Pooled Analysis of external-beam RADiotherapy parameters in phase II and phase III trials in radiochemotherapy in Anal Cancer (PARADAC).

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Abstract

PURPOSE: Concomitant external-beam radiochemotherapy (5-Fluorouracil-Mitomycin C) has become the standard of care in anal cancer since the '90s. A pooled analysis of individual patient data from 7 major trials was performed quantifying the effect of RT-related parameters on the outcome of patients with anal cancer.

MATERIALS AND METHODS: Pooling databases from combined modality trials, the impact of RT parameters (total dose, gap duration, OTT: overall treatment time) on outcome including locoregional failure (LRF), 5-year progression-free-survival (PFS) and toxicities were investigated. Individual patient data was received for 10/13 identified published studies conducted from 1987-2008(n=3031). A Cox-regression model was used (landmark=3 months post-RT for first follow-up).

RESULTS: After data inspection indicating severe heterogeneity between trials, only 1343 patients from the 7 most recent studies (since 1994) were analyzed (median follow-up=4.1 years). A higher overall 5-year LRF rate [22.8% (95%CI 22.3-27.3%)] significantly correlated with longer OTT ($p=0.03$), larger tumor size ($p<0.001$) and borderline significantly with male gender ($p=0.045$). Though significant differences were not observed, subset analyses for LRF (dose range:50.4-59Gy) seemed to favor lower doses ($p=0.412$), and when comparing a 2 week gap versus 3 (dose:59.4Gy), results suggested 3 weeks might be detrimental ($p=0.245$). For a 2 week gap versus none (dose range:55-59.4Gy) no difference was observed ($p=0.89$). Five-year PFS was 65.7% (95%CI: 62.8-68.5%)]]. Higher PFS rates were observed in women ($p<0.001$), smaller tumor sizes ($p<0.001$) and shorter OTT

($p=0.025$). Five-year OS [76.7%(95%CI: 73.9%-79.3%)] correlated with female gender ($p<0.001$), small tumor size($p=0.027$) and short OTT($p=0.026$). Descriptive toxicity data is presented.

CONCLUSION: For patients receiving concurrent external-beam doublet chemoradiation a longer OTT seems detrimental to outcome. Further trials involving modern techniques may better define optimal OTT and total dose.

Pooled Analysis of external-beam RADiotherapy parameters in phase II and phase III trials in Anal Cancer (PARADAC).

Introduction

Anal cancer is a rare tumor arising from the gastrointestinal tract. Over the past decades an increase in incidence has been observed for *in situ* and squamous cell anal carcinoma^{1, 2}. The most important risk factors are: previous gynaecological or blood related cancer, smoking, sexually transmitted diseases (HPV, HIV, herpes, etc.), sexual partners exceeding 10, long-term immunosuppression and receptive anal intercourse².

Until the seventies abdominoperineal resection remained the standard of care, with an operative mortality rate of about 6-8 percent³. Five-year overall survival (OS) rates of 40 to 70% were reported, with 5-year recurrence rates of approximately 40%^{4, 5}. After radiation therapy (RT), whether or not followed by surgery, similar disappointing results were reported⁴. The concomitant use of chemotherapy, 5-Fluorouracil (5-FU) with Mitomycin C (MMC), with usually split course RT dramatically improved local control (LC) and colostomy free survival (CFS). Thus, radical surgery was replaced with primary chemoradiation as the standard of care^{3, 6, 7}. Almost two thirds of patients could be cured and their sphincter preserved with this approach^{3, 6, 7}. Nevertheless, the prognosis remained poor for patients with advanced disease or lymph node involvement. Despite attempts to improve on this treatment, the standard treatment for locally advanced disease remained unchanged for years with the most recent contributions confirming the

efficacy of RT with 5-FU and MMC⁷⁻¹⁰. The most concrete improvement in the treatment of this disease is the introduction of new modalities of RT delivery, Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), allowing a better toxicity profile with comparable outcomes¹¹⁻¹⁶. However, many questions remain a matter of debate.

A pooled analysis of individual patient data from 7 major prospective trials was performed with the aim to quantify the effect of RT-related parameters on the outcome of patients with anal cancer to improve guidelines for future RT combined modality studies.

Materials and methods

Selection criteria:

A consensus meeting was held at the European Organization for the Research and Treatment of Cancer (EORTC) Headquarters on March 6th, 2008, with representatives of European countries and collaborative groups active in the field of radiochemotherapy for advanced anal cancer: the Italian group, Spanish Group, Nordic Group, *UK Co-ordinating Committee for Cancer Research* (UKCCR) and the *French Federation Nationale des Centres de Lutte Contre le Cancer* (FNCLCC). The aim of the meeting was to agree on the design of the next phase III randomized trial testing improved radio-therapeutic regimes. To prepare, the group reviewed available evidence from phase II and III studies for anal cancer, including the then recently closed phase III trials, such as ACCORD-03¹⁷. The studies identified at the time are detailed in Table 1.

Table 1. Phase II and III studies in anal cancer. Individual patient data was received for all studies in bold.

