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Induction chemotherapy followed by chemoradiation in locally advanced cervical cancer: Quality of life outcomes of the GCIG INTERLACE trial

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ABSTRACT

Aim: Induction chemotherapy (IC) added to chemoradiation (CRT) in locally advanced cervical cancer (LACC) improves survival at the expense of adverse events (AEs), 99 % with IC/CRT vs 95 % CRT alone, 59 % vs 48 % G3/4 AEs. We investigated the impact of this on quality of life (QoL).

Methods: 500 women with FIGO 2008 stage IB1 node positive, IB2, II, IIIB and IVA cervical carcinoma were randomised to CRT alone or IC (6 weeks carboplatin AUC2 paclitaxel 80mg/m^2) followed by CRT. QoL questionnaires (EORTC QLQ-C30 v3, QLQ-CX24) were completed at baseline, D1 week 4 IC, D1 CRT, D1 week 3 CRT, 4 weeks post CRT and all follow up visits. Mixed modelling for repeated measures was used to compare the groups during trial treatment to 2 years follow up (adjusting for baseline).

Results: QoL (global health status, physical and social functioning) slightly worsened during IC and symptom experience slightly improved. Emotional functioning improved during IC.

Peripheral neuropathy was slightly worse with IC/CRT. Fatigue and nausea/vomiting worsened from baseline to week 4 IC whilst pain and diarrhoea improved, consistent with reported AEs. Over the whole period, mean differences for these symptoms between the treatment groups was small and not clinically significant and resolved by 12–18 months.

In all cases, mean score differences during trial treatment until 2 years post CRT showed only small differences (<5 units) not meeting the threshold for clinical relevance.

Conclusion: IC added to CRT does not adversely impact QoL compared to CRT, either during IC, during CRT or later.

1. Introduction

Cervical cancer remains the fourth most common cancer in women [1]. For patients with locally advanced cervical cancer (LACC) chemoradiotherapy (CRT) has been the standard of care for years [2–4]. The addition of induction chemotherapy (IC) with weekly carboplatin and paclitaxel has been shown to significantly reduce risk of progression and death. This is however, as expected, at the cost of an 11 % increase in risk of G3/4 adverse events [5] and an increase in grade1/2 neuropathy (54 % vs 24 %), grade 1/2 alopecia (58 % vs 10 %) and fatigue, dyspnoea, and constipation. It is therefore important to assess the impact on quality of life (QoL) particularly in view of the survival advantage. The importance of QoL when considering cancer treatments value has also been emphasised by the European Society of Medical Oncology [6],

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American Society of Clinical Oncology [7] and US Food and Drug Administration [8].

In general, QoL after CRT is reported to be good [9] with physical and emotional functioning impaired at baseline and improving with treatment [10–12]. Negative effects however are seen after treatment with regards to sexual functioning and body image [9,10,12–14]. Most studies have reviewed QoL after CRT at 3–12 months from baseline with little data during CRT itself. In addition to treatment, patient-related factors impact QoL. Younger women report better QoL [10] but improved QoL has been associated with a higher level of education [10] as well as a lack of formal education [15]. With the exception of one phase 2 trial demonstrating no significant impact on QoL [16], previous studies investigating IC prior to CRT have not reported detailed QoL outcomes [17–20]. This substudy explores the impact of IC on QoL for patients treated within the INTERLACE trial.

2. Materials and methods

INTERLACE [5], was a phase III multicentre trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer (supplementary Figure 1) assessing the efficacy of IC (6 cycles of weekly carboplatin AUC2 and paclitaxel 80mg/m [2]) given prior to CRT versus CRT alone. Primary endpoints were progression-free and overall survival. Secondary endpoints were adverse events, pattern of first relapse, time to first relapse and health-related QoL. The trial was designed by the Trial Management Group with oversight by a Trial Steering Committee and an Independent Data Monitoring Committee. The trial adhered to the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulatory requirements including all local ethics approvals. All patients provided written informed consent before enrolment.

Eligible patients were women with stage IB1 node positive, IB2, IIA/B, IIIB or IVA disease (International Federation of Gynecology and Obstetrics (FIGO) staging system, 2009); squamous, adenocarcinoma or adenosquamous histology; fit for radical treatment and with no positive lymph nodes above the aortic bifurcation. Positive lymph nodes were defined as either histologically positive or PET positive, or $\geq$ 15 mm on CT or MRI. Key exclusion criteria were FIGO 2009 IIIA disease and presence of para-aortic nodes. Patients were randomised 1:1 to receive IC with 6 cycles of weekly carboplatin AUC2 and paclitaxel 80mg/m^2 immediately followed by CRT (IC/CRT) or CRT alone. In both groups, CRT comprised external beam radiation therapy (EBRT) with weekly cisplatin 40mg/m^2 for 5 weeks and brachytherapy. The EBRT dose was 40–50.4 Gy delivered in 20–28 fractions to a planned pelvic volume using 3DCRT in 59 % and IMRT in 41 %.

