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Original Article

Anal cloacogenic carcinoma has the same prognosis of the squamous cell carcinoma: case control study of 30 patients

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Abstract: Case-control study comparing overall survival and disease free survival for patients with squamous cell carcinoma of the anus (ASCC) and transitional clocacogenic carcinoma (CCA). Material and methods: 450 patients were supported between January 2001 and December 2014, cancer of the anal canal. 15 patients with CCA were selected and matched (1 for 1) by age, sex, tumor stage (clinical, radiological, and histological) and HIV infection and HPV status in patients group of ASCC. Overall survival and disease free survival in both groups were studied. After initial treatment, the persistence of the lesion histologically proven before 6 months after treatment was defined as a residual disease (MR), the occurrence of a local recurrence was defined as a lesion histologically proved after 6 months of starting treatment. Statistical analysis was done using the Chi 2 test and the Student test, and survival curves were determined using the Kaplan-Meier. Results: There were 26 women, median age was 67.5 (55-83) years. HPV and HIV infection rate was 0 and 40% respectively. The distribution of stages I, II, IIIA, IIIB and IV was 13.3% (n=4), 40% (n=12), 26.6% (n=8), 13.3% (n=4), and 6.6% (n=2) respectively. 83.3% of patients were treated with radiochemotherapy with no difference between the two groups. Six patients underwent abdominoperineal resection 4 for residual disease (2 in each group), and 2 for locoregional recurrence (1 in each group). The median overall follow-up was 41 months (3-108 months) with no difference between groups. Overall survival at 3 and 5 years was not different between the two groups and CCA group CEA respectively 85%; 75% vs. 87.5%; 73% (NS). The overall survival at 3 and 5 years without colostomy was not different between the two CCA group and CEA groups (respectively 80%; 46% vs 78.7%; 56% (NS)). Disease-free survival at 3 and 5 years was similar in both CCA and ASCC groups (respectively 84%, 46% vs 69%; 46% (NS)). Conclusion: This study demonstrates that stage equivalent prognosis of ASCC and CCA is comparable.

Keywords: Cloacogenic carcinoma, anal cancer, overall survival

Introduction

Anal cancer accounts for 2% of all cancer digestive system malignancies in the United States [1] Squamous cell carcinoma represents (ASCC) 80% of those. Transitional clocacogenic carcinoma is rare and represents only 2.7% of anal [2]. The tumor arises from the transitional epithelium of the pectinated lines [3]. The prognosis of anal cloacogenic carcinoma (ACC) compared to that of ASCC, is still unclear. In fact, although dismal prognosis has been usually reported [1, 4], available data do not allow reliable evaluation because of several limitations (heterogenous histological diagnosis criteria; variability of therapeutic approaches, small series of patients) [1, 4]. In order to clarify the prognosis of this histological rare form of anal carcinoma ACC, we performed a case control study between ACC and ASCC. The aim of the

Table 1. Characteristics of study populations

	Anal Squamous Cell carcinoma (ASCC) "reference group" (n=15)	Anal Cloacogenic carcinoma (ACC) investigational group (n=15)	Total (n=30)	*P* values
Gender male/female (n)	2/13	2/13	4/26	1.000
Median age (years)	66 (50-90)	68 (45-83)	67.5 (45-83)	0.180
HPV infection n (%)	0	0	0	1.000
HIV infection n (%)	6 (40%)	6 (40%)	12 (40%)	1.000
Radiological Stage n (%)				1.000
I	2 (13.3%)	2 (13.3%)	4 (13.3%)	
II	6 (40%)	6 (40%)	12 (40%)	
IIIA	4 (26.6%)	4 (26.6%)	8 (26.6%)	
IIIB	2 (13.3%)	2 (13.3%)	4 (13.3%)	
IV	1 (6.6%)	1 (6.6%)	2 (6.6%)	