Group	Study Name	Phase	No. Patients	No. eligible patients	Inclusion Stage	No. N0/N1	NACT	Concurrent CT	Consolidation CT	Pelvic Dose (Gy)/fr. [†]	Boost Dose(Gy)/fr.	Inguinal Dose (Gy)	Inguinal. dose N+ (Gy)	Gap (weeks)
EORTC	22861 ⁵	III	110	103	All T > 4cm and/or all N+; M0	57/53	No	± 5-FU - MMC	No	45/25	15 if CR 20 if PR EBRT or BT	0	45 + 15/20	6
	22953 ¹⁸	II	44	43	All T > 4cm and/or all N+; M0	25/18	No	± 5-FU - MMC	No	36/20	23.4/13 EBRT or BT	0	59.4	2
	22011 ¹⁹	II	88	76	All T > 4cm and/or all N+; M0	50/38	No	5-FU – MMC vs. Cisplatin – MMC	No	36/20	23.4/13 EBRT or BT	0	36 + surgery	2
UKCCCR	ACT I ^{20, 21}	III	585	577	All (except T1N0); M0	cN+: 31 pts	No	± 5-FU - MMC	No	45/20 or 25	15/6 EBRT or 25Gy;10Gy/day,BT if R > 50%	± 45	-	6
	EXTRA ²²	II	31	31	All	23/8	No	Capecitabine - MMC	No	30.6/17	19.8/11	30.6	50.4	0
	ACT II ⁹	III	940	935	All; M0	609/302	No	5-FU – MMC vs. 5-FU - Cisplatin	± 2 cycles 5-FU-Cisplatin	30.6/17	19.8/11	30.6	50.4	0
RTOG	87-04 ²³	III	310	289	All T & N; M0	240/51	No	5-FU ± MMC	No	45/25 [‡]	5.4/3	45	50.4	0
	92-08 ²⁴	II	46 and 20	66	All T > 2 cm; M0	41/6	No	5-FU - MMC	No	45/25 [‡]	14.4/8	45	59.4	2 and 0
	98-11 ^{8, 25}	III	682	638	All except T1; M0	448/196	± 5-FU - Cisplatin	5-FU – MMC vs. 5-FU - Cisplatin	No	45/25	10-14/5-7	45	55-59	0
FNCLCC	^{26 **}	II	80	80	T> 4 cm and/or N+; M0	18/62	5-FU - Cisplatin	5-FU - Cisplatin	No	45/25	15 if CR 20 if PR EBRT or BT	0	60-65	4-8
	ACCORD -03 ^{17**}	III	307	307	All T > 4cm and/or all N+; M0	182/120	± 5-FU - Cisplatin	5-FU - Cisplatin	No	45/25	15 or 20-25 (20 if R > 80%) EBRT or BT	± 45	surgery + 45 or 60-65	3
ECOG-ACRIN	42-92 ²⁷	II	32	32	All; M0	17/12	No	5-FU - Cisplatin	No	45/25 ^x	14.4/8	36	59.4	2
CALGB	9281 ²⁸	II	45	45	T3 > 5cm; T4 and all N+	-	5-FU - Cisplatin	5-FU - MMC	5-FU-Cisplatin if PR or N2/N3	45/25 [‡]	14.4/8	30.6	50.4	2

* No. of eligible patients with analyzable data

** published in 2012, ongoing at the time of the meeting

[†]in fractions of 1.8 Gy for all studies, except for ACT I in fractions of 1.8 Gy or 2.25 Gy. RTOG 98-11 advises the boost to be given in fractions of 2 Gy.

[‡]field reduction at 30.6 Gy and at 36 Gy. If after the full treatment there was a residual histologically confirmed primary or inguinal lymph node, addition of a second boost (9 Gy).

[‡]field reduction at 30.6 Gy.

^x field reduction at 30.6 Gy and at 36 Gy.

Abbreviations: No., number; Gy, NACT, neoadjuvant chemotherapy; CT, chemotherapy; fr., fractions; Gy, Gray; EORTC, European Organization for the Research and Treatment of Cancer; UKCCCR, UK Co-ordinating Committee for Cancer Research; RTOG, Radiation Therapy Oncology Group; FNCLCC, French Federation Nationale des Centres de Lutte Contre le Cancer; ECOG-ACRIN, ECOG-ACRIN Cancer Research Group; CALGB, Cancer and Leukemia Group B; 5-FU, 5-fluouracil; MMC, Mitomycin C; CR, complete response; PR, partial response; el., electrons; ph., photons; BT, brachytherapy; R > 50%, response > 50%; EBRT, external beam radiotherapy.

Studies:

ACCORD-03, examined the impact of therapeutic intensification by induction chemotherapy and/or high dose RT¹⁷. Several studies (EORTC 22011, RTOG 98-11 and ACT II) evaluated the feasibility of different chemotherapy schemes in combination with RT, with or without induction or maintenance chemotherapy^{8, 9, 19, 25}. The EORTC 22953 trial investigated the effect of a reduction of the gap (16-days) in combination RT and 5-FU-MMC treatment for anal cancer versus a standard 6 weeks gap¹⁸. In the UKCCCR EXTRA trial intravenous 5-FU was replaced by Capecitabine²². ECOG-ACRIN 42-92 studied the feasibility of Cisplatin replacing MMC with a 2 week gap²⁸.

A consensus emerged that it was not timely to start a new trial, given the number of existing projects in the various countries that were still maturing at the time, and the difficulty to finance such academic trials. Considering the rarity of the disease, an international European or worldwide collaboration was needed for a successful phase III study.

A proposal was made for pooling databases from existing trials to explore the impact of specific RT parameters and toxicities on outcome. It was acknowledged that to address these questions would entail between-trial protocol comparisons. The questions that emerged revolved around the impact of overall treatment time (OTT, affected by the duration of the gap) and RT dose on local recurrence. The relationship between irradiated pelvic volume and pelvic recurrence rates, the total dose to the elective inguinal area and inguinal control, long term toxicity related to irradiated volume/total dose and of prognostic factors for long term outcome in relation with the baseline patient and disease characteristics was assessed.

Data collection and extraction:

For each included study, the protocol and publication of results were obtained. The following individual patient data were requested for each patient:

- **Patient-related:** Age; gender; date of entry/randomization.
- **Tumor-related:** Date of diagnosis; cT; cN; cM; maximum tumor size; tumor localization (i.e. anal margin involved); inguinal node involvement (if involved, number and size); pelvic nodal involvement (if involved, number and size).
- **Treatment-related:** Treatment arm; RT parameters [date of start, total dose to the primary tumor (number of fractions), total dose to positive lymph nodes (number of fractions), total dose to the elective pelvic area (number of fractions), Total dose to the elective inguinal area (number of fractions), OTT (tumor; positive nodes; elective), gap duration]; chemotherapy (if given, date of start, drugs used (5-FU, MMC, Cisplatin, other).
- **Outcomes:** Last follow up date; survival status; local recurrence and date (if any); pelvic recurrence status and date; inguinal recurrence status and date; distant recurrence status and date; date of colostomy (if performed); date of lymph node resection and procedure (if performed).
- **Late Toxicity:** Bladder; bone; skin; intestine; anus (worst grade, date of start, scale).

