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Les Carcinomes adénosquameux de la sphère ORL: à propos de 20 cas et revue de la littérature

THESE

préparée sous la direction du Professeur Esat Mahmut Ozsahin

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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Les Carcinomes adénosquameux de la sphère ORL: à propos de 20 cas et revue de la littérature

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Madame le Professeur Stephanie Clarke
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RESUME

Le but de cette étude rétrospective et descriptive était de déterminer les aspects cliniques et anatomopathologiques ainsi que les modes de presentation et de récidive des carcinomes adénosquameux de la sphere ORL, traités de manière curative, et recensés entre le 1er janvier 1989 et le 31 décembre 2010 au sein des Institutions du Rare Cancer Network.

Nous avons retenu 20 cas de patients traités par chirurgie (S), et/ou radiothérapie (RT), avec ou sans chimiothérapie (CT) concomitante. L'âge médian etait de 59.5 ans au moment du diagnostic (étendue, 48-73). La classification selon le TNM montrait des stades avancés pour la majorité des patients, avec un, deux, cinq et 11 patients présentant respectivement une tumeur de stade I, II, III, et IVa. Les sites anatomiques incriminés étaient la cavité orale (n=4), l'oropharynx (n=5), l'hypopharynx (n=2), le larynx (n2), les glandes salivaires (n=2), le vestibule nasal (n=2), les sinus maxillaires (n=2) et enfin le nasopharynx (n=1). Seize patients ont bénéficié d'une chirurgie, et 17 d'un traitement combiné (S+RT chez 13, RT+CT chez deux, et les trois modalités chez les deux derniers patients).

Apres un suivi médian de 16 mois (étendue, 9-62), 3, 1, 1, 1, 2 and 4 patients ont développé une récidive à distance, régionale, locale, locorégionale, locorégionale + à distance, et régionale + à distance. Toutes les récidives locales sont survenues dans le champ d'irradiation. Au dernier suivi, neuf patients étaient vivants sans maladie. La survie globale, la survie sans maladie, et le contrôle locorégional médians et à 3 ans étaient respectivement de 39 mois et 52% (95%[CI]:28-75%), 12 mois et 32% (95%[CI]:11-54%) et enfin 33 mois et 47% (95%[CI]:20-74%). L'analyse multivariée a montré que la survie sans maladie était inversement corrélée à la présence d'effractions capsulaires (p=0.01) et aux stades avancés (IV versus I-III, p=0.002).

D'une manière générale, nous avons confirmé que le pronostic global des carcinomes adénosquameux de la sphère ORL est sombre, ceci étant majoritairement dû à la survenue précoce de métastases ganglionnaires et à distance, lesquelles surviennent chez plus de la moitié des patients. En revanche, nous avons pu montrer que le contrôle local obtenu par un traitement combiné de radio-chimiothérapie permet aux patients diagnostiqués à un stade précoce de bénéficier d'une survie sans maladie tout à fait favorable.

Les Carcinomes adénosquameux de la sphère ORL: À propos de 20 cas et revue de la littérature

Introduction - Généralités :

Les cancers ORL sont essentiellement les cancers des voies aérodigestives supérieures (VADS) développés aux dépens de la cavité buccale, du pharynx, du larynx et des cavités nasosinusiennes. Leur incidence est estimée entre 2003 et 2007 à 22,9 chez l'homme et 7,1 chez la femme. Ils représentent environ 15 % de la totalité des cancers chez l'homme et 2 % chez la femme[1]. Leur maximum de fréquence se situe entre 45 et 70 ans. Ces tumeurs sont dues essentiellement à l'association de deux substances cancérigènes : tabac et alcool. Cependant, ces dernières années, l'infection à papillomavirus a été identifiée comme un facteur majeur responsable de l'émergence de certains cancers de l'oropharynx, notamment chez l'adulte jeune[2].

Les signes d'appel peuvent être discrets, à type de gêne pharyngée unilatérale apparaissant à la déglutition, ulcération persistante, trouble de la voix ou de la déglutition, otalgie réflexe unilatérale. Les cancers des VADS s'accompagnent souvent d'adénopathies excepté le cancer glottique.

A l'histologie il s'agit le plus souvent de carcinomes épidermoïdes plus ou moins différenciés.

Le traitement fait appel à toutes les techniques oncologiques isolées ou le plus souvent associées, après décision d'un comité multidisciplinaire (associant chirurgiens, oncologues et radiothérapeutes). La stratégie thérapeutique est discutée selon la topographie et le stade de la

tumeur mais aussi l'état général du patient et son choix éclairé. Les deux modalités curatives de première intention sont la chirurgie et/ou la radiothérapie (associées ou non à la chimiothérapie).

Le pronostic dépend du stade. Dans les formes localisées la survie à 5 ans est de 40 à 50 %[3].

Présentation de l'article : Enjeu

Les carcinomes adénosquameux de la sphère ORL ont été décrits pour la première fois en 1968 par Gerughty et al[4]. Il s'agit d'une histologie rare et seulement quelques dizaines de cas ont été reportés dans la littérature à ce jour[5]. Il semble que le pronostic soit plus sombre que celui des carcinomes épidermoïdes[6,7], mais, étant donné la faible incidence de cette histologie, on ignore toujours la meilleure stratégie thérapeutique à adopter. En particulier, faut-il privilégier la radiothérapie par rapport à la chirurgie ? Faut-il d'emblée proposer une radiothérapie postopératoire ? Irradier à titre systématique les aires ganglionnaires, même pour les stades précoces ? Une chimiothérapie concomitante à la radiothérapie permet-elle d'obtenir un bénéfice de survie ou de contrôle local ?

Le but de cette étude est d'établir le profil clinique de cette néoplasie, son mode de récidive et les facteurs pronostics éventuels chez les patients traités à visée curative, en cherchant à établir si le mode de traitement (radiothérapie, chirurgie, chimiothérapie, seules ou en association) peut influencer les taux de guérison.

Afin de répondre à ces interrogations, nous avons fait appel au Rare Cancer Network (RCN) et lancer une étude rétrospective multicentrique. Le RCN (http://rarecancer.net/) est un réseau scientifique et médical international dont le siège administratif est basé au Centre Hospitalier

Universitaire Vaudois, à Lausanne, et dont l'objectif est de recueillir, analyser et publier des données portant sur des tumeurs rares (ou des tumeurs plus fréquentes mais dont le mode de présentation est peu commun), ne pouvant par définition faire l'objet d'études prospectives. Plus 50 centres hospitaliers dans 25 pays sont activement membres du RCN[8].

