Pediatric salivary gland malignancy: NCI experience

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Citation

ABSTRACT

Background: Salivary glands malignancies are not common among pediatric populations less than 16 years old. These tumors represent less than 10% of head and neck tumors among pediatric population. Pediatric parotid malignancies represent most of them with mucoepidermoid carcinoma as the most common malignant variant. Methods: This study is a retrospective cohort study included 32 pediatric patients with salivary glands lesions who were treated and followed up at the National cancer institute, Cairo University, from January 2008 to January 2018, The primary end point for this study is to present our institutional experience with the evaluation and management of pediatric major salivary glands malignant tumors, and to evaluate the incidence types, presentation, imaging characteristics, pathological features and treatment outcomes of pediatric major salivary glands malignant tumors. Results: The median age of the patients was 10 years old (range: 2 – 13 years), 13 cases (40.6%) were female and 19 cases (59.37%) were male, investigations were done for all patients in the form of radiological and pathological investigations; radiological workup was CT & MRI in 2 cases (6.25%), ultrasound & CT in 30 cases (93.75%); pathological workup was FNAC alone in 26 cases (81.25%), FNAC and true cut biopsy in 6 cases(due to inadequate FNAC) (18.75%), 14 cases (43.75%) were in the left parotid gland, 2 cases (6.25%) were in the left submandibular gland, 14 cases (43.75%) were in the right parotid gland and 2 cases (6.25%) were in the right submandibular gland. Pathological results: mucoepidermoid carcinoma in 19 cases (59.37%), adenoid cystic carcinoma in 4 cases (12.5%), Hodgkin lymphoma in 2 cases (6.25%), rhabdomyosarcoma (anaplastic variant) in 2 cases (6.25%), rhabdomyosarcoma (embryonal variant) in 4 cases (12.5%) and acinic cell carcinoma in 1 case (3.1%). Conclusion: Among 32 pediatric patients with malignant salivary neoplasms, parotid gland represented the most common site for these tumors (87.5%), mucoepidermoid carcinoma represented the most common variant (59.37%).

Keywords: Salivary glands malignancies, mucoepidermoid carcinoma, ultrasound, malignant tumors
1. INTRODUCTION
Salivary glands neoplasms are rare in children; these tumors represent about 3% of all head and neck tumors (Guzzo et al., 2006; Shapiro & Bhattacharyya, 2006), and less than 10% of pediatric head and neck tumors (Rahbar et al., 2006; Mehta & Willging, 2006). Pediatric salivary glands neoplasms represent about 5% of salivary glands tumors in general population (Guzzo et al., 2006; Shapiro & Bhattacharyya, 2006; Ellies et al., 2006). These tumors in pediatric age group are noticed to have inclination to affect female children more frequently especially between 10 and 18 years old (Shapiro & Bhattacharyya, 2006; Ethunandan et al., 2003). The parotid gland represents the most common location for these tumors in the pediatric population (Luna et al., 1991). The incidence of these tumors in the pediatric age group increases as they become older within the second decade of life (Ribeiro et al., 2002). The most common malignant pediatric parotid neoplasm is mucoepidermoid carcinoma, followed by Adenoid cystic carcinoma, Acinic cell carcinoma and rhabdomyosarcoma (Guzzo et al., 2006; Kupferman et al., 2010; Juneja et al., 2020). Surgery is the standard choice for treatment of pediatric salivary glands neoplasms. The principles of surgery vary according to pathological variant of tumor, size of tumor, local extension and neck metastases. The facial nerve is spared unless it is invaded (Castro et al., 1972). Adjuvant radiotherapy is considered in certain malignant cases such as positive surgical margins, persistent lymph node involvement, perineural invasion or high grade tumor. The risk of post-irradiation complications such as facial deformities, secondary malignancies, trismus and hyposialia should be considered (Bhide et al., 2009; Rebours et al., 2017). Neoadjuvant chemotherapy is indicated for malignant variants of parotid tumors which are rapidly progressing, recurrent, metastatic and non-resectable lesions (Goyal et al., 2015). Most of the studies in literature, addressing pediatric salivary glands neoplasms, are based on retrospective studies with small numbers of cases and case reports with none of them focusing on malignant neoplasms. Our goal of this study is to present our institution’s experience in evaluation and management of pediatric salivary glands malignant neoplasms with slightly larger number of cases, and focusing on factors and variables influencing disease free survival and loco-regional control.

