



Original Article

Impact on Health-Related Quality of Life of Induction Chemotherapy Compared With Concurrent Cisplatin and Radiation Therapy in Patients With Head and Neck Cancer



D. Adkins^{*†}, J. Ley[†], P. Oppelt^{*†}, H.A. Gay^{*‡}, M. Daly^{*‡}, R.C. Paniello^{*§}, R. Jackson^{*§}, P. Pippkorn^{*§}, J. Rich^{*§}, J. Zevallos^{*§}, K. Trinkaus^{*||}, W. Thorstad^{*‡}

^{*}Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri, USA

[†]Division of Medical Oncology, Washington University School of Medicine, St. Louis, Missouri, USA

[‡]Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri, USA

[§]Department of Otolaryngology, Washington University School of Medicine, St. Louis, Missouri, USA

^{||}Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri, USA

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Abstract

Aims: Organ preservation, an important goal in the treatment of head and neck squamous cell carcinoma (HNSCC), may include induction chemotherapy and cisplatin with radiation therapy (CRT). To our knowledge, no reports have directly compared the impact of induction chemotherapy with that of CRT on health-related quality of life (HRQOL).

Materials and methods: In a phase II trial, we assessed the HRQOL of patients treated with induction chemotherapy followed by CRT. Eligible patients had stage III–IV HNSCC. HRQOL questionnaires were administered at baseline, the end of induction (EOI), the end of CRT (EOCRT) and after CRT. Functional Assessment of Cancer Therapy (FACT version 4) assessed HRQOL. We carried out a comparison of changes in HRQOL from baseline to EOI and from EOI to EOCRT. This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01566435).

Results: Thirty patients were enrolled in the study. Most HRQOL questionnaires were completed (88%). The mean total FACT scores did not differ from baseline to EOI (general: 83.8 versus 79.1, $P = 0.08$; head and neck: 109.7 versus 105.8, $P = 0.33$; Total Outcome Index: 69.7 versus 62.3, $P = 0.03$; respectively, using $P \leq 0.01$ to adjust for multiple simultaneous tests of differences). However, total FACT scores significantly worsened from EOI to EOCRT (79.1 versus 62.3, $P = 0.01$; 105.8 versus 74.2, $P < 0.01$; 62.3 versus 34.2, $P = 0.01$; respectively). Within domains, the head and neck cancer subscale score did not differ from baseline to EOI (median 28.5 versus 27.0, $P = 0.69$), but significantly worsened from EOI to EOCRT (27.0 versus 9.5, $P < 0.01$). Swallowing, oral pain and voice quality improved from baseline to EOI, but worsened from EOI to EOCRT. Physical and functional scores worsened from baseline to EOI and from EOI to EOCRT. The emotional well-being score improved from baseline to EOI but worsened from EOI to EOCRT.

Conclusions: Overall, HRQOL did not significantly change from baseline to EOI but dramatically worsened from EOI to EOCRT.

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Key words: Head and neck; induction; quality of life

Introduction

Health-related quality of life (HRQOL) is a subjective measure of a patient's experience of the impact of cancer

and cancer treatment on their life. Head and neck squamous cell carcinoma (HNSCC) can have a profound impact on a patient's HRQOL, adversely affecting their voice, swallowing, nerve function and appearance. Treatment also adversely impacts HRQOL. The changes in HRQOL caused by HNSCC and its treatment may be temporary or permanent. Education of patients and health care providers about the effect of HNSCC and its treatment on HRQOL can influence treatment decisions.

Author for correspondence: D. Adkins, Division of Medical Oncology, Washington University School of Medicine, 660 South Euclid, Campus Box 8056, St. Louis, MO, 63110, USA. Tel.: +1-314-747-8475; Fax: +1-314-747-1411.

E-mail address: dadkins@wustl.edu (D. Adkins).

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Radiation therapy is an integral component of the treatment of locally advanced HNSCC. Many patients treated with radiation therapy will also be candidates for concurrent systemic therapy. A large body of literature exists reporting the HRQOL in patients with HNSCC treated with radiotherapy with or without chemotherapy; this literature was recently reviewed [1]. Overall HRQOL scores dramatically declined after radiation therapy and then returned to baseline within 1 year. However, substantial variability in the depth of decline and the pace of recovery occurred among HRQOL domains. In some cases, adverse changes were long-lasting. One example is xerostomia, which adversely affects swallowing function, dental health, speech and sleep. The shift from conventional three-dimensional and two-dimensional radiation therapy to intensity-modulated radiation therapy (IMRT) reduced patient-reported xerostomia and had a broad positive effect on several HRQOL domains [2–5].

