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Review

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

Eleonor Rivin del Campo [a,*], Oscar Matzinger [b], Karin Haustermans [c], Didier Peiffert [d], Robert Glynne-Jones [e], Kathryn A. Winter [f], Andre A. Konski [g,h], Jaffer A. Ajani [i], Jean-François Bosset [j], Jean-Michel Hannoun-Levi [k], Marc Puyraveau [l], A. Bapsi Chakravarthy [m], Helen Meadows [n], John Northover [o], Laurence Collette [p], Melissa Christiaens [c], Philippe Maingon [q]

[a] *Department of Radiation Oncology, Tenon University Hospital, Sorbonne University, Paris, France*
[b] *Department of Radiation Oncology, Genolier Clinic, Genolier, Switzerland*
[c] *Department of Radiation Oncology, UZ Leuven University Hospital, Leuven, Belgium*
[d] *Department of Radiation Oncology, Institut de Cancérologie de Lorraine, Nancy, France*
[e] *Department of Radiation Oncology, Mount Vernon Cancer Centre, Northwood, United Kingdom*
[f] *NRG Oncology Statistics and Data Management Center, American College of Radiology, Philadelphia, PA, USA*
[g] *Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine, Leonard Davis Institute of Health Economics, West Chester, PA, USA*
[h] *Department of Radiation Oncology, The Chester County Hospital, West Chester, PA, USA*
[i] *Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA*
[j] *Department of Radiation Oncology, Jean Minjoz University Hospital, Besançon, France*
[k] *Department of Radiation Oncology, Centre Antoine Lacassagne, Nice, France*
[l] *Department of Statistics, Jean Minjoz University Hospital, Besançon, France*
[m] *Department of Radiation Oncology, Vanderbilt University Medical Center, Nashville, TN, USA*
[n] *Cancer Research UK & UCL Cancer Trials Centre, London, United Kingdom*
[o] *Department of Surgery, The London Clinic and St Marks Hospital, London, United Kingdom*
[p] *Department of Statistics, EORTC Headquarters, Brussels, Belgium*
[q] *Department of Radiation Oncology, La Pitié Salpêtrière – Charles Foix University Hospital, Sorbonne University, Paris, France*

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* *Corresponding author*: Department of Radiation Oncology, Tenon University Hospital – Hôpitaux Universitaires Est Parisien, Sorbonne University, 4 rue de la Chine, 75020, Paris, France. Fax: +33 156016599.
E-mail address: eleonor.rivindelcampo@aphp.fr (E. Rivin del Campo).

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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 radiation therapy (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 were received for 10/13 identified published studies conducted from 1987 to 2008 (n = 3031). A Cox regression model was used (landmark = 3 months after RT for first follow-up).
Results: After data inspection indicating severe heterogeneity between trials, only 1343 patients from 7/10 studies received were analysed (the most recent ones, since 1994; median follow-up = 4.1 years). A higher overall 5-year LRF rate [22.8% (95% confidence interval [CI] 22.3–27.3%)] significantly correlated with longer OTT ($p = 0.03$), larger tumour size ($p < 0.001$) and male gender ($p = 0.045$). Although significant differences were not observed, subset analyses for LRF (dose range: 50.4–59 Gy) seemed to favour lower doses ($p = 0.412$), and when comparing a 2-week gap versus 3 (dose: 59.4 Gy), results suggested 3 weeks might be detrimental ($p = 0.245$). For a 2-week gap versus none (dose range: 55–59.4 Gy), 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 tumour sizes ($p < 0.001$) and shorter OTT ($p = 0.025$). Five-year overall survival [76.7% (95% CI: 73.9%–79.3%)] correlated positively with female gender ($p < 0.001$), small tumour size ($p = 0.027$) and short OTT ($p = 0.026$). Descriptive toxicity data are 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.

1. Introduction

Anal cancer is a rare tumour 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 intercourse [2].

Until the '70s, abdominoperineal resection remained the standard of care, with an operative mortality rate of about 6–8 percent [3]. Five-year overall survival (OS) rates of 40–70% 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 reported [4]. 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 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 MMC [7–10]. The most concrete improvement 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 outcomes [11–16]. 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.