No specific format for data collection was specified. Since many trials were historical, not all data could be obtained for all studies, depending on the data collection system used (see results).

Statistical analysis:

Recognizing that treatment effects of interest in the analysis required assessments across studies, but were essentially fixed by each trial protocol, a Cox model was developed to adjust for patient specific factors in a subgroup of the data selected to minimize systematic heterogeneity due to protocol specific criteria (e.g. eligibility criteria) and included factors representing RT dose and OTT. The model included adjustment for age (continuous linear effect), gender, tumor localization (anal margin, anal canal or both), N stage (pelvic N0/N+ without inguinal involvement/ pelvic N+ with inguinal involvement/ pelvic N+ with unknown inguinal status) and tumor size within N categories within tumor location. The latter was to accommodate for interaction effects and to fulfill the proportional of hazard assumptions. The OTT was modelled as a continuous effect, whereas the total dose was assessed in categories (≤ 50.5 Gy, >50.5 to 55 Gy, >55 to 59 Gy, >59 to 59.4 Gy and >59.4 Gy). The categories were created to accommodate the intrinsically discrete set of total doses planned in the study protocols (Appendix A: Figure 1).

Appendix A. Figure 1. Overall treatment time according to the total dose to the anal canal.

Online only.

For the analysis of locoregional failure (LRF), our primary endpoint, a landmark of 3 months was used to homogenize the timing of first disease assessment during follow-up in the studies, and the time was censored at 5 years to harmonize the duration of follow-up.

The adequacy of the Cox regression model was evaluated by performing the graphical and numerical methods of Lin, Wei and Ying²⁹. Based on intermediate study results that showed a single model could not fit the early trials that used RT alone $\pm$ one chemotherapeutic drug and the more recent studies that used RT $\pm$ a doublet of drugs, the primary analysis set was restricted to patients treated with doublet chemotherapy after 01/01/1994.

The analysis was exploratory and two-sided tests were used with a 5% significance level.

Results

Merging data

Data was provided by 10/13 trials, amounting to 3031 patients. Assessment of data received and of study protocols revealed severe heterogeneity in patient selection criteria, the staging system used and the capture of the RT treatment data. An attempt was made to harmonize the data from the trials, to allow merging of the databases while excluding as few patients as possible (Figure 1).

Patients were recruited during a two decade period (1987-2008) (Appendix A, figure 2). The difference in terms of data collection, patient staging, treatments and patient follow-up was particularly evident between the first 3 trials (EORTC 22861, ACT I and RTOG 87-04), conducted with RT $\pm$ two chemotherapeutic drugs (RT + single or doublet chemotherapy for the RTOG trial), and the later trials which assessed RT + doublet chemotherapy (RT $\pm$ doublet chemotherapy for the EORTC 22953 trial)^{6, 20, 21, 23}. Heterogeneity was such that no model could fit both groups of studies together. Since current treatment involves doublet chemotherapy with RT, the analysis was restricted to the more recent studies (Figure 1; Appendix A, figure 2).

Certain parameters (e.g.: planned RT dose, OTT) were specified inside a trial, but varied between trials. Thus it was essential to minimize any systematic differences in other factors that would also be confounded with the trial effect in our models. We assessed the eligibility criteria of the studies and selected patients for the analysis fitting the most stringent criteria across protocols, excluding patients >75 years or patients with unknown age, T1N0 and M1 or Mx disease from the analysis.

For many patients important data [e.g. N-stage, dose to the anal canal, OTT, tumor localization, gap duration, total dose to the pelvis, etc.] could not be retrieved or derived. In

particular, OTT and total dose could not be calculated for patients who received brachytherapy. Since these factors were key to the analysis, these patients were excluded. Also, very short treatment times (<30 days) or very low dose (<36Gy) could result from excess toxicity or very poor prognosis or performance status (30 patients) or from protocol planned dose adaptations triggered by intermediate assessment of the response to treatment (21 patients). We applied a landmark of 90 days to not overestimate the association between treatment and outcome (due to the exclusion of the 21 patients during the landmark) and harmonize the timing of the first visit in the studies.

Toxicity was also scored heterogeneously between trials. Some trials systematically reported late toxic events at each follow-up, whereas others only reported one event (the worst grade) per patient in the received data files. The scales used for grading were also very heterogeneous (RTOG/EORTC, SOMA-LENT, NCI CTC different versions) (Appendix A. Table 1). A common scale for toxicity was applied and was based on the ‘RTOG/EORTC Late RT Morbidity Scoring Scheme’ as it was the most used. The toxicities were classified into groups and scored into mild/moderate vs. severe). Late toxicity was considered as starting more than 90 days after the start of treatment.

Results pooled analysis:

A total of 1343/3031 patients were eligible for the pooled analysis (Figure 1). Their characteristics and RT-related parameters are presented in Table 2. The overall median duration of follow-up within these trials was 4.1 years (Appendix A: Figure 3).

In total, 419 patients (31.2%) developed clinical failure during follow-up (local, inguinal or locoregional relapse, distant metastases or death).

An inguinal recurrence was recorded in 4 studies (ACCORD-03, EORTC 22011, EXTRA and ACT II), occurring in 54 of the 741 patients evaluable in these studies (7.3%). At treatment initiation; 21 of the 54 patients had N0 disease, while 33 had positive nodes, of which 6 had no positive inguinal nodes.

LRF was described in 295 patients (22%). LRF was defined as a local recurrence, a regional recurrence or local surgery (abdominoperineal resection or colostomy). The 5-year cumulative rate of LRF was 22.8% [(95%CI 22.3-27.3%) Figure 2]. Lymph node resection surgery was not considered as an event (this data was only available on the 3 EORTC trials, only 3 patients had a lymph node resection before documented LRF).

LRF was significantly correlated with OTT ($p=0.03$), tumor size ($p<0.001$) and borderline significantly associated with gender ($p=0.045$). OTT and total dose were not markedly different between males and females (Appendix A: Table 2).