The standard of care non-operative treatment of locally advanced HNSCC is concurrent chemotherapy and radiation therapy (CRT). Induction chemotherapy given before CRT failed to show a survival benefit [6–8]. However, induction chemotherapy is sometimes used as an organ-preservation strategy to direct patients to CRT if the cancer favourably responds, or to surgery if not [9]. In contrast to CRT, there are few data about the effect of induction chemotherapy on HRQOL in patients with HNSCC. Docetaxel, cisplatin and 5-fluorouracil (TPF) is the standard induction regimen for patients treated with radiation therapy [10] or carboplatin and radiation therapy [11]. In two phase III trials, overall survival was better in patients treated with TPF compared with PF. Swallowing and coughing problems were lower and weight gain was higher after TPF compared with PF [12], and global HRQOL was better at 6 months after radiation therapy in the TPF arm [12]. These data show that induction chemotherapy regimens can be selected that have a lower adverse impact on HRQOL and improve efficacy outcomes.

Better induction regimens are needed because relapse of disease was the most common cause of treatment failure after TPF [11]. We reported excellent efficacy of a novel induction regimen that included *nab*-paclitaxel [13]. In this phase II trial, *nab*-paclitaxel, a nanoparticle albumin-bound taxane that may improve drug delivery into tumour [14,15], was added to cisplatin and 5-fluorouracil (APF) followed by CRT. The relapse rate was only 3%. Two-year overall survival was 94% in human papillomavirus (HPV)-related oropharynx squamous cell carcinoma (SCC) and 92% in HPV-unrelated HNSCC.

To the best of our knowledge, there are no reports that have directly compared the impact of induction chemotherapy with that of CRT on HRQOL of patients with HNSCC. We prospectively assessed the HRQOL in patients with HNSCC treated with APF followed by CRT [13]. Self-reported HRQOL questionnaires were administered at baseline, the end of induction (EOI) APF, the end of CRT (EOCRT) and at 3, 6 and 12 months after CRT. Here we compare the impact of induction APF with that of CRT on self-reported HRQOL.

Materials and Methods

Study Design and Participants

We carried out a phase II single-centre trial. Patient selection criteria, study design and assessments of efficacy end points and adverse events have been previously reported [13]. In brief, eligible patients were aged 18 years or older with untreated HNSCC stages III, IVa and IVb [16] (T₁ excluded) that originated in the oropharynx, larynx or hypopharynx. Other criteria included adequate performance status (ECOG 0–2) and vital organ function. The Washington University Human Research Protection Office approved the protocol and all study participants signed informed consent forms.

APF consisted of cycles of *nab*-paclitaxel, cisplatin and 5-fluorouracil every 3 weeks. After three cycles of APF, patients proceeded to CRT. IMRT was used in all patients. Patients with serum creatinine <2.0 mg/dl received high-dose bolus cisplatin with IMRT. Patients who failed to meet this criterion received cetuximab. Baseline assessments, follow-up assessments and monitoring of adverse events were carried out as previously reported [13].

Procedures

All patients were asked to complete a validated questionnaire of HRQOL before treatment, at EOI, EOVRT and at the 3-, 6- and 12-month follow-up visits after CRT. The questionnaire was administered to the patient in the clinic by a clinical research coordinator. Patients were asked to answer each question based on their experience over the last 7 days preceding completion of the questionnaire.

The HRQOL questionnaire used in this protocol was the Functional Assessment of Cancer Therapy - Head and Neck (FACT-H&N, version 4), a 4 page questionnaire that assesses physical, social, emotional and functional well-being domains through questions designed specifically for patients with head and neck cancer [17]. FACT-H&N includes 39 questions: seven in the physical well-being domain, seven in the social/family well-being domain, six in the emotional well-being domain, seven in the functional well-being domain and 12 additional questions in the head and neck cancer subscale (HNCS) domain. These questions were scored from 0 (not at all) to 4 (very much). Higher scores indicated worse physical and emotional well-being and better social/family and functional well-being. The relationship of scores on additional questions of the HNCS domain varied based on each question (worse for questions 2, 3, 6, 8, 9 and 12 and better for questions 1, 4, 5, 7, 10 and 11). Subscale scores for each of the five domains, the FACT-H&N Trial Outcome Index (TOI), the FACT-G Total Score and the FACT-H&N Total Score were calculated based on the FACT-H&N scoring guidelines [17]. The FACT-H&N TOI (range 0–96) measures the total score for the physical, functional and HNCS domains but excludes the emotional and social domains. The FACT-G Total Score (range 0–108) measures the sum of the physical, social, emotional and

functional domains but excludes the HNCS domain. The FACT-H&N Total Score (range 0–148) measures the sum of the physical, social, emotional, functional and HNCS domains. The maximum score of 148 reflects the best quality of life (QOL). A clinically significant change in score is 7 for an increase and 14 for a decrease [18].

