

ORIGINAL ARTICLE

Weekly kilovoltage cone-beam computed tomography for detection of dose discrepancies during (chemo)radiotherapy for head and neck cancer

BREGTJE C.M HERMANS¹, LUCAS C.G.G PERSON¹, MARK PODESTA¹,
FRANK J.P HOEBERS¹, FRANK VERHAEGEN^{1,*} & ESTHER G.C TROOST^{1,2,3,4,*}

¹Department of Radiation Oncology (MAASTRO clinic), Maastricht University Medical Centre, Maastricht, the Netherlands, ²Helmholtz Zentrum Dresden-Rossendorf, Germany, ³OncoRay, National Center for Radiation Research in Oncology, Dresden, Germany and ⁴Department of Radiation Oncology, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

ABSTRACT

Background. Use of highly conformal radiotherapy in patients with head and neck carcinoma may lead to under-/overdosage of gross target volume (GTV) and organs at risk (OAR) due to changes in patients' anatomy. A method to achieve more effective radiation treatment combined with less toxicity is dose-guided radiotherapy (DGRT). The aim of this study was to evaluate discrepancies between planned and actually delivered radiation dose in head and neck patients and to identify predictive factors.

Methods. In this retrospective analysis, 20 patients with cT2-4 N0-3 M0 carcinoma originating from oropharynx, oral cavity, larynx and hypopharynx (Cohort 1), and seven patients with cT1-4 N0-3 M0 nasopharyngeal carcinoma (Cohort 2) treated with primary (chemo)radiotherapy and undergoing weekly kV-CBCT scans were included. Radiation dose was recalculated on 184 kV-CBCT images, which was quantified by $D_{95\%}$ (GTV), D_{mean} (parotid and submandibular glands) and $D_{2\%}$ (spinal cord). Predictive factors investigated for changes in these dose metrics were: gender, age, cT/N-stage, tumor grade, HPV-status, systemic therapy, body mass index at start of treatment, weight loss and volume change over the duration of the radiotherapy.

Results. There was no significant difference between the planned and delivered dose for GTV and OARs of Week 1 to subsequent weeks for Cohort 1. In Cohort 2, actually delivered D_{mean} to parotid glands was significant higher than planned dose (1.1 Gy, $p = 0.002$). No clinically relevant correlations between dose changes and predictive factors were found.

Conclusion. Weekly dose calculations do not seem to improve dose delivery for patients with tumors of the oral cavity, oropharynx, larynx and hypopharynx. In patients with nasopharyngeal carcinoma, however, mid-treatment imaging may facilitate DGRT.

Squamous cell carcinomas of the head and neck region can originate from different subsites, e.g. larynx, hypopharynx, oropharynx, oral cavity and nasopharynx. Depending on the subsite and disease stage, treatment with curative intent comprises surgery and/or (chemo)radiotherapy. Surgery in general entails a greater degree of mutilation, whereas radiotherapy is more often organ preserving, but may be

harmful for healthy tissue (may lead to, e.g. swallowing problems and secondary cancers) [1].

Volumetric modulated arc therapy (VMAT) is a highly conformal radiation technique where the shape of the beam, gantry angle and dose rate are continuously varied throughout the delivery of the beam(s). This method enables the irradiation of patients with a high dose to the tumor and a low dose

*Both authors contributed equally.

Correspondence: E. Troost, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany. E-mail: esther.troost@uniklinikum-dresden.de

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to the surrounding normal tissues, using steep dose gradients [2]. This implicates that a small difference in positioning of the patient or a small anatomical change in the patient may result in dose differences negatively affecting either the local tumor control or treatment-related side effects.

To overcome the problem of misalignment, image-guided radiotherapy (IGRT) is used [3]. In daily clinical practice, shortly before the delivery of radiation, (orthogonal) x-ray images are acquired with an onboard imager (electronic portal imaging device; EPID) or a kilo voltage cone-beam CT (kV-CBCT) scan is performed. According to the imaging, the position of the patient is adjusted if necessary.

