GALA-5: An Evaluation of the Tolerability and Feasibility of combining 5-Amino-Levulinic Acid (5-ALA) with Carmustine Wafers (Gliadel) in the Surgical Management of Primary Glioblastoma.

This is a single arm feasibility study to evaluate the safety and tolerability of combining 2 technologies, 5-ALA resection and Gliadel insertion, in the surgical management of patients with GBM and subsequent standard therapy. Having less than 85% of patients who complete chemoradiotherapy would not be acceptable, and our target is at least 95%. Using an exact sample size calculation with one-sided test of statistical significance of 5% and 80% power, 60 patients need to be given 5-ALA and Gliadel wafers.

The primary objective was to establish that the combined use of 5-ALA and Carmustine wafers is safe and does not compromise a patient from receiving or completing standard chemoRT: (i) proportion of 5-ALA resected patients who received Carmustine wafer implants (i.e. procedure compliance); (ii) proportion of patients with a new post-operative deficit or surgical complication (i.e. post-operative complication rate); (iii) number of patients with chemoRT delay due to surgical complications; (iv) number of patients failing to start chemoRT due to surgical complications; (v) number of patients failing to complete chemoRT without interruption; (vi) proportion of patients with a lower WHO performance status at first post-operative clinic visit.

The secondary objective was to gather preliminary evidence that the combination has the potential to improve clinical outcome: (i) progression-free survival; (ii) overall survival; (iii) patient-reported quality of life.

Survival curves are presented using the Kaplan-Meier method, patients were censored using the date they were last seen if no event had occurred. Analyses were carried out on all eligible patients unless otherwise stated, and generated using SAS software version 9.3 (SAS Institute, Cary NC).

RESULTS

PATIENTS

Seventy-two patients were recruited from 8 UK sites between July 2011 and May 2013; 64 patients (64/72, 88.9%) received Carmustine wafer implants and 59 patients (59/72, 81.9%) were found to be eligible after surgery (Figure 1). Eight patients (8/72, 11.1%) did not receive Carmustine wafer implants due to GBM not diagnosed peri-operatively (n=4), ventricular breach (n=3), and peri-operative deterioration (n=1); a further 5 patients were ineligible due to GBM not diagnosed post-operatively (n=4), and simultaneous diagnosis of unrelated cutaneous sebaceous carcinoma (n=1). Patient characteristics of all eligible patients are shown in Table 1.

TREATMENT COMPLIANCE & SAFETY

There were 9 surgical complications in 7 eligible patients (7/59, 11.9%): wound infections were reported in 5 patients (5/59, 8.5%) and cerebrospinal fluid leakage in 4 patients (4/59, 6.8%). Forty-six patients (46/59, 78.0%) received chemoRT; two patients (2/59, 3.4%) were not able to begin chemoRT due to surgical complications, one wound infection and one cerebrospinal fluid leakage.

Four patients (4/46, 8.7%) were not able to begin chemoRT within 6 weeks of surgery due to surgical complications, three wound infections and one cerebrospinal fluid leakage. Concomitant chemoRT was interrupted in 18 patients (18/46, 39.1%); 12 patients (12/46, 26.1%) chemotherapy was interrupted due to toxicity and 13 patients (13/46, 28.3%) radiotherapy was interrupted due to logistical reasons (n=9) and toxicity (n=4). Forty-three patients (43/46, 93.5%) continued to adjuvant chemotherapy, one patient progressed before and two patients were lost to follow-up.

Adjuvant chemotherapy was completed without interruption in 24 patients (24/43, 55.8%), 19 patients (19/43, 44.2%) were unable to complete adjuvant chemotherapy without interruption due to: toxicity (n=11), disease progression (n=5), administrative failure (n=2), and unknown (n=1).

Thirty-four patients (34/59, 57.6%) have reported 79 adverse events of grade 3 or higher, the most common of which were muscle weakness and seizure which were each reported in 5 patients (5/59, 8.5%). None of these adverse events were likely related to 5-ALA, whilst 7 were at least 'possibly' related to the Carmustine wafers: wound infection (n=2), sepsis (n=2), cerebrospinal fluid leakage (n=1), edema cerebral (n=1), seizure (n=1). Reported grade 3 or higher adverse events are shown in Table 2.

