THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (May–June 2017) 67(3):196–201
DOI 10.1007/s13224-016-0935-6

ORIGINAL ARTICLE

Adenoid Cystic Carcinoma of Vulva-11 Years' Single-Institution Experience

Leena Rose Johnson[1] · Rema Prabhakaran Nair[2] · Suchetha Sambasivan[2] · Rari P. Mony[2] · Jayapriya Gangadharan[2] · Aswin Kumar[2] · Iqbal M. Ahamed[2]

Received: 17 June 2016 / Accepted: 12 August 2016 / Published online: 19 September 2016

About the Author

Dr. Leena Rose Johnson is a qualified Obstetrician and Gynaecologist with 8 years of clinical experience. She has undergone fellowship training in Gynecologic Surgical Oncology from Regional Cancer Centre, Thiruvananthapuram, Kerala, India, and is presently employed as Assistant Professor of Obstetrics and Gynecology at SUT Academy of Medical Sciences, Thiruvananthapuram, Kerala.

Leena Rose Johnson has done her MBBS, DGO, DNB(OBG). She is Assistant Professor of Obstetrics and Gynecology at SUT Academy of Medical Sciences,Thiruvananthapuram. Rema Prabhakaran Nair is Additional Professor, Division of Surgical Oncology, Regional Cancer Centre; Suchetha Sambasivan is Associate Professor, Division of Surgical Oncology, Regional Cancer Centre; Rari P. Mony is Senior Resident, Division of Pathology, Regional Cancer Centre; Jayapriya Gangadharan is Senior Resident, Division of Pathology, Regional Cancer Centre; Aswin Kumar is Additional Professor, Division of Radiation Oncology, Regional Cancer Centre; Iqbal M. Ahamed is Professor and Head of the Department, Division of Surgical Oncology, Regional Cancer Centre.

The study was conducted during her tenure as Senior Resident in Gynecologic Surgical Oncology at Regional Cancer Centre, Thiruvananthapuram.

This study has been approved by the Institutional Review Board, Regional Cancer Centre, Thiruvananthapuram.

Abstract

Introduction Adenoid cystic carcinoma of vulva (ACC-vulva) is an extremely rare entity with <100 cases reported in the literature so far.

Objective To study the clinical profile and outcome of ACC-vulva treated at a tertiary cancer care centre in South India.

✉ Leena Rose Johnson
leonroop@gmail.com

[1] Department of Obstetrics and Gynecology, SUT Academy of Medical Sciences, Thiruvananthapuram, Kerala, India

[2] Division of Surgical Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India

Methods This is a retrospective, record-based study of histopathologically confirmed cases of ACC-vulva treated at our centre from January 2005 to March 2016.
Results Only four patients were diagnosed with ACC-vulva during the 11-year period under study. The longest duration of follow-up was 129 months. The age at diagnosis ranged from 32 to 43 years, with a median of 40 years. All patients were married, parous and premenopausal and presented with a painless unilateral vulval swelling. All patients had involvement of the Bartholin's gland site with normal overlying skin. In all patients, wide excision was performed. Unilateral inguinal node dissection was done in one case. Perineural infiltration was documented in two cases, while positive excision margins were present in three cases. None of the patients had any lymph node involvement at diagnosis or during follow-up. Two patients had recurrence of disease. The disease-free interval was 23 months for one patient and 118 months for the other. In both, local (vulval) and distant (multiple lung) metastases were detected simultaneously.
Conclusion Adenoid cystic carcinoma of vulva is an extremely rare, slowly progressing neoplasm mostly involving the Bartholin's gland. The usual treatment includes wide excision and adjuvant radiotherapy (if required). There may be late local and distant recurrence.

Keywords Bartholin's cyst · Vulvar neoplasm · Bartholin's gland carcinoma · Vulval carcer

Introduction

Adenoid cystic carcinoma of vulva (ACC-vulva) is an extremely rare entity with fewer than 100 cases reported in the literature so far [1].

In general, ACC affects the exocrine glands. First described by Theodor Billroth (1856), the currently accepted terminology ACC was proposed by Foote and Frazell (1953) [2]. Fifty-eight percent of these tumours occur in the oral cavity—major and minor salivary glands, palate, floor of the mouth, gums, lips, tongue and pharynx. Besides the oral cavity, ACC also occurs in the nose, nasal cavity, sinus, larynx, trachea, bronchus, lung, oesophagus, ear, lacrimal gland, brain, skin, breast, Bartholin's gland, vulva and cervix.