2. Materials and methods

2.1. Selection criteria

A consensus meeting was held at the European Organization for the Research and Treatment of Cancer (EORTC) headquarters on 6th March 2008, with representatives of European countries and collaborative groups active in the field of radiochemotherapy for advanced anal cancer: the Italian group, Spanish Group,

Table 1
Phase II and III studies in anal cancer.

Group	Study name	Phase	No. of patients	No. of eligible patients[a]	Inclusion stage	No. N0/N1	NACT	Concurrent CT	Consolidation CT	Pelvic dose (Gy)/fr.[c]	Boost dose (Gy)/fr.	Inguinal dose (Gy)	Inguinal. dose N+ (Gy)	Gap (weeks)
EORTC	**22861** [6]	III	110	103	All T > 4 cm 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 [20]	II	44	43	All T > 4 cm 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 [18]	II	88	76	All T > 4 cm 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** [24,25]	III	585	577	All (except T1N0); M0	cN+: 31 pts	No	±5-FU −MMC	No	45/20 or 25	15/6 EBRT or 25 Gy:10 Gy/day, BT if R > 50%	±45	-	6
	EXTRA [21]	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** [26]	III	310	289	All T & N; M0	240/51	No	5-FU ± MMC	No	45/25[d]	5.4/3	45	50.4	0
	92-08 [54]	*II*	*46 and 20*	*66*	*All T > 2 cm; M0*	*41/6*	*No*	*5-FU−MMC*	*No*	*45/25*[e]	*14.4/8*	*45*	*59.4*	*2 and 0*
	98-11 [8,19]	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	*[55]* [b]	*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] [b]	III	307	307	All T > 4 cm 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** [56]	II	32	32	All; M0	17/12	No	5-FU −Cisplatin	No	45/25[f]	14.4/8	36	59.4	2

CALGB	*9281 [22]*	*II*	*45*	*45*	*T3 > 5 cm; T4 and all N+*	*-*	*5-FU– Cisplatin*	*5-FU–MMC*	*5-FU– Cisplatin if PR or N2/N3*	*45/25[e]*	*14.4/8*	*30.6*	*50.4*	*2*

Abbreviations: No., number; NACT, neoadjuvant chemotherapy; CT, chemotherapy; fr., fractions; Gy, gray; EORTC, European Organization for the Research and Treatment of Cancer; UKCCCR, UK Coordinating 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 Leukaemia Group B; 5-FU, 5-fluorouracil; MMC, mitomycin C; CR, complete response; PR, partial response; el., electrons; ph., photons; BT, brachytherapy; R > 50%, response > 50%; EBRT, external-beam radiotherapy.
Individual patient data were received for all studies in bold. No data was received for those in Italics.

[a] No. of eligible patients with analysable data.
[b] Published in 2012, ongoing at the time of the meeting.
[c] In fractions of 1.8 Gy for all studies, except for ACT 1 in fractions of 1.8 Gy or 2.25 Gy. RTOG 98-11 advises the boost to be given in fractions of 2 Gy.
[d] 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, a second boost was added (9 Gy).
[e] Field reduction at 30.6 Gy.
[f] Field reduction at 30.6 Gy and at 36 Gy.

Nordic Group, *UK Coordinating 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 concur on the design of the next phase III randomised trial evaluating improved radiotherapeutic 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-03 [17]. The studies identified at the time are detailed in Table 1.

2.2. Studies

ACCORD-03 examined the impact of therapeutic intensification by induction chemotherapy and/or high-dose RT [17]. 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 [8,9,18,19]. 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-week gap [20]. In the UKCCCR EXTRA trial, intravenous 5-FU was replaced by capecitabine [21]. ECOG-ACRIN 42-92 studied the feasibility of cisplatin replacing MMC with a 2-week gap [22].

A consensus emerged that it was not timely to start a new trial, given the number of existing projects in various countries that were still maturing 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, resulting in a need to obtain a more homogeneous patient group (Figs. 1 and 2). 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 relationships between irradiated pelvic volume and pelvic recurrence rates, the total dose to the elective inguinal area and inguinal control, of prognostic factors for long-term outcome in relation with the baseline patient and disease characteristics, as well as long-term toxicity, were assessed.