An additional four question HRQOL survey (modified FACT-GOG NTX-4) assessed symptoms of peripheral neuropathy [19], a side-effect often seen with *nab*-paclitaxel and cisplatin. These four questions scored numbness/tingling or discomfort in the hands or feet from 0 (not at all) to 4 (very much).

Outcomes

The primary and secondary efficacy end points of the clinical trial have been previously described [13]. A key secondary end point was HRQOL, prospectively and sequentially assessed in patients treated with APF followed by CRT.

Statistical Analyses

A comparison of changes in HRQOL over time was carried out. Estimated means and 95% confidence intervals were calculated for FACT-TOI, FACT-G Total Score, FACT-H&N Total Score and for each of the five domains. Medians and interquartile ranges (IQR) were calculated for subscale scores for each of the five domains. The FACT-TOI, FACT-G Total Score and FACT-H&N Total Score were Gaussian distributed on a linear or transformed scale, so a linear model was used to test hypotheses about the change in scores over time. The model tested whether the estimated scores and confidence intervals at EOI, EOCRT and at 3, 6 and 12 months after treatment differed from baseline and whether the change in scores from baseline to EOI was different from the change in score from EOI to EOCRT. A *P* value ≤ 0.01 was used to define a significant difference in this model to adjust for the five simultaneous tests for each time point of measurement. A similar comparison of subscale scores for each of the five domains over time was carried out. A Wilcoxon signed-rank test was used as the subscale scores were heavily skewed. A Wilcoxon rank-sum test was also used to compare the change in subscale score from baseline to EOI with that from EOI to EOCRT. A false discovery rate method was used to adjust *P* values within each subscale as each subscale had six separate tests.

Overall survival was stratified by HPV status and updated for this analysis. Overall survival (time from diagnosis to death or last follow-up alive) was estimated using the Kaplan–Meier method [20].

Role of the Funding Source

The funder had no role in the study design, data collection, data analysis, data interpretation or writing of the report. All authors had full access to all the data in the study. The corresponding author had the final responsibility for the decision to submit for publication.

Results

Between 10 August 2012 and 13 November 2013 we enrolled 30 patients into the trial. The cut-off for data analysis presented here was 14 March 2017.

Most patients were men, smokers and had advanced (T3/4 and/or N2b-3) oropharynx or larynx SCC (Table 1). All patients were treated with induction chemotherapy and 27 patients were subsequently treated with CRT. Cisplatin (*n* = 26) or cetuximab (*n* = 1) was administered during radiation therapy. Two patients declined CRT and one patient died before receiving CRT. The one treatment-related mortality event occurred in a patient who had stable disease after two cycles of APF, underwent resection and died after surgery due to bacterial sepsis.

Before treatment, three patients had tracheostomy tubes and three patients had percutaneous endoscopic gastrostomy (PEG) tubes in place. At the completion of CRT, one patient had a tracheostomy tube and 20 patients had PEG tubes. At 12 months after the completion of therapy, two patients had tracheostomy tubes and no patients had PEG tubes in place.

The updated median follow-up for all patients was 40 (19–51) months. Relapse of disease occurred in two (7%)

Table 1
Patient and tumour characteristics

Characteristic	Patients (<i>n</i> = 30)
Age (years)	
Median	57
Range	43–75
Gender	
Male	25 (83%)
Female	5 (17%)
Smoking History	
Yes	23 (77%)
No	7 (23%)
T Classification	
2	8 (27%)
3	13 (43%)
4	9 (30%)
N Classification	
0–1	5 (17%)
2	18 (60%)
3	7 (23%)
Overall stage	
III	3 (10%)
IVA	18 (60%)
IVB	9 (30%)
Primary site	
Oropharynx	18 (60%)
Larynx	9 (30%)
Hypopharynx	3 (10%)
HPV status (oropharynx only)	
p16+	17
HPV OPSCC risk group [21]	
Low	8
Intermediate	9

HPV, human papillomavirus; OPSCC, oropharyngeal squamous cell carcinoma.

patients. At the last follow-up, 26 patients were alive without relapse and four patients had died (treatment-related: one; relapse: one; co-morbidity: two). The estimated 2-year overall survival for all patients was 93% (95% confidence interval 76–98) and, when stratified by HPV status, was 94% (95% confidence interval 65–99) in HPV-related oropharynx SCC and 92% (95% confidence interval 57–99) in HPV-unrelated HNSCC.

