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R. Glynne-Jones, H.M. Meadows, A. Lopes, R. Muirhead, D. Sebag-Montefiore, R. Adams, on behalf of the ACTII study group

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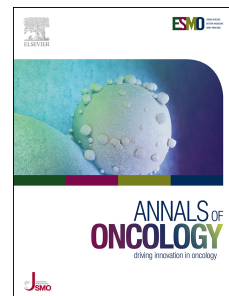
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Impact of compliance to chemoradiation on long-term outcomes in squamous cell carcinoma of the anus. Results of a post-hoc analysis from the randomized phase III ACT II trial

Authors

R. Glynne-Jones¹, H. M. Meadows², A. Lopes², R. Muirhead³, D. Sebag-Montefiore⁴, R. Adams⁵ on behalf of the ACTII study group.

¹Mount Vernon Centre for Cancer Treatment, Mount Vernon Hospital, Northwood, UK; ²Cancer Research UK & University College London Cancer Trials Centre, UCL, London, UK; ³Oxford Cancer & Haematology Centre, Oxford University Hospitals, Oxford, UK.; ⁴University of Leeds, Leeds Cancer Centre, Leeds, UK, ⁵ School of Medicine, Cardiff University, Cardiff, UK

Running title: Compliance to chemoradiation in the ACTII trial

Corresponding author:

Dr R Glynne-Jones, Mount Vernon Cancer Centre, Mount Vernon Hospital, Rickmansworth Rd, Northwood, UK HA6 2RN, E: rob.glynnejones@nhs.net, T: +44 203 826 2434

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Preliminary results of this study were presented at the American Society of Clinical Oncology meeting in 2015.

HIGHLIGHTS

- Post hoc analysis suggests compliance to chemotherapy & radiotherapy in radical chemoradiotherapy is clinically important
- Compliance should be considered as a prognostic factor in future studies
- Extending overall treatment time of radical chemoradiotherapy (50.4Gy) in anal cancer is associated with poorer outcomes
- Poor week 5 chemotherapy compliance is associated with an adverse impact on progression free and overall survival
- Careful patient selection as regards renal function and continual monitoring of toxicity is advised to maintain compliance

ABSTRACT

Purpose: Concurrent chemoradiation is standard-of-care for patients with squamous cell carcinoma of the anus (SCCA). Poor compliance to chemotherapy, radiotherapy treatment interruptions and unplanned breaks may impact adversely on long-term outcomes.

Methods: The ACT II trial recruited 940 patients with localized SCCA, and assigned patients to mitomycin (week 1) or cisplatin (weeks 1 and 5), with fluorouracil (weeks 1 & 5) and radiotherapy (50-4Gy in 28 fractions over 38 days). This post-hoc analysis examined the association between baseline factors (age, gender, site, T-stage and N-stage), and compliance to treatment (radiotherapy and chemotherapy), and their effects on loco-regional failure-free survival (LRFFS), progression-free survival (PFS) and overall survival (OS).

Compliance was categorized into groups. Radiotherapy: 6 groups according to total dose (TD) and overall treatment time (OTT). Chemotherapy: 3 groups (A = per-protocol; B = dose reduction or delay; C = omitted).

Results: 931/940 patients were evaluable for radiotherapy and 936 for chemotherapy compliance. Baseline Glomerular filtration rate (GR) <60 mL/min and cisplatin were significantly associated with poor week 5 compliance to chemotherapy (p 0.003 and 0.02, respectively). Omission of week 5 chemotherapy was associated with significantly worse LRFFS (HR 2.53 [1.33 to 4.82] p=0.005). Dose reductions/delays or omission of week 5 chemotherapy were associated with

significantly worse FPFS (HR: 1.56 [95%CI: 1.18-2.06], $p=0.002$ and HR: 2.39 [95%CI: 1.44-3.98}, $p=0.001$, respectively) and OS (HR: 1.92 [95%CI: 1.41-2.63], $p<0.001$ and (HR: 2.88 [95%CI: 1.63-5.08], $p<0.001$, respectively). Receiving the target radiotherapy dose in >42 days is associated with worse PFS and OS (HR:1.72 (95%CI:1.17-2.54), $p=0.006$).

Conclusion: Poor compliance to chemotherapy and radiotherapy were associated with worse LRFFS, PFS and OS. Treatment interruptions should be minimized, and OTT and TD maintained.

Key words: Squamous cell carcinoma of the anus, chemotherapy, radiotherapy, chemoradiation, combined modality, compliance.

275 words

Introduction

Standard treatment for localized squamous cell carcinoma of the anus (SCCA) is chemoradiation using concurrent fluorouracil and mitomycin C^{1,2}. This combination has been tested in randomized trials^{3,4,5,6,7} and results in good outcomes for cT1/T2 cancers⁷, but less so for cT3/T4 cancers^{7,8}. Loco-regional failure is the predominant pattern of relapse^{7,9}, potentially influenced by innate chemo/radio-resistance, sub-therapeutic radiotherapy total dose (TD) delivered and poor chemotherapy compliance.

Early phase III trials in SCCA planned breaks in treatment of 6-8 weeks to manage acute treatment-related toxicities^{3,4}. Evidence for the importance of overall treatment time (OTT) exists in squamous carcinomas of the head and neck (SCCHN)^{10,11}. Evidence in SCCA is inconsistent, but strict adherence to protocol achieved significantly better overall survival (OS)¹² and suboptimal compliance to the planned radiotherapy TD adversely impacted on local control and OS¹³. More recent trials, without planned radiotherapy interruptions, reported high levels of acute toxicity to both modalities^{6,7}, leading to poor compliance in some patients. With the increasing use of intensity modulated radiotherapy (IMRT), toxicity is reduced allowing a potential reduction in average OTT¹⁴.

Since chemotherapy and radiotherapy independently enhances the other, compliance for each is required for optimum results. In the second United Kingdom Anal Cancer Trial (ACT II) the intention was to deliver a standard central axis tumour dose (irrespective of stage) of 50.4Gy in 28 fractions in 38 days. Other contemporary

trials used an initial dose of 45Gy, but were permissive, according to stage and response, as regards TD and number of fractions^{6,15}.

Compliance refers to conformity to trial recommendations with respect to timing, dose, and frequency of the intended radiotherapy or chemotherapy treatment. We could find no standard definition for radiotherapy compliance (TD or OTT) within chemoradiation schedules in SCCA, although the UK contemporary national guidance in 2015 recommended a maximum of 4 days' extension to the OTT¹⁶. In contrast, the RTOG 9811 trial allowed treatment breaks up to 10 days⁶. Thus, ACT II is uniquely placed to reliably assess the impact of compliance in terms of TD, OTT and chemotherapy on cancer outcomes. The permissive design of the other randomised trials precludes such an analysis.

The present analysis aimed to quantify compliance to radiotherapy (TD and OTT) and week 5 chemotherapy. We aimed to identify independent factors to predict better or worse compliance, and to investigate the impact on oncological outcomes i.e. loco-regional failure-free survival (LRFFS), progression-free survival (PFS) and OS). This is a relevant research question, which cannot be answered by only looking at those patients with poorer compliance.

Materials and Methods

Trial design and participants

ACT II was a randomized factorial phase III trial with 940 patients enrolled between 2001-2008, which investigated whether replacing mitomycin with cisplatin in the chemoradiation schedule improves complete response rate, and the impact of maintenance chemotherapy (fluorouracil/cisplatin) after chemoradiation. Methods and results have previously been reported⁷.

Protocol Guidance and modifications for toxicity

Radiotherapy: All patients were to receive radiotherapy (50.4Gy in 28 daily fractions over 38 days), in two-phases to the International Commission on Radiation Units and Measurements (ICRU) intersection point. A Monday start for radiotherapy was recommended, but not mandated. As such, planned OTT for those commencing treatment Monday to Wednesday or Thursday to Friday would be 38 and 40 days respectively. Protocol interruptions to radiotherapy were only recommended for haematological and gastrointestinal NCI Common Toxicity Criteria (CTC) grade 3 and 4. The protocol did not encourage, but allowed clinician's discretion to interrupt radiotherapy for moist skin desquamation, gastrointestinal and haematological toxicity. There was no guidance in the protocol about how, or when, to compensate for such interruptions.

Chemotherapy: Patients received fluorouracil 1000 mg/m² per day on days 1–4 (week 1) and 29–32 (week 5) by continuous intravenous infusion with radiotherapy, and either, 12 mg/m² of mitomycin as an intravenous bolus on day 1 only (maximum single dose 20 mg), or 60 mg/m² of cisplatin by intravenous infusion on days 1 and 29 (maximum single dose of 120 mg).

Patients with a calculated GFR of 50-60 ml/min were eligible only if the subsequently tested GFR was ≥ 50 ml/min. Cisplatin and MMC dose reductions were prescribed for patients with a GFR of 50–59 mL/.

Fluorouracil doses were reduced for week 5 chemotherapy in severe toxicity following week 1. Specifically, 25% and 50% dose reductions were recommended for grade 3 and 4 haematological toxicity respectively. Omission of fluorouracil was mandated in the case of G4 diarrhoea. Week 5 cisplatin was omitted if the GFR fell below 50ml/min.

Radiotherapy interruptions for toxicity delayed chemotherapy, so that the two modalities were given together.

Treatment compliance definition

Per-protocol radiotherapy compliance was defined prior to analysis as completion of protocol radiotherapy 50.4Gy in 28 fractions within an OTT of 38-42 days (including up to 4 days for logistical problems and public holidays) i.e. 10% extension. Poor radiotherapy compliance was therefore defined as extending >42 days. **Table 1** shows how we categorized radiotherapy and week 5 chemotherapy compliance.

Statistical analysis

Categorical variables were summarized in terms of frequency and percentage, and continuous variables in terms of median and range.

The association between baseline factors and radiotherapy TD delivered was examined using Kruskal Wallis test. The OTT by groups 1-6 was evaluated using cox regression. Logistic regression assessed any association between baseline characteristics and the risk of radiotherapy interruptions due to toxicity and odds

ratios (OR), 95% CI and p-values are reported. Fisher's exact test examined whether any baseline characteristics were associated with chemotherapy compliance.

Kaplan-Meier plots and cox regression assessed the effect of radiotherapy/chemotherapy compliance (groups 1-6 and A-C) on PFS and OS with subgroup analysis by T-stage. To account for potential immortality bias, the time to event outcomes were measured as time from 7 weeks post registration until the event of interest, or date of last follow-up for censored patients. Hazard ratios (HR), 95%CI and p-values derived from cox regression are reported.

RESULTS

Radiotherapy

Of 940 patients, 931 were evaluable for radiotherapy and 936 for chemotherapy compliance respectively **[Figure 1]**. Median follow-up was 5.1 years (95%CI: 5.0-5.3). **Table 2**, shows baseline characteristics were similar amongst all patients, and amongst groups 1-6 and groups A-C, except week 5 chemotherapy delays and reductions were more common in the cisplatin arm and amongst patients with $GFR \geq 60$ mL/min.

Previously reported compliance details⁷ have been updated. **[Table 3]**. The median radiotherapy TD was 50.4 Gy (range 5.6Gy – 56.7Gy, IQR 50.4–50.4) in a median of 28 fractions (range 3-32). Median OTT for radiotherapy was 38 days (range 3-81 days, IQR 38–39). 98/931 (11%) patients had at least one day's interruption in radiotherapy documented due to toxicity, but the precise cause was not specified in 82/98 patients (84%). A further 40/931 (4%) had interruptions due to non-toxicity (19

administrative i.e. machine breakdown, transport) 11 patient choice (weather, illness) and in 10 the reason was not specified. Only 18 patients had treatment interruptions of ≥ 8 days. For the 15 patients in Group 6, the extension to OTT ranged from 1-29 days with a median of 7 days. Radiotherapy was completed as per-protocol in 379/467 (81%) in the mitomycin arm and 377/464 (81%) in the cisplatin arm, respectively. There was no evidence of an association between baseline factors, type of chemotherapy (mitomycin, cisplatin), age, gender, clinical T or N stage, GFR, WBC and radiotherapy compliance [Table A1 & A2].

Adjusting for interruptions due to toxicity, we observed a statistically significant effect of radiotherapy OTT on PFS and OS - if patients receive less than the planned target dose or if the planned target dose is extended >42 days [Figure 2 and Online Table A3, Figure A1, Figure A2]. Patients who received the planned radiotherapy dose within 38-42 days had better outcomes. If OTT was extended >42 days, there was a significant increase in the risk of PFS event and death (PFS, HR: 1.58 (95%CI: 1.12 to 2.23) $p=0.01$) (OS, HR: 1.72 (95%CI: 1.17 to 2.54), $p=0.006$).