2. METHODOLOGY
Medical records of 32 pediatric patients with major salivary glands lesions were reviewed and analyzed from January 2008 to January 2018; patients included in this study were patients less than 18 years old with parotid or submandibular lesions, patients excluded from this study were patients above 18 years old at presentation with parotid or submandibular lesion and those who presented with inflammatory lesions. The primary end point for this study is to present the experience of National cancer institute, Cairo University, in the evaluation and management of pediatric salivary gland malignancy, to evaluate the incidence, types, presentation, imaging characteristics, pathological features and treatment outcomes of pediatric salivary gland malignant lesions. The secondary end point for this study is to report disease free survival, loco-regional control and to assess postoperative complications.

Ethical issues
All patients signed consent forms by their parents before enrollment into the study along with the approval of the ethical committee. Subject identification and protection of confidentiality were assured as; Access to medical files was restricted to the individuals listed in this study, no reference of patients’ possible identifiers were included in the results, also no facial photography to be taken without obtaining patients consents on the medical photos.

Statistical methods
Data management and statistical analysis was performed using statistical package for social sciences (SPSS) vs.21. Numerical data was summarized using means and standard deviations or medians and ranges as appropriate. Categorical data was summarized as percentages.

3. RESULTS
The median age of the patients was 10 years old (range: 2 – 13 years) with mean age (8.906), 13 cases (40.6%) were female and 19 cases (59.37%) were male, all cases had negative family history for malignancy and negative past medical history for malignancy. Investigations were done for all patients in the form of radiological and pathological assessment; radiological investigations were CT and MRI in 2 cases (6.25%), ultrasound and CT were done in 30 cases (93.75%); pathological investigations were FNAC in 26 cases (81.25%), FNAC and true cut biopsy were done in 6 cases (18.75%). 14 cases (43.75%) were in the left parotid gland, 2 cases (6.25%) were in the right parotid gland and 2 cases (6.25%) were in the right submandibular gland. Pathological results; mucoepidermoid carcinoma in 19 cases (59.37%), adenoid cystic carcinoma in 4 cases...
(12.5%), Hodgkin lymphoma in 2 cases (6.25%), rhabdomyosarcoma (anaplastic variant) in 2 cases (6.25%), rhabdomyosarcoma (embryonal variant) in 4 cases (12.5%) and acinic cell carcinoma in 1 case (3.1%) table (1).

**Table 1** pathological variant of the salivary gland malignant neoplasms

<table>
<thead>
<tr>
<th>Pathological variant</th>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinic cell carcinoma</td>
<td>1</td>
<td>3.1 %</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>4</td>
<td>12.5 %</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>2</td>
<td>6.25 %</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>19</td>
<td>59.37 %</td>
</tr>
<tr>
<td>Rhabdomyosarcoma (anaplastic variant)</td>
<td>2</td>
<td>6.25 %</td>
</tr>
<tr>
<td>Rhabdomyosarcoma (embryonal variant)</td>
<td>4</td>
<td>12.5 %</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>100</td>
</tr>
</tbody>
</table>

19 cases (59.37%) were diagnosed as mucoepidermoid carcinoma, clinically 16 cases were staged as T2N0M0, 2 cases were T2N1M0 and one case was T1N0M0. Pathologically 15 cases were low grade and 4 cases were intermediate grade. 14 cases were treated via a surgical procedure of total parotidectomy with facial nerve preservation with ipsilateral extended supra-omohyoid neck dissection (levels 1, 2, 3 & 4) and among those 14 cases 4 cases were resected with positive surgical margins and 2 cases were resected with close surgical margins. 2 cases were treated via a surgical procedure of total parotidectomy with facial nerve preservation without neck dissection and both of them were resected with positive surgical margins. 3 cases were treated via a surgical procedure of submandibular sialadenectomy with ipsilateral extended supra-omohyoid neck dissection. Among 17 cases who underwent neck dissection 16 cases had negative lymph nodes (pathologically) and only one case had 5 positive lymph nodes over 24 lymph nodes dissected without capsular invasion (pathologically). All of the 19 cases didn’t receive adjuvant chemotherapy, 6 cases received adjuvant radiotherapy due to positive margins of resection in 5 cases and due to positive margins of resection and positive lymph nodes in one case. Among mucoepidermoid carcinoma cases during follow up period ranging from 2 years to 10 years with (mean value 4.947) and (median value 5); 6 cases had recurrence (table 2), 4 cases had nodal recurrence and they received adjuvant radiotherapy after the initial surgery and 2 cases had local recurrence and they didn’t receive adjuvant radiotherapy after the initial surgery, all of them underwent surgical treatment after the diagnosis of the recurrence and those with local recurrence received adjuvant radiotherapy, all of them had good response after the treatment of recurrence and are tumor free till now (figure 1).