Chacun des membres du réseau a donc été contacté par l'investigateur principal de cette étude (Ulrike Schick) via le RCN. Les différents membres ont alors interrogé leur base de données afin, dans un premier temps, de rapporter le nombre de patients diagnostiqués d'un carcinome adénosquameux de la sphère ORL entre 1970 et 2010, et traités à visée curative dans leur centre. Les histologies douteuses, les patients métastatiques d'emblée et ceux traites a visée palliative ont été autant de critères d'exclusion. Chacun des membres pouvant fournir des données cliniques a reçu un formulaire (annexe I) et y a reporté les différentes données cliniques, notamment les données portant sur les caractéristiques démographiques du patient, les caractéristiques tumorales, le traitement, le suivi du malade ainsi que les informations portant sur l'éventuelle apparition de métastases ou de récidives locales (se référer à l'article pour plus d'informations sur la méthodologie de ce travail).

Conclusions et perspectives

Au total, nous avons inclus 20 patients provenant de quatre centres hospitaliers différents, et diagnostiqués entre 1989 et 2010. Brièvement, quatre, cinq et 11 patients présentaient une tumeur de stade I-II, III et IV. Seize d'entre eux ont bénéficié d'une chirurgie d'exérèse, et 17 d'un traitement combiné.

Après un suivi médian de 15.5 mois, 12 patients ont présenté une récidive. La survie globale, la survie sans progression et le contrôle locorégional médians et à trois ans étaient respectivement de 52% et 39 mois, 32% et 12 mois, et 47% and 33 mois. L'analyse

multivariée a permis de montrer que la survie sans progression était significativement influencée par un stade avancé et la présence d'effractions extra-capsulaires.

Au total, nous avons illustré le mauvais pronostic des carcinomes adénosquameux de la sphère ORL, avec un taux de rechutes à distante survenant dans plus de la moitié des cas. Cependant, notre série montre que le contrôle local reste favorable chez les patients diagnostiqués à un stade précoce de la maladie, et traités par radio-chimiothérapie.

En revanche, et nous le regrettons, notre collectif de patients était trop restreint pour obtenir des informations complémentaires, en particulier concernant le rôle du HPV chez les patients développant cette histologie. Il est peu probable que des études prospectives incluant ces patients voient le jour, l'histologie non épidermoïde étant fréquemment un motif d'exclusion des études en cours. En conséquence, il est vraisemblable que le praticien continuera de traiter les patients présentant un carcinome adénosquameux et les patients présentant une histologie de type épidermoïde de façon similaire.

Références

1. Sturgis EM. International Head and Neck Cancer Epidemiology Consortium: Update no. 12. *Head & neck.* Oct 2013;35(10):1371-1372.
2. Klussmann JP, Weissenborn S, Fuchs PG. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *The New England journal of medicine.* Aug 2 2001;345(5):376; author reply 377.

3. Keelawat S, Liu CZ, Roehm PC, Barnes L. Adenosquamous carcinoma of the upper aerodigestive tract: a clinicopathologic study of 12 cases and review of the literature. *Am J Otolaryngol.* May-Jun 2002;23(3):160-168.

4. Gerughty RM, Hennigar GR, Brown FM. Adenosquamous carcinoma of the nasal, oral and laryngeal cavities. A clinicopathologic survey of ten cases. *Cancer.* Dec 1968;22(6):1140-1155.

5. Napier SS, Gormely JS, Newlands C, Ramsay-Baggs P. Adenosquamous carcinoma. A rare neoplasm with an aggressive course. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* May 1995;79(5):607-611.

6. Kothari RK, Ghosh A, Bhattacharyya SK, Ghosh SK. Adenosquamous carcinoma of oral cavity: a case report. *J Indian Med Assoc.* Sep 2007;105(9):531-532.

7. Sheahan P, Fitzgibbon J, Lee G, O'Leary G. Adenosquamous carcinoma of the tongue in a 22-year-old female: report of a case with immunohistochemistry. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies.* Oct 2003;260(9):509-512.

8. Patel A, Ozsahin M, Mirimanoff RO, Bhatia S, Chang K, Miller RC. The Rare Cancer Network: achievements from 1993 to 2012. *Rare tumors.* Jun 26 2012;4(3):e35.

ANNEXE I

Formulaire de recueil des données cliniques

Adenosquamous carcinoma of the head and neck
A Rare Cancer Network Study (U.Schick, M.Ozsahin)
Retrospective analysis 1985-2008 with a minimum follow-up of 6 months

(If your patient is referred to you for a relapse following surgery without postoperative RT, please fill the forms for the first treatment details (eg., pathology, no RT, etc...) and then give us the RT details concerning the RT following the relapse surgery.)

1. Hospital/Institution _____
   Investigator _____

2. Patient Initials _____
   Birth date / / (dd/mm/yyyy)
   Gender O female O male
   Previous cancer O no O yes, please specify _____
   _____

   Ethnic origin O black O white O hispanic O asian O other
   Tabacco O no O yes, years of consumption : _____
   Alcohol O no O yes, specify _____

3. Date of Diagnosis / / (dd/mm/yyyy)
   Clinical presentation _____
   Localisation: O oral cavity: _____
   O oropharynx: _____
   O hypopharynx: _____
   O larynx: _____
   O other: _____

   MRI O no O yes
   CT O no O yes
   Extension work-up O no O yes
   Clinical stage: cT__ cN__ M__ (if T4, please specify why: _____)

4. Histology O biopsy O surgical specimen

   pTNM : _____
   Tumor size: _____ (mm * mm * mm)
   Dominant component: O adenoca O squamous
   Histologic component in the lymphnodes: O adenoca O squamous
   Grade of differenciation of the adenoca component : O well O moderate O poor
   Grade of differenciation of the squamous component: O well O moderate O poor
   Presence of necrosis O no O yes
   Presence of dysplastic changes O no O yes
   Presence of in situ carcinoma O no O yes
   Presence of keratinization O no O yes
   Presence of perineural infiltration O no O yes

Presence of ca. lymphangitis O no O yes
Presence of vascular invasion O no O yes
Presence of positive margins O no O yes
Number of removed lymph nodes : _____
Number of positive lymph nodes : _____
Number of lymph nodes with extracapsular extension: _____