Brachytherapy was delivered using a 2D or 3D approach with full 3D image-guided adaptive brachytherapy (IGABT) in 30 %. The median total 2 Gy equivalent dose (EQD2) from combined EBRT and brachytherapy was 79.4 Gy and for patients treated with IGABT 87 Gy. Median overall radiation treatment time (OTT) was 45 days in both groups with 96 % competing radiotherapy in $\leq$ 56 days. In the IC/CRT group, 84 % (211/250) completed 6 weeks of IC and 92 % (230/250) completed 5 weeks. The median interval from IC completion to CRT start was 7 days [5–54 days]; with an interval of $\geq$ 15 days among 4.6 % (11/242). Regarding cisplatin, 85 % (212/250) for IC/CRT and 90 % (224/250) for CRT alone completed $\geq$ 4 cycles, with 68 % (169/250) and 79 % (197/250), respectively, completing 5 cycles.

QoL assessment was performed using the European Organisation of Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30 and the cervical cancer module QLQ-CX24. Both questionnaires were completed at baseline, day 1 of week 4 IC where applicable, day 1 of CRT, day 1 of week 3 CRT, 4 weeks post CRT and all follow up visits (3 months post CRT then 3 monthly for 2 years then 6 monthly to 5 years) (supplementary figure 2). No questionnaire was specifically done at the time of brachytherapy. Patients received questionnaires prior to their consultation or treatment appointment and were invited to answer the questions according to how they felt.

The QLQ-C30 comprises 30 questions covering five functional scales, three symptom scales, six single items and a global health status score [21]. The QLQ-CX24 includes 24 questions assessing two function scales (sexual activity and sexual enjoyment) and seven symptom scales (symptom experience, lymphoedema, peripheral neuropathy, menopause symptoms, sexual worry, body image, and vaginal/sexual functioning symptoms) [22]. A high functioning score is good indicating high functioning and high symptom scores are bad indicating a higher symptom burden.

Statistical analyses were performed on the intention-to-treat population. Questionnaire completion rates were calculated for QLQ-C30 and QLQ-CX24 at each assessment timepoint and by treatment group. These show the actual number of completed forms divided by the expected number, which includes those alive/not withdrawn at that time point.

The mean QoL scores were summarised at baseline and week 3 CRT for both groups with changes from baseline summarised at week 4 IC for the IC/CRT group. A mixed model for repeated measures was used to evaluate the treatment impact during trial treatment up to 2-years follow up and adjusting for baseline. An interaction between treatment group and time was tested using a likelihood-ratio test and included, where appropriate, in the final model. The model included a random intercept and slope with an unstructured covariance matrix. Mean scores difference was presented with the corresponding 99 % confidence interval and p-value. Clinical interpretation was as per published evidence-based EORTC guidelines [23] which define “trivial”, “small”, “medium” and “large” mean differences and effect sizes for each of the key domains, for example global QoL “trivial” mean difference is 0–4, “small” is 4–10, “medium” is 10–15 and “large is$>$ 15.

Comparisons were made at specific timepoints to account for the longer treatment duration with IC. Change from baseline was compared between treatment groups using linear regression models at 5 months after baseline $\pm$ 1 month (comparing first assessment following treatment completion), and 12 months after baseline $\pm$ 1 month (comparing follow-up). At each timepoint, mean change from baseline and standard deviation were reported and mean change difference with the corresponding 99 % CI and p-value.

Subgroup analyses for global health status, physical functioning and symptom experience were provided for age ($\leq$35, 36–65, and 66 +) and type of radiotherapy delivered (intensity modulated radiotherapy (IMRT) and 3D conformal radiotherapy (3DCRT)). The mean scores difference was presented for each level with the corresponding 99 % confidence interval. There was a p-value from a test for interaction between each factor and treatment allocation.

3. Results

Between November 8 2012 and November 17 2022, 500 patients were recruited; 76.0 % from the United Kingdon, and 20.0 % from Mexico. Median age was 46 years, [range 24–78]. 87.0 % had a performance status of 0. All stages were represented with 70.8 % FIGO 2008 stage IIB and 43.0 % were node positive. Both groups were well balanced (Table 1). Treatment compliance was reported previously [5] and the distribution between the two groups analysed here is reported in supplementary table 1.