![Survival Function](image)

**Figure 1** Graph illustrating disease free survival over years (survival function)

4 cases (12.5%) were diagnosed as adenoid cystic carcinoma, clinically 2 cases were staged as T2N0M0 and 2 cases were T1N0M0. Pathologically, 2 cases were low grade and 2 cases were high grade. 2 cases were treated via surgical procedure of superficial parotidectomy alone and two cases were treated via surgical procedure of total parotidectomy with facial nerve preservation with ipsilateral extended supra-omohyoid neck dissection. Among 2 cases that underwent neck dissection both of them had positive lymph nodes with capsular invasion (pathologically). All of the 4 cases didn’t receive adjuvant chemotherapy, 2 cases received adjuvant radiotherapy as they had positive lymph nodes and were high grade. Among adenoid cystic carcinoma cases
during follow up period ranging from 4 years to 10 years (mean value 6.5) and (median value 6), 2 cases had local recurrence within 2 years (as they were treated via superficial parotidectomy alone) and they underwent surgical resection of the recurrence (completion parotidectomy) and they are tumor free till now, 2 cases had metastatic recurrence to the lung within 2 years (high grade and positive LNs) and they received systemic chemotherapy after the diagnosis of the recurrence but with poor response and mortality occurred within 2 years from recurrence table. 6 cases (18.75%) were diagnosed as rhabdomyosarcoma, 2 cases were anaplastic variant and 4 cases were embryonal variant.

Among 2 cases of anaplastic rhabdomyosarcoma, clinically one case was staged as T2N1M0 and one case was T2N0M0, both cases received neoadjuvant chemotherapy followed by total parotidectomy with facial nerve preservation with ipsilateral extended supra-omohyoid neck dissection followed by adjuvant radiotherapy, pathologically both cases were high grade and had positive lymph nodes with capsular invasion, during follow up period between 3 years and 4 years both cases had metastatic recurrence to the lung within the second year table (2), both cases received systemic chemotherapy with poor response and mortality occurred within 1 year from recurrence for one case and within 2 years from recurrence for the other.

