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Swallowing dysfunction

# Patterns of long-term swallowing dysfunction after definitive radiotherapy or chemoradiation

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ABSTRACT

*Objectives:* To identify patterns of long-term, radiation-induced swallowing dysfunction after definitive radiotherapy with or without chemotherapy (RT or CHRT) and to determine which factors may explain these patterns over time.

*Material and methods:* The study population consisted of 238 consecutive head and neck cancer patients treated with RT or CHRT. The primary endpoint was ⩾grade 2 swallowing dysfunction at 6, 12, 18 and 24 months after treatment. Cluster analysis was used to identify different patterns over time. The differences between the mean dose to the swallowing organs at risk for each pattern were determined by using dose maps.

*Results:* The cluster analysis revealed five patterns of swallowing dysfunction: low persistent, intermediate persistent, severe persistent, transient and progressive. Patients with high dose to the upper pharyngeal, laryngeal and lower pharyngeal region had the highest risk of severe persistent swallowing dysfunction. Transient problems mainly occurred after high dose to the laryngeal and lower pharyngeal regions, combined with moderate dose to the upper pharyngeal region. The progressive pattern was mainly seen after moderate dose to the upper pharyngeal region.

*Conclusions:* Various patterns of swallowing dysfunction after definitive RT or CHRT can be identified over time. This could reflect different underlying biological processes.



Radiation-induced swallowing dysfunction is a clinically relevant late side effect after definitive radiotherapy (RT) or chemoradiation (CHRT) in patients with head and neck squamous cell carcinoma (HNSCC) which has a substantial impact on health-related quality of life (HRQoL) [1–3]. During and shortly after RT or CHRT, almost all HNSCC patients suffer from a certain degree of swallowing dysfunction. In most cases, acute swallowing dysfunction markedly improves during the first months after treatment. However, 2 years after treatment, many patients still suffer from grade 2 or higher swallowing dysfunction [4–9].

Recently, we reported on a multivariable Normal Tissue Complication Probability (NTCP) model for grade 2–4 swallowing dysfunction at 6 months after definitive RT or CHRT ($SWAL_{M6}$). In that study, the mean dose to the superior pharyngeal constrictor muscle (superior PCM) and the mean dose to the supraglottic larynx were the two most important prognostic factors for $SWAL_{M6}$ [10]. One of the limitations of that study was that the primary endpoint was taken at 6 months after completion of treatment, while other investigators showed that swallowing dysfunction may improve or deteriorate beyond 6 months. Consequently, patients may show various patterns over time [5,6,8,9], which may reflect various underlying radiobiological mechanisms. For instance, swallowing dysfunction at 6 months that gradually decreases during longer follow-up is more likely due to recovering mucositis and laryngeal edema, while progressive swallowing dysfunction after a longer period (e.g. requiring dilatation) is more likely to result from progressive fibrosis. We decided to conduct a prospective cohort study to determine which factors are related to these various patterns. After our first swallowing dysfunction analysis at 6 months, all patients remained included in a standard follow-up program,

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which included a subsequent prospective assessment of swallowing dysfunction up to 24 months after completion of treatment.

The purpose of the present study was to identify patterns of long-term, radiation-induced swallowing dysfunction after completion of definitive RT or CHRT and to determine which factors could explain these patterns.

## Methods and materials

### *Patients*

The study population of this prospective cohort study consisted of 238 consecutive patients, treated from 1997 at two medical centers in the Netherlands: the VU University Medical Center (VUMC), Amsterdam or the University Medical Center Groningen (UMCG), Groningen. For the purpose of this analysis, we only included the 238 patients with a minimal follow-up of 24 months and a maximum of 1 missing value on swallowing function. We decided to limit the analysis up to 24 months as the number of patients dropped beyond that interval due to end of follow-up or death. All patients were treated with curatively intended conventional three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT) for HNSCC, either alone or in combination with concomitant chemotherapy. All patients were subjected to a prospective standard follow-up program including assessment of toxicity and HRQoL prior to, during and at regular intervals after treatment [10–12].

Patients who previously underwent surgery, RT or CHRT, who had prior malignancies, and/or distant metastases were excluded. Patients with RTOG grade 2–4 swallowing dysfunction at baseline were also excluded to ensure that the observed swallowing dysfunction was induced by radiation treatment and not by tumor extension. The patient characteristics are listed in Table 1.

### *Endpoints*

The endpoint was defined as the grade of swallowing dysfunction according to the RTOG/EORTC Late Radiation Morbidity Scoring Criteria as assessed at 6, 12, 18 and 24 months after completion of RT or CHRT.

### *Treatment*

Until the end of 2007, the majority of patients were treated with 3D-CRT. Since 2008 patients were mainly treated with IMRT. Regions of interest, RT planning and optimization, and chemotherapy schedules were described previously in more detail [10–12].