The distinctive histopathological feature of ACC tumours is the "cribriform pattern", characterized by rounded nests of cells arranged around gland—like spaces (swiss-cheese or sieve-like pattern), which contain granular basophilic material. Most of the gland-like spaces are not true glandular spaces but instead represent extracellular cavities containing reduplicated basal laminar material as well as myxoid material produced by the tumour cells [3] (Figs. 1, 2).

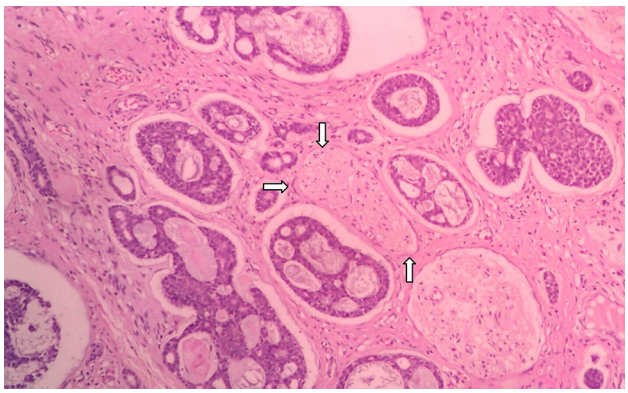

Fig. 1 Histopathological picture (×10) showing neoplasm with cribriform and tubular pattern. Tumour cell nests are seen surrounding a nerve fibre (marked by *arrows*), indicating perineural infiltration

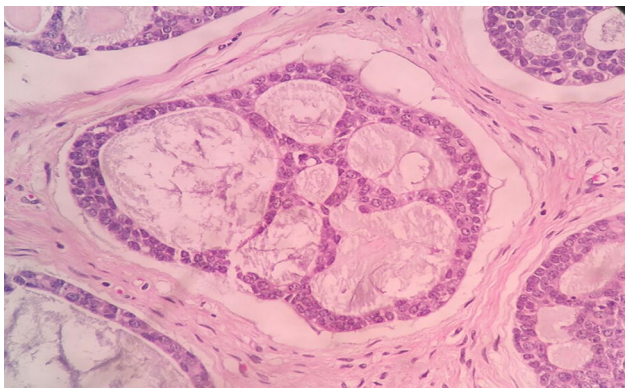

Fig. 2 High power view (×40) of cribriform pattern

Since vulva is a very uncommon site for ACC, there is limited literature on ACC-vulva. Here, we looked into the clinical profile, histopathological findings and survival of patients with ACC-vulva treated in our institution.

Materials and Methods

This is a retrospective study of all patients with ACC-vulva treated at a tertiary cancer centre in South India between January 2005 and March 2016. The medical records of the patients were examined, and relevant information related to patient demographics, clinical presentation, surgical management, histopathological findings, adjuvant treatment and disease progression was collected. The follow-up of the patients were updated till March 2016 by telephone enquiry.

Table 1 Clinical details of the four patients with adenoid cystic carcinoma of vulva treated from January 2005 to March 2016

Cases	Mrs. A	Mrs. B	Mrs. C	Mrs. D
Age at diagnosis (years)	42	32	43	38
Symptom onset-treatment interval	24 months	60 months	6 months	30 months
Maximum tumour dimension	2 cm	12 cm	2.7 cm	3.5 cm
Margin status at excision	+ve	+ve	−ve	+ve
Treatment	Wide excision + unilateral inguinal lymph node dissection + radiotherapy	Wide excision + radiotherapy	Wide excision	Wide excision + radiotherapy
Follow-up duration	129 months	51 months	11 months	8 months
Disease-free interval	118 months	23 months	10 months	6 months
Site of recurrence	Local + Lungs	Local + Lungs	–	–
Status at last follow-up	Alive with disease, 8 months post-recurrence	Died of the disease 25 months post-recurrence	Alive, disease free	Alive, disease free

