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Impact of tobacco smoking on patient's outcome after (chemo)-radiotherapy for anal cancer

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Abstract

Purpose

Anal squamous cell carcinoma is associated with multiple risk factors, including infection with human papillomavirus [HPV] and human immunodeficiency virus, immunosuppression, multiple sex partners, receptive anal sex and tobacco smoking. The aim of our study was to identify prognostic factors associated with poor outcome after radiotherapy for anal cancer.

Methods

We analyzed retrospectively the medical records of 171 patients treated by (chemo)-radiotherapy for a non-metastatic anal cancer in our institution from 2000 to 2015. Patients and tumor characteristics, treatments (chemotherapy (CT), radiotherapy (RT), and surgery) and outcomes were reported. Colostomy-free, disease-free and overall survivals at 5 years were studied. Univariate and multivariate analyses were performed by logistic regression in order to determine factors associated with poor progression-free survival (PFS).

Results

Patients characteristics were as follow: median age: 62 years (range 36-89); gender: 45 males (26%) and 126 females (74%); HIV serology: positive 21 patients (12%); tobacco smoking: 86 Pts (50%) among whom 28 Pts and 58 Pts were current and former smokers respectively. Tumors were classified as locally limited (T0-1-2, N0, M0) for 86 pts (50%) and locally advanced (T3-4 or N+, M0) for 85 pts (50%). Median total dose was 64.4 Gy (range 54-76.6), 146 patients were treated by concurrent chemoradiotherapy. Factors associated with poor PFS in univariate analysis were: tumor size >4cm, lymph node involvement, tobacco smoking, no initial surgical excision and anal warts at diagnosis. In multivariate analysis, only tobacco smoking status was significantly associated with poor PFS (HR=2.85 [1.25-6.50], p=0.013). 5-years-PFS for non-smokers, former smokers and current smokers was 88.1%, 76,7% and 73.8% respectively (p=0.038). Tobacco smoking was also associated with poor overall survival (p=0.03), locoregional-relapse-free survival (p=0.05) and colostomy-free survival (p=0.02).

Conclusions

Tobacco smoking status is associated with poor OS, LRFS, PFS and CFS in patients treated for anal cancer by high radiotherapy dose +/-chemotherapy

Keywords: anal; cancer; radiotherapy; chemoradiotherapy; tobacco; prognosis

1. Introduction

Anal cancer is a rare disease with 8,580 new cases per year estimated in the United States and 4,300 cases in Europe. It is accounting for 1%–2% of all gastrointestinal cancers and 2%–4% of colon, rectal and anal tumors [1]. Despite the rarity of anal cancer, the incidence has almost doubled in recent years, from 1.2 cases per 100,000 per year during 1973–1996 to 2.2-2.5 cases per 100,000 per year during 1997–2013 [2, 3].

Approximately 85% of anal cancer are squamous cell carcinoma and are mainly associated with human papillomavirus (HPV) infection, particularly serotypes 16 and 18 [4]. Anal cancer incidence increases with age and is higher in women than men. High-risk populations for anal cancer also include human immunodeficiency virus (HIV)-positive patients, men who have sex with men, patients who are current or former cigarette smokers, women with a history of preinvasive or invasive cervical or vulvar lesions and organ transplant recipients [5].

Localized small cancers (T1N0) are mainly treated by exclusive radiation therapy in the case of cancers of the anal canal, or by surgery in the case of cancers of the anal margin. The recommended treatment of locally advanced tumours (T2-T4, N0-N2) is definitive concomitant radio-chemotherapy [6].

Several studies reported that tobacco smoking was a risk factor for anal cancer [7-9]. Odds ratios for anal cancer among smokers versus non-smokers was between 2–4 in women and 4–5 in men [7, 10-12]. Some studies reported a correlation between pack-years of smoking and anal cancer (RR=1.9 for 20 pack years and RR=5.2 for 50 pack-years, p value <0.001) [12-14]. Constituents of tobacco may act directly as carcinogens or indirectly through suppression of the immune response to HPV. It has been reported that tobacco was associated with higher tumor relapse or lower progression free survival in cervical and bladder cancers [15, 16].

The primary aim of our study was to evaluate progression-free survival according to tobacco status. The other aims were to evaluate overall survival, disease-free survival, colostomy-free survival and identify others prognostic factors associated with progression-free survival.

2. Methods

We retrospectively identified from our medical database, 171 patients treated with radiotherapy or chemo-radiotherapy in our institution between 2000 to 2015 for non-metastatic anal cancer. To be included, patients had to have biopsy proven squamous cell anal carcinoma and non-metastatic anal carcinoma at the initial staging with 18-FDG-PET-CT (Positron emission tomography and computed tomography) or thoracic, abdominal, and pelvic CT, pelvic MRI (magnetic resonance imaging) or anal endoanal ultrasound.

