Adenoid cystic carcinoma of the head and neck: a review

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Purpose of review

This purpose of this article is to review and provide an update of current publications on the evaluation and management of adenoid cystic carcinoma.

Recent findings

Adenoid cystic carcinoma is an uncommon salivary gland malignancy that presents insidiously and is generally advanced when diagnosed. Current effective treatment modalities include surgery and irradiation, but locoregional recurrences are frequent and may present as early as 2 years. Patients survive with recurrent and metastatic disease for several years despite not being offered any treatment. Molecular analysis of the tumors is being undertaken, with optimistic results capable of selecting high-risk patients who may benefit from adjuvant treatment such as chemotherapy

Summary

Little progress has been made in advancing "curative" treatment of adenoid cystic carcinoma of the head and neck. The disease is said to have a fatal outcome. The time is now opportune for a multicenter, randomized, controlled trial to identify patients who would benefit from adjuvant radiotherapy and/or chemotherapy in the control of locoregional recurrences and the prevention of distant metastases.

Introduction

Adenoid cystic carcinoma (ACC) was first described by three Frenchmen (Robin, Lorain, and Laboulbene) in two articles published in 1853 and 1854[1]. It was they who described the cylindrical appearance of this tumor. Many articles since then have remarked that Billroth, in 1859, first described ACC under the name cylindroma, but it was he who described that ACC had a "great tendency to recur." Spies [2], in 1930, is credited with the term adenoid cystic carcinoma, in a discussion of tumors, cutaneous and noncutaneous, of the basal cell variety. The early history of this tumor, and the numerous different names given, has been reviewed by Tauxe et al. [3].

It was through the major work of Foote and Frazell [4] that an accepted classification of salivary tumors was proposed. It was they who described that adenoid cystic tumors were located in the major and minor salivary glands, they who recorded that the tumors were usually small with an incomplete capsule, and they who recorded the variations in histology that had a propensity to perineural spread. It was they who suggested that the low cure rates reflected "a relatively conservative surgical approach," and expected that a more radical surgical treatment could show considerable improvement. It is currently recognized that ACC remains an extremely difficult disease to treat. It was described by Conley and Dingman [5], as "one of the most biologically destructive and unpredictable tumors of the head and neck." It has a high, almost inevitable, predisposition to recur if a patient lives long enough, and this occurs even when radical excision has been performed [6]. In the past, radical or superradical surgery was advocated for curative intent, but it gradually became apparent that this may not improve survival and may not even reduce local recurrence rates compared with a more conservative surgical approach and postoperative radiotherapy [7-9].

Location

ACC accounts for approximately 10% of all neoplasms of the salivary glands. The parotid gland is the single most common site of origin (25%) in the head and neck. Most ACCs arise in the minor salivary glands (60%). ACC of minor salivary gland origin occurs most frequently in the oral cavity (palate). ACCs arising from the minor salivary glands are often advanced at the time of diagnosis, and complete excision is limited by their large size (with perineural extension involving the cranial base) and the proximity of the tumor to important neural and vascular structures.

Clinical behavior

The clinical behavior of ACC is a paradox: First, tumor growth is slow, but its clinical course is relentless and progressive. Second, operative intervention is usually feasible, but multiple local recurrences are the rule. Third, metastatic spread to regional lymph nodes is uncommon, but distant spread to the lungs and bones is frequent. And fourth, 5-year survival rates are optimistically high, but 10- to 20-year survival rates are dismally low [10]. Tumor stage is considered the most reliable indicator of overall outcome [11], but some authors have emphasized the importance of histologic subtyping. There is a strong positive correlation between site of origin and prognosis. The more favorable outcome with major (relative to minor) salivary gland ACC is attributed to the earlier discovery of the neoplasm at these more accessible locations. It has been reported that ACC of the nasal cavity and paranasal sinuses has a worse prognosis than in any other area of the head and neck region [12,13].