Chemotherapy

Week 1 chemotherapy was delivered without reductions/delays to 99% of patients in both mitomycin (433/465) and cisplatin arms (429/464). Chemotherapy delays or per-protocol reductions were uncommon; 32/465 (7%) in the mitomycin and 33/464 (7%) cisplatin arm

Data on week 5 chemotherapy was available for 936 patients. No chemotherapy was administered to 35/936 (3.7%), and 14% (68/471) in the mitomycin and 21% (96/465) in the cisplatin arm had delays or reductions. Completion of week 5 chemotherapy per-protocol was higher in the mitomycin arm 388/471 (82%) compared to the cisplatin arm 349/465 (75%). Poor compliance reflected acute toxicity, mainly haematological toxicity, worsening renal function, mucositis, diarrhoea and severe asthenia.

There was no association between baseline factors and week 5 chemotherapy compliance, except for baseline GFR in mL/min ($p=0.003$) (**Table A2**). Patients with baseline GFR of ≥ 60 mL/min were more likely to receive week 5 per-protocol chemotherapy, 711/891 (80%) compared with < 60 mL/min, 26/45 (58%). The week 5 chemotherapy 5FU intensity is comparable in both the mitomycin and cisplatin arms.

Dose reductions/delays or omission of week 5 chemotherapy were associated with worse LRFFS (HR:1.35 [0.92 to 1.98] $p=0.13$ and HR 2.53 [1.33 to 4.82] $p=0.005$ respectively). There was a statistically significant association between receiving per-protocol week 5 chemotherapy and PFS ($p=0.0006$) and OS ($p<0.0001$) [**Figure 3, Table A4**]. Omission of chemotherapy during chemoradiation was associated with >2 -fold increase in the risk of a PFS event (HR: 2.39 (95%CI: 1.44 to 3.98), $p=0.001$) compared with patients who completed week 5 per-protocol and an increased risk of death (HR 2.88 (95%CI: 1.63 to 5.08), $p<0.001$). Patients who received week 5 chemotherapy with delays/reductions compared with per-protocol, also had a significant increased risk of a PFS event (HR: 1.56 (95%CI: 1.18 to 2.06), $p=0.002$) and death (HR: 1.92 (95%CI: 1.41 to 2.63), $p<0.001$).

There is evidence of an interaction between chemotherapy week 5 compliance and T-stage for PFS ($p=0.04$) and OS ($p=0.04$) (**Table A4 and Fig 3**). The findings suggest patients with more advanced T-stage (T3-4) who failed to receive per-protocol week 5 chemotherapy have a worse PFS ($p<0001$) and an increased risk of death ($p<0001$) compared with per-protocol treatment (**Table A5**).

Compliance varied within the 52 participating sites, particularly in the 16 (31%) which recruited <10 patients (**Figure A3**). The impact of facility volumes and academic centres on outcomes has been highlighted in SCCHN¹⁷. In ACT II, these 16 hospitals treated 79 patients, 30 of whom (38%) did not complete per-protocol treatment, compared with 36 sites entering ≥ 10 patients where only 145/852 (17%) did not complete per-protocol treatment. Amongst sites recruiting ≥ 10 patients, the correlation between the number of patients recruited in each site and the percentage of patients who received radiotherapy as per-protocol was weak and not statistically significant (Spearman correlation coefficient= -0.20 , p value = 0.24).

Discussion

ACT II mandated a TD (irrespective of stage) of 50.4Gy in 28 fractions in 38 days. This retrospective post-hoc analysis quantifies compliance of patients treated with chemoradiation in the trial. We demonstrated that extending OTT of radiation by >42 days, and the omission of week 5 chemotherapy or reduced doses/delays are associated with inferior PFS and OS. This represents important information for clinicians treating this rare disease.

Since the protocol mandates chemotherapy and radiation are delivered concomitantly, 40% of patients who had a delay of radiotherapy OTT >42 days, also had the week 5 chemotherapy delayed and/or dose reduced, but only 4% had no chemotherapy at all. The association between better chemotherapy week 5 compliance in the patients who had RT as per protocol compared with patients who had RT prolonged with OTT >42 days (40.4% vs 13.76% [$p < 0.001$], respectively, implies that the inability to deliver the radiotherapy in a timely fashion is the main driver of the poor outcomes.

A retrospective pooled analysis of the RTOG 87-04 and RTOG 98-11 trials (Ben Josef 2010) concluded that total treatment time, but not duration of radiation therapy, has a detrimental effect on local failure and colostomy rate in anal cancer. However, a third received NACT and 62% of patients in RTOG 9811 required a treatment break resulting in an overall median OTT of 49 days and 302/644 (47%) patients received a total dose of only 45Gy. For these reasons, the data cannot be compared with our data in ACT II, which gave no NACT, used a mandated dose of 50.4Gy, and treatment breaks for skin toxicity were not permitted.

The strength of the study is that the data was collected prospectively within the ACT II trial with a large number of patients in study arms with equal distribution of age, gender, clinical stage of disease, ECOG performance status, and localization of primary tumour (canal /margin). TD, the fraction size of radiation and hence biological equivalent dose (BED) and the chemotherapy protocols were highly homogeneous. In particular, the consistency of the OTT [median 38 days (IQR 38-39

days)] in both mitomycin and cisplatin groups strengthens our conclusions. Outcomes are also mature with a 5-year median follow-up.

Quality assurance (QA) in radiotherapy has previously focussed on target delineation, dosimetry, PTV coverage or dose-volume parameters, OTT has been less rigorously assessed. Compliance has been categorized as acceptable, unacceptable and other (no radiotherapy or incomplete radiotherapy due to death, progression or refusal)¹⁸. Some trials consider a tolerance of +/- 10% as per-protocol with >10% an unacceptable deviation¹⁹. In ACT II, the QA protocol did not specify how many days extension to OTT would classify minor or major deviations.

The limitations of this study include the fact that this was an unplanned 'post hoc' retrospective analysis. The groups were retrospectively defined (based on contemporary UK recommendations and +/- 10% deviations), but the definitions were set prior to any analysis of data. Since patients are not randomized into these groups, sources of bias cannot be controlled for. Few patients failed to achieve per-protocol compliance and hence these represent small subgroup analyses.

Larger field sizes could have contributed to toxicity and compliance, but without reviewing individual field sizes in the light of staging CT and MRI scans to assess their fidelity, we are unable to provide detailed data. However, it is reassuring that median radiotherapy TD delivered, OTT for radiotherapy and risk of radiotherapy interruptions due to toxicity are similar between T1, T2, T3 and T4 tumours, and there is no evidence of a statistical difference ($p=0.68$, $p=0.47$ and $p=0.88$ respectively). **Table A1.** Reductions/delays in week 5 chemotherapy was observed

in 15% for T1/T2 and 19% for T3/T4, with no statistically significant difference ($p=0.37$) **Table A2.**

A further limitation is that we were unable to test for imbalances between the groups in human papilloma virus-associated cancer (p16+), smoking history or tumour infiltrating lymphocytes as this data was not collected and we were unable to adjust for co-morbidity.

The association between compliance groups and outcomes can reflect an outcome-by-outcome analysis, which is prone to bias as patients who complete per-protocol treatment tend to be younger, fitter, more robust, without co-morbidity and hence have a better prognosis. Any association between compliance and outcome does not therefore necessarily mean that the actual treatment received is associated with better/worse outcomes, although if other reasons such as poor adherence without toxicity and administrative issues can be shown to be responsible, then more robust associations can be drawn. Our results show no difference in the proportion of patients with an OTT >42 days for patients ≥ 65 years compared to younger patients.

There are a number of potential strategies to improve compliance. Prospective data from the RTOG 0529 trial suggest IMRT reduces acute toxicity. Significant reductions were reported in grade 2+ hematologic (73% vs. 85%; $P= .032$), grade 3+ gastrointestinal (21% vs. 36%; $P = 0.008$), and grade 3+ dermatologic events (23% vs. 49%; $P<0.0001$)¹⁴. Subsequent analyses suggested acute AEs correlated with radiation dose to the small bowel and anterior pelvic contents²⁰ in keeping with the finding of improved toxicity using IMRT. This is similar to a UK audit of SCCA, where

reduced toxicity resulted in radiotherapy interruptions falling from 8%-4% with IMRT and patients completing planned radiotherapy TD rose from 90% to 96%²¹.

Despite the use of IMRT, compliance remains an issue since treatment breaks in the 51 assessable patients in the RTOG 0529 trial were required by 49%, compared with 62% in RTOG 9811 ($P=0.09$), Median OTT with IMRT was 43 days with TD 54Gy, compared with 49 days and TD 50.4Gy in the standard fluorouracil/mitomycin arm of RTOG 9811 ($P<0.0001$)¹⁴. Additionally, 8/51 (16%) patients did not complete per-protocol chemotherapy. A recent retrospective pooled analysis of patients treated with IMRT in the UK reported failure to complete treatment or interruptions (defined as any extension >2 days over the planned OTT) as 5.2%. In multivariate analysis, a HR of 5.80 (1.96-17.29) was found in this group for persistent disease ($p=0.001$) compared with treatment delivered per-protocol²². Therefore, despite IMRT, poor compliance remains an issue.

A retrospective analysis, using the National Cancer Data Base (NCDB), compared outcomes of patients with SCCA treated with IMRT or 3D-CRT²³. They reported improved OS for those treated with shorter treatment times ($P < .0001$) and at high-volume centers [>18 cases per-year] ($P = .0011$). A more recent NCDB analysis of CRT (2004–2014), also showed prolonging RT was independently associated with reduced OS - with most effect when RT was delayed ≥ 2 days²⁴.

Additional proactive strategies could further improve compliance. First, meticulous hydration in the first cycle of chemotherapy might minimize toxicity in patients with baseline $GFR<60$. Second, the association between absolute nadir and the V10/V20

of pelvic and lumbosacral bone marrow could be addressed by bone marrow sparing, optimising constraints and plan evaluation²⁴.

Data on chemotherapy compliance in SCCA is sparse (**Table A6**). In the ACCORD 03 trial 78/82 (95%) (Arm C) and 71/75 (95%) (Arm D) received the second cycle of concurrent chemotherapy in the 157 patients, who received chemoradiation without induction chemotherapy¹⁵. However, this second cycle was adjusted (50-75%) according to early toxicity.

In ACT II, prolonged OTT in radiotherapy and poor compliance to week 5 chemotherapy were associated with worse PFS and OS outcomes. The large randomised trial dataset with standardised radiotherapy fields and the same mandated total dose, protocol-defined chemotherapy and toxicity prospectively captured, increases the likelihood that our findings are applicable to routine clinical practice, and should have a significant impact on the delivery of treatment regimens.

Although a 'post hoc' analysis is not powered for comparisons, the data can assist the design of future trials. We believe that there is an unmet need for studies to identify factors associated with compliance, and whether compliance could be used as a 'marker' predictive of the outcome. In this study, prolongation of OTT was not associated with any clinical factors, but initial GFR impacted on the ability to deliver week 5 chemotherapy in full.

This analysis strongly suggests radiotherapy should be delivered per-protocol in a timely manner in high volume facilities, avoiding interruptions, to achieve optimal

treatment outcomes. Better outcomes are observed when week 5 chemotherapy is administered in full without dose reduction or delay. Patients with poor compliance may require closer monitoring following chemoradiation to identify local recurrence at an early stage.

Contributors

RGJ, AL & HM designed this post hoc study, AL did the statistical analysis, RGJ, AL & HM wrote the paper, all authors interpreted the data and reviewed and approved the final draft.

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Disclosure

The authors have declared no conflicts of interest.