Overall, 158 of the 180 questionnaires (88%) were completed. Twenty patients completed all HRQOL questionnaires. The number of HRQOL questionnaires obtained at baseline, EOI, EOCRT and at 3, 6 and 12 months after CRT were 30, 28, 26, 25, 27 and 22, respectively. The reasons for failure to complete 22 of the HRQOL questionnaires included patient decision (three), death (six), lost to follow-up (two) and missed by staff (11).

The mean total FACT scores were not significantly different (using $P \leq 0.01$) from baseline to EOI (FACT-G 83.8 [95% confidence interval 77.1–90.3] versus 79.1 [95% confidence interval 72.3–85.7], $P = 0.08$; FACT-H&N 109.7 [95% confidence interval 99.6–119.8] versus 105.8 [95% confidence interval 96.2–115.4], $P = 0.33$ and FACT-H&N TOI 69.7 [95% confidence interval 62–77.5] versus 62.3 [95% confidence interval 54.8–69.8], $P = 0.03$; [Figure 1](#)). However, mean total FACT scores significantly decreased (worsened) from EOI to EOCRT (FACT-G 79.1 [95% confidence interval 72.3–85.7] versus 62.3 [95% confidence interval 57–67.5], $P = 0.01$, FACT-H&N 105.8 [95% confidence interval 96.2–115.4] versus 74.2 [95% confidence interval 67.1–81.3], $P < 0.0001$ and FACT-H&N TOI 62.3 [95% confidence interval 54.8–69.8] versus 34.2 [95% confidence interval 28.3–40.1], $P = 0.0052$). Similarly, mean total scores for FACT-G ($P < 0.0001$), FACT-H&N ($P < 0.0001$) and FACT-TOI ($P < 0.0001$) significantly decreased from baseline to EOCRT.

The median subscale score for the HNCS domain did not change from baseline to EOI (28.5 [IQR 18–36] versus 27.0 [IQR 21–36], $P = 0.6870$), but significantly declined (worsened) from baseline to EOCRT (28.5 [IQR 18–36] versus 9.5 [IQR 8–12], $P < 0.0001$) ([Figure 2a](#)). The change in median score from EOI to EOCRT was significantly different (worse) compared with the change from baseline to EOI ($P < 0.0001$). Most median scores that measured swallowing and voice either improved or remained stable from baseline to EOI but dramatically declined from EOI to EOCRT ([Supplementary Figure S1a](#)).

The median subscale score for the physical well-being domain declined (worsened) from baseline to EOI (26.0 [IQR 23–27] versus 20.0 [IQR 12–24], $P = 0.0013$) and from baseline to EOCRT (26.0 [IQR 23–27] versus 11.5 [IQR 9–17], $P < 0.0001$) ([Figure 2b](#)). A comparison of changes in median scores from baseline to EOI and from EOI to EOCRT was not significantly different ($P = 0.0645$). Most measures of physical well-being increased (worsened) during treatment and peaked at EOCRT ([Supplementary Figure S1b](#)). The worsening of nausea and pain was more apparent at EOCRT compared with at EOI.

The median subscale score for the functional well-being domain declined (worsened) from baseline to EOI (20.5 [IQR

14–25] versus 15.0 [IQR 10–22], $P = 0.0104$) and from baseline to EOCRT (20.5 [IQR 14–25] versus 9.0 [IQR 6–12], $P < 0.0001$) ([Figure 2c](#)). A comparison of changes in median scores from baseline to EOI and from EOI to EOCRT was not significantly different ($P = 0.1988$). The median scores for most of the functional domain assessments declined from baseline to EOI and then declined further from EOI to EOCRT ([Supplementary Figure S1c](#)).

The median subscale score for the emotional well-being domain increased (improved) from baseline to EOI (16.0 [IQR 13–20] versus 21.0 [IQR 15–23], $P = 0.0004$) but did not significantly differ from baseline to EOCRT (16.0 [IQR 13–20] versus 18.5 [IQR 15–20], $P = 0.0630$) ([Figure 2d](#)). The change (increase) from baseline to EOI was greater than the change (decrease) from EOI to EOCRT ($P < 0.0001$). Although faced with the uncertainties of a cancer diagnosis, the median score for losing hope remained low and the median score for coping remained high from baseline to EOCRT ([Supplementary Figure S1d](#)). Median scores for nervousness, worrying about dying and worsening of their condition improved from baseline to EOI.