5. First treatment intent O curative O palliative

6. Surgery O no
O yes - date: / / (dd/mm/yyyy)

O Tumor excision only
O Tumor excision and bilateral neck dissection
O Tumor excision and unilateral neck dissection
O Bilateral neck dissection
O Unilateral neck dissection

7. Chemotherapy O no
O yes
Date of start : / / (dd/mm/yyyy)
Date of end : / / (dd/mm/yyyy)

O neoadjuvant (drugs, doses, # cycles) :

O adjuvant :

O concomitant :

O palliative :

8. Radiotherapy O no
O yes
Date of start : / / (dd/mm/yyyy)
Date of end : / / (dd/mm/yyyy)

O definitive RT (with or without CT/anti-EGFR treatment)
O adjuvant
O palliative

Acute toxicity (>G2) O no O yes, specify _____
Late toxicity (>G2) O no O yes, specify _____

Irradiation volume O primary tumor alone O lymph nodes only
O primary tumor and lymph nodes

A- External beam Radiotherapy: O no O yes
Planning O 2D O 3D O IMRT
Total dose of EBRT / nb of fractions: _____

Elective RT O no O yes , dose/fx :
Beam Quality, Energy _____
Nb of beams _____
Interuption > 5 days O no O yes (cause :_____)
Number of days: _____

B- Brachytherapy O none O HDR O LDR O PDR
Radioactive source:
Total dose/ dose per fraction : _____/_____
Nb of applications : _____

9. Response to treatment : Assessement until 2-3 months after RT

O progression
O stable disease
O partial response (>50 % response)
O complete response

10. Systemic recurrence
O no
O yes Date : / / (dd/mm/yyyy)
Site : _____

11. Local recurrence
O no
O yes
Date : / / (dd/mm/yyyy)
Site : _____
O infield O outfield
Size:

Nodal recurrence
O no
O yes
Date: / /
Site: _____
O infield O oufield
Size:

12. Treatment for relapse O curative O palliative

O chemotherapy, specify _____

O radiotherapy, specify (dose, nb of fractions, date, irradiated regions)_____

O surgery, specify _____

13. Date of last follow-up* : / / (dd/mm/yyyy)

O alive without disease
O alive with disease
O dead due to disease
O dead due to another cause, specify _____

* the latest date that you heard about the patient (or date of death if died)

Please return completed forms either by mail or fax to:

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Adenosquamous carcinoma of the head and neck: report of 20 cases and review of the literature

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University Hospital of Geneva, Geneva, Switzerland; Clinic of Hirslanden, Lausanne, Switzerland; University Hospital of Bern, Bern, Switzerland; Uludag University Hospital, Bursa, Turkey; Radboud University Medical Center, Nijmegen, The Netherlands; and Lausanne University Hospital, Lausanne, Switzerland

Purpose. To assess the clinical profile and prognostic factors in patients with adenosquamous carcinoma (ASC) of the head and neck treated by surgery and/or radiation therapy with or without chemotherapy.
Methods. Data from 20 patients with stage I-II ($n = 4$), III ($n = 5$), or IVA ($n = 11$) head and neck ASC, treated between 1989 and 2010 were collected in a retrospective multicenter Rare Cancer Network study. Surgery was performed in 16 patients. Seventeen patients received combined modality treatment.
Results. After a median follow-up of 15.5 months, 12 patients recurred. The 3-year and median overall survival, disease-free survival (DFS), and loco-regional control were 52% and 39 months, 32% and 12 months, and 47% and 33 months respectively. In multivariate analysis, DFS was negatively influenced by the presence of extracapsular extension and advanced stage.
Conclusion. Overall prognosis of locoregionally advanced ASC remains poor. However, early stage ASC patients managed with combined modality treatment may have prolonged DFS. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:313-320)

Adenosquamous carcinoma (ASC) of the head and neck is a rare malignancy, with fewer than 100 cases reported in the English literature. This entity was first described in 1968 by Gerughty et al. in a series of 10 patients, where it was shown to be extremely aggressive, with 80% of the patients developing metastases.[1] For many years, it has been considered to be the same entity as salivary mucoepidermoid carcinoma (MEC). However, in 1984, Evans suggested that ASC should be considered as a distinctive neoplasm given its worse prognosis as compared to MEC, even high-grade.[2] In fact, metastasis and death from MEC are relatively uncommon. ASC is now defined in the World Health Organization (WHO) classification of tumors of the upper respiratory tract and ear as a malignant tumor with histological features of both adenocarcinoma and squamous cell carcinoma (SCC).[3] The SCC component usually predominates, can be in situ or invasive, and can range from well to poorly differentiated. The adenocarcinoma component can have a tubular, alveolar and/or glandular morphology.[4] The exact histogenesis of these neoplasms is disputed. One hypothesis is that this neoplasm arises from carcinoma in situ of minor salivary gland ductal epithelial tissues.[1] Ellis et al., on the other hand, suggested that the tumor arises synchronously from both mucosal and salivary duct epithelium, and this proposal is becoming widely accepted.[5] However, last year, Fonseca et al. suggested strongly that oral ASC is derived only from the squamous superficial epithelium, without the participation of minor salivary glands.[6] Classically, as previously mentioned, ASC has an aggressive behavior associated with a poor prognosis. Spread to cervical lymph nodes is common, and locoregional and distant recurrences after treatment are frequently reported.[7-9] Current treatment options include surgery and radiation therapy with or without chemotherapy. Given the relative rarity of these tumors, and the fact that they were mostly considered as MEC in the few reported series until recently,[10] the optimal management strategy remains unclear and there is a lack of consensus concerning both prognostic factors and recommendations for adjuvant treatment. These tumors therefore represent a challenging type of neoplasms to treat.

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Statement of Clinical Relevance

Adenosquamous carcinoma of the head and neck is considered a rare malignancy, with less than 100 cases reported in the literature. We reported 20 new cases with clinical profile, patterns of failure, and prognostic factors, helping to gain a better understanding of this rare tumor.

In order to contribute to our knowledge of this rare disease, especially regarding prognostic parameters, optimal management, and the role of external beam radiotherapy (EBRT), we conducted a retrospective multicenter review of the clinicopathological features of 20 consecutive cases and compared results with those described in the literature.