Histopathology

Histologically, ACC can be categorized into three growth patterns: cribriform, tubular, and solid. In most studies, a solid growth pattern is associated with a worse prognosis, caused by advanced stage and development of distant metastases [9,10]. A unique feature of ACC is the propensity for perineural invasion, even with early-stage tumors. Tumor is graded according to Szanto et al. [14], cribriform or tubular (grade I), less than 30% solid (grade II), or greater than 30% solid (grade III). In patients treated by similar modalities, the cribriform and tubular variants of ACC demonstrated no difference in the rate of distant metastases and overall survival. The cribriform variant demonstrated a significantly worse prognosis in terms of local recurrence rate. The patients who had a solid histologic pattern of ACC appeared to have an overall worse prognosis in terms of distant metastases and long-term survival [15]. The use of fine-needle aspiration biopsy is widely accepted in the diagnostic procedure of head and neck lesions. The cytologic typing of ACC is feasible in most cases by the finding of large globules of extracellular matrix, partially surrounded by basaloid tumor cells, but lacking characteristic globules [16]. However, one needs to be wary that the pleomorphic adenoma is the most frequent other salivary tumor confused when ACC is being considered on fine-needle aspiration.

Molecular analysis

Prognosis of ACC has been reported on histologic subtypes, presence of tumor at the surgical margins, anatomic site, and metastases, but none of these parameters has proved to be an unequivocal predictor of disease activity. The use of immunohistocytochemistry, and the staining pattern of p53, bcl-2, P-glycoprotein, glutathione Stransferase, and topoisomerase, as well as sequencing analysis of p53, because of their proved association with poor prognosis and therapy resistance, have been analyzed [17]. These results have demonstrated that p53 alteration is an independent prognostic marker and that proteins known for their association with radio- and chemotherapy resistance can be overexpressed in some ACCs, suggesting that those molecules could influence the outcome of new therapeutic approaches. ACC is known to have aggressive

tumor behavior by its ability to invade and metastasize. One such factor regulating these functions is the urokinase-type plasminogen activator and its receptor. The urokinase-type plasminogen activator receptor participates in several normal cellular processes but also influences tumor invasion and metastasis by facilitating the destruction of extracellular matrices. Clinically, cellular expression of urokinase-type plasminogen activator receptor denotes a worse prognosis for many malignancies. So far, studies of skull base ACC urokinase-type plasminogen activator receptor expression seem to be a negative prognostic factor [18]. Other factors studies showing some preliminary usefulness include the proliferating cell nuclear antigen and c-erbB-2 oncoprotein expression [19], the transmembrane tyrosine kinase receptor c-kit (CD117) [20], and the intercellular adhesion molecule-1 [21]. However, there is still a need to identify those patients who have a more aggressive ACC disease to identify them for more novel and possibly experimental therapeutic regimens. Surgical anatomy ACC is thought to arise from the mucous-secreting glands. It arises specifically from the intercalated ducts, and electron microscopy shows that it arises from cells that can differentiate into epithelial and myoepithelial cells. These mucus-secreting tumors are confined to structures derived from the foregut (that is, the parotid, submandibular, and sublingual glands, and the mucus glands throughout the upper respiratory tract). Palatal glands are not found in the midline or anterior to a line between the first molar teeth, nor on the gingiva. There are approximately 250 glands on the hard palate, 100 on the soft palate, and 10 on the uvula. These glands are also associated with the larynx (supraglottis and subglottis), as 128 Head and neck oncology well as the nasal and nasopharynx oropharynx (tonsil and posterior tongue) [6].

Treatment

The optimal therapy for ACC of the head and neck has not been established. The choice of therapy is affected by site, stage, histologic grade, and biologic behavior of the ACC. There are a number of publications that address the efficiency of surgery and radiation therapy in the treatment of ACC of the head and neck. Most ACCs arising in major salivary glands are treated surgically, with the possible addition of adjunctive radiotherapy. Parotid ACC should be treated by preservation of the facial nerve if not paralyzed preoperatively and not involved intimately by tumors at the time of surgery, followed by postoperative radiotherapy [22]. Submandibular ACC should be treated by a supraomohyoid neck dissection followed by postoperative radiotherapy [23]. ACC of the minor salivary glands should be treated by local radical excision and postoperative radiotherapy [23]. Although local recurrence appears to be decreased, a survival benefit has not been demonstrated [13]. Pathologic findings correlated with local recurrence rates, and positive resection margins were significantly associated with an increased risk of local recurrence. In patients who receive postoperative radiation therapy, an improved outcome is observed with radical surgery compared with biopsy alone.

