Tissue/Dose Compensation to Reduce Toxicity from Combined Radiation and Chemotherapy for Advanced Head and Neck Cancers

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SUMMARY This study was undertaken to quantify the reduction in normal tissue complications resulting from the aggressive management of advanced head and neck cancers (AHNCs) utilizing tissue/dose compensation (TDC). Thirty-nine patients with AHNC were treated on an intensive chemotherapy + radiation regimen. Eighteen of 39 patients were treated using TDC; the remaining 21 patients were radiated without TDC (NTDC). Acute and chronic toxicities, swallowing, speech function, and quality of life were assessed. The TDC group had a smaller radiation dose gradient across the entire treatment volume. Unscheduled treatment breaks were required in 11% of TDC patients as compared with 43% of the NTDC group ($P = 0.04$). The TDC group had fewer Grade 3 or 4 acute and chronic toxicities and lower SOMA scores. At 3 months posttreatment, patients in the TDC group had better oral intake, lower pharyngeal residue, and better oropharyngeal swallowing efficiency and were able to swallow more bolus types. Patients in the TDC group also had better articulation. Use of TDC resulted in reduced treatment-related interruptions, decreased acute and chronic toxicities, and better speech and swallowing functions. Techniques to improve radiation dose conformity around the target tissues while decreasing the radiation dose to the normal tissues should be an integral part of aggressive combined modality therapy. © 2002 Wiley-Liss, Inc.

Key words: tissue compensator; intensity modulation; head and neck cancer; toxicity

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INTRODUCTION

Radiation alone or in combination with surgery has been the standard of care in the management of advanced head and neck squamous cell carcinoma. A recently published randomized trial documents the locoregional control rate and survival as well as acute and chronic toxicities produced when radiation alone is delivered using standard fractionation or altered fractionation to treat advanced head and neck cancers (AHNCs) [1].

Over the last decade, the intensity of therapy using chemotherapy and radiation has increased, resulting in decreased locoregional failure and improved survival [2–7]. Due to the aggressive nature of these treatments, toxicities have also increased. It is essential to document such toxicities to assess the benefit of multimodality therapy. Biochemical, physical, and technical measures should be implemented to reduce the incidence of these toxicities.

This study was undertaken to test the association between the use of missing tissue compensators and the ability of forward-planned, intensity-modulated radiation therapy to deliver a uniform dose across the radiation field and decrease the rate of acute and chronic toxicities observed in the management of AHNC.

MATERIALS AND METHODS

A total of 39 patients with AHNC were entered in an intramural Phase II concomitant chemoradiation trial and an NIH-funded Cancer Control Science Program for Head and Neck Cancer Rehabilitation (CCSP-HNCR). These patients were treated fairly uniformly using parallel-opposed radiation beams that gave high doses to the swallowing and speech organs. The treatment consisted of concomitant radiation and chemotherapy delivered over a period of 5 days followed by a 9-day break. The radiation was delivered at 150 cGy BID. The chemotherapy was comprised of Paclitaxel (Taxol), 5 FU, and hydrea. The 2-week cycle was repeated four to five times. Eighteen of 39 patients were treated using tissue or dose compensation (TDC); the remaining 21 patients were radiated without tissue or dose compensation (NTDC).

The first seven of the 39 patients were alternatively assigned to the TDC (three patients) or NTDC (four patients) groups. The remaining 32 patients were prospectively randomized to the TDC or NTDC groups.

Two methods were employed to modulate the radiation beam in order to achieve a relatively uniform dose throughout the treatment volume: 1) aluminum or Cerrobend missing tissue compensators, or 2) segmented multileaf collimator (MLC) fields obtained from forward planning in order to obtain dose uniformity. The first method adjusts the beam fluence based on missing tissue while ignoring the perturbation caused by detailed scatter calculations, whereas the second method adjusts the beam fluence using sequential shrinking fields to compensate for calculated excess dose as determined from 3D scatter calculations. However, experiments with a home-made head phantom molded out of candle wax revealed that the midsagittal dose distribution, as recorded on verification film, was not significantly different for the two methods.

Dose calculations are reported in two planes: the central axis (CA) plane (Plane 1) and a plane through the thinnest part within the radiation field (Plane 2). For patients in whom compensators were used, dose calculations were made with and without the compensator for comparative purposes. The dose distribution was observed in multiple planes.

Acute treatment toxicities are reported using National Cancer Institute (NCI) common toxicity criteria (CTC) v. 2.0, while chronic toxicities are reported using Radiation Therapy Oncology Group (RTOG) criteria and the Subjective Objective Management Analytic (SOMA) scale [8,9]. To be able to fully distinguish acute from chronic toxicities, 90 days posttreatment was used to score any chronic toxicity.