The median subscale scores of social/family well-being were not significantly different from baseline to EOI (26.0 [IQR 22–28] versus 24.0 [IQR 22–28], $P = 0.9338$), from baseline to EOCRT (26.0 [IQR 22–28] versus 23.0 [IQR 21–26], $P = 0.3570$) or from EOI to EOCRT ($P = 0.3570$) ([Figure 2e](#)). A decline in sexual satisfaction did occur at EOI and at EOCRT ([Supplementary Figure S1e](#)).

Overall mean total scores for FACT-G, FACT-H&N and FACT-H&N TOI returned to baseline by 6 months after treatment ([Figure 1](#)). The median subscale scores for the HNCS domain and the physical and functional well-being domains returned to baseline by 6 months after treatment ([Figure 2a–c](#)). Within the HNCS domain, dry mouth improved after EOCRT but continued to be problematic at 12 months after treatment ([Supplementary Figure S1a](#)). In the physical well-being domain, some patients continued to be troubled by the side-effects of treatment ([Supplementary Figure S1b](#)). All measures of functional well-being returned to baseline by 6–12 months after treatment ([Supplementary Figure S1c](#)). Emotional well-being improved and social well-being remained stable 12 months after treatment ([Figure 2d, e](#)).

Twenty-three patients (77%) reported the development of neuropathy symptoms. The peak of sensory neuropathy symptoms was reported at 3 months after treatment ([Supplementary Figure S1f](#)). Sensory neuropathy persisted in all of these patients at 12 months after treatment. Clinician-reported scoring of neuropathy and other adverse events has been previously reported [13].

Discussion

To the best of our knowledge, this is the first study to compare the impact of induction chemotherapy with that of CRT on the HRQOL of patients with HNSCC. EORTC 24971/TAX 323 was the first prospective study to report HRQOL during induction chemotherapy; however, the study did not