As the dose and the gap duration were very closely related by design of the protocols with the lowest (50.4 Gy, except for the good prognosis patients in RTOG) and intermediate doses (55-59 Gy) given without a gap and the higher doses (≥ 59.4 Gy) given with a 2 or 3 week gap, no model was able to study the effect of the dose and the gap duration separately. A comparison between the lower and intermediate doses, without a gap, could be made. To avoid bias in favor of low doses, N0 patients treated at 45Gy were excluded. Only patients from the RTOG 98-11 treated at intermediate doses versus patients treated in ACT II and EXTRA at a planned dose of 50.4Gy were considered in this analysis (also adjusted for gender, age, tumor location, N-stage and tumor size). Based on 220 locoregional relapse events ($n=977$), no difference between dose levels could be seen. However, results seemed to favor a lower dose (Appendix A: Table 3). To assess the impact of the gap duration, we compared patients intended

to receive a dose of 59.4Gy with either a 2 week gap versus a 3 week gap (i.e. patients in EORTC studies versus ACCORD-03 arms 1 and 3). In this group of 232 patients 68 locoregional relapses were registered. The analysis suggests that a 3 week gap might be detrimental, although the effect was not statistically significant (Appendix A: Table 4)

A 2 week gap was compared to no gap in patients who were intended to receive a dose of 55 to 59.4Gy (EORTC studies versus RTOG 98-11). In this group, 113 events were observed among 521 patients. A supplementary sensitivity analysis was performed in this group by restricting the analysis to patients who had effectively received a dose of >56.5Gy and <60.0Gy (n=214). Only 74 events were seen. Neither analysis showed a significant difference between a 2-week gap and no gap (Appendix A: Table 5).

The 5-year progression free survival (PFS) rate was 65.7% (95% CI: 62.8-68.5%). The occurrence of a clinical event was less frequent in women ($p<0.001$) or in patients with small tumor size ($p<0.001$) or shorter OTT ($p=0.025$). The 5-year OS was 76.7% (95%CI: 73.9%-79.3%) and it correlated with gender ($P<0.001$), with a higher OS for women, small tumor size ($p=0.027$) and short OTT ($p=0.026$) (Figure 2, Appendix A: Table 2).

Late toxicities (90 days or more from the start of treatment), were divided into gastrointestinal, skin or subcutaneous tissue and bladder-genito-urinary late toxicities (Table 3).

Figure 1: PRISMA flowchart of selection of eligible patients for the pooled analysis to get a more homogenous group of patients.

Appendix A. figure 2: Summary of Trials. n= number of patients included in the final analysis per trial. *Online only.*

Appendix A. Table 1. Evaluated toxicities and scales used for toxicity grading for the 10 trials data was received for. *Online only.*

Group	Study	Defined selected toxicities	Scale	Comment
EORTC	22861	Rectal discharge Rectal bleeding Anal/rectal damage Rectal stenosis Rectal incontinence Colostomy Skin reaction Fibrosis Other	RTOG/EORTC Late RT Morbidity Scoring Scheme (NCI CTC v2) scale for skin reaction and sub tissue (fibrosis) Study specific defined scales for the other categories	
	22953	Bladder/Urethra Skin/subcutaneous tissue Rectum Small intestine / Colon	SOMA/LENT	
	22011	Bladder Skin Small/large intestine Subcutaneous tissue Other	RTOG/EORTC Late RT Morbidity Scoring Scheme (NCI CTC v2)	
UKCCCR	ACT 1	Ano-rectal Skin Hip/bone.	No specified scale used, only refers to grade 3 or 4 toxicities without specifying the exact grade	
	EXTRA	Skin Large intestine Rectal or perirectal pain Pain due to radiation, Urinary frequency/urgency Other	RTOG/EORTC Late RT Morbidity Scoring Scheme (NCI CTC v2) for Skin and Large intestine, Renal / genitourinary and pain Scales of NCI CTC v2 for the other toxicities	A lot of “other” toxicities
	ACT II			
RTOG	87-04	Skin Gastrointestinal Genitourinary Stomatitis/Mucus membrane	RTOG/EORTC Late RT Morbidity Scoring Scheme (NCI CTC v2)	
	98-11	Bladder Skin Small/large intestine Subcutaneous tissue Other	RTOG/EORTC Late RT Morbidity Scoring Scheme (NCI CTC v2)	
ECOG-ACRIN	42-92	No late toxicities have been reported		
FNCLCC	ACCORD-03	Bladder/Urethra Skin/subcutaneous tissue Rectum Small Intestine/Colon	SOMA/LENT	Only some scales are pre-specified

Table 2: Patient characteristics and radiotherapy-related parameters of the group of patients included in the pooled analysis.

	Total (N=1343) N (%)
Age (years)	
Median (range)	56 (25-75)
Quartile1-Quartile3 (Q1-Q3)	48-64
Mean (SD)	55.1 (9.92)
Gender	
Male	449 (33.4)
Female	894 (66.6)
Tumor localization	
Anal margin	82 (6.1)
Anal canal or both	1261 (93.9)
T stage	
T1	23 (1.7)
T2	638 (62.4)
T3	296 (22.0)
T4	186 (13.8)
Max tumor size (cm)	
Median (range)	4.1 (1 - 20)*
Q1-Q3	3.0 – 5.5
Mean (SD)	4.7 (2.03)
N stage	
N0	865 (64.4)
N+ without inguinal invasion (N+ ing-)	202 (15)
N+ with inguinal invasion (N+ ing+)	144 (10.7)
N+ with unknown inguinal status (N+ ing?)	132 (9.8)
Planned gap duration (days)	
0	1125 (83.8)
14	105 (7.8)
21	113 (8.4)
Effective duration of the gap (days)	
Median (range)	0 (0-68)
Q1-Q3	0-0
Overall treatment time (weeks)	
Median (range)	6 (4-17.3)
Q1-Q3	5.3-8
Weeks of treatment (minus GAP duration) “effective treatment time” (weeks)	
Median (range)	5.9 (4.3-16.1)
Q1-Q3	5.3-7
Total dose to Pelvis (Gy)	
Median (range)	39.6 (0.9-60)

Q1-Q3	30.6-45
N non missing observations	1329
Total dose on anal canal (Gy)	
Median (range)	50.4 (38.6-98)
Q1-Q3	50.4-59
$\leq 50.5\text{Gy}$	716 (53.3)
$>50.5-\leq 55\text{Gy}$	169 (12.6)
$>55-\leq 59\text{Gy}$	198 (14.7)
$>59\text{Gy}-\leq 59.4\text{Gy}$	152 (11.3)
$>59.4\text{Gy}$	108 (8)

* There were 5 aberrant values.