EFFICACY

Thirty-one patients (31/57, 54.4%) were in the same or improved WHO performance status category post-surgery as at baseline, 26 patients (26/57, 45.6%) had a lower WHO performance status post-surgery of which 6 patients (6/57, 10.5%) decreased by more than one category. Two eligible patients were missing this post-surgery data.

After a median follow-up of 22.0 months, 4 patients (4/59, 6.8%) are alive without progression, 14 patients (14/59, 23.7%) are alive having progressed and 41 patients (41/59, 69.5%) have died. Causes of death were disease/progression (n=37), combination of disease and treatment related (n=2), surgical complications and stroke (n=1), and unknown as withdrew consent (n=1). Median progression-free survival was 9.5 months (95% CI: 7.9 to 9.8; Figure 2A) and median overall survival was 15.0 months (95% CI: 11.9 to 17.3, Figure 2B).

OTHER ENDPOINTS

There was a decrease in median Mini Mental Score Examination between registration and post-adjuvant chemotherapy assessment (28.0 to 26.0 points; Table 3A) and an increase in median NIH Stroke Score (0.0 to 0.5 points; Table 3B). There was no marked change in EORTC quality of life functional domains over time (p-values >.05), except for physical functioning which decreased between registration and post-adjuvant chemotherapy assessment (100.0 to 73.3 points, p<.001; Table 3C).