All organs at risk (OARs), including the salivary glands, and the swallowing organs at risk (SWOARs), including the superior, middle and inferior PCM, the cricopharyngeal muscle, the esophagus inlet muscle (EIM), the cervical esophagus (CE), the base of tongue (BOT) and the supraglottic and glottic larynx, were delineated as previously described [13,14].

### *Statistics*

In order to classify the patients into patterns of swallowing dysfunction over time, we used a two-step cluster analysis. Cluster analysis creates groups of cases that are homogeneous within themselves, but heterogeneous between each other, based on a predefined set of variables [15–17]. The degree of swallowing dysfunction at baseline and at all subsequent time points (at 6, 12, 18 and 24 months) were considered for cluster modeling based on their contribution to characterizing the patterns of long-term, radiation-induced swallowing dysfunction.

The baseline characteristics for the various pattern groups were then compared on an explorative basis, thus comparing patients with no or minor swallowing dysfunction to the other patterns, using *T*-Test or chi-squared test, whenever appropriate.

For all the SWOARs we produced DVHs for all individual patients. The differences between the mean dose to the SWOARs of each pattern were determined using dose maps. Dose maps are tables with the mean dose for each SWOAR, for each patient grouped per pattern. By using a color scale (from white (lowest $D_{mean}$) to red (highest $D_{mean}$)) the differences in delivered dose

**Table 1**
Patient characteristics.

| Characteristics | | All patients | | Low persistent | | Moderate persistent | | Severe persistent | | Transient | | Progressive | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % |
| Sex | Male | 175 | 74 | 105 | 84 | 25 | 64 | 11 | 58 | 25 | 69 | 9 | 47 |
| | Female | 63 | 26 | 20 | 16 | 14 | 36 | 8 | 42 | 11 | 31 | 10 | 53 |
| Age, years | 18–65 | 156 | 66 | 76 | 61 | 27 | 69 | 15 | 79 | 27 | 75 | 11 | 58 |
| | >65 | 82 | 34 | 49 | 39 | 12 | 31 | 4 | 21 | 9 | 25 | 8 | 42 |
| Tumor classification | T1–T2 | 161 | 68 | 98 | 78 | 25 | 64 | 7 | 37 | 19 | 53 | 12 | 63 |
| | T3–T4 | 77 | 32 | 27 | 22 | 14 | 36 | 12 | 63 | 17 | 47 | 7 | 37 |
| Node classification | N0 | 154 | 65 | 103 | 82 | 24 | 62 | 2 | 11 | 15 | 42 | 10 | 53 |
| | N+ | 84 | 35 | 22 | 18 | 15 | 38 | 17 | 89 | 21 | 58 | 9 | 47 |
| Primary Site | Larynx | 136 | 57 | 96 | 77 | 20 | 51 | 2 | 11 | 12 | 33 | 6 | 32 |
| | Oropharynx | 71 | 30 | 20 | 16 | 13 | 33 | 11 | 58 | 18 | 50 | 9 | 47 |
| | Oral cavity | 11 | 5 | 4 | 3 | 2 | 5 | 2 | 11 | 1 | 3 | 2 | 11 |
| | Hypopharynx | 12 | 5 | 3 | 2 | 1 | 3 | 3 | 15 | 4 | 11 | 1 | 5 |
| | Nasopharynx | 8 | 3 | 2 | 2 | 3 | 8 | 1 | 5 | 1 | 3 | 1 | 5 |
| Treatment modalities | Conventional RT | 33 | 14 | 21 | 17 | 3 | 8 | 2 | 10 | 4 | 11 | 3 | 16 |
| | Accelerated RT | 155 | 65 | 93 | 74 | 27 | 69 | 6 | 32 | 19 | 53 | 10 | 53 |
| | Chemoradiation | 50 | 21 | 11 | 9 | 9 | 23 | 11 | 58 | 13 | 36 | 6 | 31 |
| Radiation technique | 3D-CRT | 155 | 65 | 88 | 70 | 19 | 49 | 12 | 63 | 21 | 58 | 15 | 79 |
| | IMRT | 83 | 35 | 37 | 30 | 20 | 51 | 7 | 37 | 15 | 42 | 4 | 21 |
| Neck irradiation | No or unilateral | 66 | 28 | 48 | 38 | 9 | 23 | 0 | 0 | 4 | 11 | 5 | 26 |
| | Bilateral | 172 | 72 | 77 | 62 | 30 | 77 | 19 | 100 | 32 | 89 | 14 | 74 |
| Baseline swallowing dysfunction (RTOG) | Grade 0 | 209 | 88 | 115 | 92 | 32 | 82 | 16 | 84 | 29 | 81 | 17 | 89 |
| | Grade 1 | 29 | 12 | 10 | 8 | 7 | 18 | 3 | 16 | 7 | 19 | 2 | 11 |

*Abbreviations:* RT = radiotherapy, 3D-CRT = three-dimensional conformal RT, IMRT = intensity-modulated RT