The Role of Radiation Therapy in Pediatric Mucoepidermoid Carcinomas of the Salivary Glands

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Objective To investigate the role of radiation therapy in rare salivary gland pediatric mucoepidermoid carcinoma (MEC).

Study design A French multicenter retrospective study (level of evidence 4) of children/adolescents treated for MEC between 1980 and 2010 was conducted.

Results Median age of the 38 patients was 14 years. Parotid subsite, low-grade, and early primary stage tumors were encountered in 81%, 82%, and 68% of cases, respectively. All except 1 patient were treated by tumoral surgical excision, and 53% by neck dissection (80% of high grades). Postoperative radiation therapy and chemotherapy were performed in 29% and 11% of cases. With a median 62-month follow-up, overall survival and local control rates were 95% and 84%, respectively. There was 1 nodal relapse. Lower grade and early stage tumors had better survival. Postoperative radiation therapy and chemotherapy were associated with similar local rates. Patients with or without prior cancer had similar outcomes.

Conclusions Pediatric salivary gland MEC carries a good prognosis. Low-intermediate grade, early-stage tumors should be treated with surgery alone. Neck dissection should be performed in high-grade tumors. Radiation therapy should be proposed for high grade and/or advanced primary stage MEC. For high-grade tumors without massive neck involvement, irradiation volumes may be limited to the primary area, given the risk of long-term side effects of radiation therapy in children. Pediatric MEC as second cancers retain a similar prognosis. Long-term follow-up is needed to assess late side effects and second cancers. *(J Pediatr 2013;162:839-43)*.

According to the Surveillance, Epidemiology, and End Results public-access database, the annual incidence of salivary gland tumor (SGT) between 1973 and 2006 was 0.8 and 15 per million in children/adolescents younger than 20 years old and adults, corresponding to 0.5% of all pediatric tumors and 0.3% in adults, respectively. The clinical characteristics in children differ somewhat from those seen in their adult counterparts.[1] In particular, a firm mass in the territory of a salivary gland is 2.5-fold more likely to be malignant that in adults (ie, corresponds to malignancy in 50% of SGT in children[2,3] vs 20% in adults). Salivary gland carcinomas are exceedingly rare below age 10 years; median age is between 11 and 14 years.[1,2,4] The parotid gland seems to be the most common site of origin and almost three-fourths of the tumors are localized (confined to gland/duct of origin) with regional nodal involvement in only 10% of cases and well to moderately differentiated (grade I and II) in the majority of cases. Main risk factors include previous radiation exposure[5] and a history of cancer.[6] Noteworthy, a history of cancer may indeed be associated with a genetic predisposition to cancer, which makes irradiation accountability uncertain. Only few pediatric single-epithelial SGT histology series have been reported so far.[7] Mucoepidermoid carcinoma (MEC) seem to be the most common histology in children[7-9] as they represent 49% of pediatric cases versus 24% of adult salivary gland carcinomas.[8] Pediatric MEC have 5-year survival rates approaching 95%.[4,7] The paucity of available data on rare pediatric tumors limits the development of tailored treatment guidelines; therefore, pediatric oncologists and surgeons must follow

MEC	Mucoepidermoid carcinoma
OS	Overall survival
PNI	Perineural invasion
SGT	Salivary gland tumor
VE	Vascular emboli

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adult recommendations. However, there may be some specific pediatric treatment issues as radiotherapy is associated with a risk of craniofacial growth defect and both radiotherapy and chemotherapy may be associated with an increased risk of secondary cancer in children.

We aimed to define the impact of radiotherapy on the local and regional control of salivary gland MEC and, secondarily, the prognostic factors for local, regional, and distant failure.

Methods

We performed a multicenter (34 French pediatric oncology departments) retrospective study of salivary gland MEC in patients younger than 20 years old. Data (patient characteristics, disease characteristics, treatment modalities, and outcomes) were collected for 38 children/adolescents treated between 1980 and 2010 in 6 departments among the 34 that were questioned. The study approved by each institutions' review board. The diagnosis of MEC was made on histologic examination. When MEC occurred as a secondary cancer, the tumor and treatment characteristics for the original cancer were also recorded. Local spread of the tumors was assessed by ultrasound, computerized tomography, or magnetic resonance imaging, and none were metastatic on chest radiograph. Tumors were staged according to the TNM-classification of malignant tumors of the 2007 International Union against Cancer and graded using pathologic grading criteria established by Batsakis et al[10] for MEC. As no international therapeutic recommendations exist, management of these patients was based on a case by case approach according to physician decision. The recommendations of the Reseau d'Expertise Français des Cancers ORL Rares established in 2009 were the basis for the discussion on treatment management. Radiotherapy was 2D in the earlier years of the study and conformal thereafter. Radiation was unilateral in all cases using photons and electrons, or photons alone.