Figure 1: CONSORT flow diagram – all patients

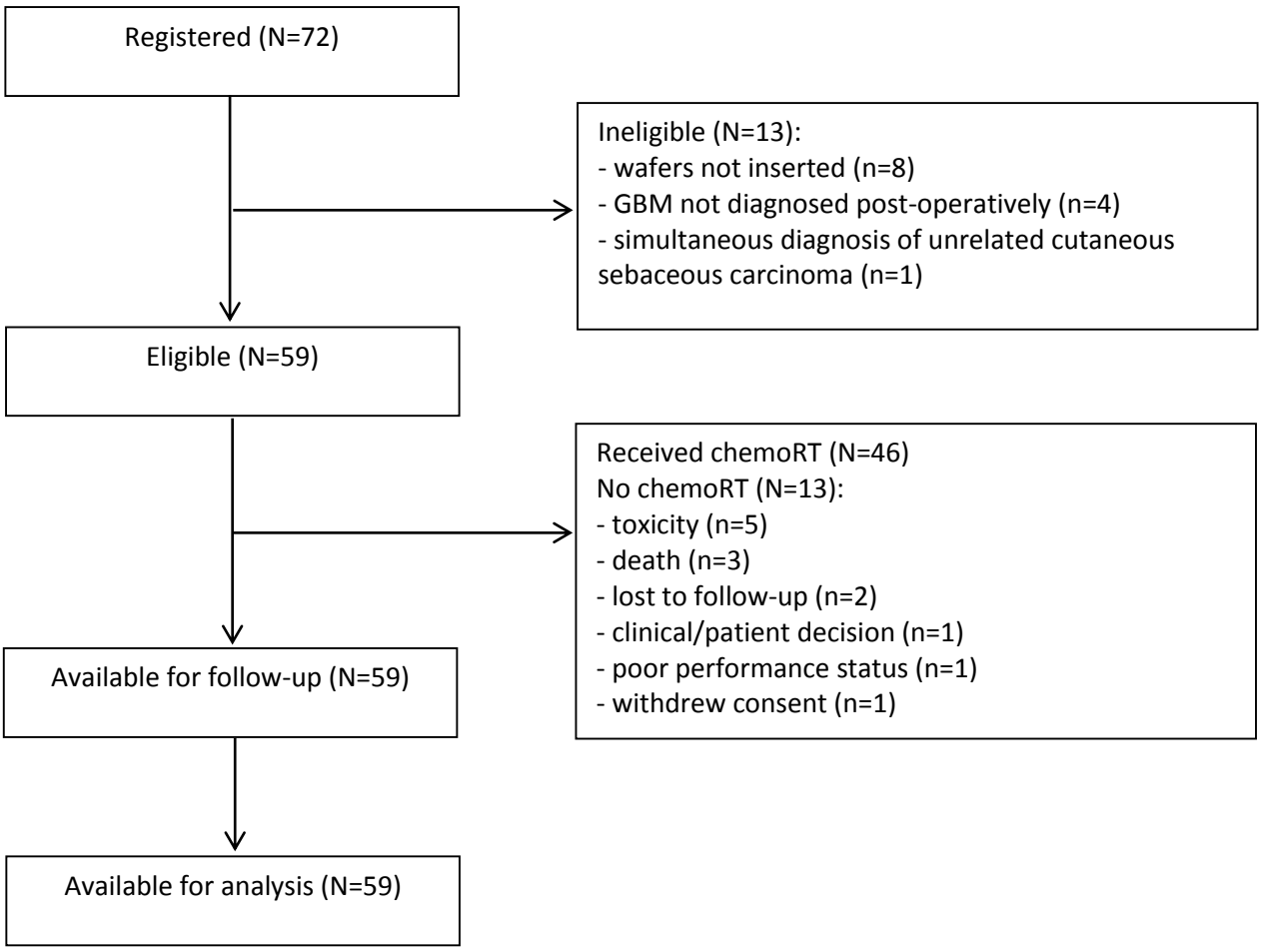
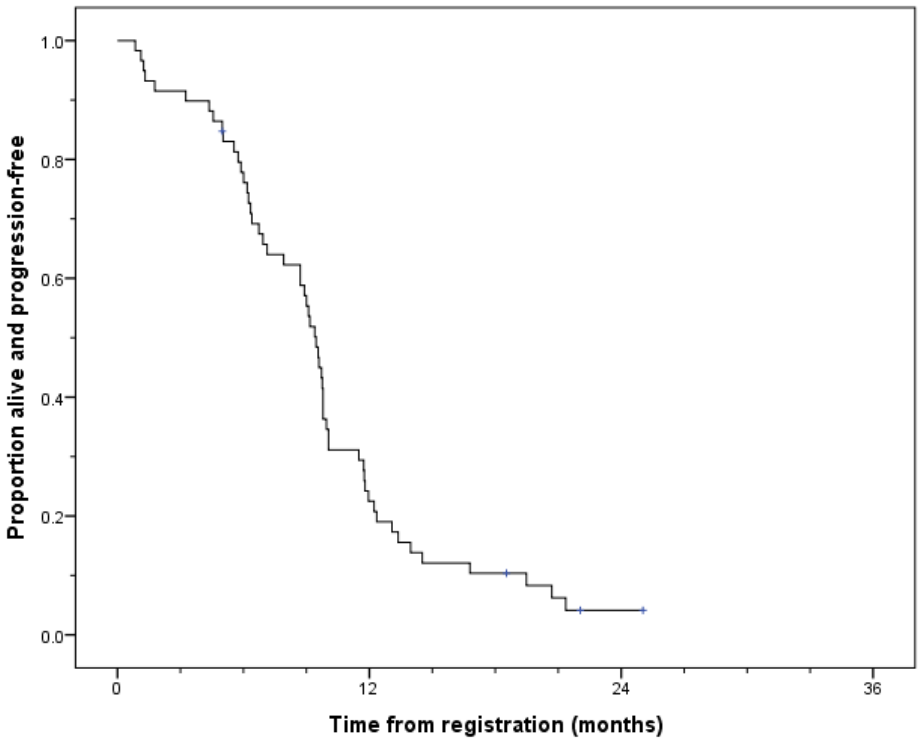


Figure 2: Kaplan Meier plots of (A) progression-free and (B) overall survival – eligible patients

(A)



(B)