However, IGRT only corrects for set-up misalignment, not for dose discrepancies due to anatomical changes occurring within the patient, e.g. resulting from weight loss or tumor shrinkage. Thus, the next step to more effective treatment combined with less toxicity to healthy tissues is dose-guided radiotherapy (DGRT). In DGRT the dose delivered to target volumes and organs at risk (OARs) is recalculated during the course of irradiation. Subsequently, the radiation treatment plan is adapted when necessary.

For patients with squamous cell carcinomas of the head and neck reports on dose discrepancies in OARs and target volumes have shown contradictory findings [4–11]. Therefore, it is not clear whether monitoring of anatomical changes and replanning is necessary in those patients. In our experience, nasopharyngeal carcinoma patients are much more likely to develop anatomical changes than patients with carcinoma in oral cavity, oropharynx, larynx and hypopharynx. Therefore, this group of patients might benefit more from replanning.

The aim of this study was to assess clinically relevant discrepancies between planned and actually delivered radiation dose to target volumes and OARs in patients with advanced stage carcinoma of oral cavity, hypopharynx, larynx and oropharynx (Cohort 1), and patients with nasopharyngeal carcinoma (Cohort 2) during the course of (chemo)radiotherapy, and to evaluate whether replanning would have been beneficial. The secondary aim of the study was to define predictive factors for the need of replanning.

Methods

Patients

In this mono-center study in MAASTRO clinic (Maastricht, the Netherlands) a retrospective analysis of prospectively obtained images was performed. For Cohort 1 patients with tumors in oral cavity, oropharynx, larynx and hypopharynx treated in 2014 were selected (Supplementary Figure 1 available

online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061210>). Inclusion criteria were cT2–4 N0–3 M0 carcinoma (TNM staging according to UICC 7th edition) [12], treatment with (chemo)radiotherapy with curative intent and availability of a planning [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan and weekly kV-CBCT scans. Exclusion criteria were cT1–T2 carcinoma of the glottic larynx treated by local radiation only, nasopharyngeal carcinoma, postoperative (chemo)radiotherapy, palliative radiotherapy, re-irradiation, primary tumor $< 10 \text{ cm}^3$ and replanning during treatment. Cohort 2 consisted of nasopharyngeal carcinoma patients treated between 1 January 2013 and 1 April 2015. Inclusion criteria for this group were cT1–4 N0–3 M0 nasopharyngeal carcinoma, treatment with (chemo)radiotherapy with curative intent and availability of a FDG PET-CT scan for planning purposes and weekly kV-CBCT scans. Exclusion criteria for this cohort were identical to those of Cohort 1 except for the minimum primary tumor volume, which was irrelevant in Cohort 2. All head and neck cancer patients received dietary counseling during the entire course of treatment and prophylactic placement of gastrostomy in the case of chemoradiotherapy.

Radiation treatment planning

Before the start of treatment FDG-PET/CT imaging was performed for radiation treatment planning purposes (planning CT) for all patients. The gross tumor volume (GTV) was delineated by two experienced radiation oncologists in consensus. For the clinical target volume (CTV) a margin of 5–10 mm was added to GTV and corrected for anatomical boundaries. The elective nodal volumes were defined per national guidelines [1]. A uniform margin of 4 mm was added to CTV to correct for systematic and random patient setup uncertainties resulting in the planning target volume (PTV). OARs (e.g. spinal cord, parotid and submandibular glands and oral cavity) were also delineated on the planning CT. All patients were treated up to a total dose of 68–70 Gy in 34–35 fractions to the PTV using a simultaneous integrated boost technique. During treatment planning, constraints to OARs were taken into account [e.g. D_{max} (maximum delivered dose) spinal cord $< 45 \text{ Gy}$, D_{max} brainstem $< 54 \text{ Gy}$, D_{mean} (mean delivered dose) parotid and submandibular glands $< 26 \text{ Gy}$, D_{mean} oral cavity $< 26 \text{ Gy}$].

All patients were planned with Varian's treatment planning system Eclipse v11 (Varian Medical Systems, Palo Alto, CA, USA) using the Acuros dose algorithm. Patients were treated with VMAT using two or three arcs with 6 MV photon beams delivered

with a Varian TrueBeam linear accelerator equipped with a 120 leaf high-definition multileaf collimator (2.5 mm leaf width for central leaves). Patients with advanced stage disease were, depending on their comorbidities and condition, concurrently treated with cisplatin (100 mg/m² on Day 1, 22, 43) or cetuximab (400 mg/m² loading dose one week prior to start of radiotherapy, followed weekly by 250 mg/m²).

