

Dysphagia

Impact on Quality of Life after Radio(chemo)therapy of Head and Neck Cancer

Julia Maurer¹, Matthias Hipp¹, Christof Schäfer², Oliver Kölbl¹

Background: In the past, xerostomia was considered one of the most important determining factors of quality of life (QoL) after radiotherapy (RT) of the head and neck region. In addition, more recent studies have shown that RT-induced dysphagia has an essential influence on the QoL.

Patients and Methods: Between September 2005 and August 2007, 35 patients with locally advanced squamous cell carcinoma of the head and neck region were included in the prospective study. Patients were treated by IMAT (intensity-modulated arc therapy) or IMRT (intensity-modulated radiotherapy) planned on 3D imaging. A total of 28 patients (80%) received concomitant chemotherapy. The evaluation of QoL (EORTC QLQ - C30, H&N C-35) and toxicities (CTC 2.0) were assessed at the beginning of, during, and after RT as well as up to 12 months after the end of therapy.

Results: At the end of therapy, 86% of the patients experienced difficulties in swallowing (62% CTC II–III^o). Twelve months after the end of treatment, 15% still suffered from dysphagia CTC II–III^o. Concomitant chemotherapy exacerbated the incidence and gravity of dysphagia, resulting in increasing dietary problems. QoL (EORTC) was significantly affected by dysphagia. In particular, the global state of health and QoL were influenced at the end of treatment ($p = 0.033$) and at a later stage ($p = 0.050$).

Conclusion: The findings of this study suggest that more emphasis should be placed on structured clinical diagnostics, therapy, and rehabilitation of deglutition problems. This means in particular to not only spare the parotids while planning the irradiation, but also to take into consideration the important structures for deglutition, like the retropharyngeal muscles.

Key Words: Carcinoma of the head and neck · Radiotherapy · Dysphagia · Quality of life

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Dysphagie – Einfluss auf die Lebensqualität nach Radio(chemo)therapie bei Kopf-Hals-Tumoren

Hintergrund: Die Xerostomie galt in der Vergangenheit als einer der wichtigsten determinierenden Faktoren der Lebensqualität (LQ) nach Bestrahlung der Kopf-Hals-Region. In aktuellen Studien hatte aber auch die radiogen induzierte Dysphagie einen wesentlichen Einfluss auf die LQ.

Patienten und Methoden: 35 Patienten mit lokal fortgeschrittenen Plattenepithelkarzinomen der Kopf-Hals-Region wurden zwischen 09/05 und 08/07 in die prospektive Studie eingeschlossen. Die Bestrahlung (RT) erfolgte 3D-CT-geplant in IMAT- bzw. IMRT-Technik. 28 Patienten (80%) erhielten eine simultane Chemotherapie. Die Evaluation der LQ (EORTC QLQ - C30, H&N C-35) und der Toxizitäten (CTC 2.0) erfolgte vor Beginn, während und im Anschluss an die RT sowie im weiteren Verlauf bis zu 12 Monaten nach Abschluss der Therapie.

Ergebnisse: Nach Abschluss der Therapie gaben 86% der Patienten Schluckbeschwerden an (62% CTC II–III^o). 12 Monate nach Behandlungsende litten noch 15% der Patienten an Dysphagie CTC II–III^o. Die Gabe einer simultanen Chemotherapie beeinflusste die Inzidenz und Stärke der auftretenden Dysphagie und führte somit zu verstärkten Ernährungsproblemen. Es zeigte sich eine deutliche Beeinträchtigung der LQ (EORTC) durch die radiogen induzierte Dysphagie. Insbesondere der globale Gesundheitszustand und die globale LQ wurden sowohl nach Abschluss der Behandlung ($p = 0,033$) als auch im weiteren Verlauf ($p = 0,050$) negativ beeinflusst.

Schlussfolgerung: Die Ergebnisse dieser Arbeit sollten Anlass sein, zukünftig einer strukturierten Diagnostik, Therapie und Rehabilitation von Schluckstörungen mehr Bedeutung zukommen zu lassen und insbesondere bei der Bestrahlungsplanung nicht nur Wert auf die Schonung der Parotiden, sondern auch auf die der am Schluckakt beteiligten Strukturen, wie z. B. der retropharyngealen Muskulatur, zu legen.

Schlüsselwörter: Kopf-Hals-Tumoren · Strahlentherapie · Dysphagie · Lebensqualität

¹Department of Radiotherapy, Regensburg University Medical Center, Regensburg, Germany,

²Department of Radiotherapy, Hospital St. Elisabeth Straubing, Straubing, Germany

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Introduction

In previous assessments of the short- and long-term adverse reactions caused by radiotherapy of the head and neck region, xerostomia was viewed as the most important determining factor of quality of life. By using intensity-modulated radiotherapy (IMRT), other toxicities (e.g., dysphagia) have become more important concerning its influence on quality of life. Several studies have shown a high impact of radiotherapy (RT)-induced dysphagia on quality of life [15, 16, 24]. The reasons for difficulties in swallowing can either lie in the tumor itself, they can result from surgery, or be caused by radiotherapy. Long-term dysphagia is generally due to changes in the muscle layer (constriction), stenosis, and ulcers. Finally, radiotherapy-induced xerostomia also considerably contributes to difficulties in swallowing. The main focus of the present paper was to elaborate on the influence of dysphagia on the quality of life [6, 29, 30, 32].

