Neck dissection findings in primary head and neck high-grade adenocarcinoma

Patrick Sheahan, M.B., A.F.R.C.S.I., Miriam Byrne, M.B., Maky Hafidh, F.R.C.S.I. (Oto.),
Mary Toner, M.B., F.R.C. Path*, Conrad Timon, M.D., F.R.C.S. (Orl.)

Abstract

Primary salivary adenocarcinoma of the head and neck is rare. In cases where cervical metastases are evident or suspected, neck dissection is likely to play a role in management. However, there is little data in the literature regarding the findings and outcome of neck dissection in these patients. The present study comprised a review of 12 patients with high-grade salivary adenocarcinoma (salivary ductal carcinoma or adenocarcinoma, not otherwise specified (NOS). Eight underwent neck dissection (four modified radical, four selective). Histological examination showed evidence of cervical metastases in five. The prevalence of occult metastases in the N_0 neck was 40 per cent. Computed tomography (CT) and magnetic resonance imaging (MRI) were not useful in detecting occult neck disease. Five patients had no evidence of disease at the most recent follow up. Neck dissection is indicated in patients with high-grade salivary adenocarcinoma, and may provide information for planning adjuvant treatment.

Key words: Salivary Glands; Adenocarcinoma; Neck Dissection

Introduction

Since carcinomas of salivary tissues take origin from the salivary duct unit, they may all be considered generically 'adenocarcinomas'.[1] However, when considering malignant salivary tumours, a number of well-defined clinicopathological entities are generally recognized and classified as distinct types of salivary carcinoma. These entities include mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, and malignant mixed tumour. Besides these principal types of salivary carcinomas, there remains a number of less frequent forms of adenocarcinoma.[1,2] These were formerly collectively embraced by the term 'adeno-carcinoma, not otherwise specified (NOS)'. More recently, the recognition of the heterogeneity that exists within this grouping has led to the definition of clinically relevant and pathologically classifiable subsets within this group, including polymorphous low-grade adenocarcinoma (PLGA), epithelial-myoepithelial carcinoma, basal cell adeno-carcinoma, and salivary ductal carcinoma. Today, the term 'adenocarcinoma NOS' refers to carcinomas, which are recognized as being of glandular origin, but which are lacking in sufficient histological

features to be recognizable as one of the subcategories of salivary adenocarcinoma.[1,2]

Batsakis has considered the subcategories of salivary adenocarcinoma according to their presumed site of origin, and has concluded that the biological aggressiveness of these carcinomas depends on this.[1] Structurally, salivary glands are composed of secretory end-pieces (consisting of serous and mucous cells), which empty into intercalated (terminal) ducts, lined by cuboidal epithelium. Several intercalated ducts join to form striated (intralobular) ducts, which in turn converge to form excretory (interlobular) ducts in the connective tissue septa between the lobules of the gland. PLGA and epithelial-myoepithelial carcinomas are believed to arise from the intercalated ducts, and generally behave as low-grade malignancies. On the other hand, salivary duct carcinoma is believed to arise from excretory ducts, and is characteristically aggressive in behaviour. Most cases of adenocarcinoma NOS are believed to arise in the excretory or striated ducts, and are thus regarded to behave in an intermediate- to high-grade fashion.[1]

Histological type and grade is well established as a prognostic factor in salivary adenocarcinoma, with high grade variants reported to have an increased incidence of cervical metastases,[3-7] increased risk of locoregional recurrence,[5] and decreased survival.[3,5,6] Because of this, neck dissection is likely to play an important role in the management of such tumours.[3,8] However, owing to the rarity of primary high-grade salivary adenocarcinoma, the use of neck dissection in the treatment of such cases is rarely reported. The purpose of the present study was to investigate the role of neck dissection and other ancillary procedures, including fine needle aspiration biopsy (FNAB) and imaging studies, in the management of patients with high-grade variants of salivary adenocarcinoma (salivary ductal carcinoma or adenocarcinoma NOS). In addition, the histological findings in the neck, and the influence of these findings on surgical outcome, are reviewed.

