World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i25.2987

World J Gastroenterol 2011 July 7; 17(25): 2987-2991
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Squamous cell carcinoma of the anus-an opportunistic cancer in HIV-positive male homosexuals

Pascal Gervaz, Alexandra Calmy, Ymer Durmishi, Abdelkarim S Allal, Philippe Morel

Pascal Gervaz, Ymer Durmishi, Philippe Morel, Department of Surgery, Geneva University Hospital and Medical School, 1211 Genève, Switzerland
Alexandra Calmy, Departments of Infectious Diseases, Geneva University Hospital and Medical School, 1211 Genève, Switzerland
Abdelkarim S Allal, Department of Radiation Oncology, Hopital Cantonal de Fribourg, 1211 Genève, Switzerland
Author contributions: Durmishi Y and Calmy A performed the literature search and critically reviewed published data; Allal AS revised the manuscript and designed the research; Gervaz P and Morel P wrote the manuscript.
Correspondence to: Pascal Gervaz, MD, Department of Surgery, Geneva University Hospital and Medical School, 4 rue Gabrielle-Perret-Gentil, 1211 Genève, Switzerland. pascal.gervaz@hcuge.ch
Telephone: +4122-372-7703 Fax: +4122-372-7707
Received: October 20, 2010 Revised: December 10, 2010
Accepted: December 17, 2010
Published online: July 7, 2011

Abstract

Squamous cell carcinoma of the anus (SCCA) is a common cancer in the human immunodeficiency virus (HIV)-infected population, and its incidence continues to increase in male homosexuals. Combined chemoradiation with mitomycin C and 5-fluorouracil was poorly tolerated by severely immunocompromised patients in the early 1990s. In the era of highly active antiretroviral therapy (HAART), however, recent data indicate that: (1) most HIV patients with anal cancer can tolerate standard chemotherapy regimens; and (2) this approach is associated with survival rates similar to those of HIV-negative patients. However, HIV-positive patients with SCCA are much younger, more likely to develop local tumor recurrence, and ultimately die from anal cancer than immune competent patients. Taken together, these findings suggest that anal cancer is an often fatal neoplasia in middle-aged HIV-positive male homosexuals. In this population, SCCA is an opportunistic disease resulting in patients with suboptimal immune function from persistent infection and prolonged exposition to oncogenic human papillomaviruses (HPVs). Large-scale cancer-prevention strategies (routine anuscopy and anal papanicolaou testing) should be implemented in this population. In addition, definitive eradication of oncogenic HPVs within the anogenital mucosa of high-risk individuals might require a proactive approach with repeated vaccination.

Key words: Anal cancer; Chemoradiation; Highly active antiretroviral therapy; Human immunodeficiency virus; Human papillomaviruse; Outcome

Peer reviewer: Dr. Benjamin Perakath, Professor, Department of Surgery Unit 5, Christian Medical College, Vellore 632004, Tamil Nadu, India

Gervaz P, Calmy A, Durmishi Y, Allal AS, Morel P. Squamous cell carcinoma of the anus-an opportunistic cancer in HIV-positive male homosexuals. *World J Gastroenterol* 2011; 17(25): 2987-2991 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i25/2987.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i25.2987

INTRODUCTION

As human immunodeficiency virus (HIV)-infected individuals continue to benefit from highly active antiretroviral therapy (HAART), their risk of dying from neoplasia, including non-AIDS-defining cancers (NADC) is increased[1]. The incidence of squamous cell carcinoma of the anus (SCCA) is not only higher in the HIV-positive population, but continues to increase in the United States[2] (Figure 1). In Australia, anal cancer is now the third most common cancer in the HIV-infected population[3]. SCCA is a sexually transmitted disease clinically related to infection with oncogenic human papillomaviruses (HPV 16-18)[4,5]. Long before the AIDS epidemics, the pivotal role of immune suppression in anal carcinogenesis was highlighted by the high incidence of these tumors in solid organ transplant

patients, irrespective of sexual practice[6,7]. In a large French HIV cohort study, the risk of anal cancer increased with the time during which the CD4 count was < 200 cells/microL and viral load was > 100 000 copies/mL[8]. Thus, both compromised immune function and HPV infection play a role in the development of anal intra-epithelial neoplasia (AIN), the precursor lesion of invasive SCCA.