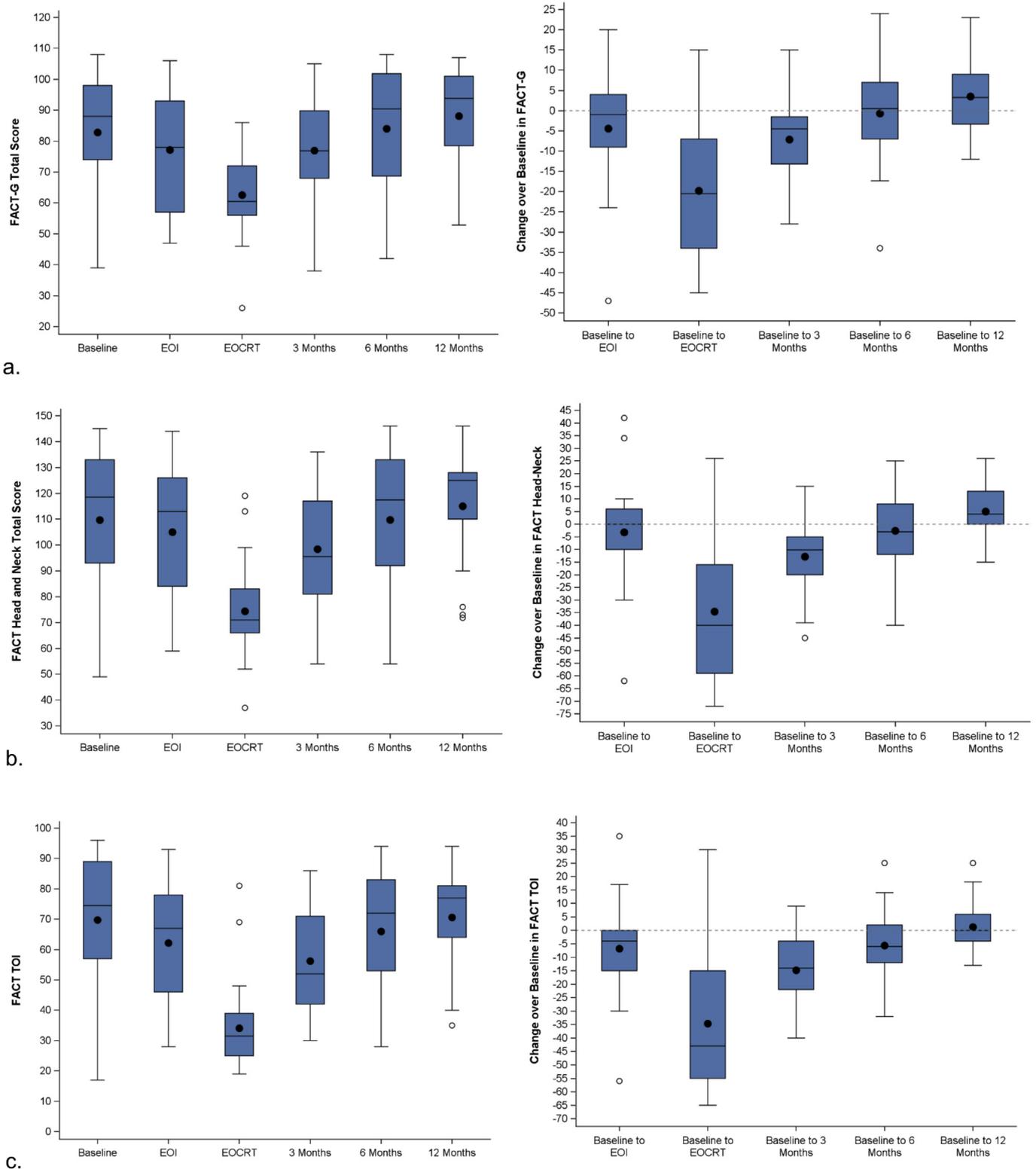


Fig 1. Overall total scores (mean [●], median [–], interquartile range [blue box], minimum, maximum and outliers [°]). EOCRT, end of cisplatin and radiation therapy; EOI, end of induction. (a) Functional Assessment of Chronic Therapy – General (FACT-G); (b) FACT-Head & Neck (FACT-H&N); (c) FACT-Trial Outcome Index (FACT-TOI).

assess HRQOL at the completion of radiation therapy [12]. In our study, we assessed HRQOL at the end of induction chemotherapy and at the end of CRT, allowing a direct comparison of the relative impact of each phase of therapy

on HRQOL. Although mean total scores for FACT-G, FACT-H&N and FACT-H&N TOI were not significantly different from baseline to EOI (when induction chemotherapy was administered), each dramatically worsened from EOI to