Patients were staged according to the 7th edition of the AJCC Cancer Staging Manual for anal cancer. In our study, we analysed factors potentially correlated with poor overall survival. Following factors were analysed: age, performance status, gender, tumor size, tumor location (anal verge, anal canal, rectal extension), lymph node involvement, tumor differentiation, HIV status, initial tumor resection, condyloma, induction chemotherapy, radiotherapy duration, smoking habits (current smoker was defined as a patient who smoked greater than 100 cigarettes in his lifetime and has smoked at the time of the anal cancer diagnostic, former smoker as a patient who has smoked greater than 100 cigarettes in his lifetime and was smoke free for 3 years at the time of anal cancer diagnostic and non-smoker as a patient who has not smoked greater than 100 cigarettes in his lifetime and did not smoke at the time of the anal cancer diagnostic).

Radiotherapy

Patients received initial irradiation to the anal canal and pelvic lymph nodes (45 Gy) followed by a boost delivered in the anal tumor and all pathological lymph nodes (14,4-19.8 Gy), in daily fractions of 1.8 Gy, 5 days per week, by high energy photon beams (≥6 MV). Most of the patients were treated with a 3D technique.

Chemotherapy

Patients with locally advanced anal tumor (tumor size ≥3cm or lymph nodes involvement) received concurrent chemotherapy by 5-fluorouracil(1000 mg/m²/d, days 1-4, days 28-31 +/- days 56-59) or capecitabine (1600 mg/m²/day, 5 days per week during all the radiotherapy treatment) and mitomycin C (12 mg/m²/day, day 1, day 28 +/- day 56). Patients with locally advanced disease could receive induction chemotherapy by 5-fluorouracil, docetaxel and cisplatin (DCF) [17].

Follow-up

Patients were followed-up at 4-month intervals for the first year, at 6-month intervals for the next 2 years and annually thereafter. The follow-up evaluation consisted of physical examination, a complete blood count, liver function test and a SCC marker. All patients had MRI at 6-month intervals for the first 2 years and annually thereafter.

Statistical analysis

Progression-free survival (PFS) was measured from the date of the first day of treatment to the date of first disease progression or death from any cause. Patients who were alive without recurrence were censored at the date of last follow-up. Locoregional-relapse-free survival (LRFS) was measured from the date of the first day of treatment to the date of locoregional disease progression or death from any cause. Local recurrence was defined as recurrence within the pelvis and regional recurrence included a pelvic or inguinal lymph node recurrence. Patients who were alive without locoregional recurrence were censored at the date of last follow-up. Colostomy-free survival (CFS) was the time period measured from the date of the first day of treatment to the colostomy or death from any cause without colostomy. Patients who were alive without colostomy were censored at the date of last follow-up. Overall survival (OS) was measured from the date of the first day of treatment to the date of death from any cause. Patients who were alive were censored at the date of last follow-up.

Survival curves were calculated by using Kaplan-Meier survival analysis. The log-rank test was used to evaluate survival differences. Comparison of continuous variables was performed using the student t-test. Cox regression analysis was used to perform a multivariate analysis, incorporating T and N stages, histology, surgery. Statistical analyses were performed using Stata 14.2 software (College Station, TX: StataCorp LP). Statistical significance was set at $p<0.05$.

3. Results

The mean age of our study population at the time of diagnosis was 62 years [Range: 36–89]. Most of the patients were women (74%). Eighty-six patients (50%) had T1-T2 and N0 tumor and eighty-five (50%) had T3-T4 and/or N+ tumor. Twenty-one patients (12%) were HIV-positive at the time of diagnosis. Data about smoking status at the time of the diagnosis was available in 163/171 patients: 58 current smokers, 28 former-smokers, and 77 non-smokers. Twenty-one patients (12%) had a

positive history of anal warts. The mean follow-up period was 4.27 years (range: 0.15–14.5). These data are summarized in table 1. Analysis of p16 expression was not systematically performed. Only very few patients had their HPV/p16 status known.

One hundred and forty-six patients (85%) received concurrent chemo-radiotherapy and 25 patients (15%) received exclusive radiotherapy. Among patients treated by chemoradiotherapy, 104 (70 %) received 5FU-Mitomycin chemotherapy, 37 (25%) received 5FU-cisplatin chemotherapy and 5 (3%) received fluoropyrimidine monotherapy chemotherapy (5-fluorouracile/capecitabine). Thirty-two patients (19%) received induction chemotherapy and 7 (5%) adjuvant chemotherapy. Radiotherapy delivered a median total dose of 64.4 Gy and a mean total dose of 64.8 Gy (range 54–76.6). The distribution of the dose was very homogeneous: 90 percent of patient received a total dose between 60 and 65 Gy. One hundred and twenty-one patients among 171 received 64.8 Gy. Fifteen patients (9%) received a boost delivered by interstitial brachytherapy.