On a therapeutic standpoint, SCCA has served as a paradigm for the successful application of chemoradiation to solid tumors[9]. Since 1974, it is admitted that: (1) A majority of anal cancers can be cured with chemoradiation therapy (CRT), using 5-fluorouracil (5-FU) and mitomycin C (MMC); and (2) Surgical excision should be restricted to patients who fail to respond to CRT[10,11]. While treatment protocols have remained virtually unchanged during the past three decades, the patients who benefit from this approach nowadays are very different from those who were treated in the 70 s and 80 s. In the 1990s, CRT was poorly tolerated by HIV-positive patients[12,13]. Today, in the Western world, up to 50% of patients with SCCA are relatively young (40-60 years) male homosexuals under HAART[14]. The aim of this paper is to review the clinical data pertaining to clinical outcome of anal cancer in HIV-positive individuals before and after the introduction of HAART.

MANAGEMENT AND OUTCOME OF SCCA IN HIV-NEGATIVE PATIENTS

Combined chemoradiation with MMC and 5-FU is poorly tolerated by immunocompromised patients, and is associated with considerable toxicity in immune competent patients. Many HIV-negative patients with SCCA require radiotherapy breaks and/or chemotherapy dose reduction. In the Memorial Sloan-Kettering Cancer Center series, > 40% (all HIV negative) of patients needed chemotherapy dose reduction of at least one agent, and 77% had at least one radiotherapy break[15]. Data from four prospective randomized trials in HIV-negative patients[16-19] also indicate: (1) a male: female ratio of 1:2; (2) a median age > 60 years; (3) a local failure rate of 30%; and (4) a 3-year overall survival rate of 70%-75% (Table 1).

A closer analysis of data reveals, however, that HIV-negative individuals with SCCA represent a relatively old population of patients who rarely succumb to anal cancer. In the UKCCCR trial[16], 54% of deaths in the chemoradiation group were due to co-morbid conditions or second malignancies, and thus were not related to SCCA. In the RTOG trial[18], out of 146 HIV-negative patients who were treated with MMC-based chemoradiation, there were 32 deaths, but only 15 (46%) were attributed to anal cancer progression. In the MD Anderson Cancer Center series, out of 167 (161 HIV-negative) patients, there were 42 deaths, and only 21 (50%) were due to anal cancer[20]. In summary, 5-year overall survival of HIV-negative patients with SCCA who undergo MMC-based chemoradiation is close to 70%, but > 50% of deaths are unrelated to anal cancer. In accordance with the initial experience of Norman Nigro reported 30 years ago[21], these data indicate that SCCA in this population has limited metastatic potential and is ultimately responsible for the death of < 20% of patients.

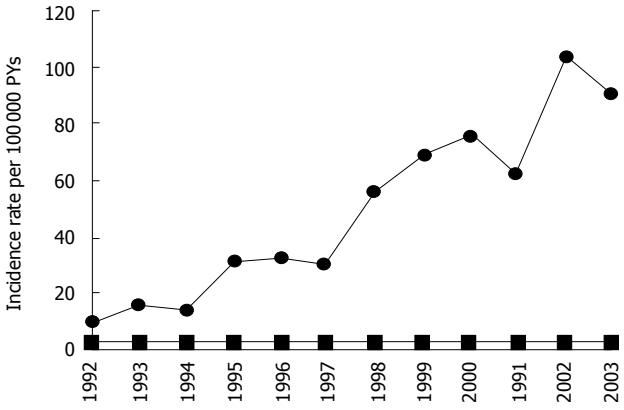

Figure 1 Annual incidence rates of anal cancer among HIV-infected persons (circles) and the general population (squares), USA 1992-2003.

MANAGEMENT AND OUTCOME OF SCCA IN HIV-POSITIVE PATIENTS IN THE HIV ERA (1982-1995)

In the pre-HAART era, HIV-positive individuals demonstrated poor tolerance to MMC-based chemoradiation protocols for anal cancer. Nonetheless, it was recommended that HIV-positive patients with CD4+ > 200/mm^3 should be treated with the standard chemoradiation regimen, whenever possible[22]. In at least seven small series[23-29], clinicians were struck by the fact that HIV-positive and HIV-negative SCCA patients differed by age (40-45 years *vs* 60-65 years), male gender (90%-95% *vs* 35%-40%), and homosexuality. Thus, the experience of treating HIV-positive patients with anal cancer prior to the development of HAART was essentially witnessing the emergence of a high-risk population (Table 2).