Table 2 Work up and management for recurrent cases

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Count</th>
<th>Column N</th>
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<tbody>
<tr>
<td>CT chest &amp; PET scan</td>
<td>2</td>
<td>16.7%</td>
</tr>
<tr>
<td>CT neck, CT chest &amp; bone scan</td>
<td>4</td>
<td>33.3%</td>
</tr>
<tr>
<td>MRI neck</td>
<td>4</td>
<td>33.3%</td>
</tr>
<tr>
<td>Ultrasound &amp; CT</td>
<td>2</td>
<td>16.7%</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>100.0%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
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<th>Count</th>
<th>Column N</th>
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<tr>
<td>FNAC</td>
<td>8</td>
<td>66.7%</td>
</tr>
<tr>
<td>None</td>
<td>4</td>
<td>33.3%</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade of recurrence</th>
<th>Count</th>
<th>Column N</th>
</tr>
</thead>
<tbody>
<tr>
<td>grade 2</td>
<td>2</td>
<td>16.7%</td>
</tr>
<tr>
<td>low grade</td>
<td>4</td>
<td>33.3%</td>
</tr>
<tr>
<td>not documented</td>
<td>6</td>
<td>50.0%</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage of recurrence</th>
<th>Count</th>
<th>Column N</th>
</tr>
</thead>
<tbody>
<tr>
<td>not documented</td>
<td>8</td>
<td>66.7%</td>
</tr>
<tr>
<td>metastatic recurrence</td>
<td>4</td>
<td>33.3%</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrence &amp; site of recurrence</th>
<th>Count</th>
<th>Column N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>4</td>
<td>12.5%</td>
</tr>
<tr>
<td>Lung (metastatic recurrence)</td>
<td>5</td>
<td>15.6%</td>
</tr>
<tr>
<td>Nodal</td>
<td>4</td>
<td>12.5%</td>
</tr>
<tr>
<td>None</td>
<td>20</td>
<td>62.5%</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Among 4 cases of embryonal rhabdomyosarcoma, clinically two cases were staged as T1N0M0, one case was T2N1M0 and one case was T3N0M0, two cases received neoadjuvant chemotherapy followed by total parotidectomy with facial nerve preservation with ipsilateral extended supra-omohyoid neck dissection Fig. (2) followed by adjuvant radiotherapy (due to positive LNs with capsular invasion) and two cases didn’t receive chemotherapy and were treated via primary surgery in the form of total parotidectomy with facial nerve preservation with ipsilateral extended supra-omohyoid neck dissection followed by adjuvant radiotherapy (due to close margins), pathologically 2 cases were low grade and had negative lymph nodes and with close negative resection margins while the other 2 cases were high grade and had positive lymph nodes with capsular invasion, during follow up period ranging from 3 years to 6 years (mean value 4.5) and (median value 4.5) one case was free of disease but lost follow up after 3 years, one case had metastatic recurrence to lung within 3rd year of follow up and received systemic chemotherapy with poor response and mortality occurred within one year of the recurrence and 2 cases were free of disease till now table (2). 2 cases (6.25%) were diagnosed as Hodgkin lymphoma, both cases did superficial parotidectomy as a diagnostic procedure and received systemic chemotherapy as a primary treatment with good response and during follow up period ranging from 4 years to 6 years both cases were disease free till now. One case (3.1%) was diagnosed as acinic cell carcinoma, clinically was staged as T2N0M0 and was treated...
via surgical procedure of submandibular sialadenectomy with ipsilateral extended supra-omohyoid neck dissection and didn’t receive either chemotherapy or radiotherapy, pathologically was low grade and had negative lymph nodes, during follow up period of 7 years the case was disease free. No major complications were reported following the management of all of our cases.

Figure 2 Female child with left parotid embryonal rhabdomyosarcoma post neoadjuvant chemotherapy, (A,B&C); preoperative images, D; radiological image via CT scan, E; intraoperative image after positioning, F; intraoperative image after total parotidectomy with facial nerve preservation with resection of the left jugulo-diagatric LN level 2B.

4. DISCUSSION

Pediatric salivary glands neoplasms are rare; they represent less than 5% of all salivary glandstumors (Bradley et al., 2007). Till now, a limited number of studies have addressed pediatric salivary glands neoplasms, and were defective in assessing the behavior and prognosis of these tumors. Most of these literatures states that about 80% of pediatric salivary glands neoplasms are benign (Orvidas et al., 2000). Liu et al. (2012), reported that pediatric salivary glands malignancy represent about 35% of all pediatric salivary gland neoplasms, with mucoepidermoid carcinoma was the most common malignant variant. Xu et al. (2017) reported that the malignant lesions of pediatric parotid neoplasms represent 67% and occur mainly in the second decade of life. Our study focused on pediatric salivary glands malignancy, and on our experience regarding the evaluation and management of pediatric salivary glands malignancy. We aimed to evaluate the incidence, types, presentation, imaging characteristics, pathological features, treatment outcomes, disease free survival, loco-regional control and postoperative complications. The parotid gland is involved in up to 90% of all pediatric salivary glands tumors, and 50% of these tumors are malignant (Bradley, 2001). In our study, 87.5% of pediatric salivary glands malignant lesions were in the parotid gland while 12.5% were in the submandibular gland. Mucoepidermoid carcinoma is the most common salivary glands malignancy in children, accounting for 50% of malignant salivary glands tumors (Hicks & Flaitz, 2000).