After a median follow-up of 48,7 months [7.5–176.2], 30 patients have died and 35 patients have relapsed.

Lung progression was a rare event in our study. Indeed, only 5 patients developed pulmonary metastases (2 smoker patients, 1 non-smoker patient and 2 patients whose smoking status was not available).

Three- and 5-year overall survival was 83.6% and 81% respectively. Three- and 5-year progression-free survival was 79.2% and 78.1% respectively. Local-tumor control at 3 and 5 years was 83.2% and 82.1% respectively. Three- and 5-year colostomy-free survival was 87% and 83.7% respectively. Among 31 patients who had a colostomy, 6 patients had a colostomy before the start of the treatment for bowel obstruction or faecal incontinence and 25 had a colostomy after radiotherapy: 18 patients for local relapse and 7 patients for faecal incontinence.

Twenty-two patients had an initial tumor resection. The mean tumor size was 3.25 cm [1–6] in this population vs 4.48 cm [1–18] in the whole population of the study.

Five-year CFS and OS was 93.3% and 90.7% for non-smokers vs 79% and 81% for smokers (p=0.02 and p=0.03 respectively) (Figure 3, Figure 4).

Prognostic factors associated with progression-free survival

Univariate analysis results have been summarized in table 2. Prognostic factor correlated to poor progression-free survival (PFS) were tumor size >4cm, lymph node involvement; tobacco smoking, no initial surgical excision and anal warts at diagnosis.

A tumor greater than 4 cm was significantly associated with a lower PFS. Five-year PFS was 85.5% for patients with a tumor less than or equal to 4 cm vs 69.2% for patients with a tumor greater than 4 cm (p=0.01).

The lymph node involvement was also associated with a lower PFS (p=0.03). 5-year PFS was 84.8% for patients staged N0, 71.1% for patients staged N1-N2 and 57.3% for patients staged N3.

Tobacco smoking status of patients was significantly associated with lower PFS. Five-year PFS was 88.1% for non-smokers vs 74.8% for current or former smokers (p=0.016) (Figure 1).

More specifically, among smoker patients, former smokers had a better PFS than current smokers. Five-year PFS was 88.1% for non-smokers vs 76.7% for former smokers vs 73.8% for current smokers (p=0.032) (Figure 2).

Initial tumor resection was also independently associated with a better PFS. Five-year PFS was 95.2% for patients who had an initial tumor resection vs 75.6% who had not (p=0.049).

Gender, HIV status, tumor location, tumor grade, histological subtype, anogenital warts, baseline SCC antigen level, median total dose, induction chemotherapy, protocol of concurrent chemotherapy did not significantly correlate with PFS.

On multivariate analysis only tobacco smoking status remained significantly correlated to PFS (HR: 2.85; 95% CI: 1.25-6.50) (Table 2).

Prognostic factors associated with colostomy free survival (supplementary data)

After univariate analysis, tumor stage, weight lost, tabaco smoking and boost by brachytherapy were statistically associated with overall survival.

After multivariate analysis, weight lost and tabaco smoking remained statistically significant (p=0.003 and p=0.017 respectively).

Prognostic factors associated with overall survival (supplementary data)

After univariate analysis, tumor stage, age ≥65, tumor length ≥4 cm, tabaco smoking were statistically associated with overall survival.

After multivariate analysis, only tabaco smoking remained statistically significant (p=0.03).

Prognostic factors associated with locoregional-relapse free survival (supplementary data)

After univariate analysis, tumor length ≥4 cm and tabaco smoking were statistically associated with locoregional-relapse free survival.

After multivariate analysis, only tabaco smoking remained statistically significant (p=0.05)

Induction chemotherapy had no detrimental effects on patients' outcome. 5-year disease-free survival rate was 84.8% vs 71.4% (p=0.11), 5-year colostomy free survival rate was 87.1% vs 71.3 (p=0.11) and 5-year overall survival rate was 82.8% vs 78.0% (p=0.25) for non-smokers and smokers patients respectively.

Treatments performed after disease progression

Among patients who experienced a disease progression, 13 patients received chemotherapy (8 smoker patients, 4 non-smoker patients, 1 patient whose smoker status was unavailable), 17 patients had a salvage abdominoperineal resection (APR) (6 smoker patients, 11 non-smoker

patients), 4 patients had lymph node dissection (3 smoker patients, 1 non-smoker patient), 1 non-smoker patient had a lobectomy and 1 smoker patient had a hepatic metastasectomy. Two non-smoker patients had lymph node radiotherapy in combination with chemotherapy and 1 patient had stereotactic radiotherapy for isolated para-aortic lymph node relapse.