Patients and Methods

Patients

A total of 35 patients with squamous cell carcinoma of the head and neck, who were irradiated between September 2005 and August 2007, were considered in the present study. The patients' characteristics are listed in Table 1. During this time, a total of 210 patients with head and neck cancer were treated in our clinic. All patients were given the chance to take part the study.

Table 1. Patients' characteristics (multiple answers permitted).

Tabelle 1. Patientencharakteristika (Mehrfachnennungen möglich).

Characteristic	Patients n (%)
Total	35 (100)
Gender	
Male	31 (89)
Female	4 (11)
Grade	
G2	28 (80)
G3	7 (20)
Stage	
I	1 (3)
II	1 (3)
III	3 (8)
IV	30 (86)
Tumor site	
Oropharynx	19 (54)
Oral cavity	7 (20)
Larynx/hypopharynx	12 (34)
Nasopharynx	2 (6)
Chemotherapy	
No	7 (20)
Yes	28 (80)
Operation	
No	21 (60)
Yes	14 (40)

Scoring

Quality of life and toxicities, especially dysphagia, were the principal point of evaluation. Therefore, the modules EORTC QLQ - C30 (versions 3.0) and H&N 35 of the EORTC were used before therapy, at the end of therapy, and after 6 and 12 months. Additionally toxicities were graded according to the criteria of CTC (version 2.0) on a weekly basis during radiation and 6 weeks after. Finally, 6 and 12 months after the end of treatment, toxicity was analyzed again using RTOG/EORTC in order to assess late radiation morbidity.

Radiotherapy

Of the 30 patients (85.7%) treated by IMAT (intensity-modulated arc therapy) [4], 21 (60%) patients were treated with a boost up to a mean total dose of 66.34 Gy (55.76–71.24 Gy), and 9 patients (25.7%) received hyperfractionated and accelerated irradiation with simultaneous integrated boost and a mean total dose of 70.6 Gy (69.6–72 Gy). Five patients (14.3%) were treated with IMRT. In 3 cases, the boost was carried out sequentially up to a total dose of 71 Gy (69.80–72.26 Gy). In 2 cases, an integrated boost was used up to a total dose of 70.2 and 74 Gy. During this period of time, the above mentioned techniques were routinely used in our clinic.

Chemotherapy

Chemotherapy was given according to three different protocols, depending on the general health condition of the patients and the preceding surgery: 19 patients (54.3%) received cisplatin monotherapy once a week (40 mg/m²) for 4–6 cycles; 7 patients (20%) were treated with a combination of 5-fluouracil (24-h infusion for 5 days in week 1 of radiotherapy) (600 mg/m²) and mitomycin (10 mg/m² weeks 1 and 5); 2 patients (5.7%) received 5-fluouracil (vide supra) in combination with cisplatin (30 mg/m²) once a week for 6 cycles.

Statistical Analysis

SPSS Windows® (LEAD Technologies, Inc., Version 15.0) was used for statistical evaluation. A p-value ≤ 0.05 was regarded as significant. A significance test was performed on time series data using the Wilcoxon test for combined samples. In order to compare sample groups with respect to certain items, the Mann-Whitney U-test was used for independent samples. Statistical correlations were tested using the Spearman and Pearson correlation coefficient, respectively. The evaluation date was August 31, 2009. At the beginning of the therapy, data of 35 patients were evaluated, at the end of therapy data of 34 patients, after 6 months data of 24 patients, and after 12 months of follow-up data of 21 patients. Stop criteria were death, relapse of the cancer, lack of compliance, or extreme toxicity (e.g., mucositis).

Results

Incidence and gravity of dysphagia over the course of time are listed in Tables 2 and 3. Before therapy, 46% of the patients reported difficulties in swallowing; at the end of therapy, 89%

Table 2. Acute dysphagia (CTC) (percent). A: before therapy, B: end of therapy, C: follow-up 6 weeks.**Tabelle 2.** Akute Dysphagie (CTC) (Prozent), A: vor Therapiebeginn, B: bei Therapieabschluss, C: 6 Wochen nach Therapie.

	CTC 0°	CTC I°	CTC II°	CTC III°	CTC IV°
A	54	37	9	0	0
B	11	27	35	27	0
C	33	26	33	8	0

Table 3. Late dysphagia (CTC; RTOG/EORTC) (percent). D: follow-up 6 months, E: follow-up 12 months.**Tabelle 3.** Chronische Dysphagie (CTC; RTOG/EORTC) (Prozent), D: 6 Monate nach Therapie, E: 12 Monate nach Therapie.