3.1. Compliance/data completeness

Out of the 500 enrolled patients, 481(96.2 %), 243 (97.2 %) IC/CRT and 238 (95.2 %) CRT alone, completed at least one questionnaire; 409 (81.8 %) patients (220 in the IC/CRT arm and 189 in the CRT alone) and 405 (81.0 %) patients (218 in the IC/CRT arm and 187 in the CRT alone arm) were included in the QLQC30 analysis and QLQCX24 analysis respectively having completed a baseline form and at least one other timepoint. Baseline characteristics of those included and excluded from

Table 1
Baseline characteristics.

Characteristic	Induction chemo + CRT (N = 250)	CRT alone (N = 250)
Median age (range) – yr	46 (26–78)	46 (24–78)
ECOG status – no. (%)		
0	214 (85.6)	221 (88.4)
1	36 (14.4)	29 (11.6)
Country – no. (%)		
UK	190 (76.0)	190 (76.0)
Mexico	49 (19.6)	51 (20.4)
Italy	5 (2.0)	3 (1.2)
India	5 (2.0)	5 (2.0)
Brazil	1 (0.4)	1 (0.4)
FIGO stage (2008) – no. (%)		
IB1	2 (0.8)	2 (0.8)
IB2	19 (7.6)	23 (9.2)
IIA	17 (6.8)	14 (5.6)
IIB	178 (71.2)	176 (70.4)
IIIB	26 (10.4)	30 (12.0)
IVA	8 (3.2)	5 (2.0)
Cell stage – no. (%)		
Non-squamous	44 (17.6)	45 (18.0)
Squamous	206 (82.4)	205 (82.0)
Nodal status – no. (%)		
Negative	144 (57.6)	141 (56.4)
Positive	106 (42.4)	109 (43.6)
Median longest tumor diameter (range) – cm	4.8 (1.3–13.5)	4.9 (1.8–12.8)

the QLQC30 analysis were summarised in supplementary table 2. No baseline form was completed for 64 (12.8 %) patients, and 12 (2.4 %) patients had completed the baseline form only (Figure 1).

Of those completing a baseline questionnaire, 387 (91.3 %) of patients analysed completed at least 5 questionnaires beyond baseline. This was balanced across the two groups. Of note, all patients analysed received treatment on trial as those who did not receive treatment did not complete questionnaires beyond baseline.

3.2. Quality of life measures during IC

During the IC treatment period, QoL became slightly worse with mean changes from baseline generally not showing clinically relevant effects (as per EORTC guidelines [23]) (Table 2). For physical functioning, role functioning, and social functioning the mean changes were trivial (-4 to −6) and for global health status the mean change was small (-5). Emotional functioning improved with a small mean score change (10). Regarding symptoms, pain improved with a small mean change (10) and fatigue increased a small amount (10) and nausea/vomiting and diarrhoea worsened with a medium mean change (9 and 13). Symptom experience, as per the cervical cancer specific module, improved with a trivial mean change (-5) and peripheral neuropathy (1) and lymphoedema (0.4) showed negligible changes.

3.3. Quality of life measure during CRT

All QoL measures (global health status, physical, role and social functioning) except emotional functioning worsened during CRT across both groups (Table 2). Emotional functioning improved in both treatment groups, but the improvement seen in the IC/CRT group during CRT compared to baseline (mean score change of +4, trivial change) was a reduction from during IC (mean score change of −6). Symptom scoring was very similar across both groups. Pain improved during CRT with mean score change of −8 from baseline in IC/CRT group versus −3 for CRT. All other symptoms worsened during CRT with fatigue, nausea, vomiting and diarrhoea exhibiting medium mean changes for both treatment groups. (Fig. 2)

3.4. Quality of life measures over whole treatment period up to 2 years follow up

Patients in the IC/CRT group experienced improved emotional functioning (p = 0.35), improved pain (p = 0.08) and improved