Chemotherapy currently is seeking a role in the management of advanced and metastatic salivary gland tumors. There is a need for biomarkers that will allow for better identification of the cohort at greatest risk of distant dissemination to make this approach cost-effective [8].

Adenoid cystic carcinoma of the skull base

ACC of the paranasal sinuses and the nasopharynx has attracted considerable amount of publications with the advent of safer techniques used in skull base surgery [24-29]. The principles of combined surgery and radiation therapy are considered the accepted standard of care for minor salivary gland malignancies, and these principles can be applied to ACCs

presenting in this area. However, the results of these new surgical technique have not resulted in an overall improvement in diseasefree survival in patients with skull base ACC [28]. Surgery appears to be palliative in most patients treated in this way with advanced skull base ACC. Thus, the morbidity of surgery needs to be tempered by this fact, with consideration given to the preservation of the functioning major neurovascular structures involved with the tumor [24]. ACC presenting or developing cervical lymph node metastases is very uncommon, and is associated almost exclusively with submandibular gland disease, and surgery for nodal disease has had little impact on overall patient survival [30].

The use of irradiation therapy

A good response is usually seen initially with photon irradiation therapy alone and most tumors will recur locally with time [31]. The best results have been obtained with the combination of radical surgery and radiation therapy. Unfortunately, there are no randomized trials that prove the value of adjunctive radiation therapy or determine which subgroups of patients are most likely to benefit [13]. Radiation, usually in doses or 60 Gy or more, may be of benefit when there is minimal residual microscopic disease. It is likely that there is frequently unrecognized perineural invasion in specimens with "negative" margins that would have benefited from the addition of radiation therapy. Therefore the use of postoperative radiotherapy has been advocated by most clinical practices to ensure locoregional control at a minimum The routine use of radiotherapy is advocated when patients are inoperable or refuse surgical treatment, in those with advanced operated tumors, or in those with distant metastases, as well as in those patients with histologically positive margins [32].

The use of fast neutron irradiation seems to have a better response to photon beam therapy because of the higher relative biologic effectiveness of neutron radiation [33,34•]. The conclusion of studies is that neutron radiotherapy is an effective treatment, compared with neutron irradiation, for patients with gross residual disease, and achieves excellent locoregional control in patients without evidence of gross disease [35].

Recurrent disease

Reports have shown that patients with ACC arising from sites in proximity to the cranial base (nasopharynx, nasal cavity, and maxilla) have a significantly increased risk of local recurrence. This is related to the difficulty of securing clear resection margins at the cranial base because of technical difficulties associated with the surgery, intracranial extension of the tumor along nerves, and restrictions on the limits of resection caused by the proximity of critical neural and vascular structures. The use of the gamma knife has been recommended for use in the treatment of recurrent salivary gland tumors involving the skull base, using a median radiosurgery dose of 15 Gy. Most patients reported an excellent symptomatic response, such as decrease in headaches or facial pain. Further repeated radiosurgery has successfully salvaged some patients previously treated [36•]. Hadad et al. [37] demonstrated that positive surgical margins are a strong predictor of poor patient outcome, and Horiuchi et al. [38] showed that radiation therapy is less effective for the treatment of macroscopic residual disease compared with microscopic disease. Pathologic findings also correlate with local recurrence rates: Positive resection margins are ACC of the head and neck Bradley 129 associated significantly with an increased risk of local recurrence, tumors located close to the cranial base and tumor grade, an increased solid component is associated with increased risk of local recurrence. Grade I tumors has also been associated with early recurrence (>1 year) and an earlier risk for development of distant metastases [15].

The pathologic detection of positive resection margins and perineural invasion for ACC may vary greatly depending on the extent of sampling of the specimen and the enthusiasm of the histopathologist.