Table 2. Treatment modalities

	Anal Squamous Cell carcinoma (ASCC) (n=15)	Anal Cloacogenic carcinoma (ACC) (n=15)	Total (n=30)	*P* values
Exclusive Radiotherapy	2 (13.3%)	3 (20%)	5 (16.6%)	1.000
Radiochemotherapy	13 (86.6%)	12 (80%)*	25 (83.3%)	1.000
Complementary radiotherapy boost	9 (60%)	4 (26.6%)	13 (43%)	0.139
Abdominoperineal resection combined with radiochemotherapy	3 (20%)	3 (20%)	6 (20%)	1.000

*Three radic hemotherapies were performed after abdominoperineal resection.

study was to compare overall and disease free survival in patients suffering from ACC and from "classical" ASCC.

Materials and methods

Between January 2001 and December 2011, 450 patients were referred to the Institute Curie (Paris, France) and to the Timone University Hospital (Marseille, France) for anal cancer. Fifteen of these consecutive patients, had anal cloacogenic carcinoma (ACC) (13 females and 2 males, median age 66 years, range 45-83). This "investigational group" was compared with a group of 15 patients with classical anal squamous cell carcinoma (ASCC) ("reference group") matched 1:1 for the following parameters age (± 5 years), gender, clinical and radiological stage HIV and HPV infection status (**Table 1**).

Primary tumor/and initial management

A local examination with biopsy under general anesthesia was performed in all patients as part of initial work up. Tumor size was measured in centimeters and the percentage of invaded circumference of the anal canal was recorded.

Pathology assessment

In the current series, ACC was defined as a poorly differentiated morphology without any definite squamous cell appearance and had been differentiated from malignant melanoma and lymphoma. Truly epithelial origin was first ascertained and differential diagnoses of malignant melanoma and lymphoma were ruled out using appropriate immunochemistry markers (cytokeratin, S-100 protein and common leukocyte antigen). Both squamous and neuroendocrine differentiations were further excluded using high molecular weight keratins, chromogranin A or synaptophysin markers. In three patients the diagnosis of ACC was made postoperatively by the examination of the surgical specimen. The diagnosis was suspected preoperatively on the clinical history of recurrent abscesses and anal mucous. Squamous differentiation was identified by a strong but focal immunoreactivity for high molecular weight keratin Any morphological remnant of glandular/adnexal differentiation was interpreted as basaloid differentiation according to Gillespie and MacKay [3]. The presence of palpable inguinal lymphadenopathy was noted and tumor involvement confirmed by lymph node biopsy.

Table 3. Patients survival

	Anal Squamous Cell carcinoma (n=15)	Anal Cloacogenic carcinoma (n=15)	Total (n=30)	*P* values
Overall survival (%)				
At 3 years	87.5	85	86	0.960
At 5 years	73	75	72	
Overall survival without stomy (%)				
At 3 years	78.7	80	79	0.964
At 5 years	56	46	49	
Disease Free survival (%)				
At 3 years	69	84	77	0.948
At 5 years	46	46	53	

Pretreatment local and distant evaluation

Initial tumor stage was assigned in accordance with the 2002 American Joint Committee on Cancer Guidelines (6th edition) TNM staging system for cancer of the anal canal based on the clinical evaluation, CT-scanner and endoscopic ultrasonography. Pre-therapeutic work up also included magnetic resonance imaging (MRI) after 2004 and FDG PET Scanner after 2006.

Treatment

Radiotherapy: (RT)-A 4 field box technique was used. The top field was located at the L5-S1 interspace and the bottom of field, 2 cm below the lowest margin of the tumor. The inguinal nodes were only covered by the anterior field. A complementary electron boost was delivered to the inguinal nodes. Dose was 50 Gy for the pelvis and 45 Gy for N0 nodes. Doses were delivered in five fractions per week and fraction does ranged from 1.8 to 2 Gy. After clinical evaluation under general anesthesia, responsive patients received a complementary boost of 15-20 Gy using either a direct perineal field or a reduced 4-field external beam radiotherapy. Patients were reviewed weekly during treatment.