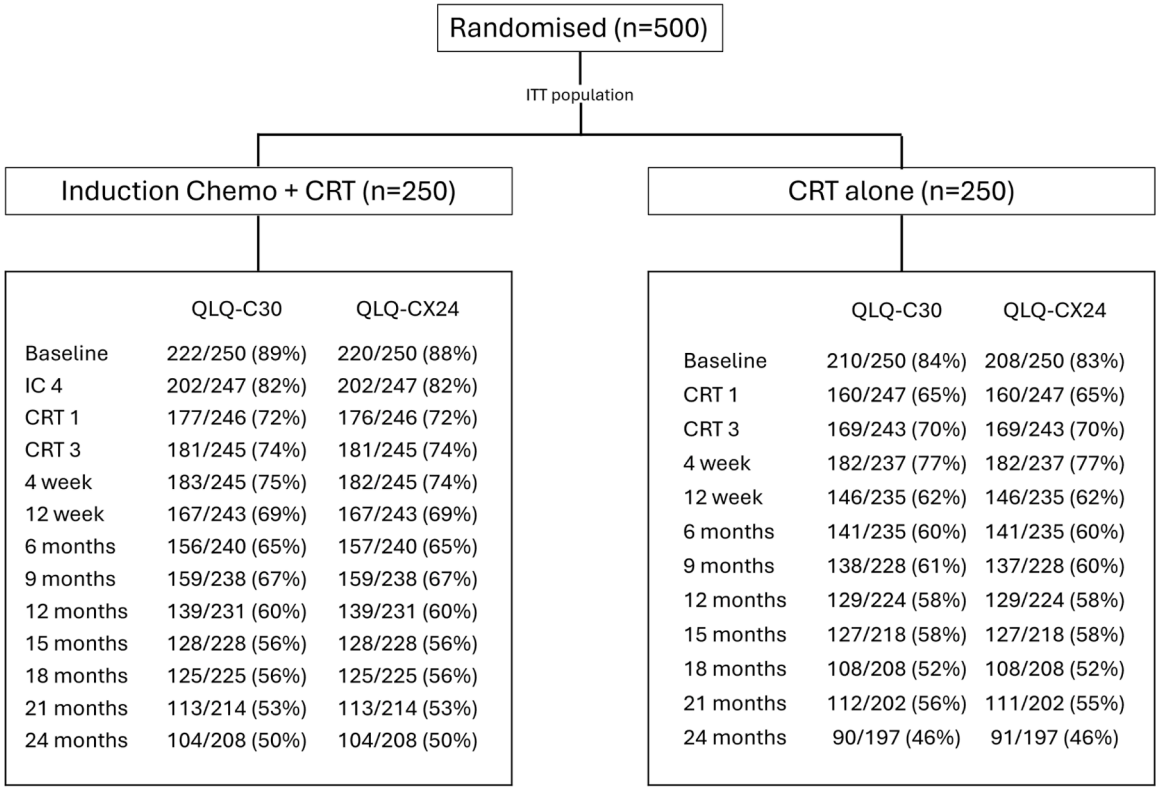

Fig. 1. CONSORT diagram for EORTC QLQ-C30 and EORTC QLQ-CX24 questionnaires.

Table 2
Mean QoL scores at baseline, changes to week 4 IC, mean score during CRT and mean difference during trial treatment up to 2 years follow up.

Domain	Mean score at baseline (SD)		Mean change in score from baseline to week 4 IC (SD)	Mean score at week 3 CRT (SD)		Mean score at 12-week follow up (SD)		From a repeated measures analysis during trial treatment to 2-years of follow-up and allowing for baseline	
	IC/CRT	CRT alone	IC/CRT	IC/CRT	CRT alone	IC/CRT	CRT alone	Difference in mean scores (99 % CI)	P-value
Global health status*	71 (21)	71 (22)	−5 (19)	55 (20)	62 (21)	75 (20)	76 (22)	−2.4 (−6.1–1.4)	0.10
Physical functioning*	89 (17)	90 (17)	−4 (17)	76 (21)	82 (21)	83 (21)	87 (19)	−2.0 (−5.4–1.4)	0.13
Emotional functioning*	73 (25)	69 (28)	10 (20)	77 (23)	79 (25)	81 (24)	77 (26)	1.5 (−2.7–5.7)	0.35
Role functioning*	84 (27)	82 (26)	−6 (27)	63 (31)	71 (30)	80 (28)	84 (26)	−3.4 (−8.5–1.7)	0.09
Social functioning*	83 (25)	82 (26)	−5 (25)	67 (30)	76 (29)	81 (27)	85 (23)	−4.0 (−8.8–0.7)	0.03
Cognitive functioning*	88 (19)	85 (23)	−1 (20)	80 (23)	83 (24)	86 (22)	85 (22)	−2.3 (−6.2–1.7)	0.15
Pain* *	29 (30)	27 (29)	−10 (28)	21 (26)	24 (27)	20 (28)	18 (25)	−3.1 (−7.7–1.4)	0.08
Fatigue* *	26 (26)	25 (26)	10 (22)	47 (27)	39 (28)	27 (27)	24 (28)	2.9 (−1.7–7.5)	0.10
Nausea/ vomiting* *	7 (15)	8 (15)	9 (21)	24 (23)	21 (21)	7 (15)	6 (16)	0.9 (−1.6–3.4)	0.34
Diarrhoea* *	6 (16)	7 (18)	13 (26)	39 (32)	41 (31)	12 (21)	17 (25)	−1.3 (−5.9–3.2)	0.45
Dyspnea* *	10 (22)	8 (18)	3 (22)	21 (26)	9 (17)	14 (24)	11 (20)	5.2 (1.0–9.4)	**0.001**
Insomnia* *	34 (34)	33 (33)	−2 (34)	32 (32)	29 (33)	29 (33)	27 (32)	−0.1 (−5.9–5.6)	0.95
Appetite loss* *	21 (28)	19 (28)	−6 (30)	27 (30)	26 (31)	14 (27)	12 (24)	0.1 (−4.3–4.5)	0.95
Constipation* *	18 (29)	16 (28)	0.4 (37)	11 (23)	17 (26)	8 (19)	8 (21)	−1.4 (−5.2–2.4)	0.35
Financial difficulties* *	21 (32)	23 (34)	1 (32)	24 (33)	19 (30)	17 (29)	17 (29)	3.6 (−1.62–8.8)	0.08
Cervical cancer specific:									
Symptom experience scale* *	18 (15)	20 (16)	−5 (13)	14 (13)	17 (14)	10 (12)	11 (12)	−2.6 (−4.9 to −0.2)	0.01
Body image scale* *	19 (27)	19 (27)	4 (24)	30 (34)	20 (25)	20 (28)	20 (27)	3.8 (−1.3–9.0)	0.05
Peripheral Neuropathy* *	9 (21)	9 (22)	1 (26)	18 (26)	9 (21)	17 (28)	10 (20)	4.7 (0.7–8.7)	**0.002**
Lymphoedema* *	3 (13)	3 (13)	0.4 (16)	5 (15)	3 (11)	5 (19)	5 (17)	0.9 (−2.0–3.9)	0.41
Menopausal symptoms* *	18 (30)	18 (27)	2 (30)	24 (32)	22 (31)	28 (37)	29 (36)	−0.9 (−7.0–5.2)	0.69
Sexual worry* *	30 (39)	28 (38)	−12 (35)	24 (36)	25 (35)	27 (36)	27 (34)	−5.5 (−11.7–0.7)	0.02
Sexual activity*	7 (18)	9 (21)	−2 (20)	3 (10)	4 (14)	8 (18)	10 (19)	−1.6 (−5.0, 1.8)	0.23
Sexual enjoyment*	60 (30)	67 (34)	−8 (41)	61 (28)	69 (40)	62 (27)	56 (28)	5.1 (−11.0, 21.2)	0.40