Distant metastases

Clinicians are all too aware that distant metastases often defeat successful treatment of patients with ACC, despite locoregional control, and are associated with a low long-term survival rate. The incidence of distant metastasis in ACC, most often the lung, is difficult to estimate, but is certainly dependent on the length of time that patients are followed, usually more than 15 to 20 years, but ranges from 35 to 50% [39]. Spiro [40] suggests that that the incidence of other sites being involved by distant metastasis is likely to be more common, because once lung metastases are detected, no further metastatic investigations are performed. The average time in a series of patients in Japan between detecting lung metastases and death was 32.3 months, and between the occurrence of metastases elsewhere and death was 20.6 months [41]. Kim et al. [42] evaluated the survival of patients in Korea with ACC with distant metastases and observed a 3-year survival rate of 41.3%, which declined to 15.5% at 5 years. Thoracotomy to excise solitary salivary malignant lung metastases may be worthwhile when the salivary histology is low grade and the disease-free interval from treatment of the primary and detection of the metastasis is measured in years. In particular, metastasectomy for ACC would seem to be highly questionable [8] and, because of the anticipated long survival in months with metastases, it has been suggested that a comparison be made of matched patients whose lung metastases have been excised with control subjects. Past experience indicates that solitary pulmonary metastases are quite unusual in these patients, and it is recognized that some metastatic lesions remain relatively stable for more than 10 years [40]. However, there are advocates for lung resection of ACC metastases who report good-quality survival, with an estimated 5-year survival rate of 84%, which continued to decline until there were no survivors after 14years [43]. An analysis of tumor doubling time of pulmonary metastases showed that metastatic deposits of ACC occurred at 86 to 1064days (average, 393 days), and the time of onset of pulmonary metastases was calculated to be much earlier (average, 227 months) before the first visit [44]. This suggests that the use of an annual chest radiograph at follow-up is not sensitive in making an early diagnosis, and rather supports the use of CT [45]. However, there is the dilemma of what useful treatment can be offered to patients who are diagnosed with lung metastases. It has been suggested that the use of chemotherapy preoperatively and/or postoperatively to reduce the incidence of distant metastases may have a role in improving patients' disease-free survival. The larger the tumor at presentation and the development of locoregional treatment failure are the two factors most predictive of distant metastases. It has been recorded that when bony metastases occur, especially in the spine, the course of disease is usually rapidly fulminant [46]. Median survival times after appearance of distant metastases among patients with isolated lung metastases and those with bone metastases with or without lung involvement were 54 and 21 months respectively [47•].

Reporting of outcomes

Most authors report patient outcome as overall survival rather than as a recurrence rate or disease-free survival. This is misleading because there is prolonged survival in many patients with residual or recurrent ACC. Despite local aggressive therapy, the majority of patients (60%) will develop recurrent disease. Approximately 50% of recurrences are clinically evident within 2 years after surgery and radiotherapy [12]. Ellis et al. [48] noted an average time to recurrence of 67 months, and Simpson et al. [49] noted a median time to recurrence of 54 months. In contrast,

Vikram et al. [50] demonstrated recurrence in half of their patients within 18 months. It is seldom stated, in most reported series, how patients are monitored after treatment, how recurrences are identified, and what treatment (if any) is offered on diagnosis. It has been suggested that one may question the benefit of long-term follow-up of a patient after surgical removal of an ACC other than for clinical curiosity [41]. It is also often stated that long-term follow-up is necessary to detect recurrent disease in patients with ACC. The routine use of radiologic examinations (especially MRI) during the postoperative period may identify changes indicative of recurrent disease months to years before it is clinically evident. It remains to be reported that early detection of recurrent disease will result in any useful or effective treatment that will result in any patient survival benefit.

Conclusion

The current therapies available for the management of patients with ACC is inadequate to achieve local control predictably by the aggressive strategy of surgery and irradiation therapy. It is unlikely that more aggressive surgery is feasible or beneficial to patients nor to result in a
 significant improvement on their quantity or quality survival. There is a need for a controlled, randomized study of patients with ACC of the head and neck to identify high-risk patients (who may develop locoregional recurrence), to address the effects of postoperative radiation therapy, and to define those groups of patients who should receive adjunctive photon or neutron irradiation and/or chemotherapy. The high incidence of local recurrences (within 2 to 3 years) suggests that such a therapeutic trial could be designed to detect a difference in local control, without the need for an extended period of observation. Currently, and until such a multicenter, randomized trail has been conducted, it seems prudent to recommend adjunctive radiation therapy for all patients with ACC, especially for those at increased risk for local recurrence, patients with tumor in proximity to the cranial base, tumors with positive resection margins, and tumors with a histologic solid growth pattern.

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