Radiochemotherapy (RT-CT): Chemotherapy, consisting of a daily continuous intravenous infusion of 5-FU (600 mg/m^2) and a daily dose of cisplatin (20 mg/m^2) for 5 consecutive days, was delivered concomitant with the first and the fifth week of radiotherapy. A total of two to three courses were given. The treatment is decided at our weekly meeting with participation of surgeons, radiation, and medical oncologists).

After completion of treatment, a physical examination was performed every 3 to 6 months. Patients were further assessed with abdominopelvic CT scan and MRI. Post-treatment biopsies were performed only in the presence of suspicious. Patients with histologically-proven carcinoma detected within 6 months of completion of RT or RT-CT were classified as presenting persistent disease (PD). Those patients who initially responded completely to RT or RTCT, but in whom a recurrence was diagnosed 6 months or more after treatment were classified as presenting locally recurrent disease (LRD).

Follow up

Postoperative follow-up included clinical, tumor maker levels squamous cell carcinoma (SCC), and radiological assessment every 3 months during the first postoperative year, then every 6 months up 5 years, and eventually every year up to 10 years of follow-up. The surviving patients were assessed for disease and site of recurrence. Follow-up information's was obtained from medical records and direct patients' consultation. The median duration of follow-up was 41 months (range: 3-108 months). The length of survival was calculated from the date of diagnosis up to march 2012.

Statistical analysis

Comparison between ASCC and CCA was performed using the chi-squared test (or the Fisher's exact test when conditions for the chi-square test was not fulfilled for categorical variables and using the *Student* t-test (or the Mann-Whitney nonparametric rank sum test in case of non-normality) for continuous variables. A Kaplan-Meier analysis was used to estimate

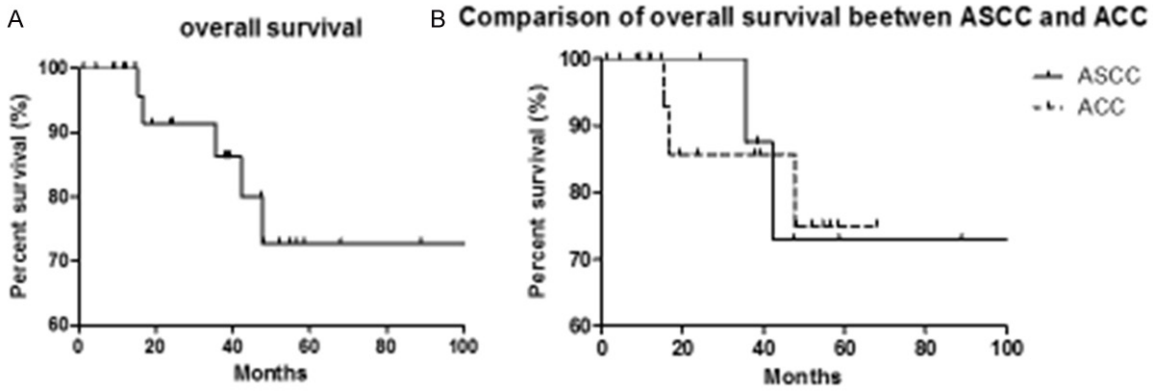

Figure 1. A. Overall survival of all population; B. Comparison of overall survival between Anal Squamous Cell carcinoma (ASCC) Anal cloacogenic carcinoma (ACC).