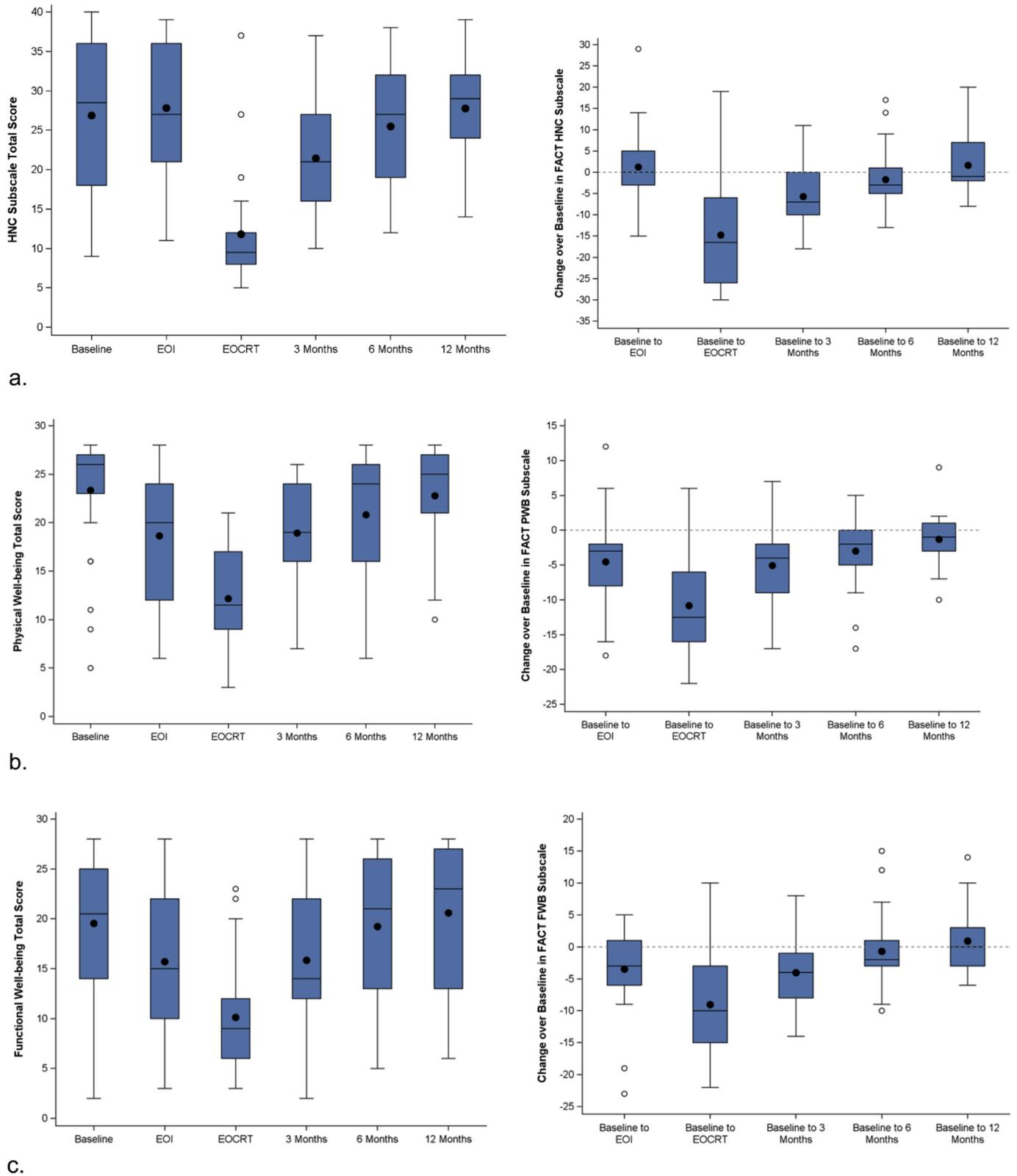


Fig 2. Domain subscale scores (median [–], mean [●], interquartile range [blue box], minimum, maximum and outliers [°]). EOCRT, end of cisplatin and radiation therapy; EOI, end of induction. (a) Head and neck cancer subscale (HNCS); (b) physical well-being (PWB); (c) functional well-being (FWB); (d) emotional well-being (EWB); (e) social/family well-being (SWB).