Swallowing function was examined with the modified barium swallowing procedure [10] using videofluorography (VFG). Each patient attempted to complete two swallows each of 1, 3, 5, and 10 ml of barium liquid and 1 ml of barium paste. Boluses were administered from a teaspoon or by slow release from a syringe. Fluoroscopic data were recorded on a 3-inch videotape at 30 frames per second. During the study, the fluoroscopy tube was focused on the lips anteriorly, the cervical vertebrae posteriorly, the soft palate superiorly, and the bifurcation of the esophagus and airway inferiorly. Speech tasks consisted of an audio recording of a 6 to 7-min conversational speech sample and a reading of the sentence version of the Fisher-Logemann Test of Articulation Competence [11]. Data reduction for swallowing and speech was completed according to methods described by Pauloski et al. [12]. Oropharyngeal swallowing efficiency (OPSE), defined as the approximate percentage of the bolus swallowed into the esophagus divided by total transit time, is a global measure that describes the interaction of the speed of movement of the bolus and the safety and efficiency of the mechanism in clearing material from the oropharynx while preventing aspiration [13].

Each patient’s salivary production was quantified pretherapy; and at several points posttherapy by taking the difference in the weight of a folded sterile
Prospective quality of life (QOL) assessment included the following well-validated instruments: the Functional Assessment of Cancer Therapy – Head and Neck Version (FACT-H&N) [15,16], the Performance Status Scale for Head and Neck Cancer (PSS-HN) [17,18], and selected items from the McMaster Radiotherapy Questionnaire [19], which assesses patients’ perceptions of treatment-related side effects [20,21]. Patients were assessed pretreatment, during treatment, and at 3 months posttreatment. QOL analyses aimed to examine the group (TDC vs. NTDC) differences at 3 months, while controlling for pretreatment values. For PSS-HN subscales and McMaster items, patients were categorized, based on a specified value indicating moderate to severe dysfunction, as having improved, stayed the same, or worsened. For example, if a patient scored above 50 on the Normalcy of Diet scale pretreatment and 50 or below posttreatment, he/she would be coded as “worsened.” Categorization was done separately for each subscale or item [18,20,21].

The TDC and NTDC groups were compared using the t-test for continuous measures and Fisher’s Exact test for dichotomous measures [22]. Swallowing and speech measures were compared between the two groups by using analysis of covariance [22] with baseline measures as the covariate. Differences in QOL measures (% improved, % same, % worse) were compared between the two groups through Fisher’s Exact test. Pretreatment minus 3-month difference scores on the FACT were compared between the two patient groups using independent sample t-tests [22], while statistical analyses were done using SAS (Cary, NC) [23].

**RESULTS**

Of 39 patients entered in this study, 18 were irradiated using tissue or dose compensation (TDC group) and 21 without tissue or dose compensation (NTDC group). There were no significant differences between the two groups with reference to gender, race, age, irradiated field, site or stage of tumors, and mean length of follow-up (Table 1). There were no statistically significant differences between the two groups in the number of chemotherapy and radiotherapy cycles, radiation field size, number of fractions, the chemotherapy drug doses, or the midplane dose at the central axis (Table 2). However, the patients treated with TDC had a smaller radiation dose gradient (Fig. 1) across the treatment volume (Plane 1 maximum dose $P = 0.01$ and Plane 2 maximum dose $P < 0.001$). Patients in the TDC group required significantly fewer unscheduled treatment breaks of 1 or more weeks (2 out of 18 or 11% of patients),
compared with 43% (9 out of 21) of the patients in the NTDC group \( (P = 0.04, \text{Table 2}) \).

**Acute Treatment Toxicity (CTC Criteria)**

Patients were monitored for local acute toxicity during and up to 90 days posttreatment. Table 3 summarizes the Grade 3 or 4 toxicities observed in the two patient groups. There were no significant differences in disorders except for the pain category. However, there was a trend toward more acute toxicities in the NTDC group. As a result of more acute toxicities, patients in the NTDC group required more treatment breaks (Table 2).

**Chronic Toxicity (RTOG)**

Chronic toxicity was defined as toxicity observed \( \geq 90 \) days posttreatment. Table 4 shows the Grade 3 or 4 worst chronic toxicities observed in TDC and the NTDC groups. Skin toxicity was statistically significantly higher in the NTDC group. In most of the organs studied there is a definite trend toward higher, Grade 3 or 4 toxicities in the NTDC group. A similar trend toward higher toxicity was observed at the last follow-up for the two groups of patients (data not shown).