*negative indicates worse symptoms * *negative indicates better symptoms

diarrhoea ($p = 0.45$) but all other scores were in favour of the CRT group. However, using the guidelines for interpreting EORTC- QLQ-C30 [23] the magnitude of mean differences for all domains were small (Table 2).

For all measures except peripheral neuropathy, scores returned either to baseline/better than baseline or to overlapping between the two groups by 12 months post treatment (Fig. 2). Global health status was improved from baseline for both groups by 12 weeks post treatment, nausea/vomiting by 4 weeks, and fatigue by 12 weeks. Physical functioning was reduced following all treatments, more so with IC/CRT but scores were overlapping by 12 months. Role functioning and social functioning both returned to close to baseline by 12 weeks for both groups and overlapping by 12 months. Emotional functioning and symptom experience both improved with both treatments, overlapping by 12 months. Of note, symptom experience improved earlier with IC/CRT. Pain also improved with both treatments, but earlier and more pronounced in the IC/CRT group, overlapping by 4 weeks. Diarrhoea, peripheral neuropathy and lymphoedema did not fully return to baseline for both groups but diarrhoea (medium difference from baseline) and lymphoedema (trivial difference) were overlapping by 15 months and 12 weeks, respectively. Peripheral neuropathy was the longest lasting with a small (4−10) increase for both treatment groups from 6 months onwards, overlapping by 15 months.

Between 4 and 6 months from baseline (after treatment had ended in both groups), role functioning, fatigue, and peripheral neuropathy were significantly worse in the IC/CRT group (small difference) compared with the CRT alone group, but 11–13 months from baseline, there was no longer a difference. No other domains showed a significant difference at these timepoints (Supplementary table 3).

3.5. *Sexual functioning*

At baseline, 14.8 % of patients reported being sexually active, reducing to approximately 10 % during treatment and by 6 months after treatment increased to above 20 %. Only 53 patients could be analysed regarding sexual/vaginal functioning (Supplementary Figure 3 and