References

1. Glynne-Jones R, Nilsson PJ, Aschele C et al: Anal Cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis treatment and follow up. *Ann Oncol. Suppl 3*:iii10-20, 2014
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Anal Carcinoma Version 1.2020 - November 19, 2019. NCCN.org (accessed January 7 2020)
3. Flam M, John M, Pajak TF, et al: Role of Mitomycin in combination with Fluorouracil and radiotherapy and of salvage chemoradiation in the definitive nonsurgical treatment of Epidermoid Carcinoma of the Anal Canal: Results of a phase III randomized Intergroup Study. *J Clin Oncol* 14:2527-2539, 1996
4. UKCCCR Anal Cancer Working Party: Epidermoid Anal Cancer: Results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil and Mitomycin. *Lancet* 348:1049-1054, 1996
5. Bartelink H, Roelofsen F, Eschwege F, et al: Concomitant Radiotherapy and Chemotherapy Is Superior to Radiotherapy Alone in the Treatment of Locally Advanced Anal Cancer: Results of a Phase III Randomized Trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 15:2040-2049, 1997
6. Ajani JA, Winter KA, Gunderson LL, et al: Fluorouracil, Mitomycin and radiotherapy vs fluorouracil, cisplatin and radiotherapy for carcinoma of the anal canal: a randomised controlled trial. *JAMA* 199:1914-21, 2008
7. James RD, Glynne-Jones R, Meadows H, et al: Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2x2 factorial trial. *Lancet Oncol* 14:516-24, 2013
8. Gunderson LL, Moughan J, Ajani JA, et al: Anal carcinoma: impact of TN category of disease on survival, disease relapse, and colostomy failure in US Gastrointestinal Intergroup RTOG 98-11 phase 3 trial. *Int J Radiat Oncol Biol Phys.* Nov 15;87(4):638-45, 2013
9. Northover J, Glynne-Jones R, Sebag-Montefiore D, et al: Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). *Br J Cancer* 102:1123-8, 2010
10. Bese NS, Hendry J, Jeremic B. Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. *Int J Radiat Oncol Biol Phys.* 2007;68:654–61.

11. González Ferreira JA, Jaén Olasolo J, Azinovic I, Jeremic B. Effect of radiotherapy delay in overall treatment time on local control and survival in head and neck cancer: Review of the literature. *Rep Pract Oncol Radiother.* 2015;20(5):328–339.
12. Konski A, Garcia M Jr, John M, et al: Evaluation of planned treatment breaks during radiation therapy for anal cancer: Update of RTOG 92-08. *Int J Radiat Oncol Biol Phys* 72:114-118. 2008
13. Sischy B, Doggett RL, Krall JM, et al: Definitive irradiation and chemotherapy for radiosensitization in management of anal carcinoma: interim report on Radiation Therapy Oncology Group study no. 8314. *J Natl Cancer Inst.* 81(11):850-6, 1989
14. Kachnic LA, Winter K, Myerson RJ et al: RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys.* 86(1):27-33, 2013
15. Peiffert D, Tournier-Rangeard L, Gerald JP, et al: Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. *J Clin Oncol* 30:1941-4, 2012
16. Royal College of Radiologists, United Kingdom. The timely delivery of radical radiotherapy: standards and guidelines for the management of unscheduled treatment interruptions, third edition. London. The Royal College of Radiologists BFCO (08)6, 2008
17. David JM, Ho AS, Luu M, et al. Treatment at high-volume facilities and academic centers is independently associated with improved survival in patients with locally advanced head and neck cancer. *Cancer.* 2017;123:3933–42
18. Willett CG, Moughan J, O'Meara E, et al: Compliance with Therapeutic Guidelines in Radiation Therapy Oncology Group Prospective Gastrointestinal Clinical Trials. *Radiother Oncol.* 105(1):9-13, 2012
19. Abrams RA, Winter KA, Regine WF, et al: Failure to Adhere to Protocol Specified Radiation Therapy Guidelines Was Associated with Decreased Survival in RTOG 9704 - A Phase III Trial of Adjuvant Chemotherapy and Chemoradiotherapy for Patients with Resected Adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys.* 82(2):809-16, 2012
20. Olsen JR, Moughan J, Myerson R, et al: Predictors of Radiation Therapy-Related Gastrointestinal Toxicity from Anal Cancer Dose-Painted Intensity Modulated Radiation Therapy: Secondary Analysis of NRG Oncology RTOG 0529. *Int J Radiat Oncol Biol Phys.* 98(2):400-408, 2017

21. Muirhead R, Drinkwater K, O'Cathail SM, et al: Initial Results from the Royal College of Radiologists' UK National Audit of Anal Cancer Radiotherapy 2015. *Clin Oncol (R Coll Radiol)*. 29(3):188-197, 2017
22. Shakir R, Adams R, Cooper R et al., Patterns and Predictors of Relapse Following Radical Chemoradiation Therapy Delivered Using Intensity Modulated Radiation Therapy with a Simultaneous Integrated Boost in Anal Squamous Cell Carcinoma. *Int J Radiation Oncol Biol Phys* 106 (2), 329-339, 2020
23. Elson JK, Kachnic LA, Kharofa JR. Intensity-modulated radiotherapy improves survival and reduces treatment time in squamous cell carcinoma of the anus: A National Cancer Data Base study. *Cancer*. 124(22):4383-4392, 2018
24. Mehta S, Ramey SJ, Kwon D, et al. Impact of radiotherapy duration on overall survival in squamous cell carcinoma of the anus. *J Gastrointest Oncol*. 2020;11(2):277-290. doi:10.21037/jgo.2020.02.09
25. Mell LK, Schomas DA, Salama JK, et al: Association between bone marrow dosimetric parameters and acute hematologic toxicity in anal cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 70(5):1431-7, 2008

Main Figures

Figure 1: Diagram of the evaluable patients for the radiotherapy compliance and week 5 chemotherapy compliance analysis

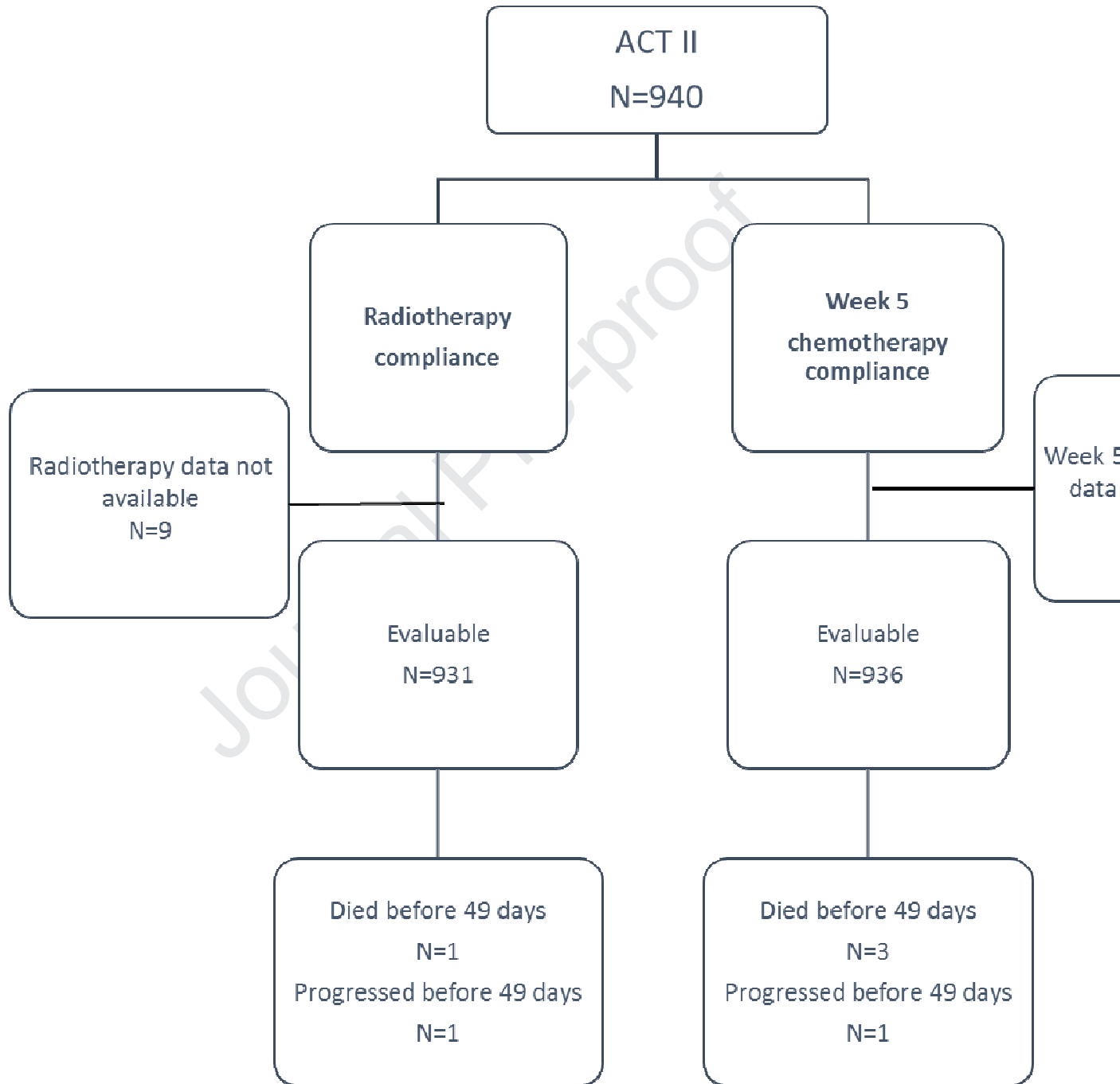
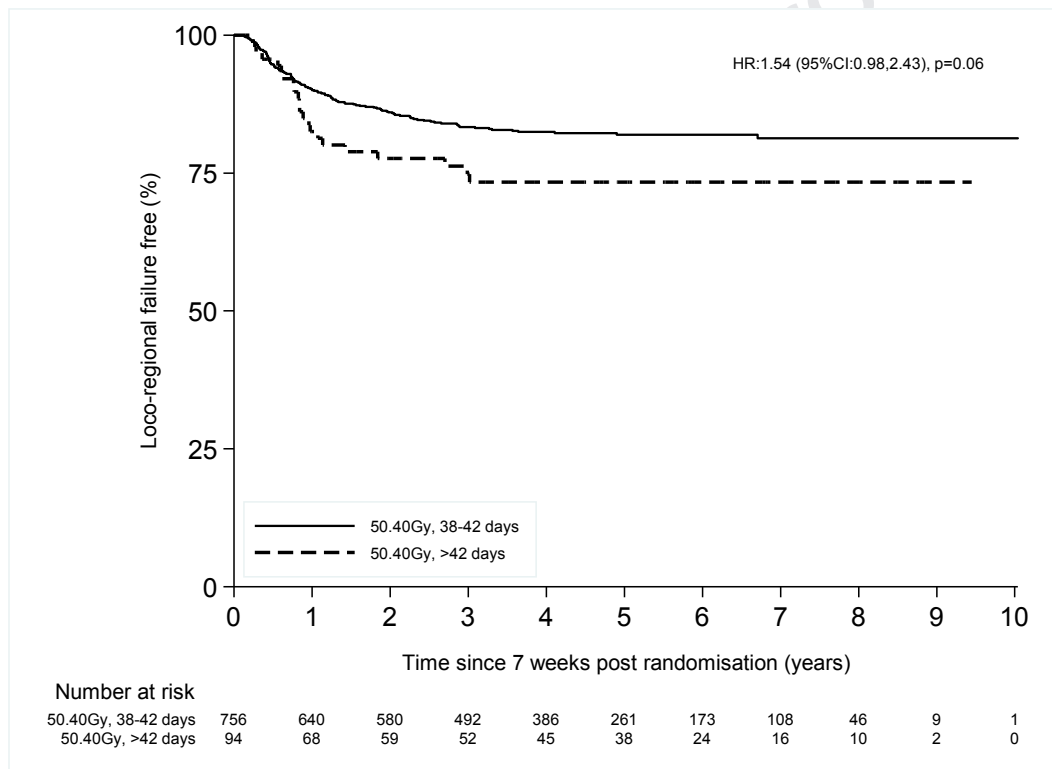