METHODS AND MATERIALS

This is a retrospective, multinational, multicenter, cooperative study conducted within the framework of the international Rare Cancer Network (RCN). The RCN is a cooperative, international consortium of investigators studying tumors too rare to be the focus of prospective trials.[11] Data from patients with ASC treated between 1989 and 2010 were collected. Five institutions from 3 countries (Switzerland, Netherlands, and Turkey) participated in the study. All investigators obtained their own institutional review board approval for patient data collection. Non-metastatic patients aged 18-80 years undergoing curative treatment for stage I-IVA (TNM 6th edition) ASC of the head and neck with a minimum of 6 months follow-up were included. The criteria used for inclusion of cases were those of the 2004 WHO classification of head and neck tumors[3]: The tumors had to harbor definitive squamous differentiation and also well-defined gland formation with or without mucin production, in the lumina or in the cytoplasm of cells. Postoperative management included observation and adjuvant treatment modalities incorporating EBRT and/or chemotherapy. The choice of adjuvant therapy was based on physician and institutional preferences. Exclusion criteria included patients with unclear histopathology, especially MEC, or patients treated with a palliative intent. The medical records of all ASC patients were reviewed to identify patient and tumor characteristics, treatment details and follow-up information including time to recurrence, salvage therapy and survival information. All original pathological reports were reviewed using the WHO classification of ASC. Acute and late treatment-induced toxicities were scored according to the Common Terminology Criteria for Adverse Events version 3.0. The cut-off date for the survival study was May 31, 2010.

Statistical analysis

Proportions were compared using the Chi-squared tests. The date of diagnosis was considered to be the time of surgery in 85% of the patients. Kaplan–Meier curves were generated from the survival data. Variables significant in the univariate analysis (log rank test) were subsequently entered into a multivariate analysis using the Cox proportional hazards ratio model. Overall survival (OS), disease-free survival (DFS), and loco-regional control (LRC) were calculated from the date of diagnosis to the date of progression, date of death, or date of last follow-up if the patient was alive. Time to any event was measured from the date of pathological diagnosis. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 18.0; SPSS Inc., Chicago, IL, USA). A P value $>.05$ was considered to be statistically significant for all tests.

Table I. Patient and tumor characteristics

Characteristics	n = *20*	*%*
Age		
Median	59.5	
≤60	12	60
>60	8	40
Gender		
Male	15	75
Female	5	25
Stage at diagnosis		
I	3	15
II	1	5
III	5	25
IVA	11	55
Extracapsular extension		
Yes	9	45
No	11	55
Perineural invasion		
Yes	8	40
No	10	50
Unknown	2	10
Site		
Oral cavity	4	20
Oropharynx	5	25
Hypopharynx	2	10
Larynx	2	10
Salivary Gland	2	10
Nasal vestibule	2	10
Maxillary sinus	2	10
Nasopharynx	1	5
Treatment modality		
Surgery alone	1	5
Surgery + RT	12	60
Surgery + RTCT	2	10
Neck dissection + RT	1	5
RT alone	2	10
RTCT	2	10

RT, radiotherapy; *CT*, chemotherapy; *RTCT*, chemo-radiotherapy.

RESULTS

Patients' demographics

Data from 22 patients were collected from their medical records. Of these, 2 cases were ineligible due to incomplete data or unclear histology. A total of 20 patients met the study requirements. Ten, six, three, and one patients were included at the Radboud University Medical Center, Nijmegen, The Netherlands, at the University Hospitals of Bern and Geneva, Switzerland, and at the Uludag University Hospital, Bursa, Turkey,

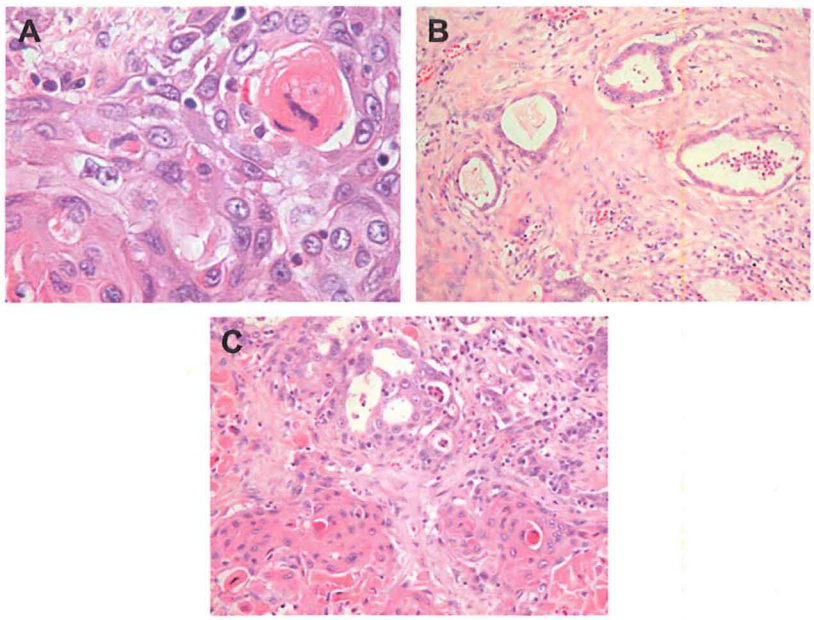

Fig. 1. Photomicrographs of a case of adenosquamous carcinoma. The tumor combines features of a well differentiated SCC with keratinization (**A**) and of an adenocarcinoma with well formed glands (**B**). An area showing both squamous and glandular differentiation is illustrated in (**C**). [Hematoxylin and eosin. (**A**): 600×; (**B-C**): 200×].

respectively. Table I depicts patient and disease characteristics. The median age at diagnosis was 59.5 years (range, 48.2-73). All patients were Caucasian. ASC was 3 times more common in men ($n = 15$) than in women ($n = 5$). All head and neck sites were included. The most common symptoms leading the patients to consult were: the presence of an abnormal mass in the head and neck or cervical lymph nodes ($n = 10$), ulceration in the oral cavity ($n = 3$), hoarseness ($n = 3$), dysphagia ($n = 2$), and nasal obstruction ($n = 2$) associated with epistaxis or deafness. Staging investigations included thoracic computed tomography or X-ray and panendoscopy in 90% and 80% of the cases, respectively. Risk factors including tobacco and alcohol were present in 55% and 50% of the patients, respectively. Smoking and alcohol habits were unknown in 3 and 2 patients, respectively.