Methods

Between September 1993 and April 2003, 237 patients underwent neck dissection at St. James' Hospital, Dublin. The pathological findings of all of these patients are reviewed. Patients were included in the present study if they had a pathological diagnosis of high-grade adenocarcinoma (salivary ductal carcinoma or adenocarcinoma NOS), and had undergone neck dissection as part of their definitive treatment because of evident, or suspected, cervical metastases. The medical records, pathological and cytological material, and imaging studies of these patients were retrospectively reviewed.

Results

Eight patients with high-grade adenocarcinoma, representing 3.4 per cent of the 237 patients undergoing neck dissection, were identified. Five of the patients were male, and three were female. Their ages ranged from 44 years to 92 years (mean age 62.8 years). All patients were smokers and drank alcohol. Three patients had salivary ductal carcinoma. The other five had adenocarcinoma (NOS). Four of the patients underwent dissection of cervical lymph node levels I to V (one bilateral), and four underwent selective (levels I, II, III) neck dissection (Table I). In addition, there were four further patients with high-grade salivary gland adenocarcinoma who did not undergo neck dissection, for a total of 12 cases during the period of review.

The site of origin of the primary tumour was the parotid gland (six cases), submandibular gland (one case), and unknown (one case) (Table I). Three of the patients with parotid primaries had salivary ductal carcinoma, and three had adenocarcinoma NOS. All patients with parotid primaries underwent parotidectomy with facial nerve preservation as part of their definitive surgery. The patient with the submandibular primary had been diagnosed with adenocarcinoma NOS of the submandibular gland one year previously, and had undergone submandibular gland removal with post-operative radiotherapy at the time, prior to referral to us. He subsequently developed bilateral neck metastases, and thus proceeded to undergo bilateral modified radical (levels I to V) neck dissection. The primary site remained unknown in one patient. This patient had undergone extensive investigation in order to rule out an occult primary, including nasal endoscopy; panendoscopy; magnetic resonance imaging (MRI) of the neck; computed tomography (CT) scans of thorax, abdomen, and pelvis; upper gastrointestinal endoscopy; prostate specific antigen (PSA) assay; and positron emission tomography (PET) scans. However, none of these investigations was indicative of a primary. Further support for a

TABLE I

CLINICAL AND PATHOLOGICAL FEATURES OF PATIENTS WITH PRIMARY CERVICAL ADENOCARCINOMA UNDERGOING NECK DISSECTION

Patient	Sex	Age	Histology	Primary	Neck levels dissected	Neck histology	Radio-therapy	Outcome
1	M	48	Adenoca NOS	Parotid	I,II,III	Negative	To parotid bed only (post op)	Well 15 mo
2	M	92	Adenoca NOS	Parotid	I,II,III	Negative	No	RIP 1 yr
3	F	61	Adenoca NOS	Parotid	I,II,III	Extra-nodal deposit	Yes (post-op)	Well 3 mo
4	M	65	Salivary ductal ca	Parotid	I,II,III,IV,V	28/33	Yes (post-op)	Recurrence 5 mo
5	F	63	Salivary ductal ca	Parotid	I,II,III	Negative	Yes (post-op)	Well 4 yrs
6	F	75	Salivary ductal ca	Parotid	I,II,III,IV,V	2/23	Yes (post-op)	Well 5 yrs
7	M	44	Adenoca NOS	Submand. gland	I,II,III,IV,V (bilateral)	2/23 (right) 2/27 (left)	Pre-op	RIP 3 mo
8	M	54	Adenoca NOS	Unknown	I,II,III,IV,V	25/70	Chemo-radiotherapy (post-op)	Well 3 mo

Adenoca NOS = adenocarcinoma not otherwise specified

presumed salivary site of origin was provided by immunohistochemistry, which showed positive staining for CK7, and negative staining for CK20 and TTS.

