. Salivary gland tumors are classified based on their histological characteristics, with the most commonly used system being the World Health Organization (WHO) classification.[5] This classification system categorizes salivary gland tumors into various subtypes, taking into account their cellular composition and architectural patterns.

Benign Epithelial Tumors

1. Pleomorphic Adenoma (ICD-O: 8940/0)

2. Myoepithelioma (ICD-O: 8982/0)

3. Basal Cell Adenoma (ICD-O: 8147/0)

4. Warthin Tumor (ICD-O: 8561/0)

5. Oncocytoma (ICD-O: 8290/0)

6. Sebaceous Adenoma (ICD-O: 8410/0)

7. Lymphadenoma

8. Ductal Papillomas (ICD-O: 8503/0)

9. Sialadenoma Papilliferum (ICD-O: 8406/0)

10. Cystadenoma (ICD-O: 8440/0)

11. Hemangioma (ICD-O: 9120/0)

12. Squamous Cell Carcinoma (ICD-O: 8070/3)

Malignant Epithelial Tumors:

1. Acinic Cell Carcinoma (ICD-O: 8550/3)

2. Mucoepidermoid Carcinoma (ICD-O: 8430/3)

3. Adenoid Cystic Carcinoma (ICD-O: 8200/3)

4. Polymorphous Adenocarcinoma (ICD-O: 8525/3)

5. Epithelial-Myoepithelial Carcinoma (ICD-O: 8562/3)

6. Basal Cell Adenocarcinoma (ICD-O: 8147/3)

7. Sebaceous Adenocarcinoma (ICD-O: 8410/3)

8. Secretory Carcinoma (ICD-O: 8502/3)

9. Salivary Duct Carcinoma (ICD-O: 8500/3)

10. Carcinoma ex Pleomorphic Adenoma (ICD-O: 8941/3)

11. Poorly Differentiated Carcinoma (ICD-O: 8020/3)

12. Carcinosarcoma (ICD-O: 8980/3)

13. Squamous Cell Carcinoma (ICD-O: 8070/3)

14. Lymphoepithelial Carcinoma (ICD-O: 8082/3)

15. Sialoblastoma (ICD-O: 8974/1)

Soft Tissue Tumors:

- Hematolymphoid Tumors: Hodgkin Lymphoma, Diffuse Large B-cell Lymphoma, Extranodal Marginal Zone B-cell Lymphoma

Secondary Tumors: These may arise as metastases or secondary tumors originating from other primary sites.

SURGICAL APPROACHES FOR SALIVARY GLAND TUMORS

Surgical intervention is a cornerstone in the management of salivary gland tumors, with the primary goal of achieving complete tumor removal while preserving important anatomical structures and maintaining optimal function. The choice of surgical approach depends on factors such as tumor location, size, histology, and the patient's overall health.[6]

Surgical Resection

Parotid surgery encompasses various surgical procedures performed on the parotid gland, which is a salivary gland located in the face. These surgeries are typically done to treat conditions such as tumors, cysts, or chronic infections of the parotid gland.[7]

Types of Parotid Surgery:

1. Extra capsular Dissection: Used for benign lesions that are not pleomorphic adenoma; facial nerve is not identified, but a facial nerve monitor is used.

2. Partial/Superficial Parotidectomy: Resection of the tumor with identification and preservation of the facial nerve; used for benign lesions and lymph node metastasis into the superficial lobe.[8]

3. Total Parotidectomy: Removal of the entire gland with identification and preservation of the facial nerve; used for aggressive malignant tumors, deep lobe tumors, vascular malformations, or large tumors where the distinction between superficial and deep lobes is unclear.

4. Radical Parotidectomy: Removal of the entire gland, including the facial nerve; used when preoperative facial paralysis is established or circumferential involvement of the nerve by malignant tumor is encountered.[9]

Surgical Technique:

Procedure performed under general anesthesia with careful monitoring of facial nerve function. Various incision options, such as the modified Blair incision or modified facelift incision, may be used. Dissection is performed to identify and preserve the facial nerve branches. Care is taken not to damage structures like the digastric muscle, tragal pointer, and tympanomastoid suture, which serve as landmarks for the facial nerve. Branches of the facial nerve are dissected proximal to the tumor. Total parotidectomy for chronic parotitis requires following Stenson's duct to the oral mucosa to prevent stone retention. Benign tumors are dissected free from the facial nerve, while malignant tumors may involve partial nerve resection. Haemostasis is crucial, and the integrity of the facial nerve is checked before closure. Complications of parotid surgery can include hematoma, facial paralysis (often temporary), seroma, surgical site infection, Frey's syndrome, first bite syndrome, loss of sensation around the ear, amputation neuroma, surgical site depression, trismus, and sialocele (salivary fistula).[10,11]

Sublingual Gland Resection: tumors originating in the sublingual gland may require the complete removal of the gland. This procedure is performed to prevent tumor recurrence and reduce the risk of malignant transformation.[12,13]

Submandibular Gland Resection**:** When tumors originate in the submandibular gland, surgical resection may involve removing the entire gland to ensure complete tumor removal. This procedure is performed with care to protect nearby structures such as the lingual nerve and facial artery.[14]