Pathological findings

In 2 patients, biopsy of the primary tumor was not performed. In these 2 cases, surgery was performed following positive fine needle aspiration cytology of a lymph node and radiology. The histological diagnosis was known before surgery in 50% of the patients. For the other half, the ASC was diagnosed on the operative pathology specimen, as the biopsy and/or cytology showed SCC only. Microscopically, the tumors had combined features of SCC and adenocarcinoma (Figure 1), generally present in distinct areas, corresponding to the WHO definition of ASC. In 1 case, the glandular features of ASC were present only in the lymph nodes metastasis but were not found in the primary tumor. In 1 case, immunohistochemical evaluation was performed with a panel of antibodies, supporting a dual squamous and glandular differentiation: the tumor cells in the squamous component expressed p63 in their nuclei (Figure 2*A*) while only few tumor cells in the glandular component were positive for p63 (Figure 2*B*). In contrast, the tumor cells in the glandular component expressed Carcinoembryogenic Antigen (CEA) (Figure 2*C*) and cytokeratin 7 (Figure 2*D*), which were both only weakly expressed or not expressed in the squamous component. Positive surgical margins were found in 3 patients and extracapsular extension was present in 9 of the 12 patients undergoing radical neck dissection (Table I). Figure 3 illustrates the macroscopic appearance of a metastatic lymph node with extracapsular extension and muscle infiltration in a radical neck dissection specimen.

Treatment

Surgery was performed in 16 patients. Four patients (20%) underwent primary tumor excision only, while 5 (25%) and 6 (30%) patients respectively had a primary tumor excision with bilateral or unilateral neck dissection. The remaining patient had a neck dissection only, followed by definitive radiotherapy (RT) to the primary tumor. Three patients were classified with stage I, 1 with stage II, 5 with stage III, and 11 with stage IVA disease (Table I). Of the 15 patients

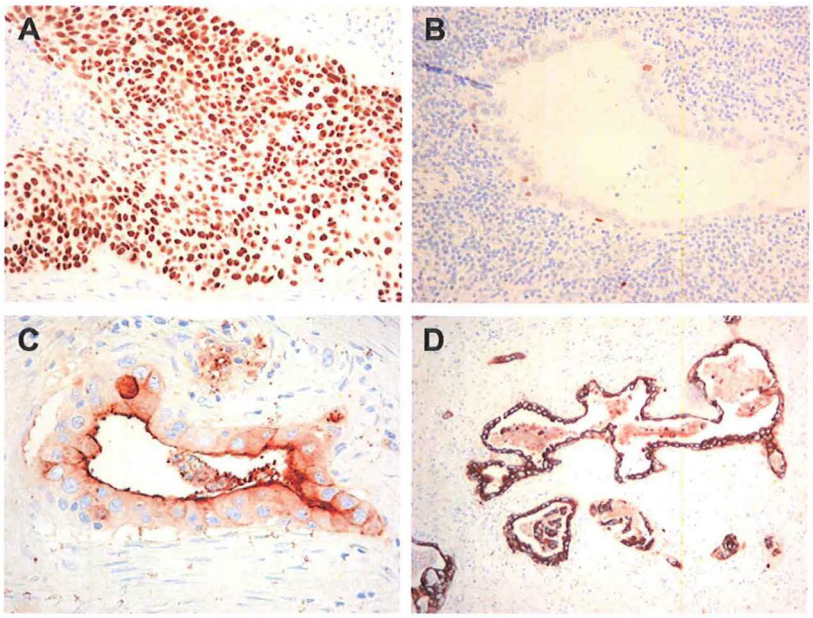

Fig. 2. Immunoprofile of a case of adenosquamous carcinoma. Tumor cells in areas with squamous differentiation diffusely express p63 in their nuclei (**A**). In contrast, only rare tumor cells in areas with glandular differentiation express p63 (**B**). Conversely, tumor cells in areas with glandular differentiation express Carcinoembryogenic Antigen (CEA) (**C**) and cytokeratin 7 (**D**), which are weakly or not expressed in squamous areas. [(**A-B**): 200×; (**C**): 400×; (**D**): 100×].

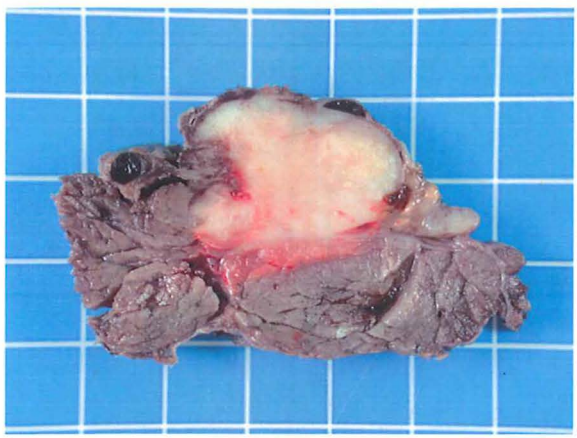

Fig. 3. Radical neck dissection specimen in a case of adenosquamous carcinoma showing a lymph node which is entirely replaced by the tumor with extracapsular extension and invasion into surrounding muscle. A square in the background represents an area of 1 cm^2.

having surgical management of the primary, 12 received adjuvant RT and 2 received adjuvant chemoradiation (with concomitant cisplatin), while only one patient had surgery alone.

Among patients not undergoing surgery, 2 received RT alone and 2 had chemoradiation with concomitant cisplatin chemotherapy (weekly, or every 3-4 weeks). Two patients underwent brachytherapy using 192Ir: the first patient received brachytherapy as a boost after external radiotherapy (21 Gy in 3 fractions) and the second patient was treated with definitive high dose rate brachytherapy to a total dose of 45 Gy in 10 fractions.

Median RT dose to the primary and the nodes was 66 Gy (range, 50-72) and 53 Gy (range 44-66), respectively (1.8-2.0 Gy/fraction, 5 fractions/week). In 4 patients, the planning treatment volume included the primary site only, while the remaining 15 irradiated patients also had treatment to the neck. Nine patients were treated with 2-dimensional RT, 7 with 3-dimensional conformal RT, and 3 with intensity-modulated RT.