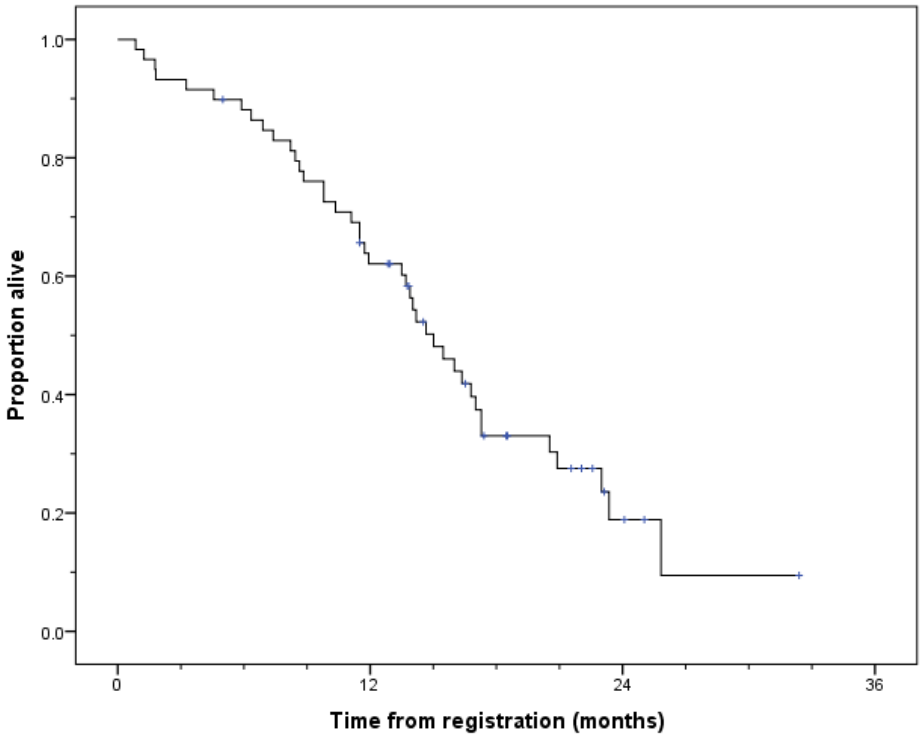


Table 1: Patient characteristics – all eligible patients

Patient characteristic	N = 59
	n (%)
Gender	
Female	22 (37.3)
Male	37 (62.7)
Karnofsky Performance Status	
100	21 (35.6)
90	29 (49.2)
80	6 (10.2)
70	1 (1.7)
60	2 (3.4)
WHO Performance Status	
Fully Active	37 (62.7)
Restricted in Physical activity	22 (37.3)
Tumour Location	
Frontal	20 (33.9)
Parietal	14 (23.7)
Temporal	14 (23.7)
Central	1 (1.7)
Occipital	1 (1.7)
Other: Frontal and Parietal	3 (5.1)
Other: Temporal and Parietal	3 (5.1)
Other: Parietal and Occipital	2 (3.4)
Other: Frontal and Temporal	1 (1.7)
Tumour Hemisphere	
Left	29 (49.2)
Right	29 (49.2)
Both	1 (1.7)
	median (range)
Age (years)	59.0 (37.0 – 71.0)
Haemoglobin (g/dL)	14.7 (11.7 – 17.7)
Platelets (x 10^9/L)	258.0 (125.0 – 475.0)
INR	0.9 (0.8 – 1.1)
Absolute Neutrophil Count (x 10^9/L)	11.1 (2.2 – 21.7)
White Blood Cell Count (x 10^9/L)	12.9 (4.9 – 25.3)