**Chronic Toxicity (SOMA Scale)**

There were no statistically significant differences in the worst toxicities between the TDC and NTDC groups using the SOMA scale (Table 5). However, there was a definite trend toward higher SOMA scale scores in the NTDC group, indicating greater toxicities in this group of patients (Table 5). The similar trend of higher toxicity was observed at the last follow-up between the two groups of patients.

**Descriptive Analysis**

In the NTDC group, four patients developed postcricoid or proximal esophageal strictures, while three additional patients developed severe complications: laryngeal strictures, laryngeal necrosis, and mandibular fracture. None of the patients in the TDC group developed strictures, necrosis, or fractures (Table 6).

**Saliva Weight**

The mean salivary weight (SEM) pretreatment and at 3 months posttreatment was 4.07 (0.51) vs. 3.90 (0.62) and 1.80 (0.75) vs. 0.79 (0.27) g in the NTDC and TDC groups, respectively. There was no significant difference in salivary secretions pretreatment and up to 3 months posttreatment between the TDC and NTDC patient groups. Salivary secretions continued to decrease with time and did not recover in either group of patients.

**Oral Intake**

Patients in the TDC group were able to maintain better oral intake at all time points, although not statistically significantly so. Table 7 summarizes the number of patients whose oral intake was \( \geq 50\% \) of their nutrition in the TDC and NTDC groups.

**Swallowing Data (VFG Studies)**

Not all patients were able to swallow all the trials of each consistency because of refusal to swallow, difficulty in swallowing, or the speech-language pathologist’s judgment that the clinical risk was too great to introduce or continue with a specific consistency during the VFG evaluation. At 3 months posttreatment, patients in the TDC group were able to swallow all tested bolus types in higher percentages than the pa-

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**Table 2. Treatment Data: Cumulative Mean RT/Chemotherapy Doses (SEM)**

<table>
<thead>
<tr>
<th></th>
<th>NTDC (n = 21)</th>
<th>TDC (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cycles:</td>
<td>4</td>
<td>4</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Taxol dose (mg)</td>
<td>864 (52)</td>
<td>836 (61)</td>
<td>0.89</td>
</tr>
<tr>
<td>5FU dose (mg)</td>
<td>27,635 (885)</td>
<td>26,552 (1035)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hydrea dose (gms)</td>
<td>27 (2)</td>
<td>26 (1)</td>
<td>0.86</td>
</tr>
<tr>
<td>Radiation field size**</td>
<td>Primary site &amp; regional nodes 16.1 (2.4)</td>
<td>15.7 (2.6)</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>Supraclavicular field 14.8 (3.3)</td>
<td>13.3 (1.6)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Midplane RT dose 7014 (113)</td>
<td>6983 (130)</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Plane 1 max. dose 7625 (151)</td>
<td>7265 (143)</td>
<td>0.01*</td>
</tr>
<tr>
<td></td>
<td>Plane 2 max. dose 8378 (165)</td>
<td>7355 (141)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Patients with treatment breaks 9 (43%)</td>
<td>2 (11%)</td>
<td>0.04*</td>
<td></td>
</tr>
<tr>
<td>Number of fractions</td>
<td>47 (1)</td>
<td>45 (2)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

* *P < 0.05.
** Equivalent square in centimeters.

TDC: tissue/dose compensation; NTDC: no tissue/dose compensation.
Fig. 1. Percent isodose distribution in the sagittal plane. A: Without tissue/dose compensation (NTDC). B: With tissue/dose compensation (TDC).
patients in the NTDC group and significantly more so with the 3 and 5 ml volumes (Table 8). There were no statistically significant differences in the swallowing measures between the TDC and NTDC groups at 3 months posttreatment. However, there was a definite trend of better swallowing measures, including the global measure of oropharyngeal swallowing efficiency (OPSE) in the group of patients treated with TDC (Table 9).

**Speech Measures**

Table 10 summarizes the speech data for the TDC and NTDC groups at 3 months posttreatment. There were no statistically significant differences between the two groups. However, individual consonant speech sounds were consistently more correctly produced in the TDC group. The difference in correct articulation of all consonants approaches significance in favor of the TDC group.

**Quality of Life**

Of the 39 patients enrolled in the study, pretreatment and 3-month follow-up data are available on 26, 13 in each group. Table 11 presents the number and percentage of patients by group whose symptoms or performance was worse at 3 months when compared to pretreatment. Eight patients (62%) in the NTDC group had more restricted diets at 3 months than pretreatment (i.e., went from above 50 to 50 or below on the diet scale), compared to five (38%) patients in the TDC group. The pattern of change in difficulty with swallowing was statistically significantly different between the two groups, with more patients in the NTDC group getting worse (9 vs. 5). On many of the
other performance outcomes and functions/symptoms evaluated, there was a trend for more patients in the NTDC group to be more symptomatic at 3 months posttreatment than they were pretreatment. In contrast, there were no significant differences nor trend towards differences on any of the FACT subscales or on the overall FACT.