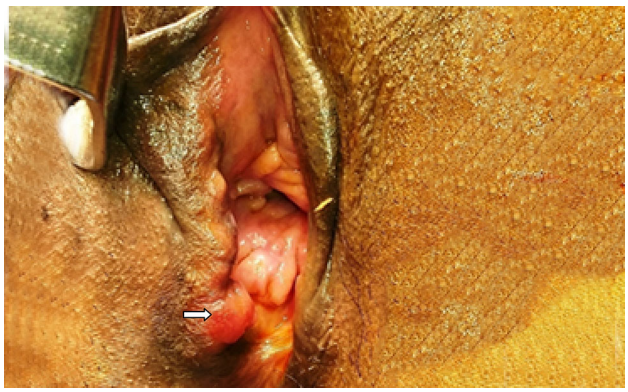

Fig. 3 Swelling (marked by *arrow*) in the posterior aspect of right labia in a patient with ACC-vulva

Results

There were 102 patients with carcinoma of vulva during the period under study (January 2005–March 2016). Only four (3.9 %) had histopathology of adenoid cystic carcinoma (Table 1). The longest duration of follow-up was 129 months. The age at diagnosis ranged from 32 to 43 years, with a median of 40 years. All patients were married, parous and premenopausal and presented with a painless unilateral vulval swelling. As the swelling slowly progressed in size, two of them had associated pain, burning sensation on micturition and pruritus. The duration of symptoms prior to surgical treatment ranged from 6 months to 5 years with a median of 30 months. All patients had involvement of the Bartholin's gland site with normal overlying skin (Fig. 3). In all patients, wide excision was performed. Three patients who were managed initially in a peripheral hospital had to undergo repeat surgery with wide excision due to positive margin. Unilateral inguinal node dissection was done in one case. The maximum tumour dimension ranged from 2 to 12 cm (in those who underwent re-wide excision, the initial maximum tumour dimension was added on to the maximum tumour dimension of the second specimen). Perineural infiltration was documented in two cases, while positive excision margins were present in three cases (despite re-wide excision in two of them). One patient had lymphovascular space and skeletal muscle involvement at the time of diagnosis. None of the patients had any lymph node involvement at diagnosis or during follow-up. Patients with positive margins were treated with adjuvant radiotherapy.

Disease recurrence was confirmed in two patients after a disease-free interval of 23 and 118 months respectively. Both patients were not on regular follow-up after primary treatment, which included surgery and radiotherapy. Both had simultaneous detection of local (vulval) and distant (multiple lung) metastases (Figs. 4, 5). Despite extensive pulmonary metastases as seen in Fig. 5, the patient had mild exertional dyspnoea as the only respiratory symptom. The vulval tumour was fixed to the bone and not resectable at presentation. Both were treated with a short course of radiotherapy. One of them received a short course of Gefitinib, which was soon discontinued due to financial constraints. Compared to the patient who had a disease-free interval of 118 months, the patient with disease-free interval of 23 months had a longer symptom onset-to-treatment interval (5 vs. 2 years); larger tumour size (12 vs. 2 cm) and perineural infiltration at diagnosis. The patient with shorter disease-free interval died of the disease 25 months after detection of recurrence.

Discussion

Adenoid cystic carcinoma of vulva usually originates from the Bartholin's gland, but may rarely occur in the rest of the vulva. ACC constitutes only 10 % of Bartholin's gland

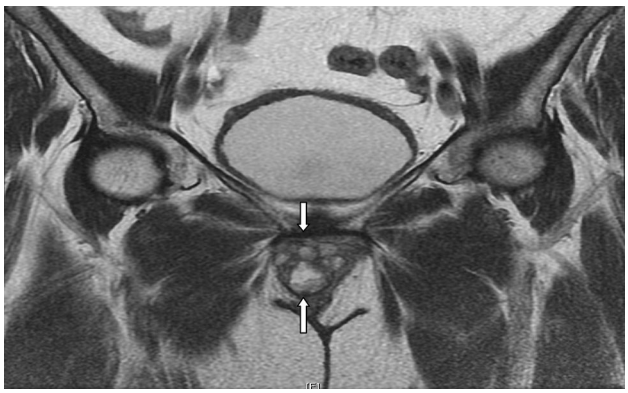

Fig. 4 MRI of a patient with ACC-vulva recurrence showing coronal T2 image with T2 hyperintense, heterogeneous lesion (marked by *arrows*) involving right labia and lower 1/3rd of vagina