Histological examination of the resected specimens showed evidence of metastatic neck disease in five patients. Three of these had palpable cervical disease pre-operatively. One patient (with no evidence of palpable disease pre-operatively) had a solitary extranodal deposit without evidence of nodal disease. The other four patients (including one with no evidence of palpable disease pre-operatively), had multiple nodal metastases, affecting multiple levels. The incidence of occult cervical disease in patients clinically staged N_0 was 40 per cent (two out of five) (Table I).

Fine needle aspiration (FNA) had been performed pre-operatively on five patients. In one patient, this had been reported as showing adenocarcinoma. Diagnosis in this case was aided by immunocytochemistry, which showed positive staining for CK7 (cytokeratin 7), and negative staining for CK20. In three cases, the FNA was reported as showing high grade carcinoma. FNA was unhelpful in one patient.

Pre-operative imaging studies (CT and / or MRI scanning) were performed in all patients. These were suggestive of cervical metastases in three patients, and metastases were confirmed histologically in all of these. Three of the five patients with no radiological evidence of cervical metastases had no metastases histologically. Two patients with no radiological evidence of neck disease were found to have metastases on histological examination.

Five patients underwent adjuvant post-operative radiotherapy to the neck. Four of these had histologically confirmed cervical metastases. One had no evidence of cervical metastases, but proceeded to undergo radiotherapy in view of the aggressive histology of the primary tumour (salivary ductal carcinoma). A sixth patient with a parotid adenocarcinoma NOS received radiotherapy to the parotid bed only, as the neck was free of disease histologically. The patient with the submandibular adenocarcinoma NOS had already undergone adjuvant cervical radiotherapy subsequent to having undergone submandibular gland removal, prior to his referral to us, and thus did not undergo further radiotherapy after salvage neck dissection. Finally, one patient with a parotid adenocarcinoma NOS elected not to undergo radiotherapy, on account of advanced age (92 years) and frail condition.

Five patients had no evidence of disease at the most recent follow up. This included three patients with histologically proven neck metastases. Two of these had adenocarcinoma NOS, however, the length of follow up in both cases was short (three months). One of the patients with salivary ductal carcinoma of the parotid gland developed regional recurrence shortly after completing radiotherapy. Finally, two patients died. One of these was the patient with the submandibular adenocarcinoma NOS and bilateral nodal metastases; he died from a pulmonary embolus three months after undergoing neck dissection. The other was the 92-year-old man with a parotid adenocarcinoma NOS without cervical metastases; it is unclear whether or not he had recurrent disease at the time of his death.

Discussion

Considerable heterogeneity of clinical behaviour and prognosis exists within the grouping of salivary adenocarcinomas. More recently, the definition of pathologically classifiable and clinically relevant subsets of 'adenocarcinoma NOS' has enhanced the identification of the more aggressive variants. However, owing to the rarity of these tumours, there is little data in the literature regarding the findings or outcome of neck dissection in such cases. In many studies, the recently defined subsets of salivary adenocarcinoma have been included together with other histological types of salivary carcinoma. The object of the present paper was to study the findings and outcome of neck dissection in the less well-described subtypes of high-grade salivary adenocarcinoma. To this end, cases of muco-epidermoid carcinoma, adenoid cystic carcinoma, and acinic cell carcinoma were excluded. Salivary ductal carcinoma is a clinico-pathologically distinct tumour that is generally considered to be a high-grade salivary neoplasm,[1,9] although low-grade variants are recognized.[9] Cases of high-grade salivary ductal carcinoma were thus included along with cases of high-grade adenocarcinoma NOS in the present study.

