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Review

Current thinking in the management of adenoid cystic carcinoma of the head and neck

Montey Garg *, Ben Tudor-Green, Brian Bisase

Department of Oral and Maxillofacial Surgery, Queen Victoria Hospital NHS Foundation Trust, Holtye Road, East Grinstead, RH19 3DZ

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Abstract

Adenoid cystic carcinoma (ACC) is an aggressive, rare, malignant tumour that accounts for about 1% of all head and neck neoplasms and 10% of all salivary gland tumours. It is characterised by frequent local recurrences and distant metastases. Growth is slow but relentless, and progression poses a challenge to head and neck clinicians. Many small retrospective studies have described its clinical management, but the lack of multicentre, randomised, controlled trials has resulted in inconsistencies in management globally. We have focused on three key management-related controversies: the role of elective neck dissection (END) for the N0 neck; the role of adjuvant treatment or radiotherapy; and finally, the follow-up protocol, particularly cross-sectional surveillance imaging of the full body or chest computed tomography (CT) alone, and options for treatment if metastases are found. The paucity of published studies may reflect the inconsistencies that exist in the management of ACC of the head and neck in the UK. The collaboration of head and neck centres would, we think, help to correct the imbalance in these three domains of care.

Keywords: Head and neck adenoid cystic carcinoma; Neck management in ACC; Follow-up in H&N ACC; Management of H&N ACC

Introduction

Adenoid cystic carcinoma (ACC) accounts for about 1% of all head and neck malignancies and 10% of all the salivary gland tumours, and is the most commonly reported malignant tumour of the minor salivary glands.[1]

Robin, Lorain, and Laboulbène first described it in 1853 and 1854 in reports of two nasal tumours and a parotid tumour. Billroth later suggested the term "cylindroma",[1] and the current name was introduced by Spies in 1930. Dockerty and Mayo established its malignant nature.[1]

ACC arises within glands, most commonly the major and minor salivary glands of the oral cavity (50% and 35%, respectively).[2] Rare occurrences, however, have been reported in other sites including the external ear, oropharyngeal and nasopharyngeal spaces, trachea, breast, skin, and lower female genital tract.[2]

The disease is characterised by local recurrences and haematogenous metastases to lung, bone, and liver.[1] The lungs are the most common site, and perineural invasion, even with early-stage tumours, is common.[3] Operation is generally the preferred primary treatment and adjuvant therapy is often recommended, but the extent of the operation, type of adjuvant therapy, and follow-up protocols, can vary considerably.

In this paper we have focused on three key management-related controversies in ACC of the head and neck: the role of elective neck dissection (END) for the N0 neck, the role of adjuvant therapy or radiotherapy, and long-term follow up of the chest.

ACC is considered a clinically high-grade neoplasm.[1] It is predominantly a tumour of adulthood with a peak

* Corresponding author at: 86, Beeches Way, Faygate, Horsham, West Sussex, RH12 0AD.

E-mail addresses: montey.garg@nhs.net (M. Garg), ben.green4@nhs.net (B. Tudor-Green), brian.bisase@nhs.net (B. Bisase).

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incidence in the fourth to sixth decades, and a female preponderance.[4]

There are three morphological patterns: cribriform, tubular, and solid. The most common and characteristic is the cribriform, multicystic, or "swiss-cheese" pattern, which comprises 44% of all lesions. The tubular pattern comprises 35%, and the solid pattern 21%. Solid ACC is a high-grade lesion with a reported recurrence of up to 100%.[5]

Spiro and Huvos did not consider the histological features of ACC to be important predictors of clinical behaviour, and thought that clinical factors such as stage, large tumour size, and involvement of the lymph nodes, were more predictive of distant metastasis, and ultimately of prognosis.[6] It should be borne in mind that if operation is the mainstay of treatment, the histological pattern will not be known in most cases until complete resection of the tumour. One could argue, however, for a more aggressive approach (depending on the histological reports) when locoregional control is more difficult, but at present no consensus exists.