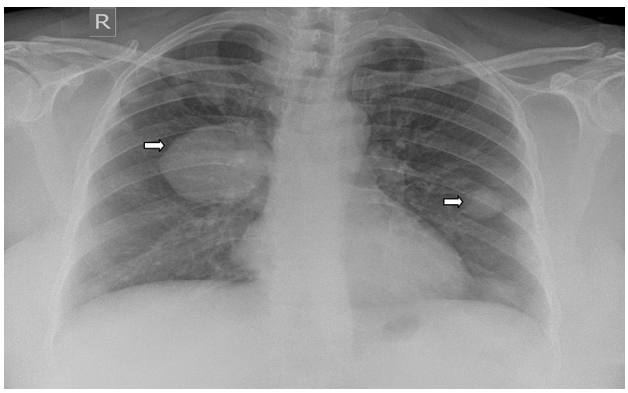

Fig. 5 Chest X-ray of a patient with ACC-vulva recurrence showing multiple pulmonary metastases (marked by *arrows*)

carcinomas, which in turn, constitute only 0.1–7 % of vulval malignancies [1].

At our centre, there were four cases of ACC-vulva during the study period of 11 years and 2 months. In comparison, a study on Bartholin's gland carcinomas at Queensland Centre for Gynaecological Cancer, Australia, described only one case of ACC-Bartholin's gland in 23 years [4]. Yoon et al. [5] reported the highest number of cases of ACC-Bartholin's gland from a single institution—five in 14 years at Samsung Medical Center, Seoul, Republic of Korea.

The median age in this study is 40 years. Following a review of 49 articles (79 cases), Alsan et al. [6] have reported the median age as 48 years (range 25–80 years).

The clinical picture is characterized by its insidious onset and slow, indolent but relentless progression. The points in this study that suggest ACC-vulva to be a slow-growing neoplasm are:

1. the symptom onset-treatment interval ranged from 6 month to 5 years, with none of the patients having features of systemic metastasis at the time of initial presentation;
2. in the two patients with adequate follow-up, the disease-free intervals were 23 and 118 months, respectively;
3. one patient survived for 25 months after the detection of local recurrence with multiple lung metastases.

Initially, all the patients in this study had painless labial swelling at the site of the Bartholin's gland (posterolateral aspect of the vaginal introitus) as shown in Fig. 3. In two patients, pain and pruritus developed when the disease progressed. This initial clinical presentation can easily be confused with a benign Bartholin's cyst, and there is a potential for misdiagnosis and delay in treatment [7]. The prolonged symptom onset-treatment interval in this study may be the result of such a delay. Jones et al. [4], in a case series on Bartholin's gland carcinomas, report a case of ACC-vulva initially diagnosed as a Bartholin's cyst, leading to a 2-year delay in diagnosis. Yoon et al. have reported a case of ACC-Bartholin's gland which was diagnosed only 8 months after marsupialization of a Bartholin's abscess. Asymptomatic small Bartholin's cysts in women <40 years of age are usually managed conservatively. However, in this study, there were two patients who were <40 years of age with malignancy mimicking a benign Bartholin mass in its early stage. Three of the patients in this study had excision in a peripheral hospital and had to undergo re-wide excision at our centre due to positive margin. This poses the question whether there is an effective method for pre-operative diagnosis. Imaging by ultrasound and MRI can help only when the infiltrative margins of the tumour are discernible. Aspiration cytology has been found to be useful in ACC at other sites, but false negative cases have also been reported [2, 8].

In view of the above, all indurated masses at the Bartholin site warrant at least a biopsy to rule out malignancy. Biopsy may be done at the time of marsupialization/drainage of a Bartholin cyst, especially when unusual features like induration and infiltrative margins are detected intraoperatively.

Surgical resection of the neoplasm with clear margins is the primary treatment. Tumour grade, stage, lymph node metastasis, invasion of major nerves and margin status are important prognostic factors. The observations of Fordice et al. in ACC of head and neck seem to hold true in ACC–vulva, too. They suggested that there may be two patient populations in ACC: one doomed to rapid death from aggressive tumour and another doomed to a prolonged course measured in decades. A 5-year survival rate of 71–100 % and a 10-year survival rate of 59–100 % have been reported [9].