Only two patients could not receive a curative treatment and received palliative care: 1 smoker patient had a colostomy without APR and 1 non-smoker patient had best supportive care for multiple lung metastases.

Salvage surgery

Among 17 patients who experienced a relapse, 14 patients had salvage abdominoperineal resection, 3 patients had salvage abdominoperineal resection with inguinal lymph node dissection, 4 patients had inguinal or internal iliac lymph node dissection, 1 patient had a lobectomy and 1 patient had a hepatic metastasectomy.

Toxicity

Forty-six patients had G3+ acute skin toxicity (26.9%), 9 patients had G3+ acute gastrointestinal toxicity (5.26%) and 2 patients had G3 acute urinary toxicity (1.16%). Among patients who had severe acute toxicity (G3+), 20 patients were non-smokers and 26 were smokers.

There was no statistical correlation between severe acute toxicity (G3+) and tobacco smoking status ($p=0.784$).

We did not find any correlation between severe acute toxicity (G3+) and locoregional-disease-free progression, disease-free progression and colostomy-free survival ($p=0.761$; $p=0.801$ and $p=0.116$ respectively).

4. Discussion

In this large monocentric study, we have found that cigarette smoking was the strongest prognostic factor correlated with PFS for patients treated by RT+/-CT for anal cancer. Moreover, we have also observed a worse cancer treatment outcome between current and former smoker patients. Some others studies have reported worse outcome in smoker patients after anal cancer treatment. Bowzyk Al-Naeeb et al. have reported in a monocentric retrospective study of 105 patients treated by chemoradiotherapy at Cambridge hospital in UK that cigarette smoking increased the risk of recurrence with an Odds-Ratio of 17.4 (p=0.008) [18]. A retrospective review of 64 cases of anal carcinoma from San Diego in California reported that current smokers had higher carcinoma recurrence rates than non-smokers (32% vs 20%). Smokers patients also died more frequently from recurrence than non-smokers patients with 45% of smokers dead compared to only 20% of non-smokers by 5 years after treatment [19]. A retrospective study of 63 patients treated for anal carcinoma mainly by chemoradiotherapy at Washington University Hospital reported a significant worse overall survival in ever-smokers than in never-smokers: 2-years overall survival was 75.4% vs 87.1% ($p<0.05$) [20]. In a retrospective study of 68 patients treated by chemoradiotherapy for anal carcinoma at the University of Heidelberg in Germany, Mai et al. find a statistically significant difference in local control between smokers and non-smokers (74% vs 94%, $p = 0.03$) but not in disease-specific survival and colostomy free survival ($p=0.19$ and $p=0.15$ respectively) [21].

Tobacco smoking is a significant risk factor for anal cancer as well as has a significant impact on anal cancer disease control and survival. This factor overcame all prognosis factors after multivariate analysis.

Past and current smoker status is not easy to determine and lack of difference observed between past and current smokers in our study should be analyzed with caution. Indeed, data regarding smoking habits are usually based on self-reports and not on biochemical tests for validation of information. It appears that self-reports regarding smoking habits have been found to be accurate in most studies. However, when taking into consideration subgroups of patients with smoking-related

diseases, self-reports are less reliable. One of the main reasons for this contradiction might be that smokers feel under strong pressure to discontinue smoking, whilst at the same time they are unable to achieve this goal [22].

How does tobacco smoking may contribute to cancer recurrence and worse outcome after (chemo)-radiotherapy?

Diminished immune function and impaired tissue oxygenation may be involved at least in part.

It has been observed that chronic inhalation of cigarette smoke alters a wide range of immunological functions, including innate and adaptive immune responses [23]. In a review of literature, Norum et al. reported that tobacco smoking patients with non-small-cell lung carcinoma generally had a higher PD-L1 tumour proportion score and probably a higher mutational burden due to smoking, they also experienced a better overall response rate of immunotherapy than non-smokers [24].

Cigarette smoking is also known to induce hypoxia, which may impact the oxygen-dependant effects of chemoradiation and may affect chemotherapy drugs delivery to tumor cells [25, 26].

As reported by others authors, we did not find a worse outcome among HIV-infected patients treated for anal cancer in our study [27].

A detailed smoking history should be part of future clinical evaluations in anal carcinoma. At least three levels of smoking status should be ascertained (never smoker, former smoker and current smoker). Our data and the literature showed patients must be encouraged to stop smoking once a diagnosis of anal carcinoma is made. Indeed, smoking status at the time of the diagnosis overcame all prognostic factors. A prospective study to determine if smoking cessation during treatment alters cancer outcomes could be meaningful. Immune checkpoint therapy in combination with chemoradiotherapy may be an interesting treatment approach in smoker patients with locally advanced anal cancer. Tumor mutational burden should be evaluated in anal cancer to predict

immune checkpoint blockade efficacy as it has become a useful biomarker in some cancer types for identification of patients that will benefit from immunotherapy.