Outcome

The median follow-up time was 15.5 months (range 2-2). All but 2 patients had a complete response to initial treatment. These 2 patients developed distant metastases a few weeks after initial management. During the follow-up, 9 patients presented rapid systemic progression within a few months (lung, bone, mediastinum, and liver), associated in 6 patients with simultaneous local and/or regional recurrence. One patient had a local relapse only. In another patient, recurrence occurred in the cervical lymph nodes only. At last follow-up, 7 patients were alive with no evidence of disease, and 12 had died: 10 due to ASC and 2 due to other reasons (secondary lung cancer and heart failure). Of the 4 local relapses observed, all occurred in the planning treatment volume. Among the 8 nodal recurrences, 6 were

Table II. Relapse characteristics

Case	*Age*	*Stage*	*Site*	*Treatment*	*Margins*	*LR*	*Infield LR*	*RR*	*Infield RR*	*SR*	*Sites*	*Further treatment*	*OS*	*Status*
1	61	4a	Base of tongue	Surgery + RT	−	No		No		Yes	Lung		4	DoD
2	64	4a	Larynx	Surgery	−	No		No		No			3	DOC
3	71	4a	Floor of mouth	Surgery + RT	+	Yes (maxilla)	Yes	Yes	Yes	Yes	Lung, bone		7	DoD
4	54	4a	Nasopharynx	RT	NA	Yes (nasopharynx)	Yes	No		No		PCT (MTX)	42	DoD
5	60	4a	Maxillary sinus	Surgery + RT	+	No		Yes	No	Yes	Lung	PCT	39	DoD
6	60	3	Oral cavity	Surgery + RT	+	No		No		Yes	Lung		9	DoD
7	58	4a	Sublingual gland	Surgery + RT	−	No		Yes	Yes	Yes	Lung, liver		11	DoD
8	68	3	Tongue	Surgery + RT	−	No		No		No			10	AWOD
9	61	4a	Tonsil	RTCT	NA	No		No		No			38	AWOD
10	54	1	Vestibule	Surgery + RT	−	No		No		No			59	AWOD
11	60	3	Oral cavity	Surgery + RTCT	−	No		No		No			62	AWOD
12	53	3	Hypopharynx	Surgery + RT	−	Yes	Yes	Yes	Yes	Yes	Lung, pleura	Laryngectomy, ND, RT	49	DoD
13	65	3	Submandibular gland	Surgery + RT	−	No		No		Yes	Lung, bone	Palliative RT	17	DoD
14	57	1	Vestibule	RT	NA	No		No		No			40	AWOD
15	58	4a	Oropharynx	ND + RT	−	No		No		No			10	DOC
16	48	4a	Hypopharynx	Surgery + RTCT	−	Yes (pharynx)	Yes	Yes	Yes	No		RT neck 38 Gy	9	AWD
17	73	1	Larynx	Surgery + RT	−	No		No		No			21	AWOD
18	52	4a	Tonsil	Surgery + RT	−	No		Yes		Yes	Lung, mediastinum	PCT (CCPD/5FU/cetuximab), RT 20 Gy	13	DoD
19	57	4a	Maxillary sinus	Surgery + RT	−	No		Yes	No	No		RT neck 60 Gy	52	AWOD
20	59	2	Tonsil	Surgery + RT	−	No		Yes	Yes	Yes	Lung	ND	14	DoD

LR, local relapse; *RR*, regional relapse; *SR*, systemic relapse; *OS*, overall survival; *CT*, chemotherapy; *RT*, radiotherapy; *RTCT*, chemoradiotherapy; *ND*, neck dissection; *MTX*, Methotrexate; *PCT*, palliative chemotherapy; *CCDP*, Cisplatin; *5FU*, 5 Fluorouracil; *DoD*, dead of disease; *DOC*, dead due to other cause; *AWOD*, alive without disease; *AWD*, alive with disease; *NA*, not available.