Statistical Analyses

Statistical analysis was done using SPSS version 17 (SPSS Inc, Chicago, Illinois). Overall survival (OS) curves were calculated by the Kaplan-Meier method to show the cumulative survival probability of an individual remaining free of the end point (death or recurrence) at any time from diagnosis to the date last seen. The non-parametric log-rank test was used to test the null hypothesis of no differences in survival times between the groups being studied and a two tailed P value <.05 was considered significant in all tests. ORs were used to test for the associations between the outcomes of interest (local recurrence) and possible categorical risk factors. Fisher exact test was used to test the null hypothesis of no difference between proportions of compared groups.

Results

This study enrolled 38 patients, of whom 55% were males. Table I summarizes the patient and disease characteristics. Ages ranged from 4-18 year with a median age of 14 year.

Table I. Patient and disease characteristics in patients undergoing radiotherapy for MEC or not

	Radiotherapy (n = 11)	No radiotherapy (n = 27)
Male/female	7/4	14/13
Age range (mean)	9-18 y (14.9)	4-18 y (12.9)
Parotid/submandibular or minor salivary gland	8/3	23/4
Past history of cancer*: yes/no	3/8	10/8
Previous cancer: yes	3	10
Acute lymphoblastic leukemia	1	3
Hodgkin/non-Hodgkin lymphoma	0/0	2/2
Medulloblastoma	1	1
Bilateral retinoblastoma	0	1
Rhabdomyosarcoma	0	1
Astrocytoma	1	0
Past history of radiation therapy: yes/no	2/9	7/20
T stage: T1/2/T3/4	6/5	25/2
Node status: N0/N1	6/5	27/0
Pathological grade 1/grade 2/3	6/5	20/7
Complete gross excision (R0)*: yes/no	8/3	20/5
Neck node excision*: yes/no	8/3	12/14
Nerve sacrifice*: yes/no	2/9	1/23
Extra capsular spread*: yes/no	5/6	9/16
PNI*: yes/no	1/5	2/12
Vascular invasion*: yes/no	1/5	1/13
Bone invasion*: yes/no	1/10	0/24
Chemotherapy given: yes/no	4/7	0/27
Local recurrence: yes/no	1/10	5/22
Follow-up range in months (mean)	3-109 (40.4)	1-339 (86.5)

R0, complete resection; *T*, primary stage according to the International Union against Cancer/American Joint Committee on Cancer 2007 classification.
*Data missing for some patients and does not add up to total.

Thirty-one of them originated from Eastern Europe, 3 were from Maghreb, and 4 from Africa. One child had a velocardiofacial chromosome 22q11 deletion syndrome. Most of the tumors arose in the parotid gland (81%); 76% affected the superficial lobe. A history of various cancers, mainly hematological malignancies (8/13 patients), and radiotherapy in the head and neck region was found in 34% and 24% respectively. Stage T1/2, N1, and grade 1 were found in 82%, 14%, and 68% of cases, respectively. No patient had distant metastasis. Treatment was by surgical resection in all but 1 (97%) who had relapsed medulloblastoma concurrent with the diagnosis of MEC. Unilateral neck node dissection (levels 1-3) was carried out in 53% of cases. Facial nerve involvement and section was present in 11%. Post operative pathology demonstrated perineural, vascular and, bone invasion in 11%, 5%, and 3% of cases, respectively. MEC as first cancer presented with more advanced clinical stages (stage 1-2 vs stage 3-4) (P = .03) than MEC as a second cancer.

Adjuvant Treatments

Concomitant, adjuvant, and neoadjuvant cisplatinum-based chemotherapy was given in 11% of patients due to node-positive disease (2 patients), T4 status with grade 3 (1 patient), and T4 status with marginal surgical excision (1 patient). Post-operative radiotherapy was given in 11 patients (29%) in whom 2 patients had previously been irradiated for a previous cancer, with radiation fields including the head and neck region. The doses of radiotherapy ranged