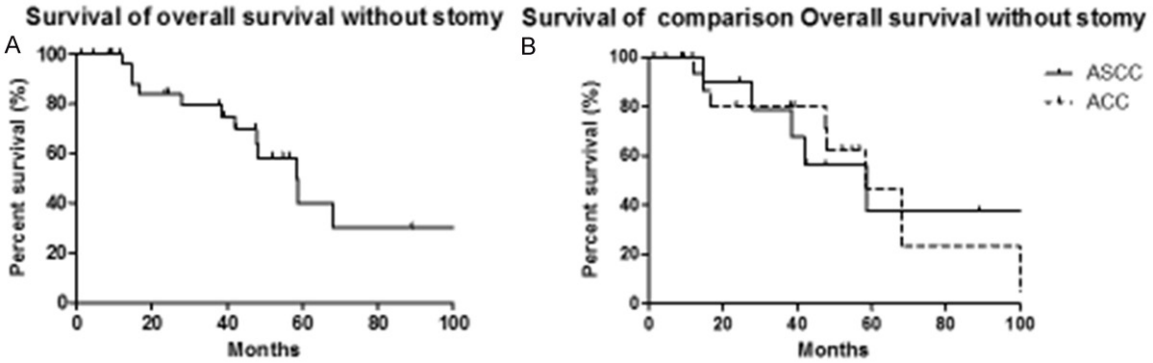

Figure 2. A. Overall survival without stomy. B. Comparison of overall survival between Anal Squamous Cell carcinoma (ASCC) Anal cloacogenic carcinoma (ACC).

the postoperative survival rate. The log-rank test was used to compare ASCC and CCA. A *p* value < 0.05 was considered statistically significant.

Results

*Clinical characteristics of population (**Table 1**)*

Between 2001 and December 2011, 15 patients with cloacogenic carcinoma (ACC) were identified among 450 consecutive patients diagnosed with anal canal carcinoma. This group of patients was compared with a group of 15 patients with "classical" anal squamous cell carcinomas (ASCC) Patient characteristics are reported in **Table 1**. No Human Papilloma Virus (HPV) infection was detected by molecular approach (detection of specific HPV DNA sequences by PCR in tumor DNA retrieved from biopsies) infection was diagnosed; concomitant HIV infection was found in 40% of patients (n=12). Initial staging for the thirty patients ranged as stage I, 13.3% (n=4), stage II, 40% (n=12), stage IIIA, 26.6% (n=8), stage IIIB, 13.3% (n=4) and stage IV, 6.6% (n=2). Two patients in each group had metastasis. Symptoms most often observed at the time of diagnosis were hematochezia and anal pain (60% and 46%, respectively) with statistically more bleeding in the group of patient with ACC (86.6% vs. 33%, P= 0.007).

Treatment modalities

Most patients were treated by concomitant radiochemotherapy 83.3% (n=25), and radiotherapy complementary boost was delivered in 43% of cases (n=13) Abdominoperineal resection was eventually performed in three patients of both groups, either because of non response to radiochemotherapy (n=4; 2 patients in both groups), either of tumor recurrence after radiochemotherapy (n=2; 1 patient in both groups). Treatment modalities are reported in **Table 2**.

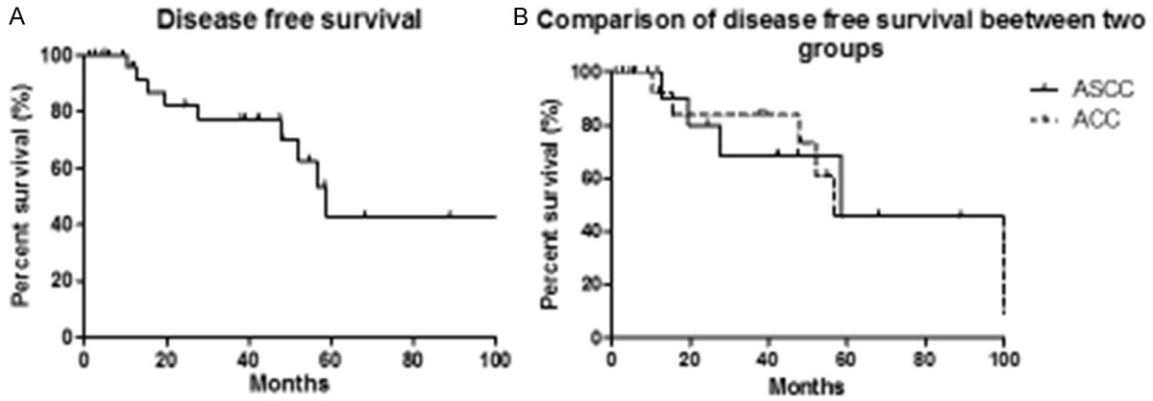

Figure 3. A. Disease free survival of all population. B. Comparison of disease free survival between Anal Squamous Cell carcinoma (ASCC) Anal cloacogenic carcinoma (ACC).