Role of elective neck dissection (END) for the N0 neck

The treatment of the N0 neck in patients with ACC is still debated. Amit et al[7] published a multicentre retrospective study on patients with ACC of the head and neck and N0 necks who had elective neck dissection (END). They collected data from nine centres worldwide and studied 457 patients who had no preoperative clinical evidence of nodal metastases on physical examination, computed tomography (CT), and magnetic resonance imaging (MRI). A total of 226 had END. In them, the overall rate of occult nodal metastasis was 17% (38/226), the highest incidences being among those with tumours of the oral cavity (66%, 25/38) and tumours that involved the major salivary glands (24%, 9/38). This finding of 17% occult nodal metastasis in ACC of the head and neck supports the case for END, as in squamous cell carcinoma (SCC) of the head and neck, which has rates of occult metastasis to the neck of between 15% and 20%. However, the authors found no significant difference in survival between the group that did not have neck dissection (n = 231) and the group that did (n = 226).[7]

In another retrospective study, Lee et al[8] reported a rate of occult metastasis of 15.38% (4/26) in patients with N0 necks, and recommended END. They studied patients with ACC of the major and minor salivary glands, and of the 57 who had N0 necks, 26 had END. There was no regional recurrence in those who had END (n = 26), whereas four of the 31 who did not, had regional recurrence. Again, there was no significant difference in the rates of survival and distant metastasis in patients who had END, but END enables accurate establishment of pathological nodal status and allows for the cellular analysis of metastases, both of which provide important prognostic information.[8]

In a smaller number of patients (n = 16), Iyer et al[9] reported an incidence of occult metastasis in 25% of patients, and suggested ipsilateral selective neck dissection.[9] Prophylactic treatment of the neck in N0 ACC was also recommended by Szanto et al, Barrett and Speight, and Cianchetti et al[10–12]Bhayani et al[13] reported regional metastasis in 23.3% of patients with early-stage T1-2/N0 disease of the major glands.[13] In their study of the risk factors for nodal metastasis, particularly in patients with ACC of the salivary glands, Megwalu and Sirjani[14] reported an overall rate to the lymph nodes of 17%. Advanced disease (T3 and T4) was associated with an increased risk, and the presence of nodal metastases was associated with worse overall and disease-specific survival.[14]

Min et al[15] noted that the site of the primary tumour and presence of peritumoural lymphovascular invasion were significantly associated with metastasis to the cervical lymph nodes. The general incidence of this was almost 10% and was associated mainly with sites such as the mobile tongue, base of the tongue, and floor of the mouth.[1,15] Jang et al[3] did not show any strong evidence that nodal status was a predictor of recurrence or survival. In their group of 70 patients, only 8.1% had nodal disease.[3]

Management of the N0 neck remains debatable, but studies have shown that in patients with ACC, node-positive disease is positively correlated to increased metastasis and decreased survival.[16–19] In reality, patients with T3 and T4 disease that involves the submandibular gland or floor of the mouth, often require END for the N0 neck. Management of the N0 neck, however, in those with T1 and T2 tumours of the parotid gland is particularly controversial.

Bhayani et al[13] suggested that END of the first echelon lymph nodes should be considered, particularly in cases of "solid" tumours. This is in line with the growing use of sentinel node biopsy to stage the neck without the morbidity of a full dissection, and sentinel node biopsy may be applicable in this respect.