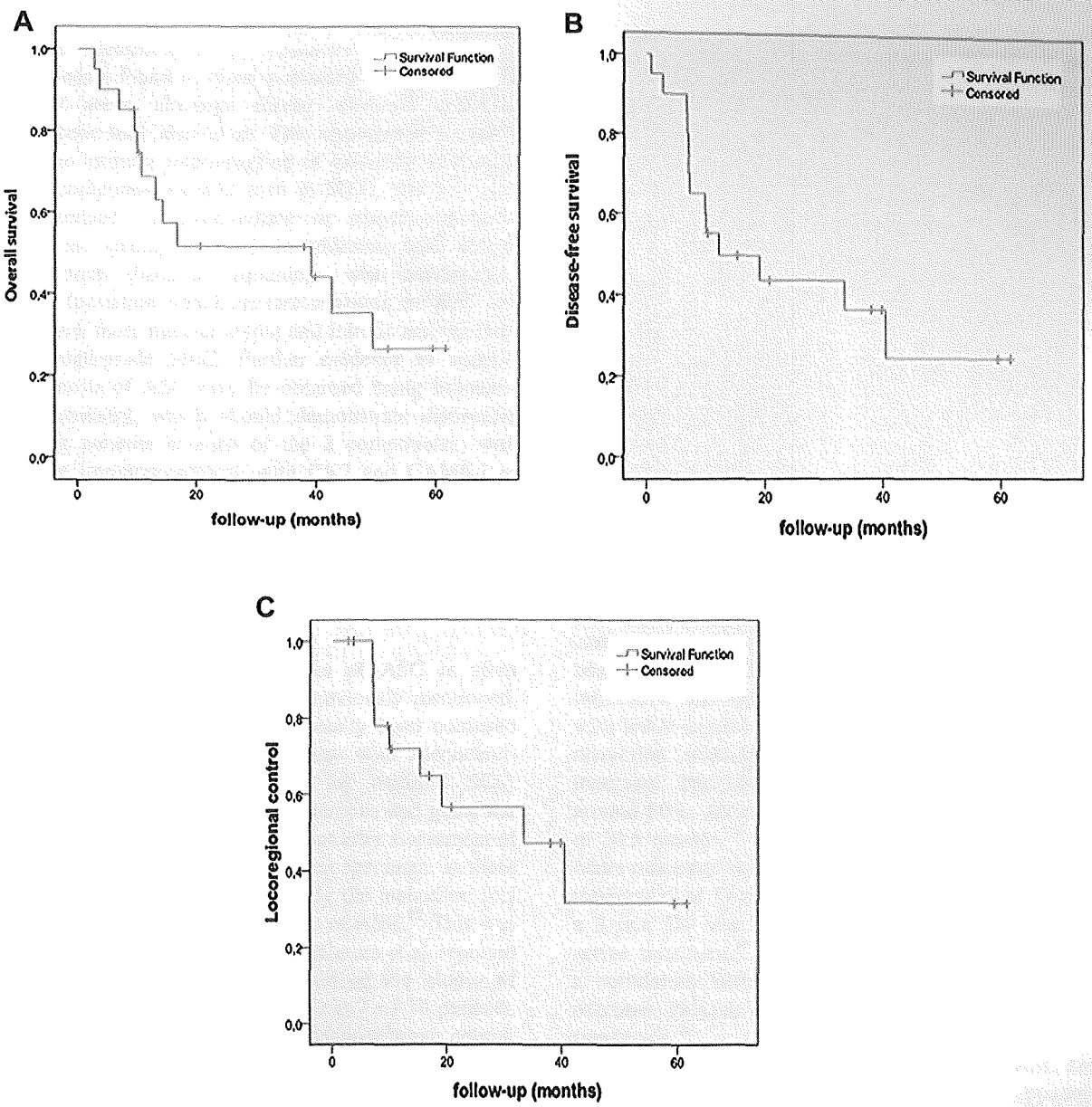

Fig. 4. (**A**): Overall survival. (**B**): Disease-free survival. (**C**): Locoregional control.

likewise in-field, while 2 were found to be outside the initial radiotherapy volume. Table II illustrates recurrences data and salvage treatment when possible.

The 3-year OS, DFS, and LRC rates were 52% [95% CI (confidence interval): 28%-75%], 32% (95% CI: 11%-54%), and 47% (95% CI: 20%-74%) respectively, while median OS, DFS, and LRC were 39, 12, and 33 months respectively (Figure 4). In univariate analysis, DFS was negatively influenced by the presence of extracapsular extension ($P = .035$) and advanced stage (I-III versus IVA, $P = .028$). None of the other analyzed variables, namely gender, age, presence of vascular invasion, and margin status had a significant influence on DFS, LRC, or OS. The multivariate analysis confirmed extracapsular extension and stage as independent variables for DFS [hazard ratio (HR) = 1.16 and 1.14, $P = .0016$ and .0137, respectively].

Grade >1 acute toxicity was observed in 10 patients. Grade 3 mucositis and dysphagia occurred during radiation in 7 patients. Only one of the 19 patients who underwent RT presented grade 3 late radiation-related toxicity (complete dryness).

DISCUSSION

ASC is a rare entity, not only in the head and neck area, but also in other organs, accounting for 0.6% and 0.1% of lung and colon cancers, respectively.[12,13] Cases have also been reported in the uterine cervix, the pancreas,

and the esophagus.[14,15] Histological diagnosis depends on the identification of squamous and glandular components found in close proximity but generally in distinct areas, although mixed areas or areas of confluence may also exist. This appearance contrasts with the intimate intermingling of glandular and squamous component usually seen in MEC, which is also characterized by intermediate or transitional cells, which are lacking in ASC. In addition, ASC should show areas distinctly squamous with extracellular keratin formation, which are rare or absent in MEC, and will show more nuclear atypia and mitotic activity than even high-grade MEC. Further evidence to support a diagnosis of ASC may be obtained using immunohistochemistry, which should demonstrate distinctive staining patterns in each of the 2 components, with positive immunoreactivity with CK7 and CAM5.2 in the adenocarcinoma component, and positive immunoreactivity with pancytokeratin or p63 but negative immunoreactivity with CK7 and CAM5.2 in the SCC component.[9,16] This feature is not seen in adenoid/acantholytic SCC which may mimic ASC due to the acantholysis of the tumor cells.

Still, the histological diagnosis of ASC is often difficult for the pathologist. As previously mentioned, the tumor on the biopsy might easily been confused with salivary gland MEC, but also with adenocarcinoma and adenoid/acantholytic or basaloid SCC. Moreover, evidence of a dual squamous and glandular differentiation may only be apparent after assessment of the complete tumor on the resection specimen, as these features may be focal. Rarely, only the metastatic foci may reveal the dual differentiation of ASC.[17] This was the case in one of our patient. Yoshimura et al. reported a rate of incorrect histology based on the biopsy of 68.5%[18]: First diagnosis was SCC in 7 of 19 patients. This was the case in 50% of the patients in our cohort. This is likely due to the fact that only the squamous cell component was seen in some biopsy specimens, with the glandular component only subsequently identified in metastatic nodes. In a primary tumor, the adenocarcinoma portion is often found in the deepest portion of the lesion and is less accessible to small biopsies. This suggests that ASC might be more common than the literature suggests, and this could be one of the reasons for failure after curative treatment in a subset of presumed SCCs of the head and neck.

The demographics in our series are representative of the already published literature. The median age was 59.5 years. Most of the published cases have occurred in middle-aged and elderly patients. However, ASC may also occur in younger patients as reported by Sheahan et al., who described an ASC involving the tongue in a 22-year-old woman.[9] In another series of 12 cases published by Keelawat et al., the median age was 65.5 years, but 2 of their patients presenting with a locally advanced ASC of the oral cavity (palate and floor of mouth) were only 34- and 38-year-old, respectively.[19] We also found a male predilection (3:1), which has also been described by some authors previously.

The common sites of occurrence in the head and neck appear to be the larynx and the oral cavity. So far, only 8, 9, and 2 cases of ASC have been described in the oropharynx, nasal cavity/paranasal sinus, and hypopharynx, respectively. The larynx was less frequently involved in our series, with only 2 cases, while the oropharynx was more represented.

The aggressiveness and treatment resistance of ASC of the head and neck have been reported in the literature. However, because of the rarity of the tumor, neither preoperative diagnostic procedure nor management strategies have yet been standardized. Izumi et al. reported the case of a 78-year-old women presenting with an ASC of the tongue, which progressed during adjuvant radiochemotherapy leading to the death of the patient 4 months after treatment.[20] Most of the reported cases in the oral mucosa and maxillofacial region have been locally extremely aggressive showing marked infiltration and destruction of the surrounding tissues, with lethal issues in most of them, despite radical neck dissection, wide excision of the tumor, and adjuvant treatment. The 2-year survival rate in the literature is around 50%. Alos et al. reported a mean survival time of 34.5 months.[16] Patients in our study had a slightly better outcome with a 3-year OS rate of 52% and 3-year median OS of 39 months, while Yoshimura et al. found a 5-year OS rate of 61% in patients who underwent active treatment.[18] As might be expected, we found a correlation between the stage of the disease and outcome. This has also been described by Damiani et al. previously.[10]

The reasons for the aggressive behavior of ASC are unclear, but it could be explained by an apparent propensity to spread by perineural invasion. This pathological feature has been observed in 6 of 12 cases in a series described by Keelawat,[19] and in 75% of the patients reported by Sheahan et al. In our series, 40% of ASC harbored perineural invasion, which could have contributed to explain the slightly better prognosis of our cohort.