Appendix A. Figure 3: Duration of follow up in the pooled analysis. *Online only.*

Figure 2. (a) Cumulative incidence of locoregional failure (b) Progression free survival and (c) Overall survival.

(a) Locoregional failure

(b) Progression-free survival

(c) Overall survival

Appendix A. Table 2: Models of overall treatment time and dose of radiation therapy for

(a) Locoregional failure (b) Progression free survival (c) Overall survival and (d)

Treatment parameters by gender . *Online only.*

(a) Locoregional failure

			HR	HR 95% CI		P	Best if
Overall treatment time	Dose ≤50.5 Gy		1.15	0.99	1.34	0.065	Time ↓
(weeks)	Dose 50.51 Gy - 55 Gy		0.98	0.72	1.34	0.908	
P=0.03 (df=5)	Dose 55.01 Gy - 59 Gy		1.23	1.04	1.45	0.017	Time ↓
	Dose 59.01 Gy - 59.4 Gy		1.14	0.88	1.47	0.309	
	Dose >59.4 Gy		1.14	0.96	1.36	0.128	Time ↓
Total dose on anal canal	50.51 Gy - 55 Gy vs. ≤50.5 Gy		2.00	0.20	19.79	0.552	
P=0.937 (df=4)	55.01 Gy - 59 Gy vs. ≤50.5 Gy		0.68	0.14	3.40	0.643	
	59.01 Gy - 59.4 Gy vs. ≤50.5 Gy		0.76	0.06	8.88	0.825	
	>59.4 Gy vs. ≤50.5 Gy		0.73	0.08	6.26	0.774	
Age (years)			0.99	0.98	1.00	0.234	
P=0.234							
	Tumor size (cm) in:						
	P<0.001 (df=6)						
	Anal margin	N0	0.83	0.60	1.15	0.257	
	Anal margin	N+ ing-	1.00				
	Anal margin	N+ ing+	0.96	0.73	1.26	0.761	
	Anal margin	N+ ing?	1.00				
	Anal canal	N0	1.11	1.05	1.18	0.001	Small
Anal canal	N+ ing-	1.19	1.06	1.34	0.004	Small	
Anal canal	N+ ing+	1.22	1.09	1.38	0.001	Small	
Anal canal	N+ ing?	0.99	0.85	1.16	0.926		
N stage	N+ ing- vs. N0		0.94	0.44	2.04	0.883	
P=0.377 (df=3)	N+ ing+ vs. N0		1.04	0.47	2.31	0.927	
	N+ ing ? vs. N0		2.28	0.89	5.87	0.087	
	Tumor loc	Anal canal vs. Anal margin		0.30	0.08	1.10	0.07
P=0.07							
Gender	Female vs. Male		0.78	0.61	0.99	0.045	Female*
P=0.045							

* there was no significant difference between treatment duration or total dose between males and females.

(b) Progression free survival

			<i>HR</i>	<i>HR 95% CI</i>		<i>P</i>	<i>Best if</i>
Overall treatment time	Dose ≤50.5 Gy		1.15	1.01	1.31	0.031	Time ↓
(weeks)	Dose 50.51 Gy - 55 Gy		1.06	0.83	1.35	0.662	
P=0.025 (df=5)	Dose 55.01 Gy - 59 Gy		1.14	0.98	1.32	0.095	
	Dose 59.01 Gy - 59.4 Gy		1.19	0.96	1.48	0.105	
	Dose >59.4 Gy		1.14	0.98	1.33	0.1	
Total dose on anal canal	50.51 Gy - 55 Gy vs. ≤50.5 Gy		1.28	0.20	8.35	0.799	
P=0.937 (df=4)	55.01 Gy - 59 Gy vs. ≤50.5 Gy		1.32	0.32	5.36	0.7	
	59.01 Gy - 59.4 Gy vs. ≤50.5 Gy		0.51	0.06	4.12	0.528	
	>59.4 Gy vs. ≤50.5 Gy		0.73	0.11	4.91	0.75	
Age (years)			1.00	0.99	1.01	0.927	
P=0.927							
Tumor size (cm) in:							
P<0.001 (df=6)	Anal margin	N0	0.90	0.71	1.16	0.424	
	Anal margin	N+ ing+	1.01	0.81	1.26	0.927	
	Anal canal	N0	1.12	1.07	1.18	<0.001	Small
	Anal canal	N+ ing-	1.16	1.04	1.29	0.006	Small
	Anal canal	N+ ing+	1.19	1.07	1.32	0.001	Small
	Anal canal	N+ ing?	0.99	0.87	1.12	0.87	
N stage	N+ ing- vs. N0		1.10	0.56	2.13	0.784	
P=0.055 (df=3)	N+ ing+ vs. N0		1.42	0.73	2.78	0.305	
	N+ vs. N0		2.79	1.31	5.94	0.008	
	Tumor loc	Anal canal vs. Anal margin		0.49	0.17	1.43	0.191
P=0.191							
Gender	Female vs. Male		0.67	0.54	0.82	0.001	Female
P<0.001							