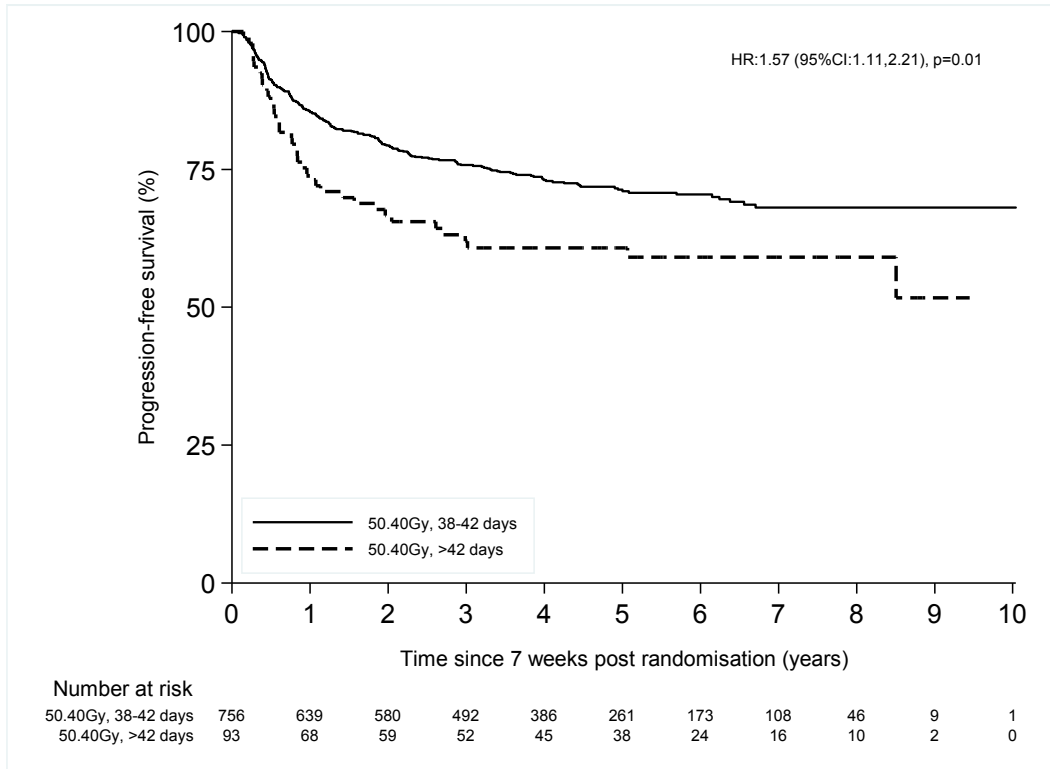
Figure 2 Association between compliance with Overall radiotherapy treatment time (OTT) and Loco-regional failure free survival (A), progression-free survival (B) and overall survival (C)

Kaplan-Meier estimates of (A) loco-regional failure free survival (LRFFS), (B) progression-free survival (PFS), and (C) overall survival (OS) in the assessable population for mandated dose of 50.4Gy in 28 fractions over 38-42 days versus 50.4 Gy with OTT >42 days. HR, hazard ratio CI confidence interval.

A. Loco-regional failure free survival



B. Progression free survival



C. Overall survival

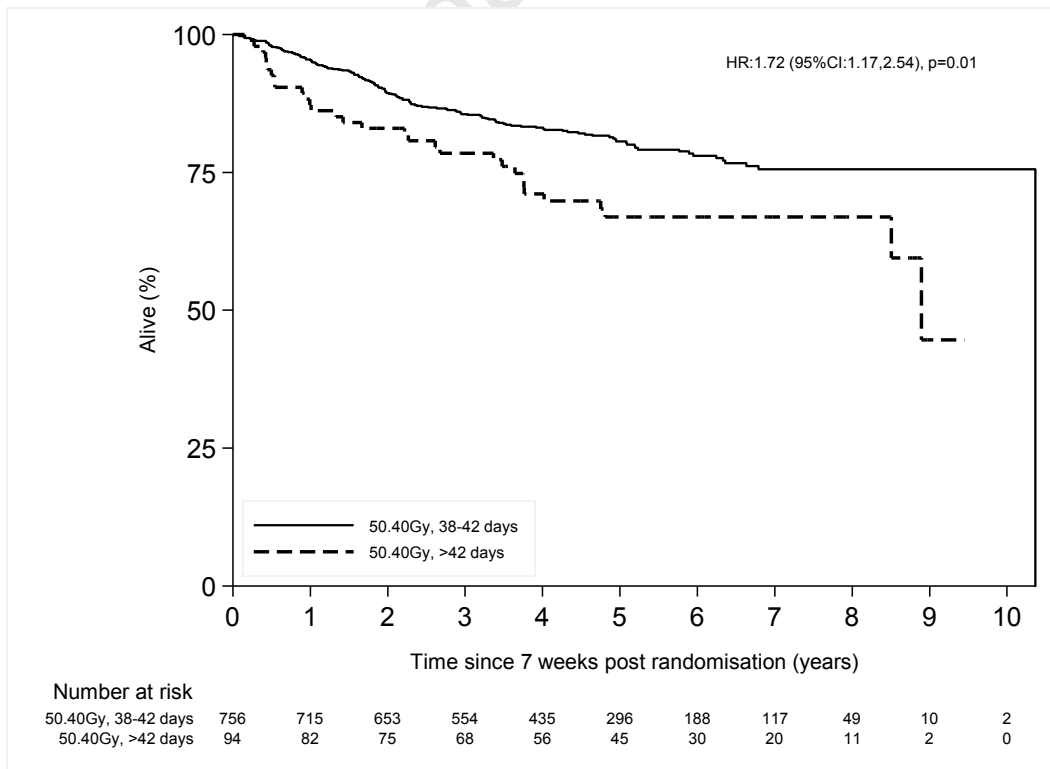
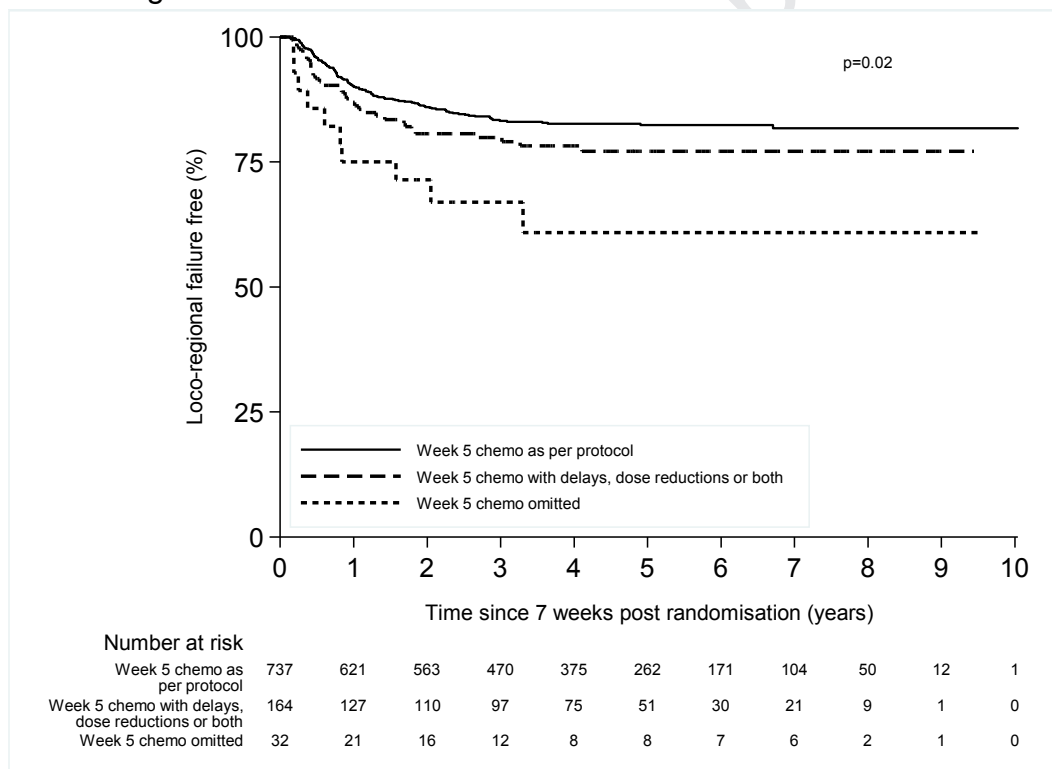


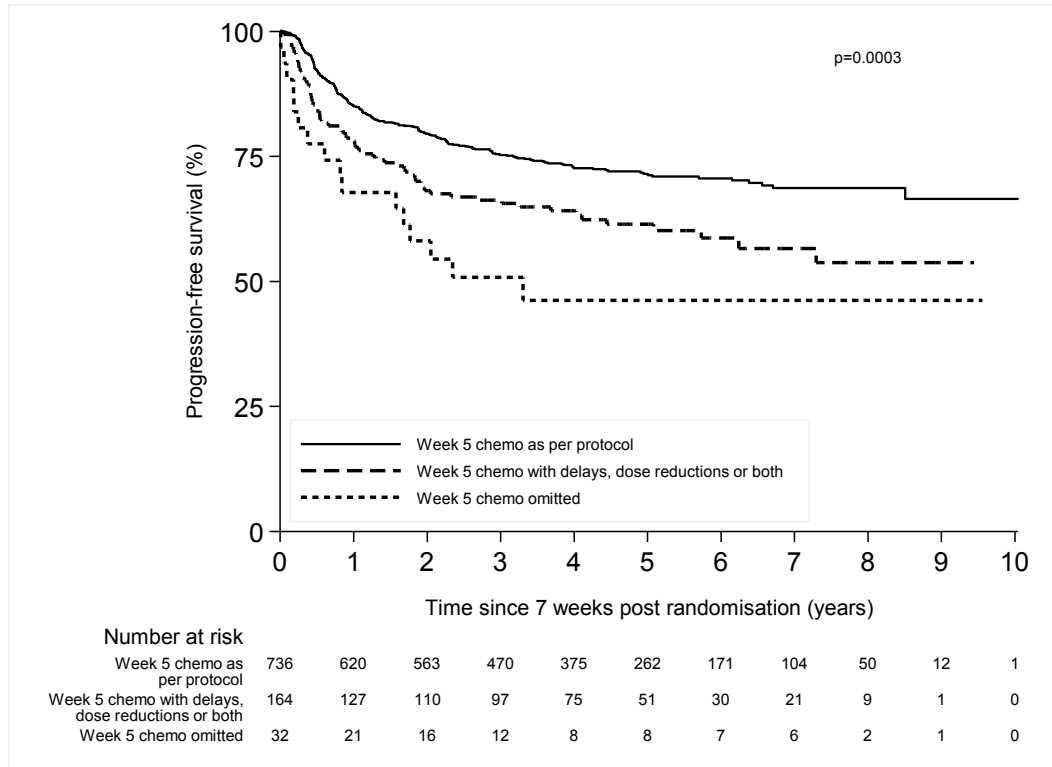
Figure 3. Association between compliance with week 5 chemotherapy and loco-regional failure free survival (A), progression-free survival (B) and overall survival (C)

Kaplan-Meier estimates of (A) loco-regional failure free survival (LRFFS), (B) progression-free survival (PFS), and (C) overall survival (OS) in the assessable population for week 5 chemotherapy delivered per protocol, for week 5 with reductions delays or both, and for week 5 chemotherapy omitted HR, hazard ratio CI confidence interval.

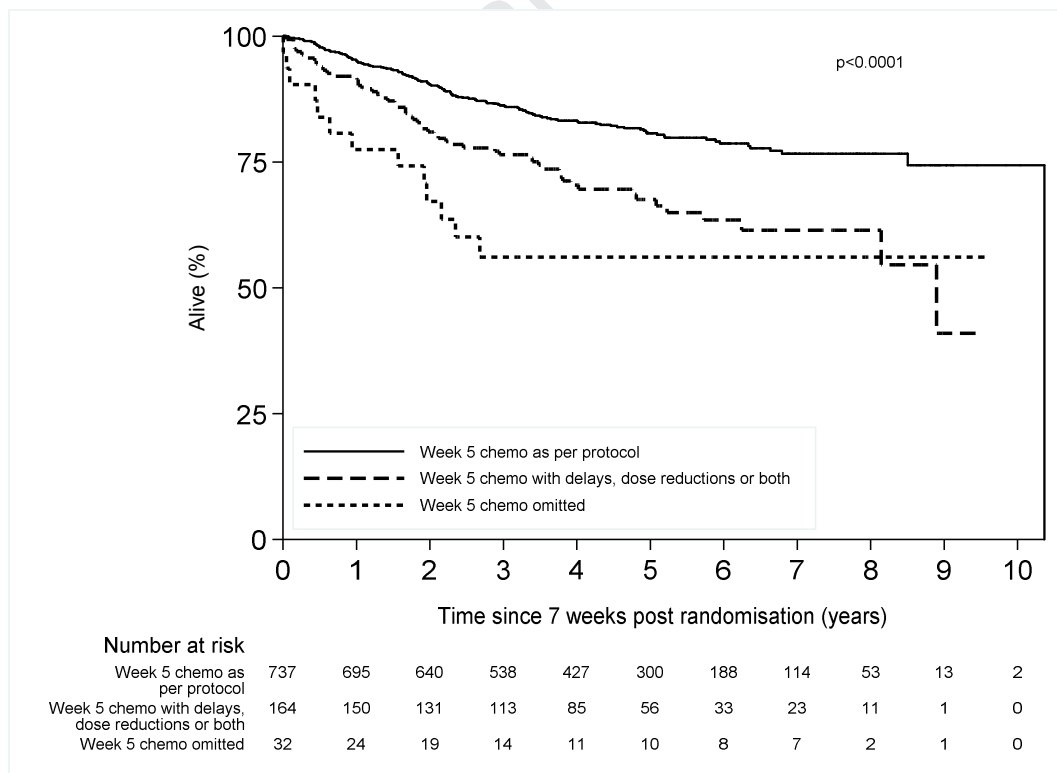
A Loco-regional failure free survival



B Progression Free Survival



C Overall Survival



Main Tables

Table 1: Categorisation of radiotherapy compliance and week 5 chemotherapy compliance