In recent years, there has been mounting evidence of the role for human papillomavirus (HPV) as an etiologic agent in a subset of head and neck cancers.[21] Moreover, HPV positivity is now considered as a favorable and strong independent prognostic factor in head and neck cancer radiotherapy.[22] ASC of the cervix has been shown to be related to HPV,[23] but the role of HPV infection in head and neck ASC in still unclear. Recently, Masand et al. found that only a small

minority of ASC is HPV-related (25%) but that these patients appear to have clinical outcomes comparable to those of patients with HPV-positive SCC.[4] These findings need to be confirmed in future studies. Unfortunately, the HPV status was not available in our cohort.

In conclusion, overall prognosis of locoregionally advanced ASC remains poor, and distant metastases and nodal relapse occur in almost half of the cases. However, local control in our series of patients managed mostly with combined modality treatment was favorable and early stage ASC patients had prolonged DFS.

REFERENCES

1. Gerughty RM, Hennigar GR, Brown FM. Adenosquamous carcinoma of the nasal, oral and laryngeal cavities. A clinicopathologic survey of ten cases. *Cancer.* 1968;22:1140-1155.
2. Evans HL. Mucoepidermoid carcinoma of salivary glands: a study of 69 cases with special attention to histologic grading. *Am J Clin Pathol.* 1984;81:696-701.
3. Barnes L, Tse LLY, Hunt JL. Tumors of the hypopharynx, larynx, and trachea: introduction. In: Barnes EL, Eveson JW, Reichart P, Sidransky D, Kleihues P, Sobin LH, eds. *Pathology and Genetics of Head and Neck Tumours, World Health Organization Classification of Tumours.* Lyon (France): IARC Press; 2005:11.
4. Masand RP, El-Mofty SK, Ma XJ, Luo Y, Flanagan JJ, Lewis JS Jr. Adenosquamous carcinoma of the head and neck: relationship to human papillomavirus and review of the literature. *Head Neck Pathol.* 2011;5:108-116.
5. Ellis GL, Auclair P, Gnepp DR, Goode RK. *Adenosquamous Carcinomas. Surgical Pathology of the Salivary Glands.* Philadelphia: WB Saunders; 1991:455-459.
6. Fonseca FP, Ramos LM, Vargas PA, de Almeida OP, Lopes MA, Santos-Silva AR. Oral adenosquamous carcinoma: evidence that it arises from the surface mucosal epithelium. *Histopathology.* 2012;61:321-323.
7. Napier SS, Gormely JS, Newlands C, Ramsay-Baggs P. Adenosquamous carcinoma. A rare neoplasm with an aggressive course. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1995;79:607-611.
8. Kothari RK, Ghosh A, Bhattacharyya SK, Ghosh SK. Adenosquamous carcinoma of oral cavity: a case report. *J Indian Med Assoc.* 2007;105:531-532.
9. Sheahan P, Fitzgibbon J, Lee G, O'Leary G. Adenosquamous carcinoma of the tongue in a 22-year-old female: report of a case with immunohistochemistry. *Eur Arch Otorhinolaryngol.* 2003;260:509-512.
10. Damiani JM, Damiani KK, Hauck K, Hyams VJ. Mucoepidermoid-adenosquamous carcinoma of the larynx and hypopharynx: a report of 21 cases and a review of the literature. *Otolaryngol Head Neck Surg.* 1981;89:235-243.
11. Patel A, Ozsahin M, Mirimanoff RO, Bhatia S, Chang K, Miller RC. The rare cancer network: achievements from 1993 to 2012. *Rare Tumors.* 2012;4:e35.
12. Fitzgibbons PL, Kern WH. Adenosquamous carcinoma of the lung: a clinical and pathologic study of seven cases. *Hum Pathol.* 1985;16:463-466.
13. Frizelle FA, Hobday KS, Batts KP, Nelson H. Adenosquamous and squamous carcinoma of the colon and upper rectum: a clinical and histopathologic study. *Dis Colon Rectum.* 2001;44:341-346.
14. Kardon DE, Thompson LD, Przygodzki RM, Heffess CS. Adenosquamous carcinoma of the pancreas: a clinicopathologic series of 25 cases. *Mod Pathol.* 2001;14:443-451.
15. Lam KY, Loke SL, Ma LT. Histochemistry of mucin secreting components in mucoepidermoid and adenosquamous carcinoma of the oesophagus. *J Clin Pathol.* 1993;46:1011-1015.
16. Alos L, Castillo M, Nadal A, et al. Adenosquamous carcinoma of the head and neck: criteria for diagnosis in a study of 12 cases. *Histopathology.* 2004;44:570-579.
17. Mokhtari S, Mohsenifar Z. Diagnostic histological features of metastatic lymph nodes in adenosquamous carcinoma. *Pathol Res Pract.* 2012;208:360-362.
18. Yoshimura Y, Mishima K, Obara S, Yoshimura H, Maruyama R. Clinical characteristics of oral adenosquamous carcinoma: report of a case and an analysis of the reported Japanese cases. *Oral Oncol.* 2003;39:309-315.
19. Keelawat S, Liu CZ, Roehm PC, Barnes L. Adenosquamous carcinoma of the upper aerodigestive tract: a clinicopathologic study of 12 cases and review of the literature. *Am J Otolaryngol.* 2002;23:160-168.
20. Izumi K, Nakajima T, Maeda T, Cheng J, Saku T. Adenosquamous carcinoma of the tongue: report of a case with histochemical, immunohistochemical, and ultrastructural study and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;85:178-184.
21. Klussmann JP, Weissenborn S, Fuchs PG. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2001;345:376.
22. Lassen P, Eriksen JG, Hamilton-Dutoit S, Tramm T, Alsner J, Overgaard J. Effect of HPV-associated p16INK4A expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2009;27:1992-1998.
23. Yasuda S, Kojima A, Maeno Y, et al. Poor prognosis of patients with stage Ib1 adenosquamous cell carcinoma of the uterine cervix with pelvic lymphnode metastasis. *Kobe J Med Sci.* 2006;52:9-15.

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