5. Conclusions

Tobacco smoking at the time of anal cancer diagnosis is associated with increased risk for cancer recurrence, colostomy and death when compared with non-smokers. Future trials should be specifically designed for patients with HPV-negative and HPV-positive disease in smokers and non-smokers according to different TNM staging. Regarding the worse disease outcome after treatment, immune checkpoint therapy in combination with chemoradiotherapy may be an interesting treatment approach in smoker patients with locally advanced anal cancer.

Conflict of interest declarations

The authors declare that they have no conflict of interest regarding the present article

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Figure legends

Figure 1
Progression-free survival according to smoking status

Figure 2
Progression-free survival according to three levels of smoking status

Figure 3
Colostomy-free survival according to smoker status

Figure 4
Overall survival according to smoker status

Figure 1

Progression-free survival according to smoking status

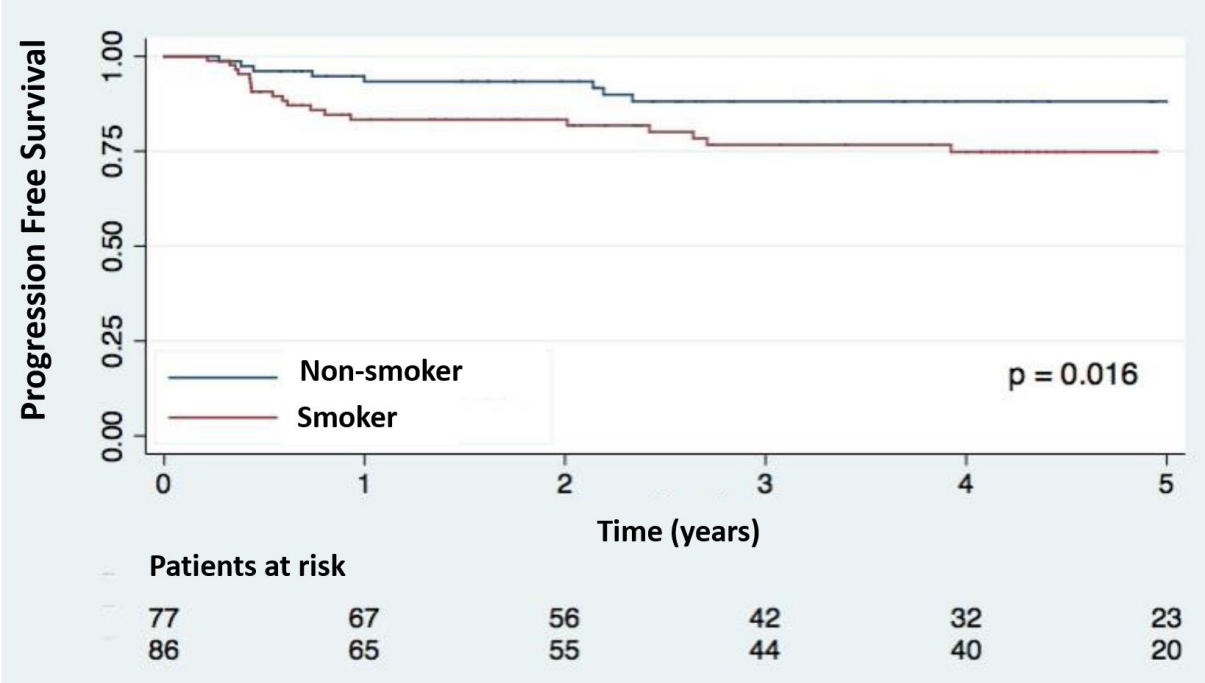


Figure 2

Progression-free survival according to three levels of smoking status

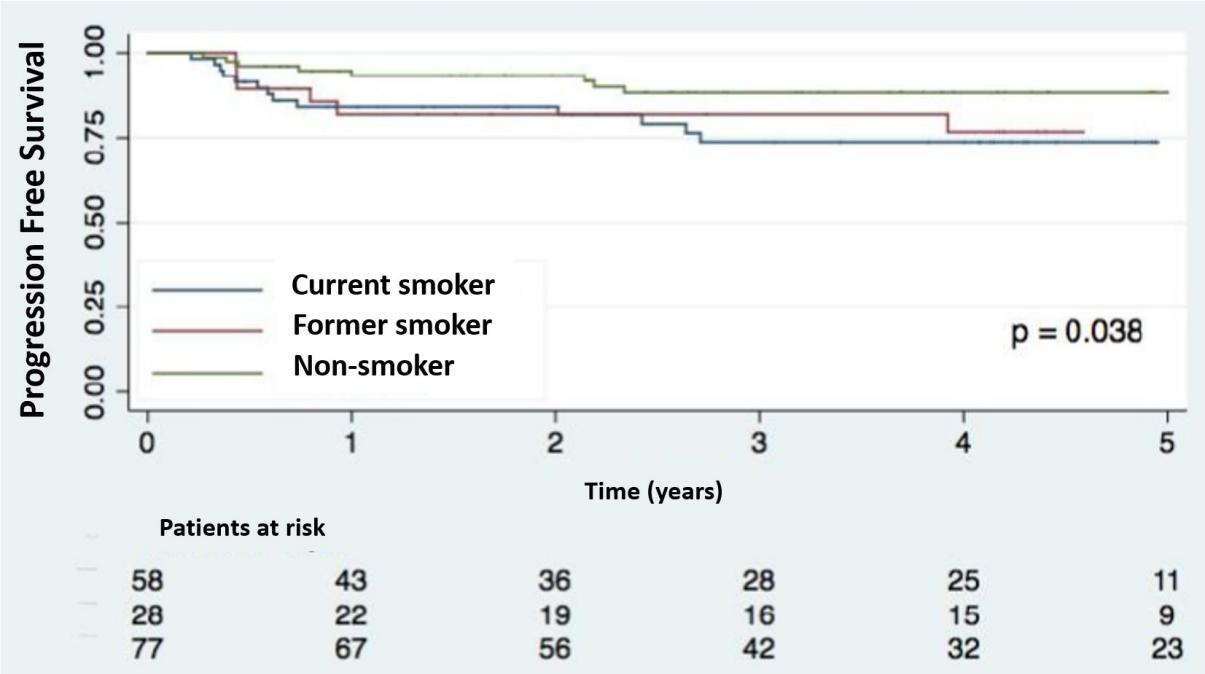


Figure 3

Colostomy-free survival according to smoker status

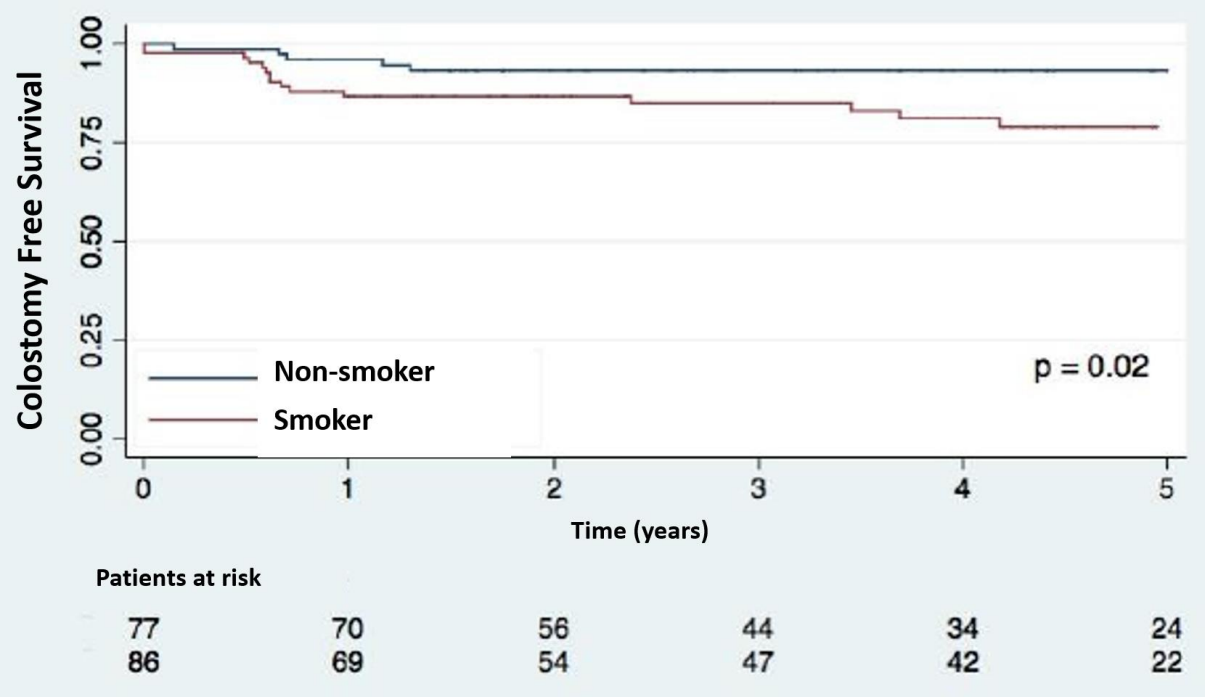


Figure 4

Overall survival according to smoker status

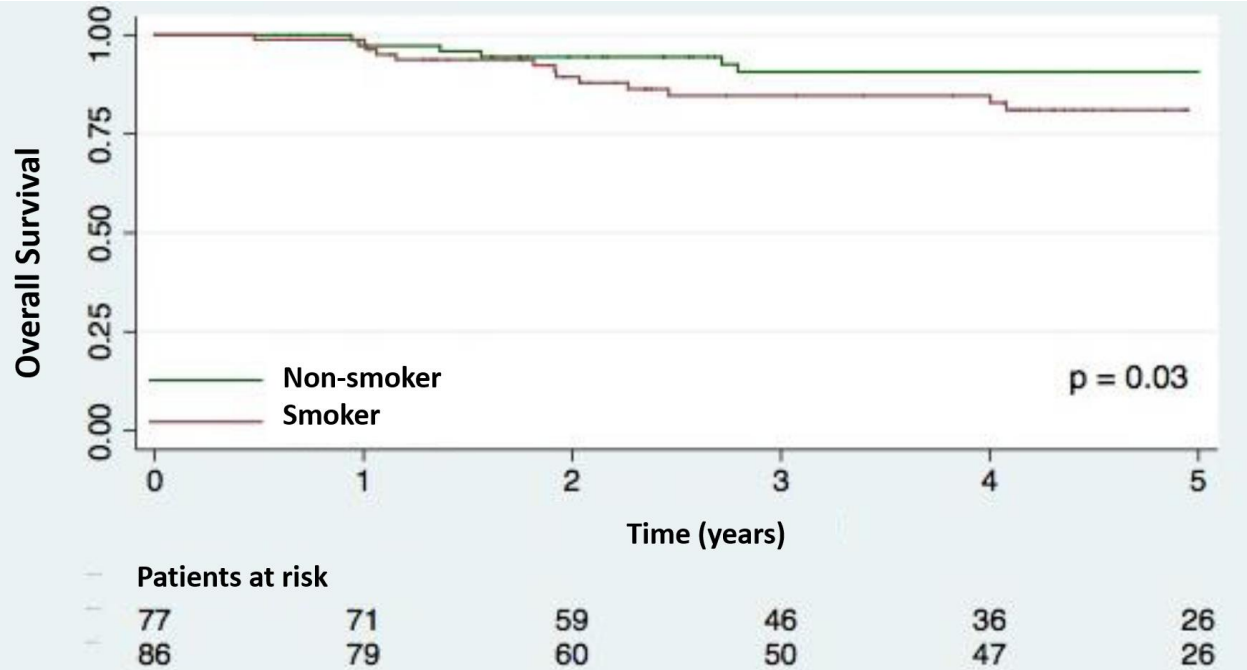


Figure 5

Locoregional-relapse-free survival according to smoker status

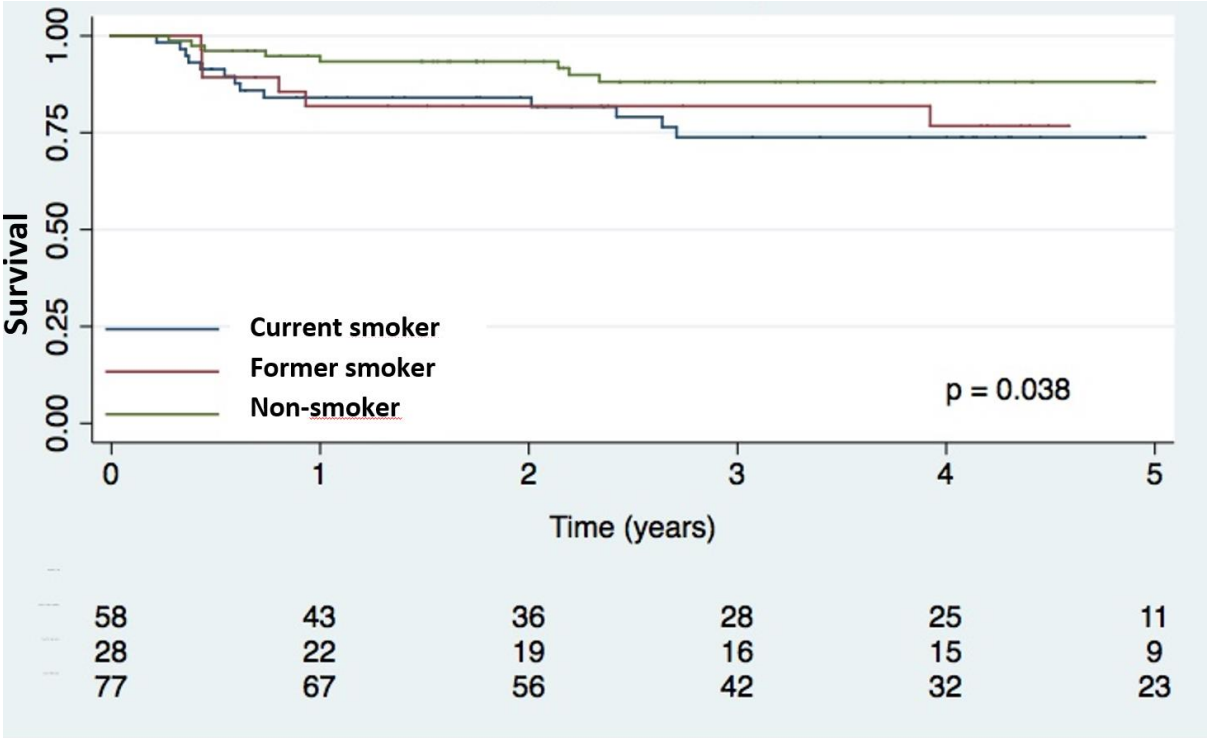


Table 1

Patient characteristics

		Number of patients	percentage
Gender	Man Woman	45 126	26.3 73.7
Age (years) Mean [range]	62 [36–89]		
Performans status	0 1 2 Unknown	115 37 11 8	67.3 21.6 6,.4 4.7
HIV status	Positive Negative Unknown	21 60 90	12.3 35.1 52.6
T stage	T1 T2 T3 T4	23 103 39 6	13.5 60.2 22.8 3.5
N stage	Nx N0 N1 N2 N3	1 101 23 26 20	0.6 59.0 13.5 15.2 11.7
Tumor group	T1-T2 and N0 T3-T4 or N+	86 85	50 50