Compliance group	Description
Radiotherapy compliance	
1	included patients who received radiotherapy treatment according to protocol (ie 50.4Gy in 38-42 days, normally done over 28 fractions of 1.8Gy), which acted as the reference group.
2	included patients who received radiotherapy treatment but to a lower total dose of ≤ 40 Gy.
3	included patients who received radiotherapy treatment to an intermediate dose between >40 Gy to <48.60 Gy in 20-28 fractions
4	included patients who received the full radiotherapy treatment of 50.4Gy but within less than 38 days
5	included patients who received the full radiotherapy treatment of 50.16 to 51.5 Gy but delivered in longer than 42 days (ie a treatment interruption or gap with no compensation for potential accelerated repopulation)
6	had an extended overall treatment time and had an increase in total dose ≥ 52.2 Gy-56.7Gy in 29-32 fractions
Week 5 chemotherapy compliance	
A	Patients received week 5 chemotherapy as per protocol
B	Patients received week 5 chemotherapy with a dose reduction or delay
C	Patients where week 5 chemotherapy was omitted

Table 2: Baseline characteristics

Baseline characteristics	All N=940	Radiotherapy compliance N=931						Week 5 chemotherapy compliance N=936		
		≤40Gy (G2) N=8	>40Gy to <48.60Gy (G3) N=25	Received 50.40Gy			>52.20Gy (G6) N=15	As per protocol N=737	With delays/ reductions N=164	Omitted N=35
				<38 days (G4) N=33	38-42 days (G1) N=756	>42 days (G5) N=94				
Age										
<65 years	699 (74%)	4 (50%)	19 (76%)	22 (67%)	565 (75%)	70 (74%)	13 (87%)	554 (75%)	115 (70%)	26 (74%)
≥65 years	241 (26%)	4 (50%)	6 (24%)	11 (33%)	191 (25%)	24 (26%)	2 (13%)	183 (25%)	49 (30%)	9 (26%)
Sex										
Female	587 (62%)	5 (63%)	16 (64%)	21 (64%)	477 (63%)	56 (60%)	10 (67%)	449 (61%)	112 (68%)	24 (69%)
Male	353 (38%)	3 (38%)	9 (36%)	12 (36%)	279 (37%)	38 (40%)	5 (33%)	288 (39%)	52 (32%)	11 (31%)
Site of primary tumour										
Canal	787 (84%)	7 (88%)	20 (80%)	28 (85%)	631 (83%)	81 (86%)	12 (80%)	607 (82%)	145 (88%)	32 (91%)
Margin	132 (14%)	1 (13%)	5 (20%)	4 (12%)	110 (15%)	10 (11%)	2 (13%)	113 (15%)	16 (10%)	3 (9%)
Not reported	21 (2%)	0 (0%)	0 (0%)	1 (3%)	15 (2%)	3 (3%)	1 (7%)	17 (2%)	3 (2%)	0 (0%)
T stage										
T1	91 (10%)	2 (25%)	5 (20%)	5 (15%)	73 (10%)	4 (4%)	2 (13%)	71 (10%)	17 (10%)	3 (9%)
T2	395 (42%)	4 (50%)	9 (36%)	6 (18%)	325 (43%)	43 (46%)	7 (47%)	322 (44%)	57 (35%)	14 (40%)
T3	295 (31%)	2 (25%)	5 (20%)	18 (55%)	234 (31%)	26 (28%)	5 (33%)	220 (30%)	59 (36%)	15 (43%)
T4	135 (14%)	0 (0%)	5 (20%)	4 (12%)	106 (14%)	18 (19%)	0 (0%)	108 (15%)	24 (15%)	3 (9%)
Tx/Not reported	24 (3%)	0 (0%)	1 (4%)	0 (0%)	18 (2%)	3 (3%)	1 (7%)	16 (2%)	7 (4%)	0 (0%)
Nodal stage										
Negative	587 (62%)	7 (88%)	17 (68%)	14 (42%)	481 (64%)	58 (62%)	5 (33%)	464 (63%)	98 (60%)	23 (66%)
Positive	305 (32%)	1 (13%)	8 (32%)	14 (42%)	238 (31%)	33 (35%)	8 (53%)	237 (32%)	60 (37%)	7 (20%)
Nx/Not reported	48 (5%)	0 (0%)	0 (0%)	5 (15%)	37 (5%)	3 (3%)	2 (13%)	36 (5%)	6 (4%)	5 (14%)
GF rate in mL/min										
<60	45 (5%)	1 (13%)	3 (12%)	2 (6%)	34 (4%)	3 (3%)	1 (7%)	26 (4%)	16 (10%)	3 (9%)
≥60	895 (95%)	7 (88%)	22 (88%)	31 (94%)	722 (96%)	91 (97%)	14 (93%)	711 (96%)	148 (90%)	32 (91%)
Differentiation										
Well	121 (13%)	1 (13%)	3 (12%)	3 (9%)	102 (13%)	10 (11%)	2 (13%)	102 (14%)	14 (9%)	5 (14%)
Moderate	395 (42%)	5 (63%)	10 (40%)	14 (42%)	307 (41%)	51 (54%)	5 (33%)	311 (42%)	75 (46%)	8 (23%)
Poor	277 (29%)	1 (13%)	6 (24%)	7 (21%)	229 (30%)	26 (28%)	4 (27%)	214 (29%)	49 (30%)	14 (40%)

Unknown/Not reported	147 (16%)	1 (13%)	6 (24%)	9 (27%)	118 (16%)	7 (7%)	4 (27%)	110 (15%)	26 (16%)	8 (23%)
Tumour type										
Basaloid	108 (11%)	0 (0%)	3 (12%)	7 (21%)	88 (12%)	9 (10%)	1 (7%)	85 (12%)	20 (12%)	3 (9%)
Cloacogenic	14 (1%)	0 (0%)	1 (4%)	0 (0%)	12 (2%)	1 (1%)	0 (0%)	11 (1%)	3 (2%)	0 (0%)
Squamous	769 (82%)	8 (100%)	19 (76%)	25 (76%)	615 (81%)	81 (86%)	13 (87%)	601 (82%)	135 (82%)	30 (86%)
Not reported	49 (5%)	0 (0%)	2 (8%)	1 (3%)	41 (5%)	3 (3%)	1 (7%)	40 (5%)	6 (4%)	2 (6%)
Pretreatment colostomy										
No	806 (86%)	7 (88%)	21 (84%)	28 (85%)	649 (86%)	80 (85%)	13 (87%)	641 (87%)	133 (81%)	30 (86%)
Yes	131 (14%)	1 (13%)	4 (16%)	5 (15%)	104 (14%)	14 (15%)	2 (13%)	94 (13%)	31 (19%)	5 (14%)
Not reported	3 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0%)	0 (0%)	0 (0%)	2 (0%)	0 (0%)	0 (0%)
WBC in x 10⁹/l										
<11	739 (79%)	5 (63%)	21 (84%)	28 (85%)	599 (79%)	67 (71%)	14 (93%)	575 (78%)	138 (84%)	25 (71%)
≥11	189 (20%)	2 (25%)	4 (16%)	5 (15%)	151 (20%)	26 (28%)	1 (7%)	159 (22%)	25 (15%)	4 (11%)
Not reported	12 (1%)	1 (13%)	0 (0%)	0 (0%)	6 (1%)	1 (1%)	0 (0%)	3 (0%)	1 (1%)	6 (17%)
Treatment										
Mitomycin	472 (50%)	3 (38%)	11 (44%)	16 (48%)	379 (50%)	51 (54%)	7 (47%)	388 (53%)	68 (41%)	15 (43%)
Cisplatin	468 (50%)	5 (63%)	14 (56%)	17 (52%)	377 (50%)	43 (46%)	8 (53%)	349 (47%)	96 (59%)	20 (57%)

Table 3: Descriptive statistics for radiotherapy and week 5 chemotherapy compliance

Radiotherapy			
Radiotherapy	Total		
	N=931		
	(Median, range)		
Total dose delivered Gy	50.4 (5.4 – 56.7)		
Time on radiotherapy	38 (3-81)		
Number of fractions	28 (3-32)		
Radiotherapy Interruptions	N (%)		
Due to toxicity	98 (11%)		
Due to other reasons	40 (4%)		
Chemotherapy at week 5			
	Mitomycin	Cisplatin	Total
	N=472	N=468	N=940
	N (%)	N (%)	N (%)
Completed week 5 as per protocol	388 (82%)	349 (75%)	737 (78%)
Any delays, dose reduction or both	68 (14%)	96 (21%)	164 (17%)
No chemo during chemoradiation	15 (3%)	20 (4%)	35 (4%)
Insufficient data	1 (<1%)	3 (1%)	4 (0%)

SUPPLEMENTARY Appendix for online only

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Table A1: Association between baseline factors and radiotherapy compliance

Explanatory factors	Outcome of interest								
	Radiotherapy total dose delivered N=931			Patients who received the target dose 50.40 Gy					
	N	Median (range)	p*	Radiotherapy duration in days N=883			Radiotherapy interruptions due to toxicity N=883		
N				Median (range)	p**	Events/N (%)	OR (95%CI)	p***	
Age									
<65 years	693	50.4 (16.2 to 56.7)	0.91	657	38 (29 to 81)	0.82	61/657 (9%)	1.00	0.56
≥65 years	238	50.4 (5.4 to 55.8)		226	38 (32 to 59)		24/226 (11%)	1.16 (0.71 to 1.91)	
Gender									
Female	585	50.4 (5.4 to 56.7)	0.79	554	38 (29 to 81)	0.88	51/554 (9%)	1.00	0.58
Male	346	50.4 (9 to 54)		329	38 (33 to 56)		34/329 (10%)	1.14 (0.72 to 1.8)	
Site of primary tumour									
Canal	779	50.4 (5.4 to 56.7)	>0.99	740	38 (29 to 81)	0.38	72/740 (10%)	1.00	0.99
Margin	132	50.4 (30.6 to 52.2)		124	38 (33 to 50)		12/124 (10%)	0.99 (0.52 to 1.89)	
T stage									
T1	91	50.4 (5.4 to 55.8)	0.68	82	38 (29 to 49)	0.47	8/82 (10%)	1.00	0.88
T2	394	50.4 (9 to 52.2)		374	38 (32 to 56)		38/374 (10%)	1.05 (0.47 to 2.33)	
T3	290	50.4 (30.6 to 56.7)		278	38 (32 to 59)		26/278 (9%)	0.95 (0.41 to 2.2)	
T4	133	50.4 (43.2 to 51.39)		128	38 (33 to 81)		10/128 (8%)	0.78 (0.3 to 2.08)	
Nodal stage									
Negative	582	50.4 (5.4 to 54)	0.53	553	38 (32 to 57)	0.8	53/553 (10%)	1.00	0.96
Positive	302	50.4 (30.6 to 56.7)		285	38 (32 to 81)		27/285 (9%)	0.99 (0.61 to 1.61)	
GF rate in mL/min									
<60	44	50.4 (34.2 to 55.8)	0.77	39	38 (32 to 46)	0.47	3/39 (8%)	1.00	0.68
≥60	887	50.4 (5.4 to 56.7)		844	38 (29 to 81)		82/844 (10%)	1.29 (0.39 to 4.29)	
Differentiation									
Well	121	50.4 (16.2 to 52.2)	0.87	115	38 (34 to 56)	0.62	12/115 (10%)	1.00	0.97
Moderate	392	50.4 (9 to 56.7)		372	38 (32 to 57)		36/372 (10%)	0.92 (0.46 to 1.83)	
Poor	273	50.4 (5.4 to 55.8)		262	38 (33 to 81)		26/262 (10%)	0.95 (0.46 to 1.95)	
Tumour type									
Basaloid	108	50.4 (43.2 to 52.2)	0.95	104	38 (32 to 51)	0.43	11/104 (11%)	1.00	0.81
Cloacogenic	14	50.4 (46.8 to 50.4)		13	38 (38 to 43)		2/13 (15%)	1.54 (0.3 to 7.85)	
Squamous	761	50.4 (5.4 to 56.7)		721	38 (29 to 81)		71/721 (10%)	0.92 (0.47 to 1.81)	
Pretreatment colostomy									
No	798	50.4 (5.4 to 56.7)	0.85	757	38 (29 to 57)	0.51	76/757 (10%)	1.00	0.22
Yes	130	50.4 (21.6 to 54)		123	38 (33 to 81)		8/123 (7%)	0.62 (0.29 to 1.33)	