Table 2: Reported grade 3 or higher adverse events – all eligible patients

Adverse event	N=59	
	No.	**(%)**
Any toxicity (each patient counted once)	*34**	*(57.6%)*
Muscle Weakness	5	(8.5%)
Seizure	5	(8.5%)
Nausea	4	(6.8%)
Neutrophil Count Decreased	4	(6.8%)
Platelet Count Decreased	4	(6.8%)
Thrombolytic event	4	(6.8%)
Lethargy	3	(5.1%)
Vomiting	3	(5.1%)
White blood cell decreased (Leukopenia)	3	(5.1%)
Wound infection	3	(5.1%)
Back pain	2	(3.4%)
Hyperglycemia	2	(3.4%)
Sepsis	2	(3.4%)
Alanine aminotransferase increased	1	(1.7%)
Aspiration pneumonia	1	(1.7%)
Bilateral Retinal detachment	1	(1.7%)
Bilateral pitting ankle oedema	1	(1.7%)
Blurred vision	1	(1.7%)
Cerebral Abscess	1	(1.7%)
Cerebrospinal Fluid Leakage	1	(1.7%)
Chest infection	1	(1.7%)
Concentration Impairment	1	(1.7%)
Confusion	1	(1.7%)
Dizziness	1	(1.7%)
Edema Cerebral	1	(1.7%)
Fractured humerus - right	1	(1.7%)
Haematoma	1	(1.7%)
Headache	1	(1.7%)
Hyponatremia	1	(1.7%)
Infection (unknown origin)	1	(1.7%)
Infection and Infestation (unknown origin)	1	(1.7%)
Intra-cranial haemorrhage	1	(1.7%)
Intra-operative neurological injury	1	(1.7%)
Intrabdominal hemorrhage	1	(1.7%)
Left sided weakness	1	(1.7%)
Lung infection	1	(1.7%)
Lymphocyte count decrease	1	(1.7%)
Neutropenic sepsis	1	(1.7%)
Paresthesia	1	(1.7%)
Pericolic Abcess sigmoid colon perforation	1	(1.7%)
Pneumonia/lung infection	1	(1.7%)
Polydipsia (due to hyperglyemia	1	(1.7%)
Pulmonary Edema	1	(1.7%)
Stroke	1	(1.7%)
Urinary tract infection	1	(1.7%)
Vasovagal reaction	1	(1.7%)
Visual Field loss	1	(1.7%)
Wound dehiscence	1	(1.7%)

*Grade 4 = 9 patients (15.3%); Grade 5 = 2 patients (3.4%)

Table 3: Mini Mental State Examination (A), NIH Stroke Scale (B), and Quality of Life (C&D) – all eligible patients

(A) Mini Mental State Examination

Visit	*N* = 59	median (IQR)
Registration	58	28.0 (25.0, 29.0)
Post-adjuvant chemotherapy	18	26.0 (22.0, 29.0)
Change from registration to post-adjuvant chemotherapy	18	-1.5 (-4.0, 2.0)

(B) NIH Stroke Scale

Visit	*N* = 59	median (IQR)
Registration	58	0.0 (0.0, 1.0)
Post-surgery	54	0.0 (0.0, 1.0)
Pre-radiotherapy	39	0.0 (0.0, 2.0)
Post-radiotherapy	34	0.5 (0.0, 2.0)
Mid-adjuvant chemotherapy	26	1.0 (0.0, 2.0)
Post-adjuvant chemotherapy	18	0.5 (0.0, 2.0)
12-month follow-up	14	0.5 (0.0, 2.0)
18-month follow-up	5	0.0 (0.0, 2.0)
24-month follow-up	5	1.0 (0.0, 1.0)
30-month follow-up	2	0.5 (0.0, 1.0)
Change from registration to post-adjuvant chemotherapy	18	0.0 (0.0, 0.2)