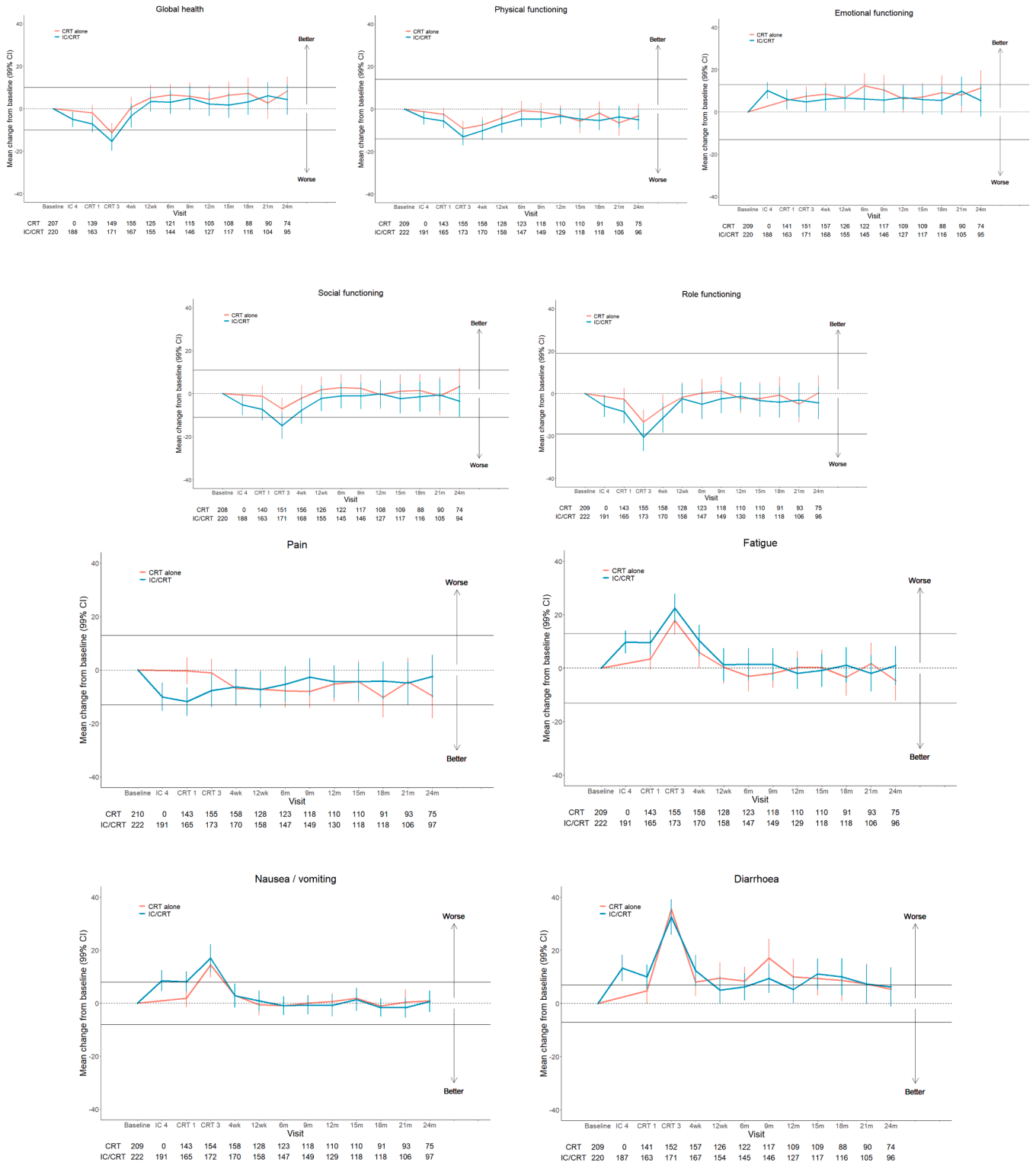

Fig. 2. A: QLQC30 global health status and functional scales over time. Solid lines represent the region of "trivial" or "small" mean difference according to EORTC guidelines [23] for interpreting these values. Any values outside of these solid lines indicate a "medium" or "large" mean difference. **B**: QLQC30 symptom scales and items over time. Solid lines represent the region of "trivial" or "small" mean difference according to EORTC [23] guidelines for interpreting these values. Any values outside of these solid lines indicate a "medium" or "large" mean difference. **C**: QLQCX24 symptom scales and items over time. Solid lines represent the region of "trivial" or "small" mean difference according to EORTC guidelines [23] for interpreting these values. Any values outside of these solid lines indicate a "medium" or "large" mean difference.