Patients survival

Median of follow up was 41 months (3-108) without difference between the two groups. Persistent disease rate (PR) was 13.3% (n=4), 13.3% (n=4) required abdominal resection without statistical significant difference between the two groups. Survival, overall survival without colostomy and disease free survival are reported in **Table 3**. They were similar in both groups. Actuarial curves for these parameters are shown in **Figures 1**-**3** respectively.

Discussion

Transitional clocacogenic carcinomas accounted for 2.7% of all anorectal carcinomas in the series of Klotz [2]. It is four times less common than ASCC in this center. This tumor subtype was described under different names such as "basaloid", "basal cell" carcinomas, "mucoepidermoid carcinomas" and 'adenoacanthoma" [2]. The presence of transitional epithelium in the region of the pectinate line of the anorectum was first pointed out by Hermann and Desfosses in 1880. Grinvalsky and Helwig in 1956 then drew attention to this epithelium and proposed that it was a remnant of the embryonic cloaca giving rise to neoplasms with a variety of patterns and they named these tumors "transitional cloacogenic carcinoma". The heterogeneity of the group of the "transitional cloacogenic carcinoma" explains the difficulty of histologic definition. We used a extended definition which included squamous differentiation and glandular differentiation interpreted as basaloid differentiation according to Gillespie and MacKay [3].

This definition could allow to match data of patients with ASCC and ACC. In order to determine the impact of the transitional cloacogenic carcinoma on the overall survival we used stage as parameter for matching. As study of Wolber 15 cloacoenic carcinoma has negative for HPV 16/18. Differential expression of HPV DNA in these lesions may be a manifestation of separate mechanisms of pathogenesis. That's explain we used HPV as parameter for matching in our study [5]. Indeed some studies reported poor prognosis for transitional cloacogenic carcinoma compared to ASCC, and others did not find any difference between the two groups [4]. The apparent discrepancy might be explained by the delay of diagnosis of 'transitional cloacogenic carcinoma" due to possible "atypical" clinical presentation such as anal fistula and chronic anal abscesses. Moreover, some of the studies reported a more aggressive treatment of ACC patients including radiochemotherapy and abdominoperineal resection, a therapeutic approach unlikely to be justified. Furthermore, prognosis of ACC was only based on tumor staging. Since 1980, there has not been any report in the literature comparing ACC and ASCC by matching stage of tumor. In the present study we show for the first time that the prognosis is the same between ACC and ASCC patients.

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Disclosure of conflict of interest

None.

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References

[1] Beahrs OH, Wilson SM. Carcinoma of the anus. Ann Surg 1976; 184: 422-8.

[2] Klotz RG Jr, Pamukcoglu T, Souilliard DH. Transitional cloacogenic carcinoma of the anal canal. Clinicopathologic study of three hundred seventy-three cases. Cancer 1967; 20: 1727-45.

[3] Gillespie JJ, MacKay B. Histogenesis of cloacogenic carcinoma. Fine structure of anal transitional epithelium and cloacogenic carcinoma. Hum Pathol 1978; 9: 579-87.

[4] Levin SE, Cooperman H, Freilich M, Lomas M. Transitional cloacogenic carcinoma of the anus. Dis Colon Rectum 1977; 20: 17-23.

[5] Wolber R, Dupuis B, Thiyagaratnam P, Owen D. Anal cloacogenic and squamous carcinomas. Comparative histologic analysis using in situ hybridization for human papillomavirus DNA. Am J Surg Pathol 1990; 14: 176-82.