(c) Overall survival

			HR	HR 95% CI	P	Best if
Overall treatment time (weeks) P=0.026 (df=5)	Dose ≤50.5 Gy		1.13	0.95	1.33	0.159
	Dose 50.51 Gy - 55 Gy		1.21	0.88	1.66	0.231
	Dose 55.01 Gy - 59 Gy		1.16	0.98	1.38	0.089 Time ↓
	Dose 59.01 Gy - 59.4 Gy		1.31	0.95	1.80	0.1
	Dose >59.4 Gy		1.22	1.00	1.50	0.05 Time ↓
Total dose on anal canal P=0.937 (df=4)	50.51 Gy - 55 Gy vs. ≤50.5 Gy		0.39	0.03	4.56	0.456
	55.01 Gy - 59 Gy vs. ≤50.5 Gy		1.03	0.19	5.56	0.976
	59.01 Gy - 59.4 Gy vs. ≤50.5 Gy		0.16	0.01	3.69	0.255
	>59.4 Gy vs. ≤50.5 Gy		0.26	0.02	3.29	0.3
Age (years) P=0.639			1.00	0.99	1.02	0.633
Tumor size (cm) in: P=0.027 (df=6)	Anal margin	N0	0.99	0.75	1.31	0.956
	Anal margin	N+ ing+	1.11	0.87	1.42	0.384
	Anal canal	N0	1.10	1.03	1.18	0.007 Small
	Anal canal	N+ ing-	1.14	1.00	1.29	0.043 Small
	Anal canal	N+ ing+	1.12	0.96	1.31	0.164 Small
	Anal canal	N+ ing?	1.01	0.87	1.17	0.882
N stage P=0.079 (df=3)	N+ ing- vs. N0		1.08	0.46	2.54	0.859
	N+ ing+ vs. N0		2.23	0.95	5.75	0.065
	N+ ing ? vs. N0		2.62	1.04	6.63	0.041
Tumor loc P=0.954	Anal canal vs. Anal margin		1.04	0.28	3.84	0.954
Gender P<0.001	Female vs. Male		0.56	0.43	0.72	<0.001 Female

Abbreviations: N+ ing-: N+ without inguinal invasion; N+ ing+: N+ with inguinal invasion; N+ ing?: N+ with unknown inguinal status.

d. Treatment parameters by gender

	Gender	
	Male (N=449)	Female (N=894)
Overall treatment time (days) including boost		
Median (range)	39 (30 - 107)	43 (30 - 121)
Q1-Q3	37 – 52	37 – 57
Total dose on anal canal (Gy)		
Median (range)	50.4 (39.6 - 75)	50.4 (38.6 - 98)
Q1-Q3	50.4 - 57.4	50.4 – 59
Effect of treatment being a woman		
Median (range)	5.6 (4.3 - 15.3)	6 (4.3 - 16.1)
Q1-Q3	5.3 - 6.6	5.3 - 7
Duration of the gap		
Median (range)	0 (0 – 44)	0 (0 – 68)
Q1-Q3	0 – 0	0 – 0

Appendix A: Table 3: Locoregional failure model comparing doses of 50.4 Gy vs. 55-59 Gy without a Gap (N=977) (RTOG 98-11, ACT II and EXTRA) *Online only.*

			<i>HR</i>	<i>HR 95% CI</i>		<i>P</i>	<i>Best if</i>
Planned Dose	anal canal	55-59 vs 50.4 Gy	1.14	0.84	1.54	0.159	Lower*
P=0.412							
Age (years)			0.99	0.98	1.01	0.468	
P=0.468							
Tumor size (cm) in: P=0.002 (df=4)	Anal margin	N0	0.77	0.54	1.11	0.165	
	Anal margin	N+ ing-	1.00			0.384	
	Anal margin	N+ ing+	0.99	0.74	1.31	0.921	
	Anal margin	N+ ing?	1.00				
	Anal canal or both	N0	1.11	1.05	1.19	0.001	Small
	Anal canal or both	N+ ing-	1.18	1.04	1.33	0.009	Small
	Anal canal or both	N+ ing+	1.25	1.08	1.19	0.003	Small
	Anal canal or both	N+ ing?	1.01	0.86	2.97	0.542	
N stage P=0.333 (df=4)	N+ ing-		1.08	0.46	2.54	0.859	
	N+ ing+		2.23	0.95	5.75	0.065	
	N+ ing?		2.62	1.04	6.63	0.041	
Tumor localization P=0.033		Anal canal or both	0.21	0.05	0.88	0.032	Both
Gender P=0.574		Female vs. Male	0.92	0.69	1.23	0.577	Female

Abbreviations: N+ ing-: N+ without inguinal invasion; N+ ing+: N+ with inguinal invasion; N+ ing?: N+ with unknown inguinal status.

Appendix A: Table 4: Locoregional failure model: 3week vs 2week gap at 59.4Gy intended dose (EORTC studies and ACCORD-03)). *Online only.*

			<i>HR</i>	<i>HR 95% CI</i>		<i>P</i>	<i>Best if</i>
Planned gap	21 d vs 14 days		1.37	0.81	2.34	0.245	
P=0.245							
Age (years)			0.97	0.95	1.00	0.02	Young
P=0.02							
Tumor size (cm) in: P=0.377 (df=4)	Anal canal or both	N0	1.19	0.93	1.53	0.173	
	Anal canal or both	N+ ing-	1.10	0.83	1.47	0.49	
	Anal canal or both	N+ ing+	1.13	0.88	1.45	0.333	
N stage P=0.468	N+ ing-		1.70	0.25	11.68	0.589	
	N+ ing+		3.21	0.50	20.55	0.218	
Gender P=0.228	Female vs. Male		0.71	0.41	1.23	0.228	Female
n = 332							

Abbreviations: N+ ing-: N+ without inguinal invasion; N+ ing+: N+ with inguinal invasion; N+ ing?: N+ with unknown inguinal status.