In a recent paper, Xiao et al[20] studied 2807 patients with ACC from the US National Cancer Database (NCDB) who were treated surgically. Of them, 636 (22.7%) had END, which was done most often in those with disease of the salivary glands and tongue. To our knowledge, this is the first study to show an association between END and overall survival in patients with ACC. On univariate Kaplan–Meier analysis, END was associated with significantly extended overall survival in patients with advanced (T3-T4) ACC of the major salivary glands when compared with those who had resection alone. The authors concluded that there was a significantly increased risk of occult nodal metastasis among patients with clinically negative nodal disease of the major salivary glands and tongue, and suggested that there was a need for END in this group. They also recommended it in patients with advanced disease because of the improvement in overall survival.[20]

On the other hand, in a recent systematic review and meta-analysis, Ning et al[21] found that the overall rate of metastasis to the cervical lymph nodes was 25% in patients with ACC of the minor salivary glands, and they recommended END in these cases.[21]

Role of adjuvant treatment or radiotherapy

Anecdotally, adjuvant radiotherapy is considered more important in ACC than in other malignant salivary gland diseases, as only low-stage disease can be salvaged if there is a recurrence. Recurrences in other salivary gland malignancies, can pose a threat to local structures, particularly the facial nerve, but do not normally threaten the life of the patient, as they are relatively reluctant to metastasise to distant organs. In comparison, ACC of the head and neck has a propensity for early distant metastasis with a low tumour load. A recurrence in the head and neck implies that the disease has been present since the original operation and there is a real risk that it will metastasise with a lethal result. The stakes therefore are much higher, and the threshold for adjuvant radiotherapy low. As it is not possible to obtain clear margins in T3 and T4 disease, postoperative radiotherapy is given in all such cases. The dilemma concerning its use mainly presents in patients with T1/T2 N0 tumours of the parotid and a few discrete T1 lumps in the buccal mucosa, submandibular gland, or other intraoral sites such as the palate.

Some authors have suggested that adjuvant radiotherapy is the best treatment for parotid tumours that retain a close deep surgical margin (particularly when peeled off the facial nerve) and there is concern about microscopic disease.[22,23]

In their retrospective study, Ko et al[4] reported radiation therapy with a median of 58.1 Gy as adjunctive treatment in 28 patients with positive surgical margins.[4] ACC may have a dose-response relation with radiation.[6,24] Chen et al,[24] reported that 64% of 140 patients had postoperative radiation with a median (range) dose of 64 (54-71) Gy, and concluded that combined operation and radiation with doses of over 60 Gy should be considered standard in patients with ACC of the head and neck.[24] In a review, Bradley found no randomised controlled trials that proved the value of adjuvant radiotherapy, or showed which patients would be most likely to benefit from it.[25] Such treatment may be helpful in residual microscopic disease and (frequently unrecognised) perineural invasion in specimens with apparently clear margins, so it has been advocated to ensure locoregional control.[25,26] Other authors have recommended its routine use in patients with inoperable disease, distant metastases, advanced tumours after resection, and histologically invaded margins.[25,26]

In their series of 87 patients who had operations for ACC, and after adjusting for T stage, Ali et al[27] reported a 13-fold increased risk of local failure in those who did not have postoperative radiotherapy compared with those who did ($p = 0.003$).[27] Indications for postoperative radiotherapy in their study included stage III/IV cancers and adverse pathological factors such as close or positive margins, and perineural invasion. However, they recommended that it should be considered in all patients, possibly with the exception of those with small T1 tumours and no adverse pathological features.[27] Two studies, one by Ellington et al,[28] which looked at 3026 patients from the Surveillance, Epidemiology, and End Results (SEER) database, and another population-based study by Lloyd et al,[29] suggested that postoperative radiotherapy conferred no survival benefit. However, in a large retrospective study of 1784 patients with ACC of the major salivary glands, Lee et al[30] showed that it was associated with significantly improved survival in patients with pT1-2N0, pT3-4N0, and pT(any)N+ disease, and those with positive margins, but not in those with negative margins.[30]

Based on small retrospective studies, the US National Comprehensive Cancer Network guidelines[31] have suggested that adjuvant radiotherapy should be offered to patients with risk factors for recurrence such as intermediate or high-grade tumours, close or positive margins, perineural invasion, lymph node metastases, lymphovascular invasion, and T3-4 tumours (evidence category 2B).[31]

Based on these reported findings, some patients may not benefit from postoperative radiotherapy, but will still experience the short and long-term side effects. The main area of controversy may be around cases with negative margins, and collaborative work and future trials may help delineate the evidence-based options.