(C) Quality of Life: EORTC QLQ-C30

Visit	*N* = 59	QLQ-Q30 Status: QL	QLQ-Q30 Function: PF	QLQ-Q30 Function: RF	QLQ-Q30 Function: EF	QLQ-Q30 Function: CF	QLQ-Q30 Function: SF
Registration	58	66.7 (50.0, 83.3)	100.0 (86.7, 100.0)	83.3 (50.0, 100.0)	79.2 (66.7, 91.7)	66.7 (66.7, 83.3)	83.3 (66.7, 100.0)
Pre-radiotherapy	36	66.7 (50.0, 83.3)	80.0 (62.5, 93.3)	66.7 (33.3, 100.0)	83.3 (66.7, 95.8)	75.0 (66.7, 83.3)	66.7 (50.0, 83.3)
Post-radiotherapy	34	66.7 (50.0, 83.3)	76.7 (53.3, 93.3)	66.7 (33.3, 100.0)	83.3 (66.7, 100.0)	66.7 (50.0, 83.3)	66.7 (33.3, 100.0)
Mid-adjuvant chemotherapy	29	66.7 (50.0, 83.3)	73.3 (60.0, 93.3)	66.7 (33.3, 100.0)	83.3 (66.7, 100.0)	66.7 (50.0, 83.3)	66.7 (33.3, 100.0)
Post-adjuvant chemotherapy	20	75.0 (50.0, 91.7)	73.3 (60.0, 86.7)	66.7 (33.3, 100.0)	75.0 (66.7, 100.0)	83.3 (66.7, 83.3)	66.7 (50.0, 100.0)
12-month follow-up	12	66.7 (50.0, 83.3)	80.0 (63.3, 93.3)	66.7 (66.7, 91.7)	79.2 (66.7, 91.7)	75.0 (50.0, 100.0)	66.7 (66.7, 100.0)
18-month follow-up	4	75.0 (62.5, 91.7)	83.3 (66.7, 96.7)	83.3 (58.3, 100.0)	83.3 (75.0, 95.8)	83.3 (75.0, 91.7)	83.3 (33.3, 100.0)
24-month follow-up	4	66.7 (41.7, 91.7)	83.3 (53.3, 93.3)	100.0 (50.0, 100.0)	91.7 (66.7, 95.8)	83.3 (58.3, 83.3)	75.0 (41.7, 91.7)
Change from registration to post-adjuvant chemotherapy	20	8.3 (-25.0, 25.0)	-20.0 (-40.0, 0.0)	0.0 (-33.3, 33.3)	0.0 (-20.8, 8.3)	0.0 (-16.7, 16.7)	-16.7 (-41.7, 0.0)

Visit	*N* = 59	QLQ-Q30 Symptom: FA	QLQ-Q30 Symptom: NV	QLQ-Q30 Symptom: PA	QLQ-Q30 Symptom: DY	QLQ-Q30 Symptom: SL	QLQ-Q30 Symptom: AP	QLQ-Q30 Symptom: CO	QLQ-Q30 Symptom:
Registration	58	22.2 (11.1, 44.4)	0.0 (0.0, 0.0)	0.0 (0.0, 16.7)	0.0 (0.0, 33.3)	33.3 (0.0, 66.7)	0.0 (0.0, 0.0)	0.0 (0.0, 33.3)	0.0 (0.0, 0.
Pre-radiotherapy	36	33.3 (27.8, 55.6)	0.0 (0.0, 0.0)	0.0 (0.0, 16.7)	0.0 (0.0, 33.3)	33.3 (16.7, 66.7)	0.0 (0.0, 0.0)	0.0 (0.0, 33.3)	0.0 (0.0, 0.
Post-radiotherapy	34	44.4 (33.3, 66.7)	0.0 (0.0, 16.7)	0.0 (0.0, 16.7)	0.0 (0.0, 33.3)	0.0 (0.0, 33.3)	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.
Mid-adjuvant chemotherapy	29	33.3 (22.2, 55.6)	0.0 (0.0, 0.0)	0.0 (0.0, 16.7)	0.0 (0.0, 33.3)	33.3 (0.0, 33.3)	0.0 (0.0, 33.3)	0.0 (0.0, 33.3)	0.0 (0.0, 0.
Post-adjuvant chemotherapy	20	33.3 (16.7, 55.6)	0.0 (0.0, 8.3)	0.0 (8.3, 16.7)	0.0 (0.0, 0.0)	33.3 (0.0, 33.3)	0.0 (0.0, 33.3)	0.0 (0.0, 33.3)	0.0 (0.0, 0.
12-month follow-up	12	33.3 (22.2, 33.3)	0.0 (0.0, 8.3)	0.0 (0.0, 16.7)	0.0 (0.0, 0.0)	33.3 (0.0, 66.7)	0.0 (0.0, 33.3)	0.0 (0.0, 33.3)	0.0 (0.0, 0.
18-month follow-up	4	33.3 (22.2, 38.9)	0.0 (0.0, 8.3)	0.0 (0.0, 16.7)	0.0 (0.0, 0.0)	0.0 (0.0, 50.0)	0.0 (0.0, 16.7)	0.0 (0.0, 16.7)	0.0 (0.0, 0.
24-month follow-up	4	38.9 (22.2, 61.1)	0.0 (0.0, 0.0)	0.0 (0.0, 8.3)	16.7 (0.0, 50.0)	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.
Change from registration to post-adjuvant chemotherapy	20	22.2 (0.0, 33.3)	0.0 (0.0, 8.3)	0.0 (-8.3, 8.3)	0.0 (0.0, 0.0)	0.0 (-33.3, 0.0)	0.0 (0.0, 33.3)	0.0 (0.0, 16.7)	0.0 (0.0, 0.