WBC in x 10⁹/l									
<11	734	50.4 (9 to 56.7)		694	38 (29 to 59)		69/694 (10%)	1.00	
≥11	189	50.4 (5.4 to 52.2)	0.88	182	38 (37 to 81)	0.25	15/182 (8%)	0.81 (0.45 to 1.46)	0.49
Treatment									
Mitomycin	467	50.4 (21.6 to 55.8)		446	38 (29 to 81)		43/446 (10%)	1.00	
Cisplatin	464	50.4 (5.4 to 56.7)	0.93	437	38 (32 to 57)	0.67	42/437 (10%)	1 (0.64 to 1.56)	0.99

* derived from Kruskal Wallis test

** derived from cox regression

*** derived from logistic regression

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Table A2: Association between baseline factors and week 5 chemotherapy compliance

Explanatory factors	Week 5 chemotherapy compliance			Fishers' exact test p
	Per protocol N=737	With delays/ reductions N=164	Omitted N=35	
Age, N (%)				
<65 years	554 (80%)	115 (17%)	26 (4%)	0.39
≥65 years	183 (76%)	49 (20%)	9 (4%)	
Sex, N(%)				
Female	449 (77%)	112 (19%)	24 (4%)	0.16
Male	288 (82%)	52 (15%)	11 (3%)	
Site of primary tumour, N (%)				
Canal	607 (77%)	145 (18%)	32 (4%)	0.11
Margin	113 (86%)	16 (12%)	3 (2%)	
T stage, N (%)				
T1	71 (78%)	17 (19%)	3 (3%)	0.37
T2	322 (82%)	57 (15%)	14 (4%)	
T3	220 (75%)	59 (20%)	15 (5%)	
T4	108 (80%)	24 (18%)	3 (2%)	
Nodal stage, N (%)				
Negative	464 (79%)	98 (17%)	23 (4%)	0.29
Positive	237 (78%)	60 (20%)	7 (2%)	
GF rate in mL/min, N (%)				
<60	26 (58%)	16 (36%)	3 (7%)	0.003
≥60	711 (80%)	148 (17%)	32 (4%)	
Differentiation, N (%)				
Well	102 (84%)	14 (12%)	5 (4%)	0.076
Moderate	311 (79%)	75 (19%)	8 (2%)	
Poor	214 (77%)	49 (18%)	14 (5%)	
Tumour type, N (%)				
Basaloid	85 (79%)	20 (19%)	3 (3%)	0.96
Cloacogenic	11 (79%)	3 (21%)	0 (0%)	
Squamous	601 (78%)	135 (18%)	30 (4%)	
Pretreatment colostomy, N (%)				
No	641 (80%)	133 (17%)	30 (4%)	0.12
Yes	94 (72%)	31 (24%)	5 (4%)	
WBC in x 10⁹/l, N (%)				
<11	575 (78%)	138 (19%)	25 (3%)	0.14
≥11	159 (85%)	25 (13%)	4 (2%)	
Treatment, N (%)				
Mitomycin	388 (82%)	68 (14%)	15 (3%)	0.02
Cisplatin	349 (75%)	96 (21%)	20 (4%)	

Table A3: Association between radiotherapy compliance and overall survival/progression-free survival

Factors of interest	Outcome of interest							
	Overall Survival (OS)*				Progression-free survival (PFS)**			
	Total events / No of patients	3 years rate %	HR (95%CI) Cox regression	p	Total events / No of patients	3 years rate %	HR (95%CI) Cox regression	p
Radiotherapy compliance groups								
1) 50.40Gy, 38-42 days	146/756	86%	1.00 (reference)		212/756	76%	1.00 (reference)	
2) ≤40Gy	5/7	29%	8.24 (3.35 to 20.27)	p<0.001	5/7	29%	5.43 (2.24 to 13.21)	p<0.001
3) >40Gy to <48.60Gy	12/25	70%	3.12 (1.73 to 5.63)	p<0.001	13/25	63%	2.12 (1.21 to 3.72)	0.009
4) 50.40Gy, <38 days	6/33	87%	0.95 (0.42 to 2.16)	0.91	9/33	72%	1.00 (0.51 to 1.95)	>0.99
5) 50.40Gy, >42 days	31/94	78%	1.72 (1.17 to 2.54)	0.006	38/93	62%	1.57 (1.11 to 2.21)	0.01
6) >52.20Gy	4/15	73%	1.57 (0.58 to 4.25)	0.37	6/15	59%	1.60 (0.71 to 3.59)	0.26
Total dose delivered in Gy (continuous variable) in groups 1 to 6	204/930	84%	0.95 (0.93 to 0.98)	p<0.001	283/929	73%	0.96 (0.94 to 0.99)	0.006
Duration of radiotherapy in weeks amongst groups 1), 4) and 5)								
Unadjusted			1.34 (1.06 to 1.68)	0.01			1.27 (1.02 to 1.59)	0.03
Adjusted for interruptions due to toxicity	183/883	85%	1.36 (1.07 to 1.74)	0.01	259/882	74%	1.20 (0.92 to 1.57)	0.19

* Measured from 7 weeks post registration until death or time of last follow-up recorded. Patients who had the event of interest before 7 weeks or a follow-up of less than 7 weeks were excluded

** Measured from 7 weeks post registration until occurrence of PFS event or time of last follow-up recorded. Patients who had the event of interest before 7 weeks or a follow-up of less than 7 weeks were excluded

Table A4: Association between compliance with week 5 chemotherapy and overall survival/progression-free survival

Compliance with week 5 chemotherapy	Total events/ No of patients	3 years rate %	HR (95%CI)	p
Overall Survival (OS)*				
Completed week 5 as per protocol	139/737	86%	1.00 (reference)	
Any delays, dose reduction or both	55/164	77%	1.92 (1.41 to 2.63)	p<0.001
No chemo during chemoradiation	13/32	56%	2.88 (1.63 to 5.08)	p<0.001
Progression-free survival (PFS)**				
Completed week 5 as per protocol	206/736	75%	1.00 (reference)	
Any delays, dose reduction or both	65/164	66%	1.55 (1.17 to 2.04)	0.002
No chemo during chemoradiation	16/32	51%	2.37 (1.43 to 3.95)	0.001

* Measured from 7 weeks post registration until death or time of last follow-up recorded. Patients who had the event of interest before 7 weeks or a follow-up of less than 7 weeks were excluded

** Measured from 7 weeks post registration until occurrence of PFS event or time of last follow-up recorded. Patients who had the event of interest before 7 weeks or a follow-up of less than 7 weeks were excluded

Table A5

A: Overall Survival by week 5 chemotherapy compliance in T stage 1 & 2 and T-stage 3 & 4

Overall Survival	Interaction p*	T-stage 1 & 2				T stage 3 & 4			
		N=483 Events/N	3 years rate (%)	HR (95%CI)	p	N=427 Events/N	3 years rate (%)	HR (95%CI)	p
Completed week 5 as per protocol		62/394	89%	1 (base)		77/328	82%	1 (base)	
Any delays, dose reduction or both	0.035	14/74	94%	1.17 (0.66 to 2.10)	0.59	40/83	60%	2.43 (1.66 to 3.56)	p<0.0001
No chemo during CRT		7/16	54%	3.84 (1.75 to 8.41)	0.001	6/16	58%	2.11 (0.92 to 4.85)	0.078

B: Progression-free Survival by week 5 chemotherapy compliance in T stage 1 & 2 and T-stage 3 & 4

Progression-free Survival	Interaction p*	T-stage 1 & 2				T stage 3 & 4			
		N=483 Events/N	3 years rate (%)	HR (95%CI)	p	N=426 Events/N	3 years rate (%)	HR (95%CI)	p
Completed week 5 as per protocol		62/393	81%	1 (base)		76/327	68%	1 (base)	
Any delays, dose reduction or both	0.042	14/74	86%	1.03 (0.62 to 1.71)	0.91	40/83	47%	2.04 (1.44 to 2.87)	p<0001
No chemo during Chemoradiation		7/16	49%	3.01 (1.46 to 6.22)	0.003	6/16	53%	1.99 (0.97 to 4.09)	0.06

* Interaction between T-stage* Chemo compliance

Adjusting for the patient characteristics in table 2, the interaction between T-stage and chemotherapy compliance for PFS is p=0.05 and for OS p=0.05.

Table A6: title Summary of 3D chemoradiation trials in SSCC

Trial	Arms (number of patients)	Chemo compliance		CHEMORADIATION (CRT) compliance	
				Median RT total dose (Range)	Median OTT in Days (Range)
RTOG 9811 (Ajani 2008)	5FU/MMC Arm (341)	95%		55Gy (9-69 Gy) IQR 45.9-59	49 (not given) IQR 42-56
	NACT + 5FU/cisplatin Arm (341)	Induction NACT 94%		55Gy (14.4- 70.2) IQR 45-59	45 (not given) IQR 37.5-52
Accord 03 (Peiffert 2012)	Arm A (75)			45Gy (39.6-47.3)	35 (26-81)
	Arm B (75)	Induction NACT		45Gy (39.4-47.3)	36 (25-91)
	Arm C (82) standard	78/82 (95%)		45Gy (42.4-50.0)	35 (30-65)
	Arm D (75)	71/75 (95%)		45Gy (34.2-47.3)	35 (25-74)
ACT II (James 2013)	chemoradiation 5FU/MMC (472)	1	2	50.4Gy (IQR 50.4–50.4)	38 (IQR 38–39)
		92%	82%		
	chemoradiation 5FU/cisplatin (468)	1	2	50.4Gy (IQR 50.4–50.4)	38 (IQR 38–39)
		92%	75%		

NACT = neoadjuvant chemoradiation

MMC = mitomycin

5FU = 5fluorouracil

Table A7 Patients who had RT as per protocol and compliance with chemo week 5

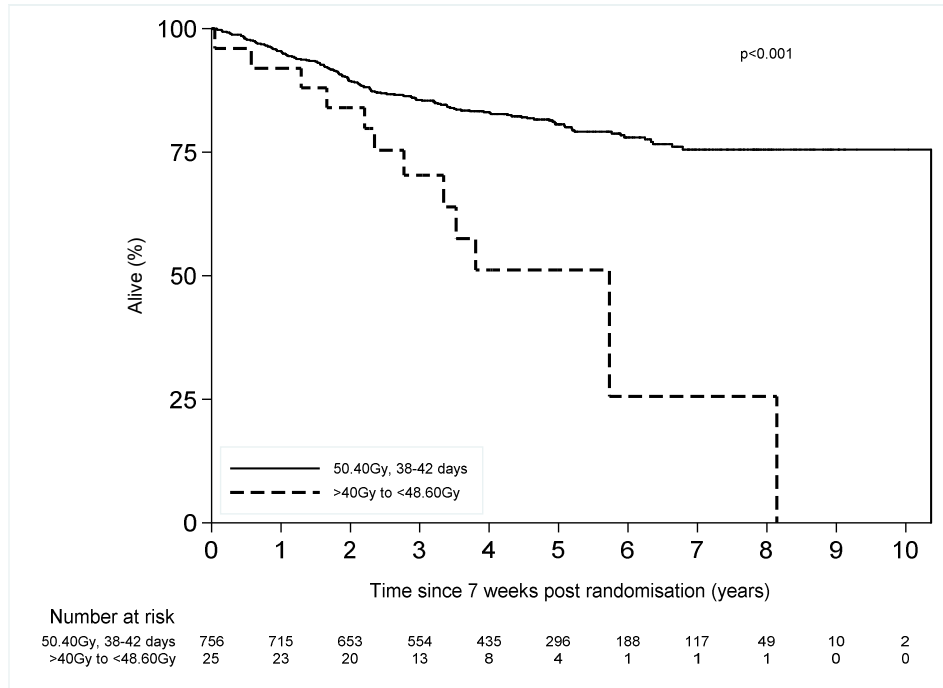
Compliance Chemo week 5	N	%
1. Completed week 5 as per protocol	631	83.47
2. Any delays, dose reduction or both	104	13.76
3. No chemo during CRT	18	2.38
4. Insufficient data	3	0.4