There is little data in the literature regarding the role of neck dissection in primary salivary adenocarcinoma, however, where cervical metastases are evident or suspected, neck dissection is likely to play an important role in management. Spiro retrospectively studied 204 patients with adenocarcinoma of salivary origin who were registered on the Memorial Sloan-Kettering Cancer Centre tumour registry between 1939 and 1968. Cervical metastases were evident at presentation in 17 per cent of patients, and developed subsequently in another 10 per cent. The risk of cervical metastases and death from disease was reported to be associated with the histological grade of the tumour. Radical neck dissection was performed in 45 patients, 28 of whom had palpable lymphadenopathy. Of note was that metastases were present in five of the 17 neck dissections of patients without palpable lymphadenopathy.[5] However, although large, there are several reasons why this series may not be pertinent to modern practice. In the first instance, this series was reported prior to the subclassification of adenocarcinoma into subcategories. In addition, this series included 47 sinonasal adenocarcinomas, many of which may have originated from surface mucosa rather than from salivary tissue,[10] and which are generally regarded as being of low-grade malignancy.[11] It is thus likely that the number of cases that would be considered to represent true cases of high-grade adenocarcinoma NOS by today's standards may be considerably lower than that reported. Thirdly, compared to

modern practice, very few patients (nine) received radiotherapy, and it is likely that the scarcity of this treatment modality may have affected both the indications and outcome of neck dissection. Fourthly, all patients in Spiro's series who underwent neck dissection underwent radical neck dissection. Finally, there is no information given regarding the outcome of the patients who underwent neck dissection.

In cases of malignant salivary tumours, where clinically apparent cervical metastases are present, it is generally accepted that neck dissection is indicated.[8,12] Less clear is the role of elective neck dissection in the case of the N_0 neck. Most salivary malignancies are reported to have an incidence of manifest cervical metastases of less than 15–30 per cent,[5,6,13-15] however, a higher incidence of neck disease has been reported in cases of adenocarcinoma.[3,13] Armstrong reported on 407 patients with salivary cancers and clinically negative necks, 90 of whom underwent elective neck dissection. Occult cervical metastases were present in 34 neck specimens. In addition, 13 patients not undergoing neck dissection had metastatic involvement of periglandular or intraglandular lymph nodes. The overall incidence of occult nodal metastases among the entire series of 407 patients was 12 per cent, however, the incidence of occult metastases among patients with adenocarcinoma was 18 per cent (seven out of 38).[3] Therkildsen reported occult metastases to be present in 10 of 32 patients with salivary carcinoma undergoing elective neck dissection, however, five of 11 patients with intermediate or high grade adenocarcinoma, mucoepidermoid carcinoma, or squamous cell carcinoma had metastases,[16] while Santos reported occult metastases to be present in 68 per cent of patients with high-grade mucoepidermoid carcinoma, adenocarcinoma, salivary ductal carcinoma, undifferentiated carcinoma, and squamous cell carcinoma.[4] In the present study, only high-grade variants of adenocarcinoma NOS and salivary ductal carcinoma are included, and the incidence of occult metastases was 40 per cent.

The incidence of neck conversion developing in patients with salivary cancers once the primary tumour has been adequately controlled has been reported to be very low.[13,17] Patients are more likely to succumb to failure at the primary site or late-appearing distant metastases.[13] It is also notable that patients who have had a high-grade salivary carcinoma treated and who survived without locoregional recurrence have the same risk of distant metastases as those patients who have locoregional recurrence.[18] These observations would argue against the performance of routine elective neck dissection in cases of salivary cancer and a clinically negative neck. Moreover, in cases where post-operative radiotherapy is likely to be administered on the basis of stage or grade of the primary tumour, the need for elective neck dissection may be obviated.[12,13,15] On the other hand, there are several arguments to be made supporting the case for elective neck dissection in patients with high-grade salivary adenocarcinoma and a clinically negative neck. A selective neck dissection, with clearance of levels I, II, and III, is easily incorporated into the surgical approach to the parotid or submandibular glands.[13] The information gained from examination of the neck specimen may be used to guide the need for post-operative radiotherapy.[15] Furthermore, an increased incidence of occult cervical metastases is reported in adenocarcinoma and other high-grade salivary carcinomas,[3,4,16] while the presence of cervical metastases has been reported to be an important negative prognostic factor in salivary ductal carcinoma.[19] Recognizing the increased risk of cervical and distant metastases associated with high-grade adenocarcinomas and salivary ductal carcinomas, Ferlito recommended that the decision to perform a neck dissection in patients with salivary adenocarcinoma and a clinically negative neck should be based on the oncotype of the primary tumour.[20]