(D) Quality of Life: EORTC QLQ-BN20

Visit	*N* = 59	QLQ-BN20 Domain: FU	QLQ-BN20 Domain: VD	QLQ-BN20 Domain: MD	QLQ-BN20 Domain: CD
Registration	58	33.3 (16.7, 58.3)	0.0 (0.0, 22.2)	11.1 (0.0, 22.2)	16.7 (0.0, 33.3)
Pre-radiotherapy	36	25.0 (16.7, 50.0)	5.6 (0.0, 22.2)	22.2 (11.1, 33.3)	11.1 (0.0, 27.8)
Post-radiotherapy	34	29.2 (8.3, 50.0)	5.6 (0.0, 22.2)	16.7 (0.0, 33.3)	11.1 (0.0, 33.3)
Mid-adjuvant chemotherapy	29	16.7 (8.3, 41.7)	0.0 (0.0, 11.1)	11.1 (0.0, 22.2)	11.1 (0.0, 33.3)
Post-adjuvant chemotherapy	18	16.7 (8.3, 41.7)	0.0 (0.0, 11.1)	11.1 (0.0, 33.3)	11.1 (0.0, 22.2)
12-month follow-up	12	25.0 (8.3, 58.3)	0.0 (0.0, 22.2)	11.1 (5.6, 27.8)	16.7 (0.0, 44.4)
18-month follow-up	4	20.8 (8.3, 33.3)	0.0 (0.0, 5.6)	5.6 (0.0, 22.2)	0.0 (0.0, 11.1)
24-month follow-up	4	16.7 (4.2, 37.5)	0.0 (0.0, 22.2)	11.1 (5.6, 22.2)	22.2 (11.1, 38.9)
Change from registration to post-adjuvant chemotherapy	18	-8.3 (-25.0, 16.7)	0.0 (0.0, 0.0)	0.0 (0.0, 22.2)	0.0 (0.0, 11.1)

Visit	*N* = 59	QLQ-BN20 Single: H	QLQ-BN20 Single: S	QLQ-BN20 Single: Dr	QLQ-BN20 Single: HL	QLQ-BN20 Single: IS	QLQ-BN20 Single: WL	QLQ-BN20 Single: BC
Registration	58	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	33.3 (0.0, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Pre-radiotherapy	36	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	33.3 (0.0, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)
Post-radiotherapy	34	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	33.3 (0.0, 33.3)	0.0 (0.0, 33.3)	0.0 (0.0, 33.3)	33.3 (0.0, 66.7)	0.0 (0.0, 0.0)
Mid-adjuvant chemotherapy	29	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 33.3)	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)
Post-adjuvant chemotherapy	18	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	16.7 (0.0, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	16.7 (0.0, 33.3)	0.0 (0.0, 33.3)
12-month follow-up	12	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 33.3)	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 16.7)	0.0 (0.0, 0.0)
18-month follow-up	4	16.7 (0.0, 33.3)	0.0 (0.0, 0.0)	33.3 (33.3, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	16.7 (0.0, 50.0)	0.0 (0.0, 16.7)
24-month follow-up	4	16.7 (0.0, 50.0)	0.0 (0.0, 0.0)	33.3 (16.7, 66.7)	0.0 (0.0, 0.0)	0.0 (0.0, 16.7)	0.0 (0.0, 50.0)	0.0 (0.0, 0.0)
Change from registration to post-adjuvant chemotherapy	18	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)