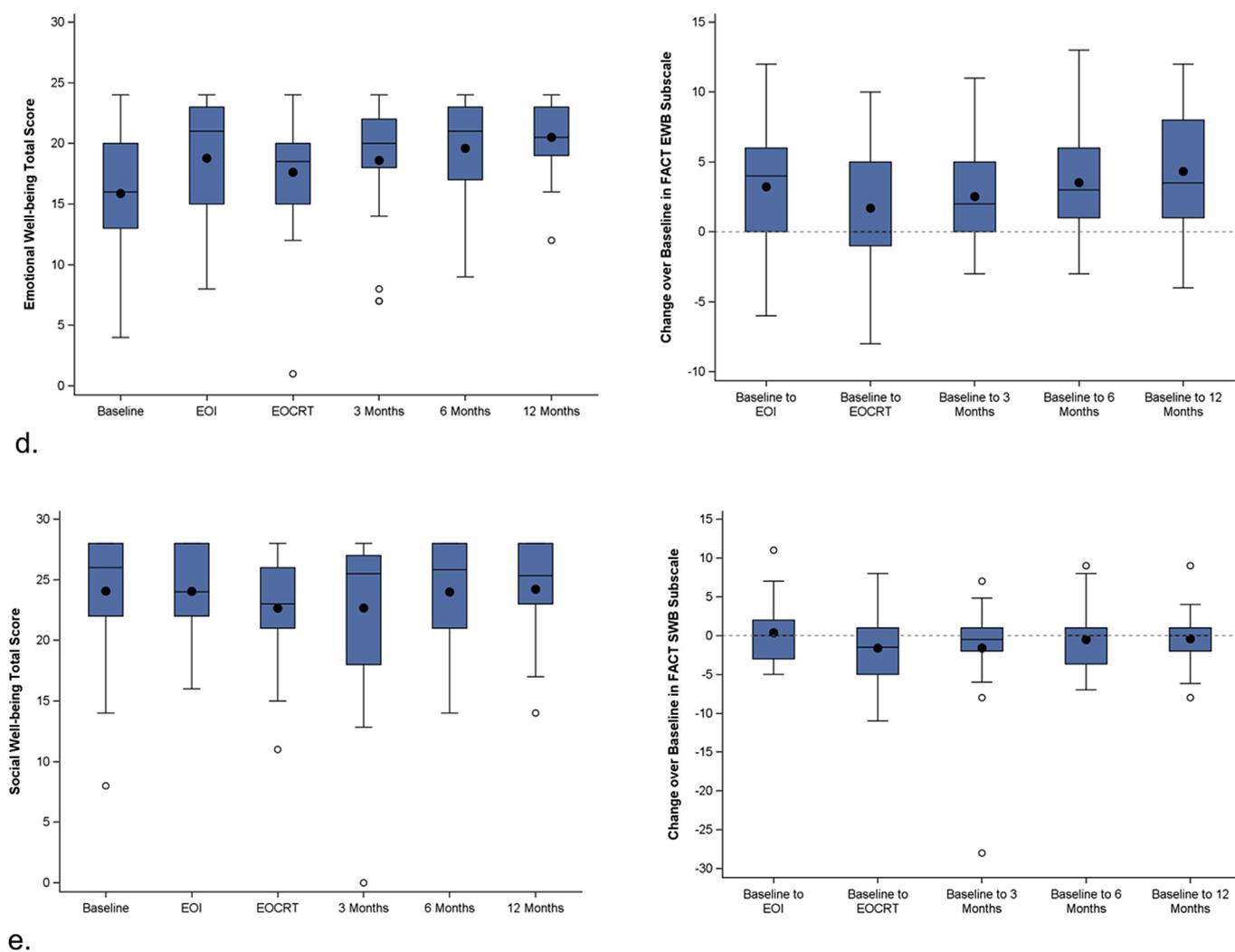


Fig 2. (continued).

EOCRT (when CRT was administered). Although both phases of therapy adversely impacted specific elements of HRQOL, CRT resulted in a substantially greater adverse effect on overall HRQOL compared with induction chemotherapy.

The results of this prospective trial show that overall HRQOL, measured by FACT-H&N, did not significantly change from baseline to the completion of APF induction chemotherapy. However, based on this sample and its limitations, there is insufficient evidence to reject the null hypothesis that there is no difference. Significant improvement in the emotional well-being domain occurred from baseline to EOI, but was counterbalanced by reductions in the physical and functional well-being domains. However, within the HNC domain, important specific measures of HRQOL, such as swallowing, oral pain and voice quality, improved from baseline to EOI. The EORTC 24971/TAX 323 trial showed that global HRQOL trended towards improvement during induction chemotherapy [12]. Selected measures, such as pain, swallowing, speech and cough, improved during induction chemotherapy. These two trials showed overall HRQOL was not significantly

compromised by the administration of induction chemotherapy to patients with HNSCC.

In our trial, the completion rate of HRQOL questionnaires was high (88%). One of the most challenging problems in interpreting QOL data is attrition of form completion, which results in bias. In the EORTC 24971/TAX 323 study, only 76% of QOL forms were completed at EOI and 45% were completed at 9 months after radiation therapy [12]. Many factors contribute to attrition; however, two key causes are relapse of disease and death. In the EORTC 24971/TAX 323 study, relapse occurred in 57–65% of patients and 2-year overall survival was 32–43%. The low rate of relapse (7%) and high 2-year overall survival (93%) in our trial contributed to the high completion rate of the HRQOL questionnaires.

In the face of monumental stresses of a new cancer diagnosis and the adverse impact of cancer and treatment on overall HRQOL, the median subscale scores for the social/family and emotional well-being domains were remarkably well preserved or improved throughout therapy and after treatment. This observation suggests that these two domains are important players in countering the adverse

impact of cancer and therapy on overall HRQOL. The development of strategies to improve the social/family and emotional well-being domains may improve overall HRQOL in these patients.

Mean total scores for overall HRQOL returned to baseline by 6 months after treatment, similar to other studies. However, some patients continued to be troubled by the side-effects of treatment, as shown in the HNCS and physical well-being domains. The reporting of a dry mouth and sensory neuropathy persisted in most patients at 12 months after treatment. A dry mouth is probably due to the adverse effect of radiation therapy on salivary gland function; neuropathy is a common adverse effect of cisplatin and nab-paclitaxel [22,23].

The limitations of this study include the relatively small patient cohort, use of a single measure of HRQOL and lack of a pre-planned specific hypothesis test for a HRQOL end point. Also, we measured HRQOL at EOI and EOCRT in the same patients. We did not compare HRQOL in patients randomly assigned to treatment with induction chemotherapy and CRT or CRT alone. It is possible that induction chemotherapy may influence the impact of CRT on HRQOL. One of the strengths of the study was that it was a prospective trial of patients treated with a uniform approach at a large tertiary care centre with an expertise in the multidisciplinary approach of care and research for patients with HNSCC. The very high rate of completion of HRQOL questionnaires reduced bias due to attrition.

In conclusion, overall HRQOL did not significantly change from baseline to the completion of induction chemotherapy. Based on the limitations of the trial, there is insufficient evidence to reject the null hypothesis that there is no difference. HRQOL dramatically worsened from the end of induction therapy to the end of CRT. The HNCS domain was the most adversely affected by CRT; whereas, social/family and emotional domains were preserved or improved. These data provide a framework to develop strategies to improve HRQOL during each phase of treatment and after the completion of treatment.

Conflict of Interest

Celgene provided research funding for this project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clon.2019.05.007>.

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