Table A8 Patients who had RT prolongation >42 days and compliance with chemo week 5

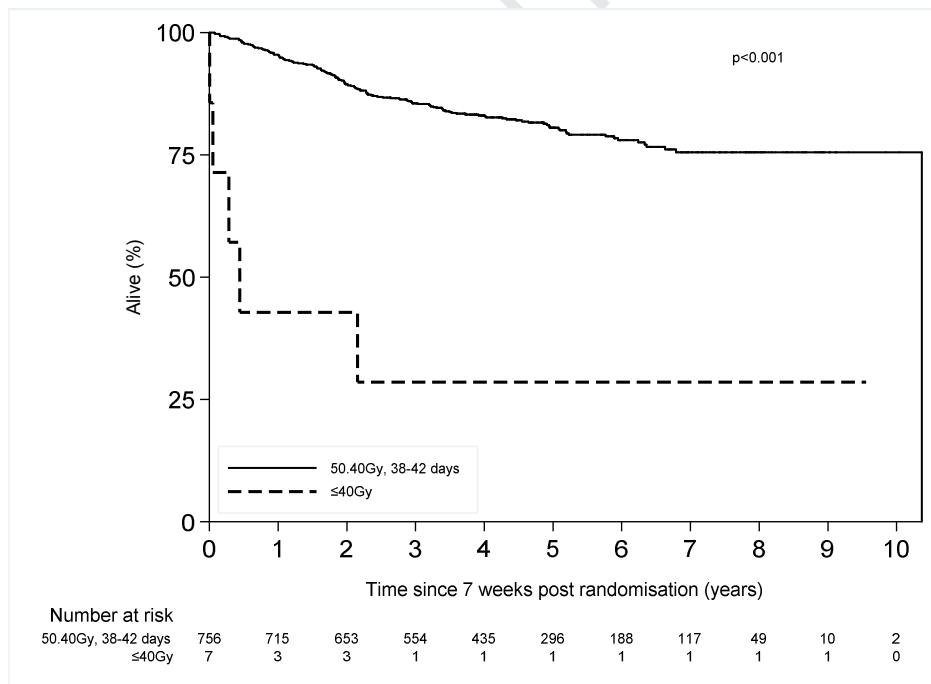
Compliance Chemo week 5	N	%
1. Completed week 5 as per protocol	52	55.32
2. Any delays, dose reduction or both	38	40.43
3. No chemo during CRT	4	4.26

Figure A1: Overall Survival by radiotherapy compliance subgroups

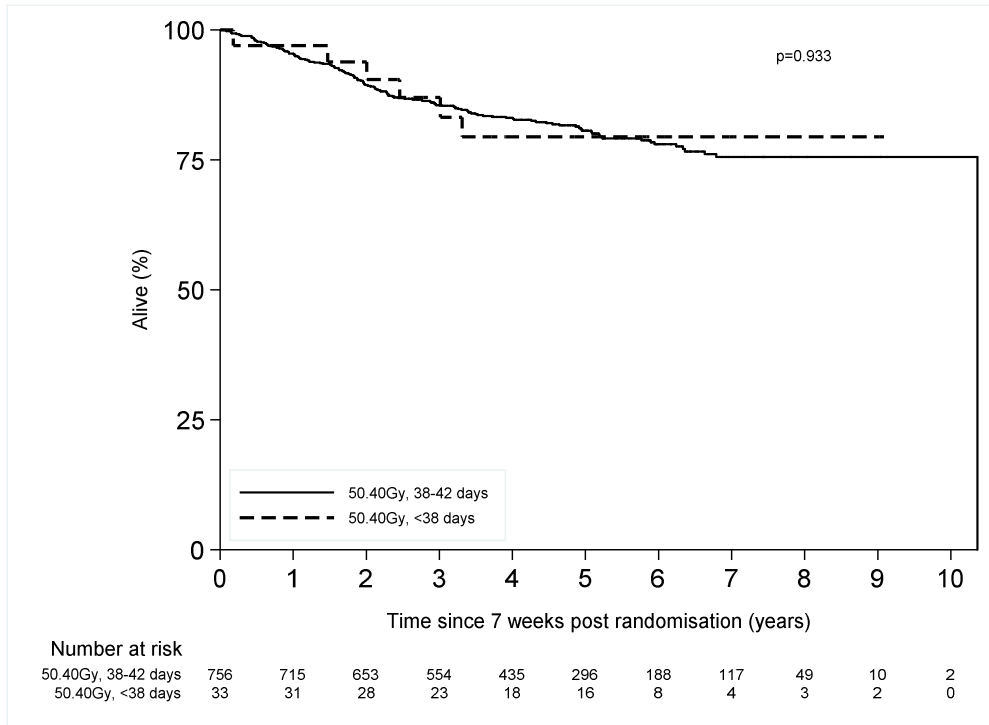
A



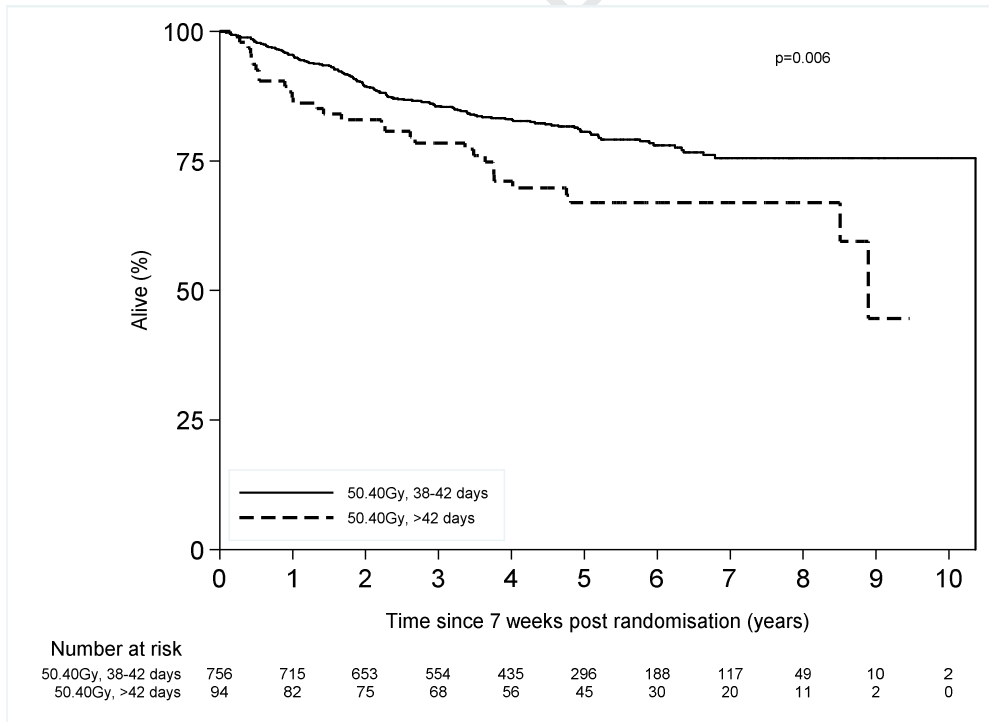
B



C



D



E

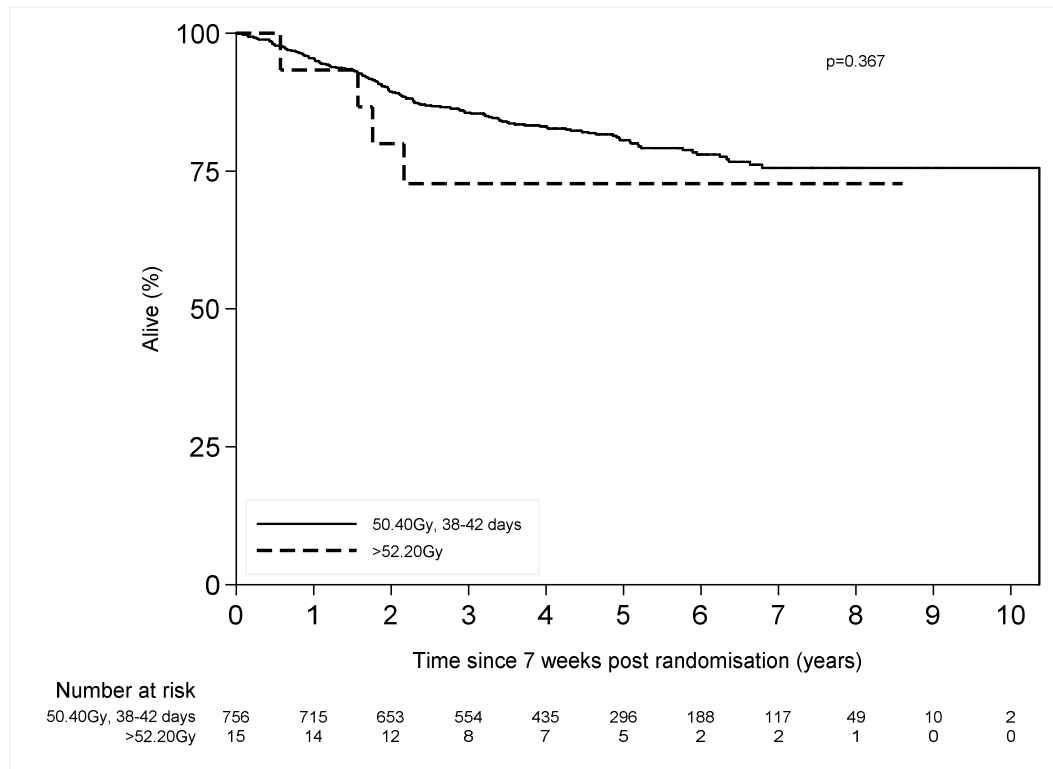
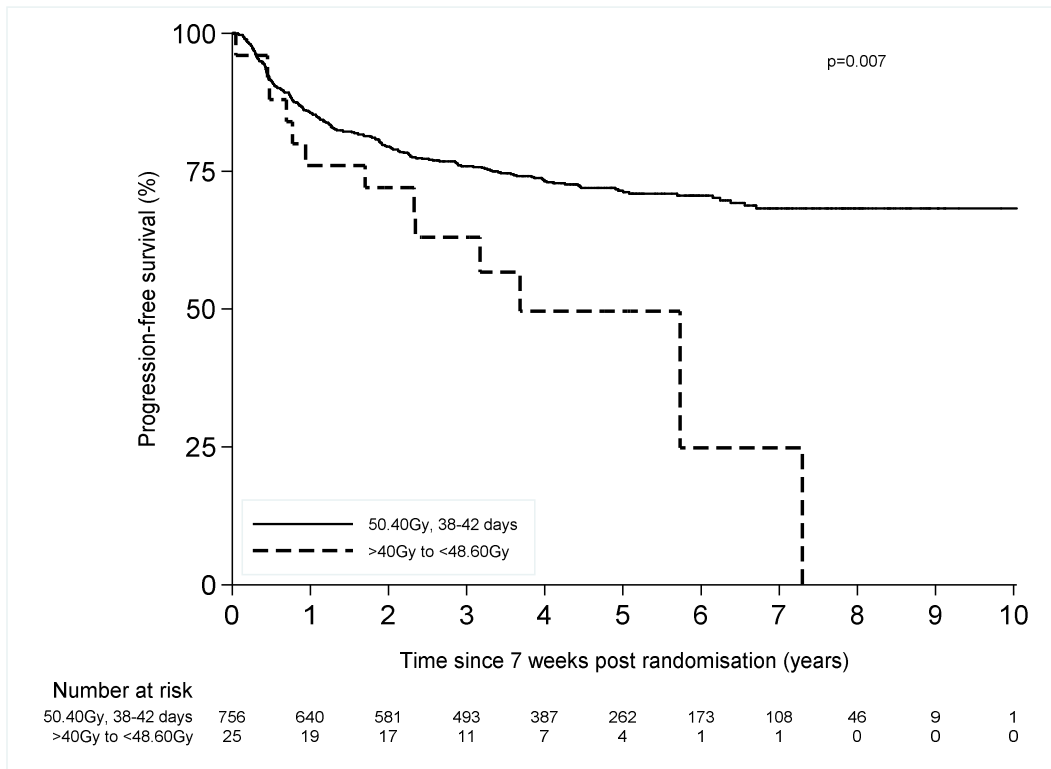
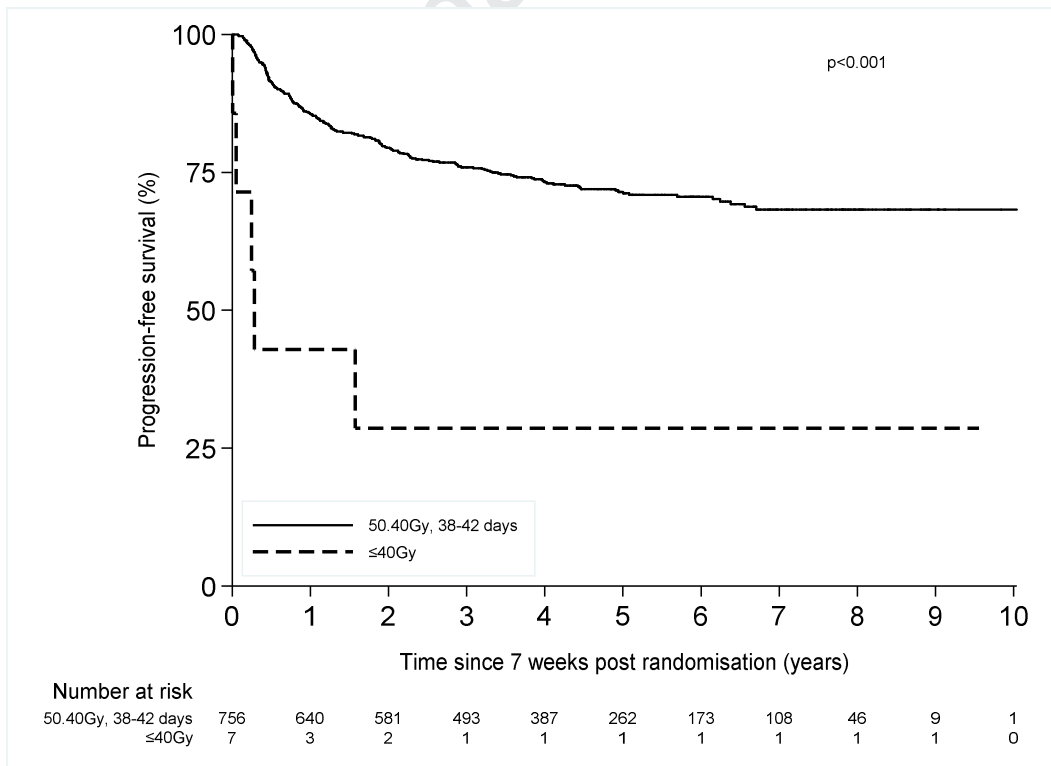