- **Primary adenocarcinoma in the head and neck is rare and the role of neck dissection in such cases is unclear**
- **This study reviews 12 cases of whom eight had neck dissection**
- **The prevalence of metastatic disease was high and, in this study, CT and MRI scanning was poor at detecting occult lesions**
- **The study concludes that neck dissection is indicated in such cases—especially since it may provide information for planning adjuvant therapy**

The outcome of metastatic adenocarcinoma to the neck from an unknown primary site is generally considered to be poor. Spiro reported on 29 such patients. Eight of these had limited disease in the upper half of the neck and underwent radical neck dissection. One of these was alive with no evidence of disease after 28 months; the others were all dead within the same timeframe. The outcome for adenocarcinoma of unknown primary origin was significantly worse than that for squamous carcinoma or melanoma. An infraclavicular primary was subsequently identified in five patients.[21] The patient in the present series with unknown primary tumour was well after three months, however, the follow up was short. Furthermore, this patient had 25 positive nodes with macroscopic extracapsular spread on histological examination, which would be suggestive of a poor prognosis. In patients with adenocarcinoma of the neck without an obvious primary site, rigorous investigation to rule out an occult infraclavicular primary is mandatory. This investigation is likely to include CT scanning of chest and abdomen, upper and lower gastrointestinal endoscopy, bronchoscopy, prostate-specific antigen assay (in males), and mammography (in females). Positron emission tomography (PET) scanning may

be a very useful adjunct in such cases. Neck dissection should be reserved for cases of predominantly upper neck involvement, where an occult salivary primary is suspected. The opinion of a medical oncologist should be sought, as such patients may also be candidates for concurrent chemoradiotherapy.

Conclusion

Adenocarcinoma of salivary origin is very rare, and little data exists regarding the management of the neck in these patients. When cervical metastases are evident, neck dissection is generally indicated. Because of the frequent involvement of multiple nodes at multiple levels, levels I to V should be dissected. Most of these patients are also likely to require adjuvant post-operative radiotherapy. In cases with a clinically negative neck, the optimum treatment is less clear. In patients with small tumours (T_1/T_2), with the less aggressive variants of adenocarcinoma, (PLGA, epithelial-myoepithelial carcinoma, and basal cell adenocarcinoma), the risk of occult cervical metastases is likely to be low. Therapeutic neck dissection may be performed in such patients who later develop neck conversion. Thus, a policy of watchful waiting may be indicated. On the other hand, among patients with salivary ductal carcinoma, and adenocarcinoma NOS, a higher incidence of occult metastases may be expected. It should, in most cases, be possible to perform selective neck dissection through an extension of the same incision, with minimal additional morbidity. Furthermore, the information obtained from the neck dissection may be of value in planning post-operative radiotherapy. Thus, neck dissection should be considered in patients with high-grade salivary adenocarcinoma or salivary ductal carcinoma as part of their definitive surgery. Finally, in cases where salivary ductal carcinoma or adenocarcinoma NOS is diagnosed post-operatively, and a neck dissection has not been performed, then patients should be considered for post-operative cervical radiotherapy.[8]

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Address for correspondence:
Patrick Sheahan,
17 Hampton Square,
Navan Road,
Dublin 7,
Ireland.

E-mail: sheahanp@eircom.net

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