**DISCUSSION**

The therapeutic gains obtained with the use of aggressive treatments are offset by the widely used standard radiotherapeutic techniques that treat irregularly shaped body parts, such as head and neck and breast areas, and result in excessive normal tissue doses that can potentially cause increased normal tissue complications [24–27]. The intensity of the radiation beam can be modulated either to deliver uniform doses to decrease dosimetric “hot spots” in the normal tissues, as done in our study, or the photon fluence can be changed over time and space to increase dose conformity to the target tissue and decrease radiation to normal tissues [28,29]. 3D conformal techniques to deliver radiation can also be employed to improve the therapeutic ratio in the management of head and neck cancers [30,31].

There are no published clinical studies of head and neck cancers that systematically document the preservation of normal tissue function with the use of TDC. Few clinical studies of head and neck cancers have utilized beam modulation, including intensity-modulated radiotherapy (IMRT), to preserve normal organ function. Eisbruch et al. [32,33] and Dawson et al. [34] used static, multisegmental IMRT to treat a group of selected patients with head and neck cancer to preserve salivary gland function without compromising target coverage. Chao et al. [35] were also able to spare salivary function and improve QOL by modulating radiation intensity. Our study systematically documents the decrease in acute and late complications and better QOL, speech and swallowing functions with the use of a 3D tissue compensator and forward-planned static multisegment radiotherapy to obtain uniform dose distribution.

In this study, there were no significant differences in patient characteristics, tumor stage and sites,

### Table 9. Swallowing Measures: Mean (SEM) for Boluses of 1 ml Liquid and Any Paste at 3 Months Posttreatment

<table>
<thead>
<tr>
<th></th>
<th>NTDC (n = 6)</th>
<th>TDC (n = 7)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharyngeal residue (%)</td>
<td>35.1 (16.0)</td>
<td>12.5 (7.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>OPSE (%/s)*</td>
<td>66 (17)</td>
<td>73 (12)</td>
<td>0.7</td>
</tr>
<tr>
<td>1 cc Paste</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngeal residue (%)</td>
<td>27.9 (8.8)</td>
<td>10.5 (3.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>OPSE (%/s)*</td>
<td>42 (7)</td>
<td>54 (5)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*OPSE: oropharyngeal swallowing efficiency (percent per second); TDC: tissue/dose compensation; NTDC: no tissue/dose compensation.

### Table 10. Correct Production of Speech Sounds: Mean (SEM) of 3-Month Speech Measures

<table>
<thead>
<tr>
<th></th>
<th>NTDC (n = 9)</th>
<th>TDC (n = 6)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>/b, b/</td>
<td>100 (0)</td>
<td>100 (0)</td>
<td>—</td>
</tr>
<tr>
<td>/d, d/</td>
<td>90.9 (0)</td>
<td>90.9 (0)</td>
<td>—</td>
</tr>
<tr>
<td>/k, g/</td>
<td>83.3 (8.6)</td>
<td>100 (9.5)</td>
<td>0.24</td>
</tr>
<tr>
<td>/M/</td>
<td>100 (0)</td>
<td>100 (0)</td>
<td>—</td>
</tr>
<tr>
<td>/f, v/</td>
<td>91.7 (6.2)</td>
<td>100 (6.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>/θ, ð/</td>
<td>88.6 (4.6)</td>
<td>97.0 (5.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>/s, z/</td>
<td>83.3 (13.6)</td>
<td>100 (15.0)</td>
<td>0.45</td>
</tr>
<tr>
<td>/f, z/</td>
<td>70.8 (11.9)</td>
<td>83.0 (13.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>/h/</td>
<td>100 (0)</td>
<td>100 (0)</td>
<td>—</td>
</tr>
<tr>
<td>/ʃ, ʒ/</td>
<td>83.3 (12.4)</td>
<td>100 (13.6)</td>
<td>0.39</td>
</tr>
<tr>
<td>Glides</td>
<td>100 (0)</td>
<td>100 (0)</td>
<td>—</td>
</tr>
<tr>
<td>Nasals</td>
<td>100 (0)</td>
<td>100 (0)</td>
<td>—</td>
</tr>
<tr>
<td>All consonants</td>
<td>88.3 (3.9)</td>
<td>100 (4.3)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

TDC: tissue/dose compensation; NTDC: no tissue/dose compensation.