Imaging during treatment

A kV-CBCT was acquired immediately before the delivery of first fraction of irradiation and weekly in consecutive weeks as part of standard medical care for head and neck cancer patients. Weekly kV-CBCT images (125 kV) were acquired on a TrueBeam linear accelerator with full rotation panel off-set to obtain scans with a larger field of view with a maximum reconstruction diameter of 50 cm instead of 20 cm. For the used protocol a calibration was obtained with a Hounsfield Unit – electron density curve, which was established with a CIRS062 MA CBCT calibration phantom. To overcome photon scatter on the superior-inferior edges of kV-CBCT images, they were ‘stitched’ with the planning CT scan (Supplementary Figure 2 available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061210>) [13]. This resulted in scans ranging from top of the head to upper thorax level, with the volume of interest (e.g. tumor and most OARs) on the CBCT part.

Data collection

Structure delineations on the planning CT were propagated to kV-CBCT images using Varian’s SmartAdapt automatic deformation software, followed by manual adaptation whenever needed by the first author supervised by two experienced head and neck radiation oncologists (FH, ET) [14,15]. The original radiation treatment plan was copied to kV-CBCT images and recalculated. Dose metrics were extracted from dose volume histograms (DVHs); D_{95%} (minimum delivered dose to 95% of the volume) for the GTV, D_{mean} for parotid and submandibular glands and D_{2%} (delivered dose to 2% of volume) for the spinal cord. Initially, the oral cavity (as an surrogate OAR for the minor salivary glands) was also investigated, but not used in the analysis due to a large inter-observer variability of delineation of the structure on the planning CT.

The factors investigated for potential prediction of dose metric changes during a course of radiotherapy were: age, gender, clinical T- and N-stage, initial volume of GTV, tumor grade, human papillomavirus (HPV) status, body mass index (BMI) at start of

treatment, weight loss during treatment and concomitant systemic therapy. Data was collected from the electronic medical record.

Statistical analysis

As the planning CT is obtained approximately 10 days before the start of treatment, the kV-CBCT image acquired in Week 1 was chosen as baseline measurement to focus on in-treatment discrepancies. Statistical analysis was performed with SPSS Statistics for windows (version 19.0, IBM, Armonk, NY, USA). A two-sided paired t-test was used to determine significant differences in the dose to GTV and OARs between kV-CBCT in Week 1 and in subsequent weeks. Simple linear regression analysis was used to evaluate the correlation between dose metric discrepancies and the continuous variables. The correlation between dose metric discrepancy and nominal variables was investigated with a Kruskal-Wallis test. A p-value of < 0.05 is regarded statistically significant.

Individual patients

For individual patients a qualitative analysis was performed. Dose discrepancies for the GTV and OARs for cumulative dose (summation of weekly calculated actually delivered dose during the course of treatment) compared to dose on kV-CBCT in Week 1 was described. A decrease in D_{95%} to GTV (primary tumor and lymph nodes) of > 2 Gy was considered clinically relevant. As xerostomia may recover after a D_{mean} to the parotid and submandibular glands of 26 Gy to 35 Gy, the clinical relevance was set at an increase of > 2 Gy if the planned D_{mean} to one of the glands was < 35 Gy [15,16]. For the spinal cord, a D_{max} > 45 Gy increases the normal tissue complication probability [17]. Thus, an increase of > 1 Gy in D_{max} to the spinal cord was regarded as clinically relevant when the actually delivered dose was > 45 Gy.

Results

Twenty patients with carcinoma in oral cavity, oropharynx, larynx and hypopharynx were included in Cohort 1 (Table I). In Cohort 2, seven patients with nasopharyngeal carcinoma were included (Table II). Weight loss in Cohort 2 was found to be statistically significantly higher than in Cohort 1 (p = 0.011). Also, significantly more patients in Cohort 2 had a high tumor grade compared to Cohort 1 (p = 0.004). The other characteristics did not significantly differ between the groups.