Appendix A: Table 5: 2 week gap vs no gap at (a) 55-59.4Gy intended dose and b) effective dose >56.5 and <60Gy (EORTC studies vs. RTOG 98-11). *Online only.*

(a)

		<i>HR</i>	<i>HR 95% CI</i>		<i>P</i>	<i>Best if</i>
Planned gap P=0.887	2 weeks vs no gap (55-59 Gy intended dose)	1.04	0.64	1.67	0.887	
Age (years) P=0.163		0.99	0.97	1.01	0.163	
Tumor size (cm) in: P=0.004 (df=4)	Anal canal or both NO	1.09	0.99	1.20	0.077	
	Anal canal or both N+ ing-	1.02	0.80	1.29	0.903	Small
	Anal canal or both N+ ing+	1.18	1.02	1.35	0.022	Small
	Anal canal or both N+	2.25	1.24	4.06	0.007	
N stage P=0.161 (Df=3)	N+ ing-	2.44	0.61	9.81	0.208	
	N+ ing+	1.23	0.42	3.63	0.708	
	N+ ing?	0.03	0.00	1.37	0.072	
Gender P=0.573	Female	0.89	0.60	1.33	0.573	
n = 521						

(b)

		<i>HR</i>	<i>HR 95% CI</i>		<i>P</i>	<i>Best if</i>
Planned gap P=0.559	2 weeks vs no gap (effective dose >56.5 and <60Gy)	0.87	0.52	1.47	0.559	
Age (years) P=0.163		0.99	0.97	1.01	0.163	
Tumor size (cm) in: P=0.214		1.06	0.97	1.17	0.214	
N stage P=0.064 (Df=3)	N+ ing-	1.58	0.87	2.87	0.130	
	N+ ing+	2.15	1.20	3.84	0.01	
	N+ ing?	1.58	0.48	5.19	0.449	
Gender P=0.339	Female	0.79	0.49	1.28	0.339	
n = 214						

Abbreviations: N+ ing-: N+ without inguinal invasion; N+ ing+: N+ with inguinal invasion; N+ ing?: N+ with unknown inguinal status.

Table 3. Late toxicities: (a) gastro-intestinal (b) skin or subcutaneous tissue and (c) genito-urinary.

(a)	<i>EORTC 22861</i> <i>N=110</i>	<i>ACT I</i> <i>N=577</i>	<i>RTOG 87-04</i> <i>N=289</i>	<i>EORTC 22953</i> <i>N=44</i>	<i>RTOG 98-11 N=638</i>	<i>ACC-03 (1st tox) N=307</i>	<i>EORTC 22011</i> <i>N=88</i>	<i>EXTRA</i> <i>N=31</i>	<i>ACT II</i> <i>N=935</i>
Any grade	72 (65.5)		63 (21.8)	37 (84.1)	155 (24.3)	242 (78.8)	39 (44.3)	24 (77.4)	706 (75.5)
Mild	69 (62.7)		58 (20.1)	37 (84.1)	140 (21.9)	184 (59.9)	39 (44.3)	24 (77.4)	697 (74.5)
Severe	30 (27.2)	180 (31.2)	8 (2.8)	13 (29.5)	15 (2.4)	58 (18.9)	1 (1.1)	0 (0)	71 (7.6)
Grade unknown	3 (2.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

(b)	<i>EORTC 22861</i> <i>N=110</i>	<i>ACT I</i> <i>N=577</i>	<i>RTOG 87-04</i> <i>N=289</i>	<i>EORTC 22953</i> <i>N=44</i>	<i>EORTC 22011</i> <i>N=88</i>	<i>EXTRA</i> <i>N=31</i>	<i>ACT II</i> <i>N=935</i>
Any grade	14 (12.7)		15 (5.2)	29 (65.9)	22 (25)	3 (9.7)	298 (31.9)
Mild	5 (4.5)		13 (4.5)	28 (63.6)	22 (25)	3 (9.7)	288 (30.8)
Severe	4 (3.6)	39 (6.8)	2 (0.7)	18 (40.9)	1 (1.1)	0 (0)	23 (2.5)
Grade unknown	5 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Discussion

This meta-analysis of individual patient data from 10 trials evaluating results of anal cancer patients receiving combined modality treatment confirmed the effect of RT-related factors on patient outcomes. OTT and tumor size were found to have a significant impact on LRF, PFS and OS, while the effects of dose levels and gap duration were more difficult to interpret.

LRF was the predominant pattern of relapse, with a 5-year LRF rate in accordance with recent trials³⁰⁻³². Shorter OTTs were significantly associated with less LRF, as were small tumor sizes for tumors of the anal canal and female gender. For patients receiving intermediate doses (55-59 Gy, RTOG 98-11) versus 50.4 Gy (ACT II and EXTRA), no major difference of LRF was observed between dose levels. Paradoxically, patients who received the lower dose seemed to have better outcomes. This may have not reached significance due to possible remaining biases in the meta-analysis (after adjusting for patient characteristics) and to differences between protocol guidelines. These findings support current guidelines from ESMO-ESSO-ESTRO guidelines which suggest no benefit in administering RT doses >50 Gy without a gap during combined modality treatment, especially for good responders³³. The duration of the gap on LRF was assessed by comparing patients planned to receive 59.4 Gy with a 2 or a 3 week gap from the EORTC studies versus ACCORD-03 arms 1 and 3, finding that a 3 week gap could be potentially detrimental. The lack of a significant difference may be due to the small number of patients in this analysis. However, when a 2 week gap was compared to no gap for doses between 57 and 59.4 Gy (EORTC studies versus RTOG 98-11) there were no significant differences between groups. Our data suggests that if the gap is detrimental, it is for gaps ≥ 3 weeks, which also increase the OTT (significantly associated with LRF). This may explain the lack of benefit in ACCORD-03 for doses >59.4Gy, as a 3 week gap was used¹⁷. In 2011, Glynne-

Jones *et al.* advocated to avoid “split course” treatments³⁴. This was based on evidence that on one hand (TROG 99-02), if a gap was planned, it should be done as late as possible in the treatment course, and on the other hand, non-randomized retrospective data seems to indicate a worse outcome with gaps of >38 or >63 days^{34–38}.