Figure A2: Progression-free Survival by radiotherapy compliance subgroups

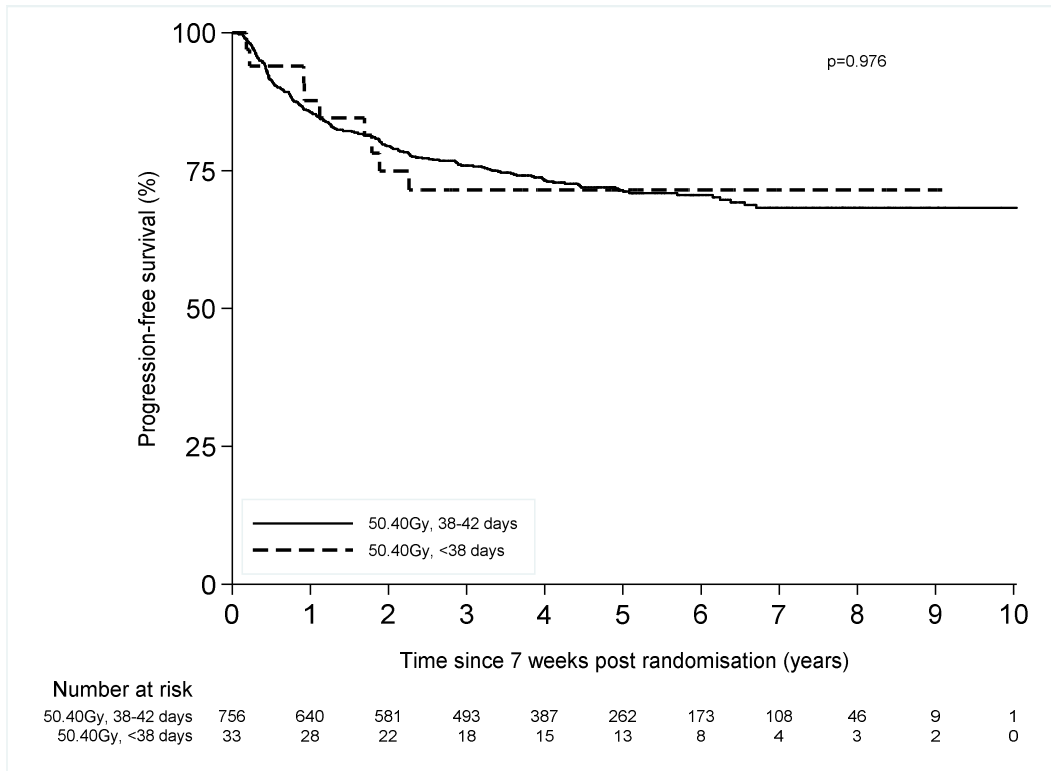
A



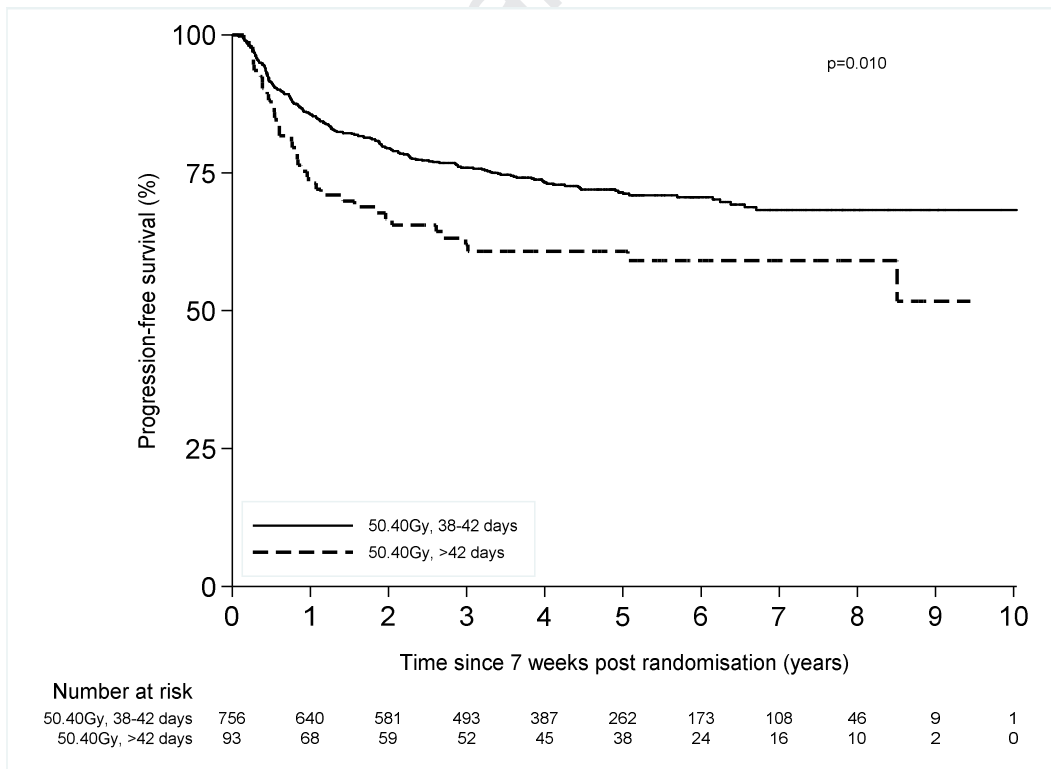
B



C



D



E

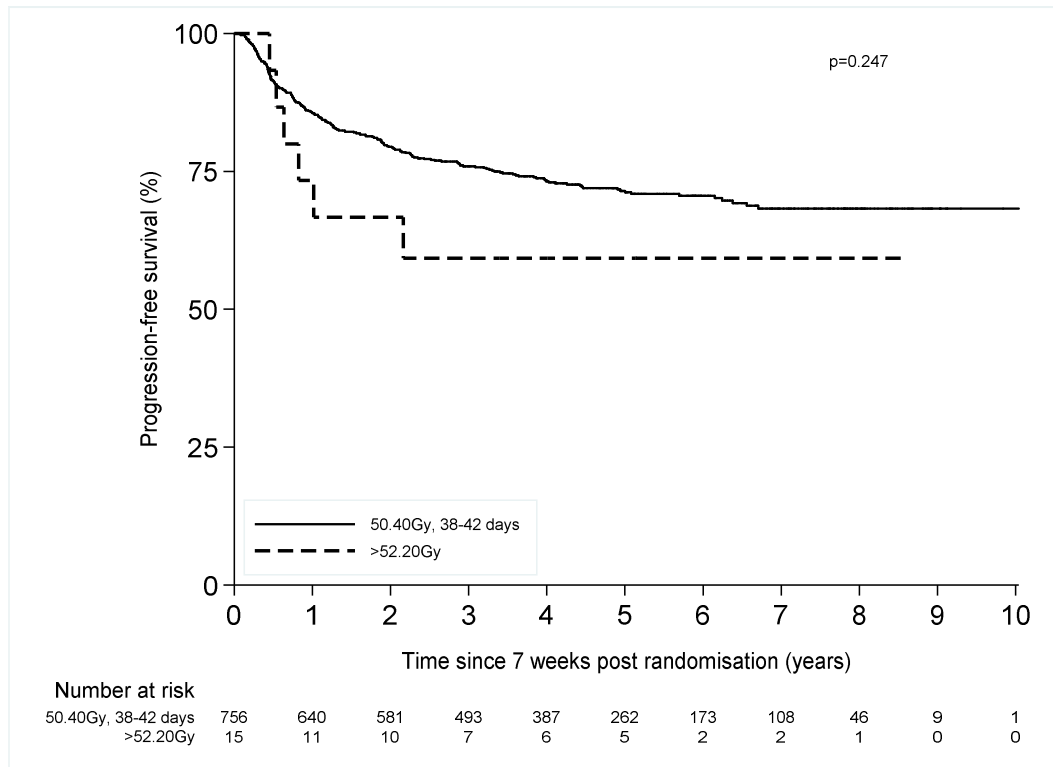
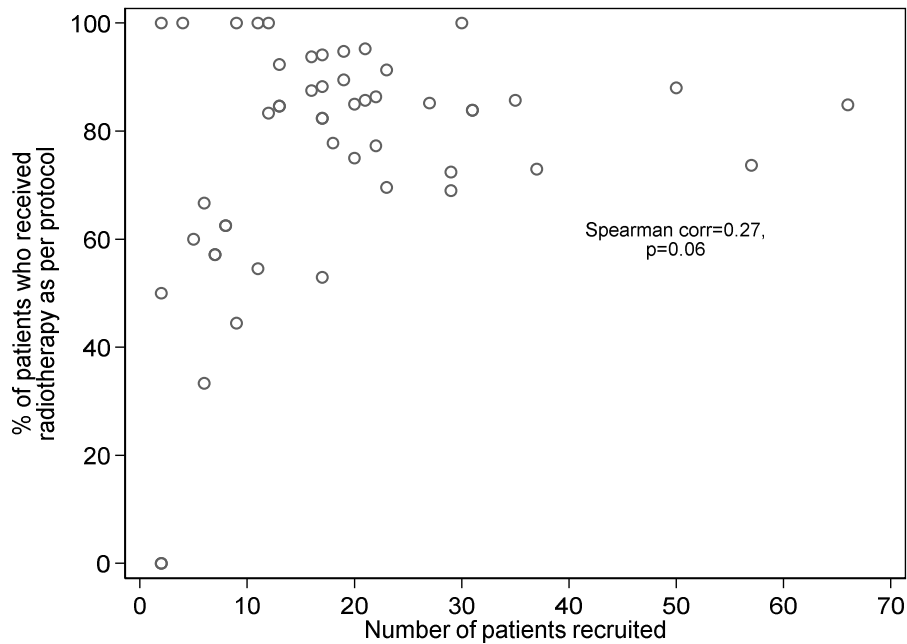


Figure A3

A: Correlation between number of patients recruited in each site and % of patients who received radiotherapy as per protocol in each site (sites that recruited >2 patients)



B: Correlation between number of patients recruited in each site and % of patients who received radiotherapy as per protocol in each site (sites that recruited >10 patients)