### Table 11. Number of Patients, by Group, with More Problems at 3-Month Posttreatment Than Pretreatment

<table>
<thead>
<tr>
<th>Performance outcome1</th>
<th>NTDC (n = 13)</th>
<th>TDC (n = 13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet (soft foods)</td>
<td>8 (62%)</td>
<td>5 (38%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Eating in public (limited)</td>
<td>7 (54%)</td>
<td>4 (31%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Speech (difficult to understand)</td>
<td>2 (15%)</td>
<td>0</td>
<td>0.48</td>
</tr>
<tr>
<td>Side effects/symptoms2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10 (77%)</td>
<td>10 (77%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>9 (69%)</td>
<td>5 (38%)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Sticky saliva</td>
<td>8 (61%)</td>
<td>8 (61%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Throat pain</td>
<td>6 (46%)</td>
<td>5 (38%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Mouth pain</td>
<td>5 (38%)</td>
<td>4 (33%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hoarse voice</td>
<td>5 (38%)</td>
<td>3 (23%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Difficulty tasting</td>
<td>2 (16%)</td>
<td>4 (31%)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

*P ≤ 0.05
1Data indicate percent of patients scoring above 50 pretreatment and 50 or below at 3 months on the Performance Status Scale for Head and Neck Cancer.
2Data indicate percent of patients reporting mild or no problems (4–7 on seven-point Likert scale) pretreatment and moderate to severe problems (1–3) at 3 months posttreatment on selected items from the McMaster Radiotherapy Questionnaire.
TDC: tissue/dose compensation; NTDC: no tissue/dose compensation.
radiated structures, radiation doses in midplane at the central axis, number of chemotherapy cycles, and doses between the TDC and NTDC groups. However, the qualitative comparison of dose distribution between the TDC and NTDC plans demonstrates that 15% to 20% of hot spots in the thin portion of the neck were reduced to within 5% of the prescribed dose with the use of TDC. This 10% to 20% higher dose over the prescribed dose in the anterior neck not only occurs on the skin surface but throughout the anterior volume, including larynx and pharynx at this location (Fig. 1). These dosimetric “hot spots” in the NTDC group resulted in increased acute and chronic toxicities, with some of the patients requiring medical interventions to manage post-cricoid strictures, laryngeal stenosis, laryngeal necrosis, and mandibular fracture. Because of acute toxicities, patients in the NTDC group required a minimum of 1 week unscheduled treatment breaks in a higher percentage than the TDC group. Due to the prolonged acute effects with the treatment regimen in our study, we used ≥90 days posttreatment, as opposed to the RTOG criteria of 90 days, from the start of treatment to score chronic toxicities. We were not able to compare dose-volume histograms between the two groups because CT data were not available for a number of the patients in the NTDC group. This information would have been helpful for further comparison between the two groups.

There was no difference in saliva weight between the TDC and NTDC patients in our study because both groups received high radiation doses to the salivary glands in excess of the threshold for permanent xerostomia [33]. We did not observe improvement in salivary secretion with time in either the TDC or the NTDC group.

Subjective and objective assessments of swallowing and speech function also revealed generally better functional outcomes in the patients in the TDC group. The patients in the TDC group experienced better QOL when assessed by various performance outcomes and symptoms. More patients in the TDC group were able to take >50% of their nutrition by oral intake than in the NTDC group. More patients in the TDC group were also able to swallow multiple bolus types, had lower pharyngeal residue, i.e., more normal OPSE, and a greater percentage of correct pronunciation of all consonants as compared with patients in the NTDC group. Data on speech and swallowing were available for only a limited number of patients due to patient dropout. Additionally, not all patients were able to swallow two trials of each food consistency, or the speech-language pathologist may have judged it risky to introduce or continue with a specific consistency during the VFG study. The swallowing dysfunctions observed in our study are similar to the ones reported by Lazarus et al. [36,37] following chemotherapy + radiation for the treatment of head and neck cancers. Impaired swallowing motility may be the result of edema, fibrosis, and reduced salivary flow caused by radiation and chemotherapy.

**CONCLUSION**

Our results suggest that there is a systematic trend toward decreased acute and chronic toxicities, better speech and swallowing function, and quality of life in the group of patients treated with TDC to decrease “hot spots” in tissues. The relatively small number of patients in the study may explain the lack of statistical significance of our observations in a number of the end-points studied. In order to reduce toxicities and maintain better functional outcomes, various techniques to improve therapeutic ratio should be evaluated and potentially become the standard of care in the treatment of head and neck cancer managed with aggressive multimodality therapy.

**REFERENCES**