2.3. 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.
- ***Tumour related:*** Date of diagnosis, cT, cN, cM, maximum tumour size, tumour localisation (i.e. anal margin

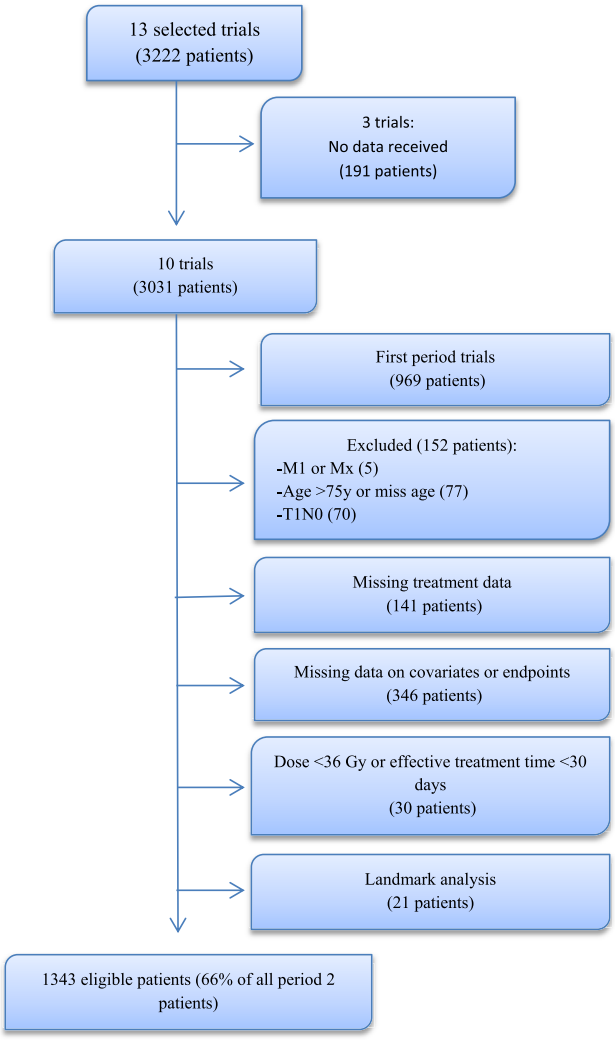

Fig. 1. PRISMA flowchart of selection of eligible patients for the pooled analysis to get a more homogenous group of patients.

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 tumour (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 (tumour; 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).

2.4. Statistical analysis

Recognising 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 minimise 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, tumour localisation (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 tumour size (modelled as an effect nested within combinations of N status and tumour location). The latter was to accommodate for interaction effects between T stage and N stage and tumour location and to fulfil the proportional of hazard assumptions. The OTT was modelled as a continuous effect, whereas the total dose was assessed in categories ($\leq$50.5 Gy, $>$50.5–55 Gy, $>$55–59 Gy, $>$59–59.4 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: Fig. 1).

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 covariate effects were summarised by their hazard ratio and its associated 95% confidence interval.

The adequacy of the Cox regression model was evaluated by performing the graphical and numerical methods of Lin, Wei and Ying [23]. Based on intermediate study results that showed a single model could not fit the early trials that used RT $\pm$ 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 the 1st of January 1994.