Ipsilateral regional inguinal lymph node involvement may be present in 10–15 % of cases. Contralateral inguinal lymph node involvement has not been reported. There is no

clear indication for inguinal lymph node dissection, except when there is clinical/radiological suspicion of nodal metastasis.

Due to the predilection for perineural invasion and skip metastasis, microscopic involvement of the resected margins is possible. In this study, three of the four patients had positive margin and underwent radiotherapy. This suggests the need for a wider excision margin when compared to squamous cell carcinoma of vulva. In the literature, 48 % of those who underwent excision of the involved vulva and 30 % of those who underwent radical vulvectomy have been reported to have positive margin. According to a review by Alsan et al. [6], simple and radical vulvectomy had been performed in 54 and 46 % of cases, respectively. Recurrence was observed in 35 % of cases with positive resection margins, and even in 10 % of those with negative resection margins.

Nowak et al. [10] also highlight the need for radical excision procedures for this disease. Quality of life issues need to be considered without compromising treatment. Radiotherapy seems to be effective in tackling the positive margin. In this study, one of the patients had a disease-free interval of 118 months despite positive margin, having probably benefitted from adjuvant radiotherapy. Alsan et al. [6] reported that the recurrence rate was 9.5 % (2/21 patients) in those undergoing radiotherapy and 37.5 % (21/56 patients) in those not receiving radiotherapy ($p = 0.01$), indicating that local recurrence was satisfactorily managed with radiotherapy. The benefit of radiotherapy is suggested by another retrospective, 14-year single-institution experience on ACC-Bartholin's gland, reported by Yoon et al. [5] Three out of five patients had positive margins. The patient who did not receive adjuvant radiotherapy had a vulval recurrence after 24 months, whereas none of the other two who received adjuvant radiotherapy and with adequate follow-up duration (71 and 106 months) had local recurrence.

The two patients in this study who developed recurrence presented when surgical intervention was not feasible (the vulval lesion was fixed to the bone, and there were multiple pulmonary metastases). Both the patients had inadequate follow-up visits after the completion of initial treatment. This highlights the need to inculcate awareness of late recurrence and long-term vigilance among the patients with ACC-vulva.

The commonest site for distant metastasis is the lungs. Other sites reported in the literature include the liver, brain and bones.

Yoon et al. [5] describe two cases of recurrence of ACC-Bartholin's gland that received aggressive surgical management to prolong survival. One of them developed first recurrence 24 months after primary surgery, which was successfully treated by radical local excision. Later, she went on to have repeated recurrences at varying intervals, for which she underwent pelvic exenteration, metastasectomy of lung and liver and chemotherapy. The patient survived for 189 months after primary surgery and had progressive disease at last follow-up. Thus, even at the time of recurrence, radical surgeries seem to have a significant role in treatment. However, the success of treatment will depend on how early the recurrence is detected. Since pulmonary metastases are common and asymptomatic, regular imaging of the chest should be incorporated in the follow-up of patients with ACC. The commonest cause of death due to ACC is systemic metastases. Unfortunately, there is no consensus on the effective systemic treatment of this condition. Chemotherapy with 5-fluorouracil, cyclophosphamide, methotrexate, doxorubicin, dactinomycin, irinotecan, have been tried in individual cases, but the efficacy of each is difficult to assess due the rarity of this condition and relatively long survival without treatment. Ramanah et al. [11] described a patient with confirmed brain and lung metastasis from ACC-vulva, treated with brain radiotherapy, lobectomy and chemotherapy with cyclophosphamide, adriamycin and cisplatin whose disease progressed to death.

Many cases of ACC were found to express c-kit receptor (CD117), the understanding of which led to trials on the role of KIT tyrosine kinase inhibitors in its treatment. Imatinib, a tyrosine kinase inhibitor (in the dose of 800 mg per day), has been evaluated by phase II trials. It seems to be beneficial in documented progressive, recurrent ACC of salivary gland, with positive CD 117 immunostaining. This form of targeted therapy may help prevent the progression of disease, occasionally evoking a partial response, rendering them amenable to surgical treatment [12, 13].

However, a few phase II trials have showed that imatinib may not be helpful in containing the disease [14, 15].