With regards to survival rates, PFS at 5 years was similar to a recent phase II study evaluating the addition of Cetuximab to 5-FU-Cisplatin concurrent chemoradiotherapy, and approximately 10% lower than in two other recent studies^{30–32}. Five-year OS (76.7%) was also similar to the results of the Cetuximab association trial, and 4-7% lower than the other two recent studies^{30–32}. Shorter OTTs, smaller tumors and female gender, again, were found to be significantly associated with a better PFS and OS. OTT is a known prognostic factor in other squamous cell carcinomas, such as cervical cancer, where every day >52 days causes a reduction of LC by 1%, as well as in head and neck cancer^{39, 40}. Although there is a paucity of data on the characteristics of proliferation of anal cancer, they seem similar to cervical cancer, with a potential median doubling-time of 4.1 days⁴¹. It is noteworthy, that clinical results of combined modality therapy in anal cancer show that OTT might have less of an impact as chemotherapy may increase the interval of growth delay of clonogenic cells⁴². An OTT >41 days was found to compromise 5-year LC, whether the treatment included a gap or not⁴³. An analysis performed on pooled data from the RTOG 87-04 and 98-11 trials found a significant impact of OTT on local and LRF (in agreement with the present meta-analysis), colostomy failure and time to failure without a correlation with CFS or OS (conversely, it correlated with OS in the present meta-analysis)⁴⁴.

Considering the impact of OTT on outcomes of combined therapy for anal cancer, strategies have been developed to shorten OTT while attempting to reduce toxicity. IMRT and

VMAT have been proven to be feasible and current results show less skin, hematological and gastro-intestinal toxicity with comparable outcomes to results from 3D-conformal RT treatments^{12-14, 16, 45}. These results should be interpreted with caution. A recent analysis of the national Veterans Affairs database compared 779 patients receiving either IMRT or 3D-conformal RT¹⁵. Indeed, they found a decrease of treatment breaks, resulting in shorter OTT in patients receiving IMRT, but without significant improvement of severe gastro-intestinal or hematological toxicity. The authors hypothesize this may be due to incorrect planning or delivery, which highlights the need to follow international guidelines and homogenize contouring practices to improve these results, not only in terms of toxicity, but also in terms of outcomes^{14, 15, 33, 46}. A single center study which reviewed 45 patients treated by 3D-conformal RT or IMRT found OTT was an independent predictor of OS and PFS⁴⁷. Additionally, simultaneous integrated boost during IMRT or VMAT treatment can considerably shorten OTT. A multicenter retrospective study evaluated 190 patients receiving either a simultaneous integrated boost (SIB) or a sequential boost for combined modality treatment for anal cancer⁴⁸. With a median follow up of 34 and 31 months for each group, median OTT was significantly lower (43 vs. 60 days) in the SIB group, as was the cumulative incidence of colostomy¹³.

Toxicity results from this meta-analysis were difficult to interpret due to heterogeneous toxicity scoring and reporting. The descriptive data from the pooled analysis show more severe gastro-intestinal toxicity in the EORTC 22861 and EORTC 22953 trials, more severe skin toxicity in the EORTC 22953 trial and more severe genito-urinary toxicity in the EORTC 22953 and ACCORD-03 trials.

A limitation of this meta-analysis is that individual patient data from only 10 of the 13 identified trials was received. Possibly, data from the 3 remaining phase II trials (in total: 191

patients) may have influenced the meta-analysis. Nevertheless, data from the large phase III trials were received and analyzed, which is a strength. For the sake of homogeneity (heterogeneous patient selection criteria, staging systems and capture of RT data), patient data from 3 of the early trials as well as 44% of the patients from the rest of the studies had to be excluded from the analysis. Also, the intrinsic design of the studies analyzed did not allow the dose and the gap duration to be evaluated separately. Approximately 25% of patients in the final analysis received neoadjuvant chemotherapy (patients from RTOG 98-11 and ACCORD-03), which might have caused an accelerated repopulation at the time of combined RT-doublet chemotherapy, eventually impacting the relevance of OTT in these patients^{8, 17}. Last, but not least, we were not able to stratify according to HPV status or smoking.

Ongoing trials may shed more light these questions, such as the PLATO protocol (ISRCTN88455282), integrating 3 trials: ACT3 for small tumors (phase II, non-randomized, local excision), ACT4 for intermediate-risk tumors (phase II, randomized, standard-dose 50.4 Gy vs. reduced-dose 41.4 Gy combined modality treatment) and ACT5 for locally advanced tumors (phase II/III, randomized, standard dose 53.2 Gy vs. 58.8 Gy and 61.6 Gy combined modality treatment) with the primary outcome of 3-year LRF. Thus, the question of dose-escalation is being tested in larger tumors, which is coherent with our results, as smaller tumors had better outcomes. A recent pooled analysis of two prospective trials including locally advanced anal cancer (tumors > 4cm) found better CFS with dose escalation⁴⁹.

Treatment outcomes may not only benefit from changes in RT schemes, but also from changes in the drugs used for combined therapy. In the aforementioned study, although the addition of cetuximab to Cisplatin/5-FU decreased local failure rates, it came at the cost of increased toxicity³². Another study testing this association had to close prematurely due to

serious adverse events⁵⁰. Future directions might include combinations with immunotherapy, such as pembrolizumab⁵¹. Ongoing trials are investigating the role of immunotherapy in the adjuvant setting, EA2165: Nivolumab After Combined Modality Therapy in Treating Patients With High Risk Stage II-IIIB Anal Cancer (NCT03233711).

As MR-Linacs become more widely available, newer techniques such as MRI-guided RT are being evaluated. Online adaptive treatment strategies may be developed using this technology, considering the clear superiority of MRI imaging for soft tissues. This technique could allow real time tumor tracking, taking into account intra-fractional motion⁵². Daily adaptive re-planning would allow effective treatment while potentially reducing toxicity⁵³.

Recent progress in the validation of a specific EORTC quality of life questionnaire for anal cancer will allow better assessment of toxicity in patients included in future trials⁵⁴. Such patient-related outcomes are essential to provide more robust evidence on toxicity outcomes.

Conclusions

This meta-analysis suggests that for patients treated with a combination of external-beam RT with 2 chemotherapeutic drugs, a longer OTT is detrimental. Further analyses suggest that in the dose range of 50.4-59 Gy lower doses seem to be preferred. Treatment gaps longer than 2 weeks appear to be detrimental. When comparing a 2 week gap to no gap (dose range: 55-59.4 Gy), there is unlikely a difference in effect between a somewhat higher dose given with a gap and a somewhat lower dose given with no gap. Further prospective trials involving IMRT/VMAT techniques or even with MRI-guided RT may better define optimal OTT and dose escalation in schedules with no gap.

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