Our study showed that 59.37% of cases were diagnosed as mucoepidermoid carcinoma. Xu et al. (2017) reported that the majority (about 84%) of mucoepidermoid carcinoma were intermediate grade as opposed to the less frequent low and high grade lesions. According to our study; about 79% of mucoepidermoid carcinoma lesions were low grade, 21% were intermediate grade, and with no cases of high grade pathology. Many studies reported that 5 years overall survival rate for pediatric parotid mucoepidermoid carcinoma was between 95% and: 100% (Xu et al., 2017; Ryan et al., 2011; Techavichit et al., 2016). Our study demonstrated that 5 years overall survival rate for pediatric parotid mucoepidermoid carcinoma was 100%, and 5 years disease free survival rate was 68.4% Fig. (1). Ryan et al. highlighted that mucoepidermoid carcinoma tends to have lymph node metastases and usually presents with advanced stage (Ryan et al., 2011). In our study, 17 cases (89.4%) of mucoepidermoid carcinoma cases underwent neck dissection; only one case had positive lymph nodes without capsular invasion. It is worth mentioning that all our cases were in early stage. Total parotidectomy was the procedure for choice for mucoepidermoid carcinoma (Orvidas et al., 2000).

Regarding cases of mucoepidermoid carcinoma in our series; surgery was the primary line of treatment. Total parotidectomy with facial nerve preservation was done in 16 cases, 3 cases were treated with submandibular sialadenectomy. Supraomohyoid neck dissection was done in 17 cases (89.4%) of all mucoepidermoid carcinoma patients. Adjuvant radiotherapy still remains debatable question for patients with mucoepidermoid carcinoma with lack of consensus regarding certain indications, and with reported side effects including radiation-induced malignancies and impediment of bone growth (Bhide et al., 2009). In our study, 6 cases with...
mucoepidermoid carcinoma received adjuvant RTH due to positive margins of resection in 5 cases, and due to positive margins of resection and positive lymph nodes in one case. Although adjuvant radiotherapy still arguable, review and analysis of literature showed that acinar cell carcinoma and adenoid cystic carcinoma are treated usually with adjuvant radiotherapy after surgery as the primary treatment (Byers et al., 1984). Our study included 4 cases with adenoid cystic carcinoma treated by surgery as the primary line of management, and 2 of them received adjuvant radiotherapy as they had positive lymph nodes and were high grade. One case was diagnosed as low grade acinic cell carcinoma; surgery was the primary line of treatment without adjuvant therapy.

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children. The head and neck region constitutes 40% of cases. In patients with localized disease, overall 5-year survival rates have improved to more than 80% with the combined use of surgery, radiation therapy, and chemotherapy. Embryonal variant is the most common variant occurring in head and neck region (Punyko et al., 2005). Our study included 6 cases (18.75%) which were diagnosed as rhabdomyosarcoma, 2 cases were anaplastic variant and 4 cases were embryonal variant. There were 4 cases which were treated via multimodality therapy; neoadjuvant CTH followed by surgery then adjuvant RTH, and 2 cases (T1 lesions) were treated via primary surgery then adjuvant RTH without neoadjuvant CTH. Poor prognosis to the anaplastic variant was noticed with metastatic disease within the second year of follow up, and a relative good prognosis to the embryonal variant with 5 years overall survival 75% and 5 years disease free survival 50% Fig. (1). Due to high incidence of pediatric salivary glands malignancies that can respond to neoadjuvant chemotherapy (8 cases: 25% in our study), we recommend mandatory preoperative pathology by guided FNAC or True cut whichever more appropriate.

5. CONCLUSION
Among 32 pediatric patients with malignant salivary neoplasms, parotid gland was representing the most common site for these tumors (87.5%); mucoepidermoid carcinoma was representing the most common variant (59.37%), preoperative pathological diagnosis of rhabdomyosarcoma is essential to start neoadjuvant chemotherapy before surgery.

Acknowledgement
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Author Contributions
Abdalwahab R. Abdalwahab: first author, corresponding author and writing paper.
Ghobrial R.E: plagiarism revision and English editing.
Mai Gad: data collection and plagiarism revision.
Mamdouh Mahmoud Mostafa, Reham Mohamed Gamal & Mostafa Selim: data collection.
Mohamed H. Zedan: senior author and statistical analysis.

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Conflict of Interest
The author declares that they have no conflict of interest.

Informed consent
Written informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval for study protocol /study design /Methodology
The study was approved by the institutional review board of Medical Ethics Committee of Cairo University (ethical approval code: 201819027.4).

Data and materials availability
All data associated with this study are present in the paper.
REFERENCES AND NOTES


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