Conclusion

Adenoid cystic carcinoma of vulva is an extremely rare, slowly progressing neoplasm mainly involving the Bartholin's gland. It usually presents as a labial swelling involving the site of Bartholin's gland, with normal appearing overlying skin. The initial clinical presentation may mimic a benign Bartholin's cyst. Misdiagnosis and delay in treatment are therefore possible. The usual treatment includes wide excision and adjuvant radiotherapy (if required). There may be late local and distant recurrence. Awareness of late recurrence and the need for long-term vigilance are to be inculcated among patients. Early detection of recurrence and aggressive surgical management of the recurrences are beneficial. Further research is

required to determine the utility of systemic treatment in patients with distant metastases.

Compliance with Ethical Standards

Conflict of interest 'Leena Rose Johnson, Rema. P, Suchetha. S, Rari P Mony, Jayapriya G., Aswin Kumar and Iqbal M. Ahamed' declare that they have no conflict of interest.'

Ethical Statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

References

1. Eriko T, Tadahiro S, Miura J, et al. Chemoradiotherapy with irinotecan (CPT-11) for adenoid cystic carcinoma of Bartholin's gland: a case report and review of the literature. Gynecol Oncol Rep. 2013;4:16–9.
2. Hosmani J, Nayak R, Kulkarni M, et al. FNAC diagnosis of adenoid cystic carcinoma of the maxillary sinus: a case report with emphasis on cytological differential diagnosis. J Dr NTR Univ Health Sci. 2013;2(2):142–6.
3. Sisodia SM, Khan WZ, Ansari SA, et al. Adenoid cystic carcinoma of Bartholin's gland: report of a case and review of literature. South Asian J Cancer. 2013;2:18.
4. Jones IS, Crandon A, Sanday K. Bartholin's gland carcinomas: a 20 plus-year experience from Queensland. Open J Obstet Gynecol. 2012;2:385–8.
5. Yoon G, Kim HS, Lee YY, et al. Analysis of clinical outcomes of patients with adenoid cystic carcinoma of Bartholin's glands. Int J Clin Exp Pathol. 2015;8(5):5688–94.
6. Alsan C, Vinh-Hung V, Eren F, et al. Adenoid cystic carcinoma of the Bartholin's gland: case report and systematic review of the literature. Eur J Gynaecol Oncol. 2011;32(5):567–72.
7. Woida FM, Ribeiro-Silva A. Adenoid cystic carcinoma of the Bartholin gland—an overview. Arch Pathol Lab Med. 2007;131:796–8.
8. Gupta R, Green C, Naran S, et al. Fine-needle aspiration cytology of adenoid cystic carcinoma of the breast. Diagn Cytopathol. 1999;20(2):82–4.
9. Lelle R, Davis K, Roberts J. Adenoid cystic carcinoma of the Bartholin's gland: the University of Michigan experience. Int J Gynecol Cancer. 1994;4:145–9.
10. Nowak M, Ryce M, Szpakowski M, et al. Interdisciplinary treatment of the patient with adenoid cystic carcinoma of the Bartholin's gland resulting in 15 years' survival: a case report and review of literature. Prz Menopauzalny. 2014;13(5):310–2.
11. Ramanah R, Allam-Ndoul E, Baeza C, et al. Brain and lung metastasis of Bartholin's gland adenoid cystic carcinoma: a case report. J Med Case Rep. 2013;7:208.
12. Faivre S, Raymond E, Casiraghi O, et al. Imatinib mesylate can induce objective response in progressing, highly expressing KIT adenoid cystic carcinoma of the salivary glands. J Clin Oncol. 2005;23(25):6271–3.
13. Alcedo JC, Fa'brega JM, Arosemena JR, et al. Imatinib mesylate as treatment for adenoid cystic carcinoma of the salivary glands: report of two successfully treated cases. Head Neck. 2004;26(9):829–31.
14. Pfeffer M, Talmi Y, Catane R, et al. A phase II study of Imatinib for advanced adenoid cystic carcinoma of head and neck salivary glands. Oral Oncol. 2007;43(1):33–6.
15. Winquist E, Lamont E, Hotte S, et al. Phase II study of Imatinib mesylate in salivary gland adenoid cystic carcinoma. Eur J Cancer Suppl. 2003;1(5):142.