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

3. Results

3.1. Merging data

Data were 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

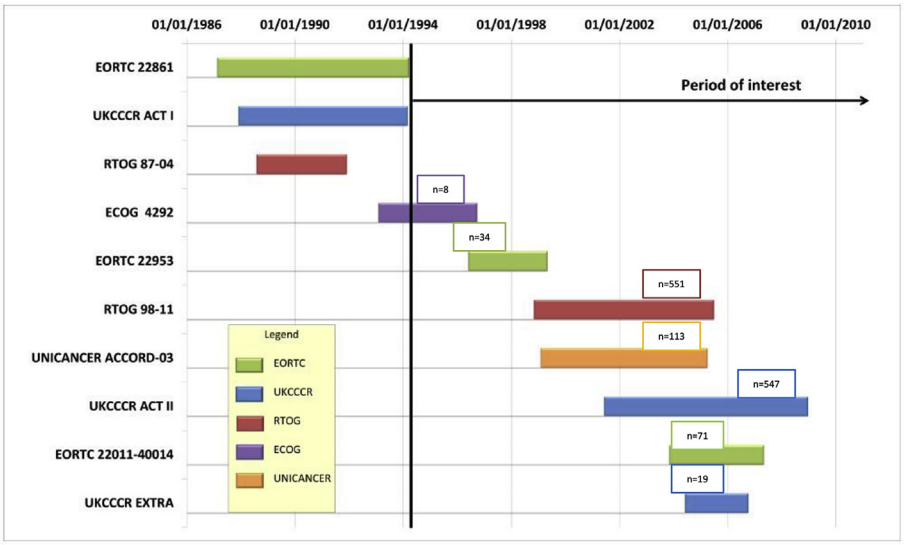

Fig. 2. Summary of trials. n = number of patients included in the final analysis per trial; EORTC, European Organization for the Research and Treatment of Cancer; UKCCCR, UK Coordinating Committee for Cancer Research; RTOG, Radiation Therapy Oncology Group.

the data from the trials, to allow merging of the databases while excluding as few patients as possible (Fig. 1).

Patients were recruited during a two-decade period (1987–2008) (Fig. 2). The difference in terms of data collection, patient staging, treatments and patient follow-up was particularly evident for the first 3 trials (EORTC 22861, ACT I and RTOG 87-04). The first two were conducted with exclusive RT versus chemo-radiotherapy with two chemotherapeutic drugs, while the RTOG 87-04 trial evaluated chemoradiotherapy with one-agent versus doublet chemotherapy. The later trials assessed RT + doublet chemotherapy [6,24–26]. 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 7 more recent studies (Fig. 1; Fig. 2).

Certain parameters (e.g. planned RT dose, OTT) were specified inside a trial but varied between trials. Thus, it was essential to minimise 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 (i.e. N-stage, dose to the anal canal, OTT, tumour localisation, 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 (<36 Gy) could result from excess toxicity, 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, LENT-SOMA, 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 [27]. 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.

3.2. Results of pooled analysis

A total of 1343/3031 patients were eligible for the pooled analysis (Fig. 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. Fig. 2).

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

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)
Quartile 1-Quartile 3 (Q1-Q3)	48–64
Mean (SD)	55.1 (9.92)
Gender	
Male	449 (33.4)
Female	894 (66.6)
Tumour 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 tumour size (cm)	
Median (range)	4.1 (1–20)[a]
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
No. of nonmissing observations	1329
Total dose on anal canal (Gy)	
Median (range)	50.4 (38.6–98)
Q1-Q3	50.4–59
≤50.5 Gy	716 (53.3)
>50.5-≤55 Gy	169 (12.6)
>55-≤59 Gy	198 (14.7)
>59-≤59.4 Gy	152 (11.3)
>59.4 Gy	108 (8)

Abbreviations: N+ ing−, N+ without inguinal invasion; N+ ing+, N+ with inguinal invasion; N+ ing?, N+ with unknown inguinal status.
[a] There were 5 aberrant values.

patients had N0 disease, whereas 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% confidence interval [CI] 22.3–27.3%; Appendix A. Fig. 3). Lymph node resection surgery was not considered as an event (these data were only available on the 3 EORTC trials, only 3 patients had a lymph node resection before documented LRF).

LRF was significantly correlated with OTT ($p = 0.03$), tumour size ($p < 0.001$) and gender ($p = 0.045$). OTT and total dose were not markedly different between males and females (Table 3).

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 favour of low doses, N0 patients treated at 45 Gy 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 50.4 Gy were considered in this analysis (also adjusted for gender, age, tumour location, N-stage and tumour size). Based on 220 locoregional relapse events ($n = 977$), no difference between dose levels could be seen. However, results seemed to favour a lower dose (Appendix A: Table 2). To assess the impact of the gap duration, we compared patients intended to receive a dose of 59.4 Gy with 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 332 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 3).

A 2-week gap was compared with no gap in patients intended to receive a dose of 55–59.4 Gy (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 >56.5 Gy and <60.0 Gy ($n = 214$). Only 74 events were seen. Neither analysis showed a significant difference between a 2-week gap and no gap (Appendix A: Table 4).

