The incidence of anal cancer in the general population has increased over the last 30 years although it remains a relatively rare entity. A number of clinical trials conducted in the 1990’s, showed that radiotherapy combined with chemotherapy can cure the disease in the majority of patients whilst preserving the anal sphincter. Trials that investigated chemotherapy combinations failed to improve over the current standard combination of mitomycin-C and 5-FU. However, different radiation strategies and schedules were used in the various phase II and phase III trials (that primarily addressed chemotherapy questions), we performed a pooled analysis of the data from all available phase II and III trials in to identify radiotherapy related parameters affecting the outcome of patients with anal cancer, resulting in new and improved guidelines for future studies and for tailormade treatment.

Methods: A total of 13 trials (7 phase II and 6 phase III) conducted were identified, totaling 3227 patients recruited between 1986 and 2010. Data from 3036 patients from 10 studies were received (94.1%). Of these studies, 3 were conducted before 1994 and randomized against radiation alone or combined with SFU only. These studies were excluded from the main analysis which focuses on radiation combined with doublet chemotherapy (N=2033). Patients not ≥75 years, not M0, or T1N0 were excluded, as well as all patients treated by brachytherapy, those who received <40 Gy of treatment (considered unfit) leaving 1343 patients in the analysis. The primary endpoint is loco-regional control within 5 years of entry on study. Loco-regional failure included events of local or regional failure and the need for local surgery. Secondary endpoints were progression-free and overall survival. A cox model adjusted by patient and disease factors was fitted to study the impact of treatment dose and duration. Statistical significance is claimed at the 5% level.

Results: The radiotherapy regimens used in the studies are described in Table 1.

Two third of the 1342 patients were women; the median age was 56 years (range: 25-75). Tumor was confined to the anal margin in 82% of the patients (6.1%). The median tumor size was 4.1 cm, 64.1% of the patients had T. The median follow-up in the studies was 4.1years. By year 5, a total of 303 events of loco-regional failure were observed with 5-year cumulative incidence of 25.1% (95%CI: 21.9-28.3%). The model included effects for sex, age (in years), N stage (N= inguinal nodes -, N+ inguinal nodes -, N+ unknown inguinal status vs N0), tumor localization (anal canal vs anal margin only), tumor size in cm (within combinations of tumor location and N category), total dose on the anal canal (=50.5 Gy vs >50.5-55Gy, >55-59 G, >59-59.4 Gy,>59.4 Gy) and overall treatment time within defined dose. This model shows a statistically significant negative impact of tumor size (<0.0026) and of prolonged overall treatment time (P=0.0126). When the overall treatment time is split between the duration of the gap and the duration of the effective treatment time only the duration of the gap remained statistically significant (P=0.0049) whether the effective duration of the treatment lost statistical significance (P=0.0786).