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# Treatment that follows guidelines closely dramatically improves overall survival of patients with anal canal and margin cancers

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ABSTRACT

*Background:* To assess relevance of ESMO-ESSO-ESTRO treatment guidelines in a retrospective analysis of patients with anal canal or anal margin cancers.
*Material and methods:* 155 patients were separated into standard treatment group (STG), treated according to or closely the guidelines, and an altered treatment group (ATG).
*Results:* The median follow-up time was 50.7 months. In the STG, the 5- and 10-year LR-DFS rates were 75.2% and 72.7%; in the ATG, they were 66.8% and 61.2%, respectively. In the STG, the 5- and 10-year OS rates were 81.8% and 68%; in the ATG, they were 63.3% and 49.5%, respectively ($p = 0.037$). In the multivariate analysis, favorable prognostic factors for OS included the standard treatment, age <60, tumor <T3, no HIV infection and a total radiation dose >50.4 Gy.
*Conclusion:* This study identifies the superiority of treatment according to standard guidelines compared to altered treatment. Our results corroborate the guidelines.


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## 1. Introduction

Anal canal cancer (ACC) and anal margin cancer (AMC) are very rare with standardized incidence ranges between 0.2/100,000 to 2.1/100,000 people (Grabar et al., 2011; Johnson et al., 2004). Since Nigro and colleagues determined the efficiency of neoadjuvant treatment, an organ-preserving policy with chemoradiation (CRT) has been considered the standard treatment of these cancers (Anonymous, 1996). The initial support for this publication has been strengthened by randomized trials, which demonstrated good loco-regional control and acceptable quality of life with this strategy while avoiding mutilating surgery and definitive colostomy (Ajani et al., 2008; Anonymous, 1996; Bartelink et al., 1997; Cummings et al., 1991; Glynne-Jones et al., 2014a; James et al., 2013).

Current guidelines for ACC and AMC tumors, published in 2014, recommend a two-sequence irradiation schedule (Glynne-Jones et al., 2014b). The first sequence is comprised of at least 45 Gy of external irradiation with concurrent chemotherapy. The most common chemotherapy protocol proposes a 5-Fluorouracil (5FU) dose at 1000 mg/m$^2$ for days 1–4 (week 1) and 29–32 (week 5) by continuous 24h IV infusions and Mitomycin C (MMC) at 12 mg/m$^2$ with IV bolus on day 1 (maximum single dose of 20 mg). The second sequence delivers a radiation boost ranging from 15 to 20 Gy. Higher doses may be required for more advanced tumors, particularly if a planned treatment gap is used, or for an observed poor response. A boost can be delivered with external irradiation or brachytherapy. However, the gap should be as short as possible according to recent literature. However, currently, it is not possible to make a definitive recommendation about total dose and use or not of a gap. Concurrent chemotherapy is not required through the second sequence irradiation. Treatment response is evaluated 6–26 weeks after CRT (Cummings et al., 1991; Glynne-Jones et al., 2014a; James et al., 2013; Moureau-Zabotto et al., 2013; Schlienger et al., 1989). According to these guidelines, surgery as an up-front treatment is clearly not permitted and is often reserved as a salvage treatment (Glynne-Jones et al., 2014b).

The patient's age and racial or socioeconomic status, the specific treatment facility, the availability of medication, the access to healthcare and individual practitioner choices can affect the adherence to the recommended guidelines (Anderson et al., 2015; Bristow et al., 2014; Carlson et al., 2014; Charlton et al., 2014; Guillerme et al., 2014). In some studies, discrepancies between the recommended guidelines and the actual treatment provided dramatically decreased the patient outcomes (Guy et al., 2014; Inwald et al., 2014; Javid et al., 2014; Nadpara et al., 2015; Olszewski et al., 2015). No comparison between the actual treatment and guideline-optimized treatment for ACC and AMC has ever been performed.

The objective of this study was to compare survival outcomes between patients optimally treated for ACC and AMC according to current guidelines and patients treated in an alternate manner throughout the 15-year radiotherapy experience at a comprehensive cancer center.

## 2. Patients and methods

### 2.1. Treatments

All patients with ACC or AMC squamous cell carcinoma (SCC) referred to our department of radiotherapy consecutively from April 1997 to March 2013 and treated with a curative intent were retrospectively included in this study. The study received approval from the institutional review board.

Tumor characteristics, size, TNM classification (UICC 2009) are described in Table 1. Since 2004, indications for CRT have been discussed among a multidisciplinary board, which includes physicians who specialize in the disease. In the cases where synchronous oligometastases were identified, patients were included in the study if treatment was performed with curative intent.

Treatment schedules were variable (Table 2). The first sequence of treatment was either radiotherapy alone (RT1) or chemoradiation (CRT1). After a time gap, which varied according to the response evaluation time and the type of treatment used, patients could receive a second sequence with radiation (RT2) or chemoradiation (CRT2). For both sequences, radiation was delivered with 3D-RT (from 1997 to 2009), intensity-modulated radiation therapy (IMRT) (since July 2009) or by brachytherapy. 3D-RT and IMRT were delivered daily, five days a week. Brachytherapy used an Iridium-192 source from wires or source projector. The source is introduced through catheters fitted into an endorectal applicator, which is then inserted into the rectum. The sources were always afterloaded. This procedure was performed in the operating room with the patient under general anesthesia. Brachytherapy duration depended on the dose rate at the physician's discretion.

For RT1 and CRT1, the total median doses delivered were 46 Gy (range: 40–65) and 45 Gy (range: 36–76), respectively. For RT2/CRT2 and brachytherapy, the total median doses delivered were 20 Gy (range: 11–26.4) and 15 Gy (range: 6.5–30), respectively.

For CRT1 and CRT2, the drug regimen and number of chemotherapy cycles were left to the discretion of the medical oncologist. A combination of 5FU and MMC was used in 45 patients with a median number of two cycles. A drug combination with a platinum component was used in 61 patients with a median of two cycles. Other chemotherapy agents were used in 9 patients.

Early surgery indications were a local or loco-regional evolution of the tumor and a lack of response to the first step of treatment. Surgical procedures included abdominoperineal excision or a pelvic exenteration.

### 2.2. Patient grouping

Based on the current guidelines, patients were included in the standard treatment group (STG) if they received both sequences "CRT1 and CRT2", "CRT1 and brachytherapy" or "CRT1 and RT2", or for stage I tumors, "RT1 and brachytherapy". CRT was considered regardless of the medication administered because during the long period in which patients have been treated, the optimized chemotherapy protocols varied. Other patients were included in the altered treatment group (ATG). The use of a gap was not considered out guidelines. Indeed, according to the literature, authors of these guidelines were not able to recommend gap duration. The criteria to include patients in the ATG were non-delivery of CRT1 for 45 patients combined or not with non-delivery of RT2 for 23 patients and anticipated abdominal surgery after CRT1 for 6 patients. This final treatment method was considered to be non-protocol because the interval between the completion of the first sequence and the decision to operate was too brief compared to the standard recommendations (i.e., between 0 and 33 days compared to the 6–26 weeks weeks recommended).

### 2.3. Mortality and morbidity

Treatment toxicity was evaluated using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v.4). If surgery was performed, short-term postoperative morbidity and 30-day