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 tumour 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 tumour size ($p = 0.027$), and short OTT ($p = 0.026$) (Appendix A. Fig. 3, Table 3).

Late toxicities (90 days or more from the start of treatment) were divided into gastrointestinal, skin, or subcutaneous tissue and bladder-genitourinary late toxicities (Table 4).

Table 3
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.

			HR	95% CI		P	Best if
(a) Locoregional failure							
Overall treatment time (weeks)	Dose ≤50.5 Gy		1.15	0.99	1.34	0.065	Time ↓
P = 0.03 (df = 5)	Dose 50.51 Gy–55 Gy		0.98	0.72	1.34	0.908	
	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							
Tumour size (cm) in:	Anal margin	N0	0.83	0.60	1.15	0.257	
P < 0.001 (df = 6)	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	
Tumour 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[a]
P=0.045							
(b) Progression free survival							
Overall treatment time (weeks)	Dose ≤50.5 Gy		1.15	1.01	1.31	0.031	Time ↓
P = 0.025 (df = 5)	Dose 50.51 Gy–55 Gy		1.06	0.83	1.35	0.662	
	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							
Tumour size (cm) in:	Anal margin	N0	0.90	0.71	1.16	0.424	
P < 0.001 (df = 6)	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	
Tumour 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							
Overall treatment time (weeks)	Dose ≤50.5 Gy		1.13	0.95	1.33	0.159	
P = 0.026 (df = 5)	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	50.51 Gy–55 Gy vs. ≤50.5 Gy		0.39	0.03	4.56	0.456	
P = 0.937 (df = 4)	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	

(continued on next page)

Table 3 (*continued*)

			HR	95% CI		P	Best if
Age (years)			1.00	0.99	1.02	0.633	
P = 0.639							
Tumour size (cm) in:	Anal margin	N0	0.99	0.75	1.31	0.956	
P = 0.027 (df = 6)	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	N+ ing− vs. N0		1.08	0.46	2.54	0.859	
P = 0.079 (df = 3)	N+ ing+ vs. N0		2.23	0.95	5.75	0.065	
	N+ ing? vs. N0		2.62	1.04	6.63	0.041	
Tumour loc	Anal canal vs. anal margin		1.04	0.28	3.84	0.954	
P = 0.954							
Gender	Female vs. male		0.56	0.43	0.72	<0.001	Female
P < 0.001							

(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

Abbreviations: N+ ing−, N+ without inguinal invasion; N+ ing+, N+ with inguinal invasion; N+ ing?, N+ with unknown inguinal status.
[a] There was no significant difference between treatment duration or total dose between males and females.

Table 4
Late toxicities: (a) gastrointestinal, (b) skin or subcutaneous tissue, and (c) genitourinary.

(a)	EORTC 22861	ACT I	RTOG 87-04	EORTC 22953	RTOG 93- 11	ACCORD-03 (1st tox)	EORTC 22011	EXTRA	ACT II
	N=110	N=577	N=289	N=44	N=638	N=307	N=83	N=31	N=935
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 (11)	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)	EORTC 22861	AGI	RT06 87-04	EORTC 22953	EORTC 22011	EXTRA	ACT II
	N=110	N=577	N=289	N=44	N=88	N=31	N=935
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 (11)	0 (0)	23 (2.5)
Grade unknown	5 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

(c)	EORTC 22861	EORTC 22953	RTOG 98-11	EORTC 22011	ACCORD-03 (1st tox)
	N=110	N=44	N=638	N=88	N=307
Any grade	7 (6.4)	15 (34.1)	54 (8.5)	10 (11.4)	108 (35.2)
Mild	4 (3.6)	14 (31.8)	51 (8.0)	10 (11.4)	77 (25.1)
Severe	2 (1.8)	4 (9.1)	3 (0.5)	0 (0)	31 (10.1)
Grade unknown	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)