In Cohort 1, there was no significant discrepancy between dose to kV-CBCT in the first week and

Table I. Patient characteristics Cohort 1 (N = 20).

	Number	Percentage
Mean age in years (range)	63 (46–81)	
Gender		
Male	10	50
Female	10	50
Mean weight in kg (range)	62.4 (34–104)	
Mean weight loss in kg (range)	2.2 (–1.5–10)	
Tumor site		
Oral cavity	2	10
Oropharynx	7	35
Larynx	7	35
Hypopharynx	4	20
cT-stage		
cT2	5	25
cT3	7	35
cT4	8	40
cN-stage		
cN0	5	25
cN1	6	30
cN2	9	45
Tumor grade		
Grade 1	1	5
Grade 2	14	70
Grade 3	3	15
Unknown	2	10
HPV-status		
Positive	4	20
Negative	8	40
Unknown	8	40
Systemic therapy		
None	6	30
Cisplatin	7	35
Cetuximab	7	35

cT-stage, clinical evaluation of size and invasion of primary tumor; cN-stage, clinical evaluation of involved lymph nodes; HPV, human papillomavirus.

actually delivered cumulative dose for GTV and OARs (Figure 1). $D_{95\%}$ to the GTV lymph nodes was significantly higher in Week 6 compared to the first week [mean difference 0.4 Gy, range (–0.3, 1.2), $p = 0.001$]. The mean dose to the submandibular glands was significantly lower in Week 2 compared to Week 1 [–0.5 Gy (–4.8, 1.4), $p = 0.038$]. For patients in Cohort 2, the cumulative actually delivered D_{mean} to parotid glands was significant higher compared to the planned dose [1.1 Gy (–0.1, 4.0), $p = 0.002$] (Figure 1). D_{mean} to parotid glands was significantly higher in Week 5, 6 and 7 [2.4 Gy (–0.2, 6.2), $p < 0.001$; 3.2 Gy (–1.9, 6.9), $p = 0.006$ and 2.8 Gy (0.9, 6.1), $p = 0.001$, respectively] (Figure 2). There was no significant dose discrepancy for GTV, submandibular glands and spinal cord in this group of patients.

In Cohort 1, none of the individual patients showed a clinically relevant decrease (> 2 Gy) of actually delivered dose to the tumor or metastatic lymph nodes (Supplementary Table I available online

Table II. Patient characteristics Cohort 2 (N = 7).

	Number	Percentage
Mean age in years (range)	58 (25–72)	
Gender		
Male	6	86
Female	1	14
Mean weight in kg (range)	75.3 (46–94)	
Mean weight loss in kg (range)	4.5 (3.4–6)	
cT-stage		
cT1	2	29
cT2	1	14
cT3	1	14
cT4	3	43
cN-stage		
cN0	2	29
cN1	2	29
cN2	2	29
cN3	1	14
Tumor grade		
Grade 3	4	57
Grade 4	1	14
Unknown	2	29
EBV-status		
Positive	5	71
Negative	0	0
Unknown	2	29
Systemic therapy		
None	2	29
Cisplatin	5	71

cT-stage, clinical evaluation of size and invasion of primary tumor; cN-stage, clinical evaluation of involved lymph nodes; EBV, Epstein-Barr Virus.

at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061210>). One patient showed a clinically irrelevant increase of > 1 Gy to the spinal cord and four patients developed a clinically irrelevant increase of > 2 Gy to one of the submandibular glands. In one of the four patients with an increased dose to the parotid glands, D_{mean} increased clinically significantly from 31.2 Gy (kV-CBCT 1) to 33.5 Gy (cumulative dose). Review of the delineation of the parotid glands on weekly kV-CBCT images revealed that the increase was caused by a medial shift of the parotid gland (Supplementary Figure 3 available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061210>). None of the individual nasopharyngeal carcinoma patients (Cohort 2) showed a clinically relevant dose decrease to target volumes or a clinically relevant increase to OARs (Supplementary Table II available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061210>).