Tobacco use	Current-smoker Former-smoker Non-smoker Unknown	58 28 77 8	34 16 45 5
Anal warts	Yes No or unknown	21 150	12.3 87.7
Initial surgical excision	Yes No	22 149	12.8 87.2
Resection margin status	R0 R1 or R2	7 15	31.8 68.2
RT dose Mean [range]	64.4 Gy [54–76.6]		
Concurrent chemotherapy	Yes No	146 25	85.4 14.6
Brachytherapy boost	Yes No	15 156	8.8 91.2

Table 2

Univariate analysis of prognostic factors for progression-free survival (PFS)

		Patients (n)	5-year PFS (%)	p
Sex	Woman Man	126 45	77.9 78.5	0.9
Age	≤ 65 years > 65 years	105 66	79.5 75.3	0.7
HIV Status	Negative or unknown Positive	150 21	78.3 74.3	0.92
Pathological subtype	Squamous Bowenoid Cloacogenic Basaloid	151 2 2 16	77.2 100 0.33 86.2	0.10
Tumor grade	I II III NR	44 46 35 46	85.6 70.0 79.3 78.1	0.34
Tumor size	≤ 4 cm > 4 cm	93 78	85.5 69.2	**0.015**
T stage	T1 T2 T3 T4	23 103 39 6	90.9 77 76.3 50	0.19
N stage	N0 N1-N2 N3	101 49 23	84.8 71.1 57.3	**0.03**
PET-CT for initial staging	No Yes	116 55	77.4 80.5	0.81
Neoadjuvant CT	No Yes	139 32	76.6 68.8	0.48