4. 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 tumour size were found to have a significant impact on LRF, PFS and OS, whereas 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 trials [28–30]. Shorter OTTs were significantly associated with less LRF, as were small tumour sizes for tumours 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 because of possible remaining biases in the meta-analysis (after adjusting for patient characteristics) and of differences between protocol guidelines. It is noteworthy that of the three trials included in this analysis, only ACT II required RT quality assurance, although the results have not been reported. If indeed the RT in ACT II was administered following quality assurance guidelines more closely, this may be a factor favouring the lower dose level used in this trial. 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 responders [31]. The duration of the gap on LRF was assessed by comparing patients planned to receive 59.4 Gy with a 2- or 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 attributed the small number of patients in this analysis. However, when a 2-week gap was compared with 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 suggest that if the gap is detrimental, it is for gaps $\geq$ 3 weeks, which also increase OTT (significantly associated with LRF). This may explain the lack of benefit in ACCORD-03 for doses >59.4 Gy, as a 3-week gap was used [17]. In 2011, Glynne-Jones *et al.* advocated to avoid "split course" treatments [32]. 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-randomised retrospective data seem to indicate a worse outcome with gaps of >38 or >63 days [32–36].

With regard 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 [28–30]. 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 [28–30]. Shorter OTTs, smaller tumours 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 [37,38]. 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 days [39]. It is noteworthy that clinical results of combined modality therapy in anal cancer show OTT might have less of an impact as chemotherapy may increase the interval of growth delay of clonogenic cells [40]. An OTT >41 days was found to compromise 5-year LC, whether the treatment included a gap or not [41]. 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) [42].

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, haematological and gastrointestinal toxicity with comparable outcomes to results from 3D-conformal RT treatments [12–14,16,43]. 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 RT [15]. Indeed, they found a decrease of treatment breaks, resulting in shorter OTT in patients receiving IMRT, but without significant improvement of severe gastrointestinal or haematological 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 [14,15,31,44]. A single-centre study that reviewed 45 patients treated by 3D-conformal RT or IMRT found OTT was an independent predictor of OS and PFS [45]. In addition, simultaneous integrated boost (SIB) during IMRT or VMAT treatment can considerably shorten OTT. A multicenter retrospective study evaluated 190 patients receiving either a SIB or a sequential boost for combined modality treatment for anal cancer [46]. 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 colostomy [13].

Toxicity results from this meta-analysis were difficult to interpret because of heterogeneous toxicity scoring and reporting. When observing the descriptive data from the pooled analysis, it appears that there was higher severe gastrointestinal toxicity for the EORTC 22861 and EORTC 22953 trials, higher severe skin toxicity for the EORTC 22953 trial and higher severe genitourinary toxicity for 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 analysed, 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 and 44% of the patients from the rest of the studies had to be excluded from the analysis. Also, the intrinsic design of the studies analysed did not allow the dose and the gap duration to be evaluated separately. Nor was the relationship between OTT and gap duration examined. 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]. Furthermore, this analysis did not evaluate the impact of which concurrent chemotherapy scheme was used (the hypothesis considered them as equivalent). Last, but not least, we were not able to stratify according to human papilloma virus (HPV) status or smoking.

Ongoing trials may shed more light on these questions, such as the PLATO protocol (ISRCTN88455282), integrating 3 trials: ACT III for small tumours (phase II, nonrandomised, local excision), ACT IV for intermediate-risk tumours (phase II, randomized, standard dose 50.4 Gy vs. reduced dose 41.4 Gy combined modality treatment) and ACT V for locally advanced tumours (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 tumours, which is coherent with our results, as smaller tumours had better outcomes. A recent pooled analysis of two prospective trials including locally advanced anal cancer (tumours $>$ 4 cm) found better CFS with dose escalation [47].

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 toxicity [30]. Another study testing this association had to close prematurely due to serious adverse events [48]. Future directions might include combinations with immunotherapy, such as pembrolizumab [49]. 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 the MR-Linac becomes more widely available, newer techniques such as MRI-guided RT are being evaluated [50]. 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 tumour tracking, taking into account intrafractional motion [51]. Daily adaptive replanning would allow effective treatment while potentially reducing toxicity [52].

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 trials [53]. Such patient-related outcomes are essential to provide more robust evidence on toxicity outcomes.

5. 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.

Conflict of interest statement

The authors declare no conflict of interest.

Disclaimers

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.022.

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