In Cohort 1, weight loss was a significant predictor for a higher cumulative $D_{95\%}$ ($p = 0.005$) in the primary tumor. A decrease in $D_{95\%}$ to the lymph nodes was predicted by a higher age ($p = 0.022$). For submandibular glands, a larger GTV at the start of

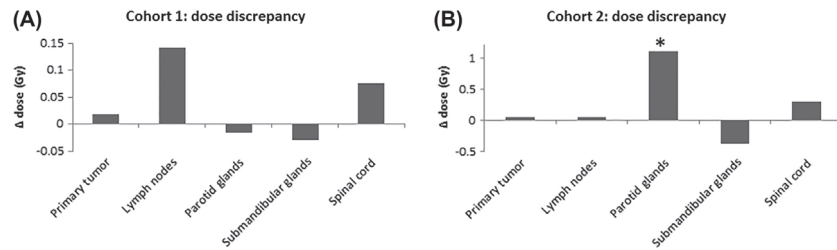


Figure 1. Mean dose discrepancy of Cohort 1 (A) and Cohort 2 (B) regarding $D_{95\%}$ (primary tumor and lymph nodes), D_{mean} (parotid and submandibular glands) and $D_{2\%}$ (spinal cord) between planned dose on kV-CBCT in first week of treatment and actually delivered cumulative dose. In Cohort 1, none of the discrepancies was significant whereas in Cohort 2, a significantly increased dose was detected ($p = 0.002$).

treatment resulted in an increase of cumulative D_{mean} ($p = 0.008$), whereas a higher cN-stage resulted in a slight decrease of the D_{mean} ($p = 0.038$). A larger initial GTV predicted for an increase of $D_{2\%}$ to the spinal cord ($p = 0.015$). For parotid glands, no correlations were found between an increase in the D_{mean} and predictive factors. In Cohort 2 no correlations were found between predictive factors and dose to target volumes and OARs.

Discussion

In patients with tumors in the oral cavity, oropharynx, larynx and hypopharynx we found no relevant discrepancies in dose to target volumes and OARs in this study. Only one patient in this cohort showed a clinically relevant increase in the mean dose to one of the parotid glands. Moreover, this study showed a significant increase in D_{mean} to parotid glands for patients with nasopharyngeal carcinoma in cumulative dose and in Week 5, 6 and 7 of treatment.

In head and neck squamous cell carcinoma (HNSCC), studies on decreased doses to target volumes and increased doses to OARs have found conflicting results [4–11]. Castelli et al. [6] calculated actually delivered dose to parotid glands on weekly CT scans and found a statistically significant

mean increase of 1.8 Gy. Bhide et al. [5] investigated weekly CT scans of 20 patients (of whom four with nasopharyngeal carcinoma) and showed a 2-Gy reduction of D_{min} to the PTV and a non-significant increase of D_{mean} to parotid glands and D_{max} to spinal cord and brainstem. Beltran et al. [4] evaluated CT scans of 16 patients obtained at two time-points during treatment and found $D_{95\%}$ and $D_{98\%}$ for PTV1 decreased significantly, whereas $D_{95\%}$ of the GTV and the D_{mean} to both parotid glands increased non-significant. Wu et al. [8] evaluated weekly CT images of 11 HNSCC patients and found as only discrepancy an increased D_{mean} to the parotid glands. Similarly, Lee et al. [7] showed a cumulative increase of the D_{mean} to parotid glands of 15% on daily CT images.

Moreover, the study by Fung et al. [19] reported a significant increase of dose to brainstem, spinal cord and parotid glands in nasopharyngeal patients. Zhao et al. [20] showed a significant increase of D_{mean} to contralateral parotid glands in 33 nasopharyngeal carcinoma patients and Lu et al. [21] described an increased D_{mean} to spinal cord, brainstem and parotid glands.

Our study indicates a risk of increased dose to parotid glands in patients with nasopharyngeal carcinoma. However, no individual patient in this group showed a clinically relevant increase of dose since most of the patients in this study had a planned $D_{\text{mean}} > 35$ Gy. Careful monitoring of patients with nasopharyngeal carcinoma and planned D_{mean} to parotid glands < 35 Gy is even more important to lower toxicity to the glands.