Concurrent CT	No Yes	146 25	76.2 87.2	0.48
CT protocol	5FU-CDDP 5FU-MMC 5FU/Capecitabine	37 104 5	67.8 79.5 76	0.57
Brachytherapy boost	No Yes	156 15	78.6 72	0.7
Radiotherapy duration	< 76 days ≥ 76 days	101 70	79.8 76.2	0.26
Tobacco status	Former smoker Current smoker Never smoker	58 28 77	76.7 73.8 88.1	**0.038**
Anal warts	No Yes	149 21	79.6 64.8	0.12
Surgical resection	Yes No	22 149	95.2 75.6	**0.0494**
SCC antigen	≤ 1.5 ng/ml > 1.5 ng/ml	68 76	78.9 78.4	0.86
Tumor sublocation	Anal margin Anal canal	8 101	87.5 82.2	0.17

	Rectal extension	62	70.7	

CT= chemotherapy ; HIV= Human Immunodeficiency Virus; Squamous Cell Carcinoma; PFS= Progression-Free Survival; PET-CT= positron emission tomographycomputed tomography

Table 3

Multivariate analysis of prognostic factors for progression-free survival (PFS)

	HR	**Z**	**P>|z|**	**IC95%**
Tobacco status	2.85	2.49	0.013	[1.25-6.50]
Tumor size >4cm	1.60	1.14	0.25	[0.71-3.57]
N stage	1.44	1.34	0.18	[0.84-2.46]
Surgical resection	0.30	-1.14	0.25	[0.039-2.34]