Many of these young homosexuals would eventually die of AIDS, with or without evidence of residual anal cancer - but the latter was rarely considered the primary cause of death at a time when median survival with a diagnosis of AIDS was only 17 mo[30]. In the series from Kaiser Permanente Medical Center in Los Angeles[25], after a median follow-up of 38 mo, half of patients were alive and disease-free, while the other half had died from complications of AIDS. Results in terms of local recurrence were disappointing, but many patients did not receive standard chemotherapy for fear of significant hematologic toxicity. Nonetheless, acute toxicity was quite frequent (> 50%), and local tumor recurrence rates were elevated (40%-50%). In addition, Kim *et al*[23] were the first to note that: (1) HIV-positive patients were more likely to die from SCCA than HIV-negative patients, who often succumbed to other, cancer-unrelated causes; and (2) the median time to cancer-related death in HIV-positive individuals was 1.4 years *vs* 5.3 years for HIV-negative patients. Since AIN progresses more quickly towards SCCA in HIV-positive patients, it was logical to hypothesize that

Table 1 Clinical characteristics and outcome of human immunodeficiency virus-negative patients with squamous cell carcinoma of the anus

Author	Trial	Yr	*n*	Male (%)	Age (range)	Local failure (%)	Overall survival
Northover *et al*[16]	UKCCCR	1987-1991	577	45	64 (26-88)	39	65% at 3 yr
Bartelink *et al*[17]	EORTC	1987-1994	103	29	60	29	69% at 3 yr
Flam *et al*[18]	RTOG 87-04	1987-1991	291	30	62 (29-85)	24	
Ajani *et al*[19]	RTOG 98-11	1998-2005	644	31	55 (25-88)	25	84% at 3 yr

Table 2 Clinical characteristics and outcome of human immunodeficiency virus-positive patients with squamous cell carcinoma of the anus before the era of highly active antiretroviral therapy

Author	Yr	*n*	Male (%)	Age (range)	Toxicity 3-4 (%)	Local failure (%)	Overall survival
Kim *et al*[23]	1985-1998	13	92	42	80	61	34% at 5 yr
Holland *et al*[24]	1980-1993	7	100	41	100	43	29% at 2 yr
Peddada *et al*[25]	1987-1995	8	100	48 (37-70)	100	12	50% at 3 yr
Hoffman *et al*[26]	1991-1997	17			64	25	
Cleator *et al*[27]	1989-1999	12	100	43 (30-53)	50	25	60% at 2 yr
Place *et al*[28]	1980-1999	14	100	42 (28-58)	50	57	20% at 5 yr
Efron *et al*[29]	1988-1999	6	100	40 (29-46)		67	

Table 3 Clinical characteristics and outcome of human immunodeficiency virus-positive patients with squamous cell carcinoma of the anus during the era of highly active antiretroviral therapy

Author	Yr	*n*	Male (%)	Age (range)	Local failure (%)	Overall survival
Stadler *et al*[37]	1998-2002	8	100	44 (34-61)	50	67% at 2 yr
Blazy *et al*[38]	1997-2001	9	100	36 (35-49)	11	100% at 2 yr
Bower *et al*[39]	1996-2003	26	100	42 (28-56)	23	47% at 5 yr
Chiao *et al*[40]	1998-2004	175	99.5	49 (43-55)		66% at 4 yr
Wexler *et al*[41]	1997-2005	32	94	45 (31-68)	16	65% at 5 yr
Oehler-Jänne *et al*[42]	1997-2006	40	93	48 (34-75)	62	61% at 5 yr
Abramowitz *et al*[43]	1998-2004	44	100	45	32	85% at 3 yr
Seo *et al*[44]	1999-2007	14	93	45 (34-59)		92% at 3 yr
Barriger *et al*[45]	1995-2008	17	100	44 (29-53)	59	50% at 5 yr
Hogg *et al*[46]	1996-2006	21	100	45	48	73% at 3 yr
Fraunholz *et al*[47]	1997-2008	21	90	45 (31-68)	41	67% at 5 yr

the molecular biology of anal cancer might differ between the two groups[31,32].