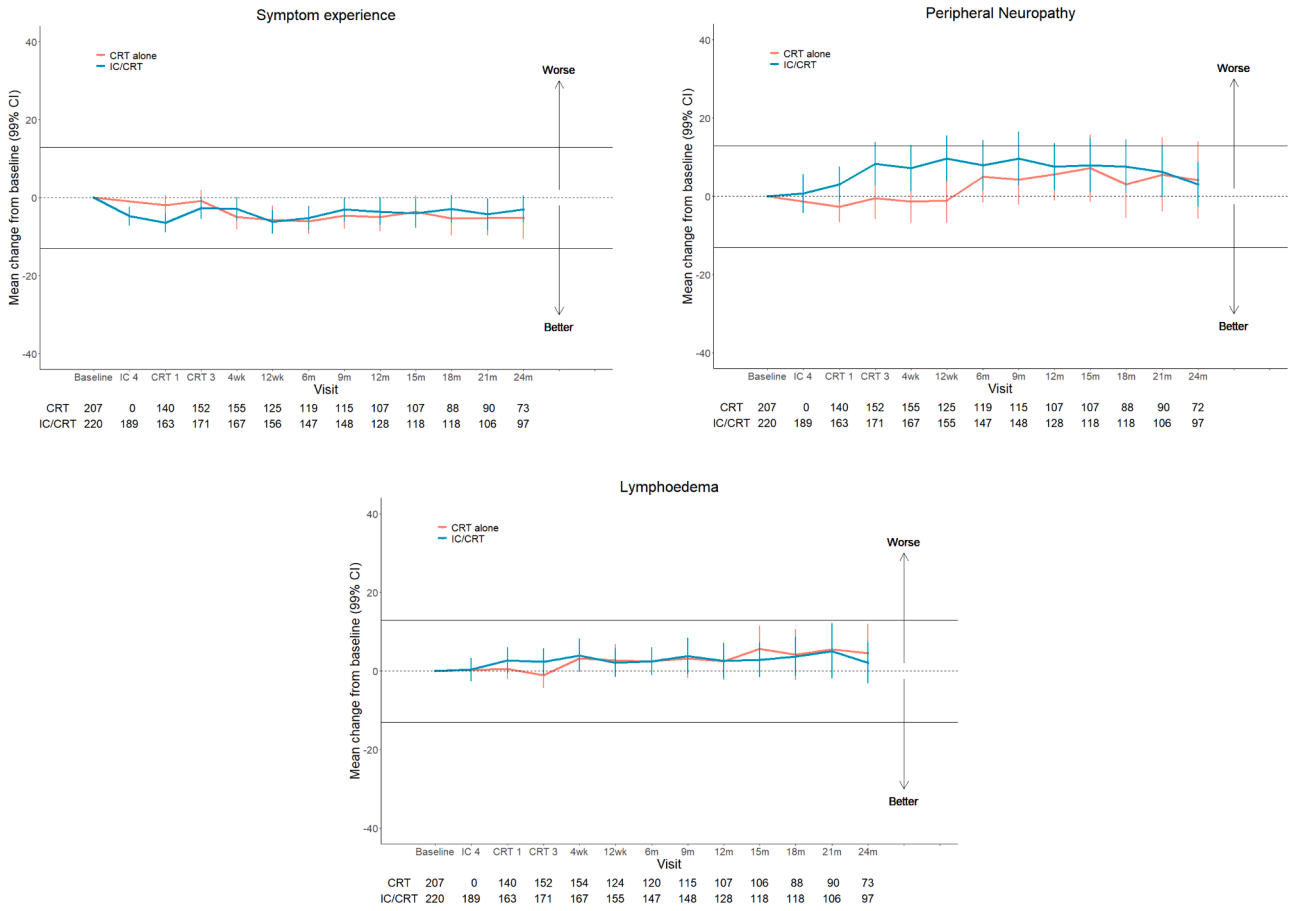

Fig. 2. (*continued*).

Table 4). The trend showed an increase in vaginal symptoms after treatment completion, suggesting a reduction in sexual QoL, with no difference between the treatment groups. Despite these increased vaginal symptoms, patients still reported more sexual activity.

3.6. Subgroup analyses

No statistical differences were seen (supplementary table 5) in global health status, physical functioning and symptom experience between IC/CRT and CRT groups across the age groups. This was despite the medium difference, as defined by EORTC guidance [23], in mean scores for the oldest age group (66 +) for global health status. Similarly, for radiotherapy, the QoL differences were similar between treatment groups for IMRT and 3DCRT separately.

4. Discussion

This data is the first to document the significant impact of CRT for LACC on QoL during and after the active treatment phase. The addition of IC does reduce QoL further than CRT alone but not to a clinically relevant level as per EORTC definitions and any differences resolved by approximately 1 year from baseline. Interestingly, symptom scales during CRT for both groups are similar despite symptoms reported during the IC phase. IC led to an earlier improvement in pain, despite no supportive management differences, and possible emotional functioning compared to CRT alone. Importantly, for both groups, changes return to baseline for global health status and some key symptoms (fatigue, nausea/vomiting) by 4–12 weeks after treatment. QoL compliance was reasonable but did drop over time. However, the largest differences were in the first 12 months and compliance was equal across both groups.