Follow-up protocol

In a UK series,[32] 40% of patients with ACC were alive at 20 years, and survival continued to drop until 30 years. Perusal of the crude data showed that 47% of patients developed a recurrence at the primary site and 12% in the neck nodes. The actuarial development of a recurrence at the primary site was 83% at 20 years, and increased to 100% at 30 years after further extrapolation.[32] This low long-term survival rate is linked to the failure to control distant disease, which most often occurs in the lung.[1] No consensus exists, however, on the type or frequency of chest imaging that is needed.

18F- FDG PET-CT does not help to rule out distant metastases if the primary salivary gland carcinoma does not show enhanced FDG uptake, a situation that is common in ACC.[1] Disease with a relatively low FDG uptake might be obscured by the normal physiological uptake in the salivary glands; conversely, salivary glands are often affected by inflammatory processes in which increased FDG uptake might result in a false-positive result.[1]

The tumour doubling time of pulmonary metastases showed that metastatic deposits of ACC occurred between a mean (range) of 393 (86 – 1064) days, and the time of onset of pulmonary metastases (tumour size 10 μm) was a long time before (around 227 months) the first visit that detected them on chest radiograph.[33] It has been shown that in general, a tumour of 10 μm grows to 1 mm in 20 doublings, 1 cm after 30, and 10 cm after 40,[34] which suggests that an annual chest radiograph is not sensitive enough to make an early diagnosis, and therefore supports the use of chest CT.[25]

The Adenoid Cystic Carcinoma Research Foundation (ACCRF) has suggested a combination of MRI and CT to check for, and to track, any residual disease or potential recurrence.[35] CT can effectively identify tumours in the lungs and hard tissues, while MRI is useful for soft tissues and the head and neck. Imaging should be done every 2-6 months in patients with evident disease, and every 6-12 months in those in whom no disease has been evident for many years. Younger patients with no evidence of disease after treatment should occasionally have radiographs to minimise their overall exposure to radiation from CT.[35] Recurrences that are missed by chest radiographs (which are known to have a low sensitivity) may be larger and more difficult to manage if a patient opts to have thoracic surgery.

The resection of pulmonary metastases in ACC has been reported. In a series of patients who had pulmonary metastasectomy, Liu et al[36] reported five-year estimated survival of 84%, which continued to decline until no survivors were left after 14 years. There was no difference in survival between those with solitary or multiple lesions, and it was unclear whether the operation had made a difference.[36] On the other hand, Kim et al[37] found that three-year survival in patients with distant metastases was 41.3%. This declined to 15.5% at five years. Their study, however, did not make clear what treatment had been given.

In a review, Winter et al[38] noted that survival in patients with pulmonary metastases from ACC was far better than it was in those with pulmonary metastases from SCC of the head and neck. In their study, six patients had pulmonary metastases from ACC and five of them had extensive disease. Five-year survival after resection was 33%. The authors concluded that survival in patients who had had pulmonary metastasectomy was significantly better than it was in those treated conservatively.[38]

In one of the largest published retrospective series, Girelli et al[39] studied 109 patients who had pulmonary metastasectomy (median age at the time of operation was 48 years). A single metastasis was found in 29 patients and multiple lesions in 80. Cumulative survival was 66.8% at five years and 40.5% at 10 years.[39] The authors concluded that pulmonary metastasectomy should be considered as a therapeutic option for disease control when two conditions are met: first, when complete resection is feasible, and secondly, when the time to pulmonary relapse after treatment of the primary tumour is more than 36 months.[39] They found no significant difference in survival between patients with single nodules and those with multiple metastases in the lungs.[39]

As pulmonary metastastectomy has a role in the management of pulmonary metastases in patients with ACC, annual monitoring of the lungs with CT may be helpful. If it is not done, patients may be denied a chance of treatment.