MANAGEMENT AND OUTCOME OF SCCA IN HIV-POSITIVE PATIENTS IN THE HAART ERA (1996-)

HAART does neither prevent the development of AIN, nor the progression of AIN towards SCCA[33,34]. The rising incidence of anal cancer in the HIV-positive population during 1996-2004 is well documented[35]. HAART certainly had a positive impact on patients' ability to tolerate chemo-radiation treatment; accordingly, many radiologists strongly caution against scaling back treatment of anal cancer in HIV-positive individuals[36]. This is also motivated by the recent recognition that SCCA is the greatest threat to these patients' lives. We have summarized, in Table 3, the results of eleven studies published since 2004, which evaluated the outcome of HIV-positive patients with SCCA in the HAART era[37-47]. With two exceptions[40,42], these small series are underpowered, and inadequate to detect survival differences between HIV-positive and HIV-negative individuals.

In the Veterans Affairs study[40], the authors concluded that in the HAART era, survival of SCCA is equivalent between HIV-positive and HIV-negative patients (overall 4-year survival 66% *vs* 62%). However, the age distribution of both groups was quite different; among HIV-positive individuals, patients aged 45-49 represented the largest percentage, whereas among HIV-negative individuals the largest percentage of patients was greater than age 75 (Figure 2). In other words, two populations with an age difference greater than 20 years have the same survival, which strongly suggests that SSCA-related mortality was higher in the HIV-positive group. This hypothesis is supported by the multicenter series reported by Oehler-Jänne *et al*[42]: five-year overall survival was similar in both groups (61% *vs* 65%), but HIV-positive individuals had a 4-fold higher risk of locoregional tumor recurrence (62% *vs* 13%), and the majority of them, unlike HIV-negative individuals with SCCA, died of anal cancer. In summary, and in the

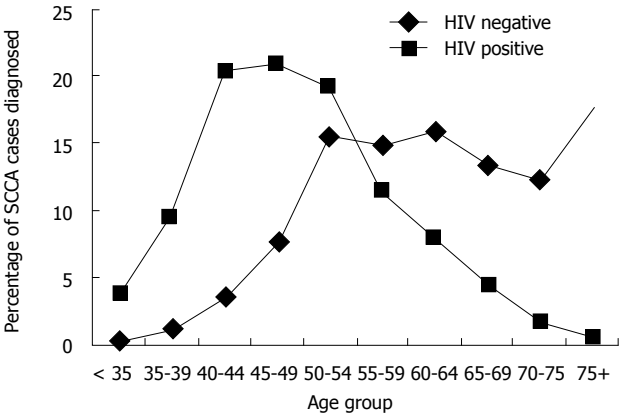

Figure 2 Percentage of anal cancer diagnosed among us veterans by age group (1998-2004). HIV: Human immunodeficiency virus.

HAART era, HIV-individuals with SCCA carry a 50% risk of local relapse and a 33% risk of dying from anal cancer.

CONCLUSION

In some countries, anal cancer is now the third most common cancer in HIV-infected individuals and its incidence continues to increase, despite (or because of) the use of HAART. It is a disease of relatively young male homosexuals, who should be considered candidates for chemoradiation, using standard doses of MMC and 5-FU, as well as pelvic irradiation. There is, however, evidence that HIV-positive patients experience a higher rate of locoregional tumor recurrence and are more likely to die from anal cancer than their HIV-negative counterparts; this explains why both HIV-positive and HIV-negative groups have similar survival, despite a > 20 years difference in age. HIV-positive male homosexuals under HAART are protected from opportunistic infections, but have an increased risk of developing, and eventually succumbing to anal cancer.

SCCA was not a frequent cause of death in HIV-positive patients before 1997-1998, and this affirmation stands true in 2010 for elderly HIV-negative patients. In contrast, for middle-aged male homosexuals under HAART, SCCA is an often fatal, opportunistic cancer which results from the combination of two factors: (1) persistent immune deficiency; and (2) persistent infection with oncogenic HPVs in the anal canal. Cancer-prevention strategies should be implemented in this population: male homosexuals should undergo routine anuscopy and an anal Papanicolaou test to detect and treat precursor lesions of SCCA. This approach, if successful, might hopefully mimic in male homosexuals, the dramatic improvement observed for cancer of the uterine cervix in women. Complete eradication of oncogenic HPVs in the anogenital mucosa might also require a proactive vaccination program for high-risk individuals[48,49]. This approach could also serve an important public health purpose, reducing the pool of susceptible individuals and contributing to the control of re-emerging HPV infection.

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