Lateral Transcervical Approach:

A 4-6 cm incision is made in the lateral neck crease, approximately 2-3 cm below the lower edge of the mandible. The facial nerve is identified and protected. The facial vein and artery are ligated, and the gland is dissected free from the surrounding structures, including the mylohyoid muscle. The lingual and hypoglossal nerves are preserved, and the submandibular duct is ligated and divided.[15]

Submental Approach:

The gland is dissected free from surrounding fascia in a subplatysmal plane. The facial vein and artery are ligated, and the gland is separated from the mylohyoid muscle and the submandibular ganglion. The submandibular duct is ligated, and the gland is removed through the incision.[16]

Retroauricular Approach:

Procedure: The incision is made in the lower part of the postauricular sulcus, transitioning into the hairline. The skin flap is raised carefully to avoid damage to hair follicles and nerves. The gland is exposed and excised similarly to other open approaches.

Transoral Approach:

Procedure: An incision is made in the floor of the mouth, and the submandibular gland is dissected and removed through this incision. Care is taken to identify and protect the lingual nerve.

Endoscopic Approaches:

Endoscopic-assisted and completely endoscopic approaches are being explored, offering advantages such as magnified visualization and reduced scarring. The endoscopic-assisted transoral approach involves endoscope-guided excision via a transoral incision, offering improved visualization without CO2 insufflation. The endoscopic-assisted submental approach uses endoscopic equipment to aid in gland excision while maintaining a smaller submental incision. The endoscopic transcervical approach involves creating an operative pocket without CO2 insufflation and offers a minimally invasive alternative. Robotic-enhanced endoscopic surgery offers three-dimensional vision and articulated instruments for improved precision.[17]

Neck Dissection: Neck dissection is indicated when there is evidence of lymph node involvement by the salivary gland tumor or when lymph node metastasis is suspected based on imaging or clinical findings. The extent of neck dissection varies and may include:

Selective Neck Dissection: Removal of only the lymph nodes at risk for metastasis.

Modified Radical Neck Dissection: Removal of a larger number of lymph nodes, while preserving key structures like the sternocleidomastoid muscle, internal jugular vein, and accessory nerve.

Radical Neck Dissection: Extensive removal of lymph nodes, muscles, and other structures in the neck, typically reserved for advanced cases.

In recent developments in ablative surgery for head and neck malignancies, transoral surgery techniques such as Transoral Laser Microsurgery (TLM) and Transoral Robotic Surgery (TORS) have emerged as valuable options. These approaches offer enhanced visualization, precise surgical control, and better maneuverability compared to traditional methods, making them particularly effective for treating certain types of squamous cell carcinomas (SCC) in the upper aerodigestive tract, notably in the oropharynx and larynx. These procedures have been proven successful in treating SCC in the larynx (TLM) and oropharynx (TORS), although their application in treating minor salivary gland carcinomas (MiSGC) in these regions is less documented. Transoral surgery is favored for its minimally invasive nature, reducing damage to surrounding tissues and leading to fewer postoperative complications, less pain, quicker recovery, shorter hospital stays, and improved functional outcomes. Comparative studies have demonstrated the advantages of transoral approaches over open surgery for oropharyngeal SCC.

For MiSGC, especially those arising in the oropharynx, procedures like radical tonsillectomy, lateral oropharyngectomy, and base of tongue (BOT) resection have been adapted from traditional TORS techniques, showcasing favorable outcomes with good functional results and low postoperative complications. Recent retrospective analyses have reported comparable survival rates and positive margin rates between TORS and non-robotic approaches for oropharyngeal MiSGC, though the readmission rate was slightly higher in TORS cases. Transoral surgery has also been explored for primary parapharyngeal space tumors originating from the deep lobe of the parotid gland, offering improved visibility and precision compared to the conventional transoral approach. However, this approach is currently limited to select cases and necessitates experienced robotic surgeons. In terms of technical advancements, the implementation of CO2-laser technology during TORS has shown promise in minimizing collateral tissue damage. A steerable CO2-laser fiber carrier has been developed to enhance the capabilities of TORS for malignant salivary gland tumors. Transnasal endoscopic surgery is another option for managing certain MiSGMTs, particularly those in the naso-ethmoidal region and nasopharynx. These approaches have demonstrated good oncological outcomes. In reconstructive surgery following radical parotidectomy, new techniques have emerged. Vascularized nerve grafts (VNGs), such as the radial forearm flap (RFF) and anterolateral thigh (ALT) flap, combined with facial nerve reconstruction, have shown potential in improving functional recovery. The use of the masseteric nerve for midface reanimation has gained popularity, providing faster and more reliable results. In some cases, a dual innervation approach combining masseteric nerve transfer and proximal facial nerve grafting may be employed. Single-stage reconstruction of complex defects after radical parotidectomy is now possible using innovative free flaps like the ALT with dual chimeric innervated vastus lateralis free flap and the thoracodorsal artery perforator and nerve flap (TAPN) flap. These flaps offer options for both skin or soft tissue reconstruction and facial nerve reconstruction, improving patient outcomes.[18]