After the initial treatment phase our results are in line with the limited published literature [12,16,24]. The anticipated improvements in functional scales and symptom experience after CRT are clearly demonstrated in both treatment groups within the INTERLACE trial. However, as indicated by the EMBRACE group [12] these improvements are potentially due to baseline scores being lower than the age matched female population due to disease burden. The only other IC trial to report QoL outcomes is the phase II CIRCE trial [16]. Other trials, such as the Brazilian Phase II trial, include QoL as a secondary endpoint but these data have not been published [18]. The CIRCE study randomised 107 patients to CRT, or 3 cycles of cisplatin and gemcitabine followed by CRT [16]. QoL questionnaires (EORTC QLQ-C30 and QLQ-CX24) were given at baseline and 0, 3-, 6-, 9- and 12-months post treatment. Most scales improved over time in both groups with worsening neuropathy and menopause symptoms in both groups. At 12 months, IC led to improved body image, sexual activity and menopause symptoms, but this cohort was younger, and the CRT alone group reported more lymphoedema and sexual worry. Among the INTERLACE patients no difference in the impact of IC on QoL was seen according to age (>46 years old versus ≤46). However, QoL compliance rates within CIRCE were low in the IC group at 40 % compared with 69 % in the CRT group. Lower compliance could indicate poorer QoL as IC in that study had a detrimental impact on outcome. QoL compliance rates within the INTERLACE trial were higher than in CIRCE with analysis of more than 80 % of patients randomised, more than 90 % of which completed 5 or more questionnaires beyond baseline. Our main findings of non-significant differences in QoL were also in line with the CIRCE trial results. Considering peripheral neuropathy, our results suggest an increase over the first 6 months then a stabilisation/slow reduction in both arms which is different to CIRCE but may be representative of our longer

analysis duration of 2 years rather than 12 months. Our results are in line with the published toxicity data [5] including the slight increase in diarrhoea seen in the CRT group.

The positive impact of IC on relapse rates could impact QoL. However, analysis excluding relapsed patients showed the same patterns and degree of differences reported.

Due to the small proportion of sexually active patients at baseline, very few patients could be included in the sexual functioning analysis. Despite this, more patients were sexually active after treatment than at baseline in line with previous reports after CRT [12,16].

Within INTERLACE, the impact of IC on QoL was similar regardless of whether external beam radiation was delivered using IMRT or 3DCRT. Within the CIRCE trial patients were only treated with 3DCRT [16] whereas EMBRACE patients were treated with both modalities and our results are in line with those reportes [12]. Any potential impact of radiotherapy technique on QoL should not affect the overall results as the techniques were balanced across both groups. However, it should be acknowledged that IMRT reduces toxicity such as diarrhoea which can reduce the negative impact of radiotherapy on QoL.

The data presented here is the first to document QoL at timepoints during and after CRT. A high proportion of patients completed questionnaires at multiple (>5) timepoints. However, it must be acknowledged that QoL and symptoms vary dynamically and quickly throughout treatment and the timepoints recorded are limited and do not include a timepoint around brachytherapy. There is also limited long term follow up although changes seem to resolve within the timeframe reported. In addition, out of the whole INTERLACE population, double the proportion of patients were excluded due to missing data in the CRT group which could impact our results. However, if this was due to poorer QoL leading to poorer compliance with questionnaires then any true QoL differences may be less than what we have reported.

Even considering these limitations, this data aids understanding of how to manage patients on CRT or IC/CRT. Along with the previously published toxicity data [5] it is clear that CRT alone causes significant toxicity and impaired QoL with good resolution by 12 weeks post treatment. The addition of IC increases this toxicity with a predominance of haematological toxicity [5] which does not impact on QoL as much as non-haematological toxicity. IC causes neuropathy which is seen here to impact patients and therefore close monitoring and management of this is important. This data also supports more intensive symptom and psychological support during the treatment period and first 12 weeks afterwards with reassurance for patients regarding the timeframe in which to expect recovery.

In conclusion, IC before CRT is not associated with a significant detriment in QoL compared to CRT alone despite the increase in toxicity reported. The small differences seen resolved by 12–18 months after treatment. This data supports the use of IC immediately prior to CRT for patients with LACC.

CRediT authorship contribution statement

Anne-Marie Hacker: Writing – review & editing. **Gemma Eminowicz:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Madhavi Adusumalli:** Writing – review & editing. **Angela Chan:** Writing – review & editing. **Anjana Anand:** Writing – review & editing. **Jenny Forrest:** Writing – review & editing. **Miguel Panades:** Writing – review & editing, Conceptualization. **Tony Mathew:** Writing – review & editing. **Mary McCormack:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Dolores Gallardo:** Conceptualization. **Christopher Kent:** Writing – review & editing. **Allan Hackshaw:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Jonathan Ledermann:** Writing – review & editing, Funding acquisition, Conceptualization. **Simran Vaja:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115375.

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