A remarkably difference between this study and previous publications is the limited weight loss in the patients with tumors in the oral cavity, oropharynx, larynx and hypopharynx. Other studies reported a mean weight loss up to 7.5 kg compared to 2.2 kg in this study [5,22,23]. In MAASTRO clinic, all HNSCC patients being irradiated are routinely offered intensive weekly counseling by dietitians. Moreover, all patients undergoing chemoradiotherapy receive a percutaneous radiologic gastrostomy

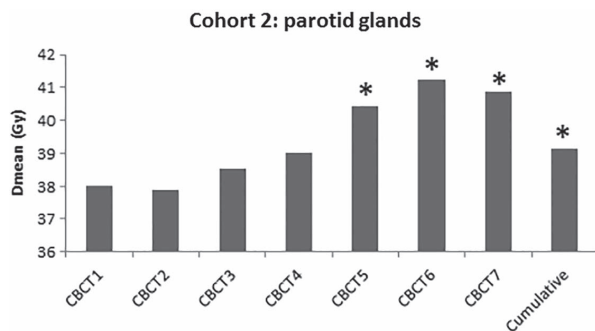


Figure 2. Cohort 2: D_{mean} (mean delivered dose) to parotid glands on weekly kV-CBCT scans in patients with nasopharyngeal carcinoma. *Significant increase of dose compared to kV-CBCT in first week of treatment.

(PRG) or percutaneous endoscopic gastrostomy (PEG) tube before start of the treatment. This may explain the lower weight loss. Notably, weight loss after the start of counseling by a dietitian in the first week was only 0.6 kg in six weeks.

As weight loss was hypothesized to be an important factor in dose differences for Cohort 1, the relatively stable weight in our study may also explain the lack of significant dose discrepancies, similar to the report by Height et al. [9].

Conversely, weight loss in patients with nasopharyngeal cancer was higher (4.4 kg), despite the same intensive counseling by dietitians. This weight loss may contribute to a dose discrepancy in this patient cohort. Notably, no correlation between weight loss and dose discrepancy to parotid glands was found, most probably due to a uniform distribution of weight loss [range (3.4, 6 kg)] or due to the low number of patients in this cohort. Multi-center studies need to reveal whether optimal nutritional support can prevent weight loss in HNSCC patients during (chemo)radiotherapy.

With this study, we demonstrated that the actually delivered dose does not seem to be inferior to the original treatment plan for the subsites oral cavity, oropharynx, larynx and hypopharynx. However, this study did not address the question whether a superior treatment plan can be generated during the course of (chemo)radiotherapy. Previous studies have shown contradictory results on the beneficial effect of replanning for head and neck patients [6,24]. Currently, MAASTRO clinic is participating in a multi-center study investigating dose-escalated radiotherapy and systemic therapy in 268 patients (the ARTFORCE study) [25]. In that study, a higher fraction and cumulative dose is given to the biological target volume (as defined by FDG-PET/CT), and therefore verification of delivered dose in close proximity to the OAR is even more important. This study may indicate if and for which patients replanning is beneficial.

Our study also has some limitations. First, in this study kV-CBCT images were used. Ideally CT scans should be used because these are more accurate than kV-CBCT images due to a higher resolution, less photon scatter and less artefacts. However, since no in-room CT scans are available in MAASTRO clinic, it was not possible to perform the study with CT scans. Second, the inter-observer variability in target volume and OAR delineation is a limitation. To reduce this variability, one single investigator manually adapted the structures according to the planning CT scan whenever necessary after these had been copied to the kV-CBCT images.

In conclusion, none of the 20 patients with tumors in oral cavity, oropharynx, larynx and hypopharynx

investigated had a potential clinical benefit from replanning: there was no relevant discrepancy between planned dose and actually delivered dose. Thus, weekly dose calculations may not be necessary for patients with tumors in these sites with no profound weight loss and no clinical signs of anatomical changes.

Patients with nasopharyngeal carcinoma showed a significant dose increase to parotid glands after Week 5 of treatment. Therefore, mid-treatment imaging may aid dose-guided treatment adaptation in this group of patients.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Appendix available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061210>.

Supplementary Figure 1–3 and Table I–II available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061210>.