Rampinelli et al[40] looked at the cumulative exposure to radiation, and lifetime attributable risk of cancer that is associated with screening for lung cancer with annual low-dose CT. They found that over 10 years, 5203 participants (3439 men and 1764 women) had 42228 low-dose CT and 635 PET-CT scans. The lifetime attributable risk of lung cancer and major cancer after 10 years of CT screening ranged from 5.5 to 1.4/10000 people screened, and from 8.1 to 2.6/10000 people screened, respectively. The authors concluded that the exposure to radiation and the risk of cancer (even if not negligible) may be acceptable in light of the substantial reduction in mortality that is associated with screening.[40] In young people, however, the risk of stochastic effects from annual chest CT should be balanced against the detection of pulmonary metastases, which may or may not be amenable to resection. It is a complex dilemma as it is difficult to ascertain the greater risk - malignancy from radiation or failure to detect a salvageable pulmonary metastasis.

In the current climate of patient-centred care and need for informed consent that includes the discussion of material risk, this information must be collected together and given to patients in context to enable them to make informed decisions about whether or not to have an annual chest CT.

It is also important to monitor patients with recurrent or metastatic disease because rapid developments in new drugs may enable better control and treatment with targeted therapies. Ferrarotto et al[41] genotyped 102 patients with pathological and clinical data. They investigated the molecular underpinning of a form of ACC with an aggressive phenotype and assessed the NOTCH1 pathway as a potential target. This pathway is involved in functions that are relevant to cancer, including cell fate specification, proliferation, and angiogenesis.[41] Whole exome sequencing has shed light on the genetics of ACC, and 11% to 29% of patients had Notch pathway alterations.[41] The authors found that NOTCH1 mutations defined a distinct, aggressive form of the disease, which was likely to be the solid subtype and to be at an advanced stage at diagnosis. These tumours had high rates of metastasis to the bone and liver, and patients had short relapse-free survival. There was appreciable inhibition of tumour growth with brontictuzumab in the ACC-derived xenograft model that harboured a Notch1 activating mutation. The authors concluded that clinical studies are needed to target Notch1 in a genotype-defined subgroup of ACC.[41]

More recently, Tchekmedyian et al[42] published findings of their phase II trial to evaluate lenvatinib, a multitargeted tyrosine kinase inhibitor, in patients with recurrent or metastatic disease. They enrolled 33 patients with histologically-confirmed recurrent or metastatic ACC of any primary site with radiographic or symptomatic progression, or both, and reported a median progression-free survival of 17.5 months. Lenvatinib was stopped in 18 patients because of drug-related issues, but the trial showed that it induced antitumour activity in recurrent or metastatic disease.[42] Clinical trials on targeted treatments are currently underway and planned for the future, so follow-up protocols will then become more important.

Conclusion

ACC is an aggressive disease that continues to challenge clinicians, and there seems to be considerable variation in the management of the primary site and regional lymph nodes, and in long-term follow up to monitor for distant disease.

However, there is a trend towards treatment of the N0 neck with END, which enables accurate staging, and provides prognostic information and locoregional control, even if it does not improve overall survival. Adjuvant radiotherapy does improve locoregional control in patients with adverse features but, as some multidisciplinary protocols adhere to historical data and all patients are given postoperative radiotherapy, those with small tumours, no adverse features, and clear margins, may be over treated and suffer unnecessary side effects. There may be a role for cross-sectional imaging of the full body, or chest CT alone, in the long-term monitoring of patients to identify distant disease. This type of surveillance has to balance the benefit of interventions when a metastasis is found (such as metastatectomy or targeted treatments) against the risk of radiation-induced tumours if none is identified.

There is a need for collaboration among centres that treat patients with cancer of the head and neck to address the uncertainty about the management of ACC. This will help multidisciplinary teams to decide on the best treatments and our patients to make more informed choices about their care.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

Not needed

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bjoms.2019.07.021.

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