NON-SURGICAL APPROACHES FOR SALIVARY GLAND TUMORS

Radiation Therapy (Radiotherapy):

- External Beam Radiation Therapy (EBRT): This approach involves precisely targeting the tumor with high-energy X-rays from outside the body. EBRT is a mainstay in treating salivary gland tumors, either as the primary treatment or as adjuvant therapy after surgery. It is particularly effective for tumors that are inoperable or located in challenging anatomical areas.
- Intensity-Modulated Radiation Therapy (IMRT): IMRT is a sophisticated form of EBRT that customizes the radiation beams to match the shape of the tumor. This precision allows for higher doses of radiation to be delivered to the tumor while minimizing exposure to nearby healthy tissues. IMRT is often employed when tumors are near critical structures like the optic nerves or brainstem.
- Proton Beam Therapy: This advanced radiation therapy utilizes protons, which have unique properties that enable precise targeting of the tumor. Proton therapy is especially valuable when treating tumors close to critical structures because it can reduce the risk of damaging surrounding healthy tissues.[19]

Chemotherapy

While chemotherapy is not typically the first-line treatment for salivary gland tumors, it may be considered in certain cases, especially for tumors that are not amenable to surgery or have metastasized to distant sites. Cisplatin is a platinum-based chemotherapy drug that is commonly used in combination with other agents. It works by interfering with the DNA inside cancer cells, preventing them from dividing and growing. Mitoxantrone is an anthracenedione chemotherapy drug. It works by inhibiting the DNA replication process in cancer cells, ultimately leading to cell death. Cyclophosphamide is an alkylating agent that interferes with the DNA of cancer cells, preventing them from growing and dividing. Paclitaxel is a taxane chemotherapy drug that stabilizes microtubules in cancer cells, inhibiting cell division and growth. Docetaxel is another taxane drug that functions similarly to paclitaxel, disrupting microtubules in cancer cells. Vinorelbine is a vinca alkaloid chemotherapy drug that inhibits cell division in cancer cells, leading to their destruction. Methotrexate is a chemotherapy drug that interferes with the growth of cancer cells by inhibiting the enzyme dihydrofolate reductase. It is used less frequently in the treatment of salivary gland tumors but may be considered in certain cases.[20,21]

Immunotherapy and Immune Checkpoint Inhibitors for Salivary Gland Cancer:

A crucial aspect of our immune system is its ability to distinguish between normal body cells and potential threats. To maintain this balance, the immune system uses specific proteins, often referred to as "checkpoints," to either activate or suppress immune responses. In cases of salivary gland cancer, these checkpoint proteins can be exploited by cancer cells to evade immune system attacks. Immunotherapy, specifically immune checkpoint inhibitors, is a form of treatment designed to counteract this evasion strategy. One notable class of immune checkpoint inhibitors targets the PD-1 protein, found on the surface of T cells in the immune system. PD-1 normally serves to prevent these immune cells from mistakenly attacking healthy cells within the body. Immune checkpoint inhibitors like Pembrolizumab (commercially known as Keytruda) work by blocking the PD-1 protein. As a result, these drugs enhance the immune response against cancer cells. This can lead to the shrinking of tumors or a slowdown in their growth. Pembrolizumab is one such drug that targets PD-1. It is considered an option for the treatment of advanced salivary gland cancers, particularly when other treatment methods have been attempted without success or when there are limited alternative treatment options available. It is essential to note that the effectiveness of Pembrolizumab may be influenced by the genetic characteristics of the cancer cells. In particular, this drug may be more suitable for cancers with a high tumor mutational burden (TMB-H), signifying the presence of numerous gene mutations within the cancer cells. Specialized testing can determine whether a patient's tumor exhibits these genetic changes. Pembrolizumab is administered through intravenous (IV) infusion and is typically given at intervals of every 3 to 6 weeks.[22]

Radiosensitizers:

Radiosensitizing drugs are substances that make cancer cells more sensitive to radiation therapy. By using radiosensitizers in combination with radiation treatment, the effectiveness of radiation can be enhanced. This approach can be particularly valuable in cases where the tumor has shown resistance to radiation alone.

CONCLUSION

Surgery remains the cornerstone of treatment for most salivary gland tumors, aiming to achieve complete resection with negative margins whenever possible. Advances in surgical techniques, including minimally invasive procedures like transoral robotic surgery (TORS), have expanded the options available to patients, reducing postoperative morbidity and improving functional outcomes. Radiation therapy, both as adjuvant treatment and primary therapy, plays a vital role in achieving local control, particularly in cases where complete surgical resection is challenging or impossible. Proton therapy offers precision in delivering radiation while minimizing damage to surrounding healthy tissue. Emerging targeted therapies and immunotherapies show promise in the treatment of recurrent or metastatic salivary gland tumors, providing new avenues of hope for patients with limited treatment options. In conclusion, while salivary gland tumors present diagnostic and therapeutic challenges, advances in surgical techniques, radiation therapy, and emerging treatment modalities offer renewed hope for patients. Early diagnosis, comprehensive evaluation, and individualized treatment plans remain essential in the quest to improve the prognosis and quality of life for those affected by salivary gland tumors.

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