	CTC 0°/ RTOG 0°	CTC I°/ RTOG I°	CTC II°/ RTOG II°	CTC III°/ RTOG III°	CTC IV°/ RTOG IV°
D	55	33	4	8	0
E	52	33	10	5	0

of the patients experienced dysphagia. After 6 months, 12% of the patients still complained about moderate to severe (CTC II–III°/RTOG II–III°) difficulties in swallowing, while 15% of the patients still reported having difficulties after 12 months. CTC-I°/RTOG I° dysphagia still appeared in an additional 33% of patients after 12 months. At no time was CTC IV°/RTOG IV° dysphagia observed.

The chronological change of the dysphagia (median) is shown in Figure 1. Discomfort caused by dysphagia already increased in week 1 of treatment (median I°, $p < 0.01$) and reached its maximum at the end of week 4 (median II°). This continued up to the end of therapy. A significant decrease in dysphagia (median I°, $p < 0.01$) occurred 6 weeks after end of therapy. The base level was reached after 6 months (median 0°).

As far as further toxicities are concerned, the following values were obtained: enoral mucositis peaked from week 5 of therapy on (97% in total, 73% CTC II–III°). As early as 6 weeks after therapy, a significant reduction became evident. After 6 months, no acute mucositis could be identified any more. The maximal xerostomia was obtained after the completion of week 4 (97% in total, 73% CTC II–III°) and remained unchanged until the end of the therapy. Twelve months after completing the therapy, a total 90% of the patients complained about a xerostomia, 28% of them with medium to heavy discomfort (CTC II–III°, RTOG/EORTC II–III° respectively). At no point were there any cases of CTC IV° toxicity.

At the end of therapy, there were statistically significant correlations between dysphagia, mucositis ($r = 0.564$; $p = 0.001$, $r =$ correlation coefficient), and xerostomia ($r = 0.406$; $p = 0.017$). Over the course of time, these correlations could not be shown anymore. Dysphagia correlated with the particular diet at all times.

Most patients already received a prophylactic feeding tube before beginning the therapy in anticipation of side effects. Before starting therapy, 72% met their nutritional needs orally, while 28% of the patients already used a feeding tube to meet

their nutritional needs. Only 2 patients (6%) depended on the exclusive use of a feeding tube at that time. At the end of therapy, the majority (80%) of the patients needed a feeding tube for additional alimentation; 30% were wholly dependent on a feeding tube. Six months after radiation, 40% of the patients were still in need of a feeding tube, and 10% were totally dependent on it. These values did not change at the 12-month follow-up.

Regarding dysphagia, there was no significant difference between adjuvant versus the primary treated patients.

Patients who had received simultaneous chemotherapy differed significantly from those who had not. Concerning the difficulties in swallowing, there was a significant difference between patients undergoing concomitant chemotherapy and the group receiving no chemotherapy treatment. Already after 4 weeks of treatment, there was a significant difference in terms of the manner of ingestion. Patients undergoing chemotherapy used a feeding tube significantly more often than patients without chemotherapy (EORTC MW 28.21 vs. 6.67, $p < 0.010$). After 6 months, dysphagia was found in patients without chemotherapy showing a median of 0° (min 0°, max 0°). Patients undergoing chemotherapy reached a median of I° (min 0°, max III°) ($p < 0.050$). The same results were obtained after 12 months. No patient without chemotherapy depended on a feeding tube after 6 and 12 months (EORTC MW 0), while patients with chemotherapy showed an average of 17.65 ($p < 0.050$).

Dysphagia has a significant impact on quality of life. At the beginning of therapy, dysphagia caused by surgery or by the tumor itself did not show any influence on global quality of life ($p > 0.050$). Before the beginning of therapy, however, an adverse effect could be shown on all functional scales of the EORTC-QLQ C 30 (physical function $p = 0.007$, $r = -0.454$; role function $p = 0.035$, $r = -0.362$; cognitive function $p = 0.004$, $r = -0.484$; emotional function $p = 0.000$, $r = -0.569$) and an influence on fatigue ($p = 0.000$, $r = 0.587$) and pain ($p = 0.001$, $r = 0.525$). No additional significant correlations were identified. At the end of the therapy, there was a significant correlation between the gravity of dysphagia and the decline in global quality of life ($p = 0.033$, $r = -0.342$). This correlation was also found up to 6 and 12 months after radiotherapy treatment compared to baseline ($p = 0.050$, $r = -0.321$). What is more, an impact on appetite could be shown after 12 months due to the dysphagia ($p = 0.041$, $r = 0.440$), but there were no additional significant impacts of single items in the questionnaire.

Discussion

Deglutition is a complicated process which involves many cranial nerves and muscles. This process proceeds automatically until it is disrupted through a tumor, an operation, or radiotherapy [7, 18, 22, 26]. Difficulties in swallowing cause diminished sensitivity and can lead to a dysfunction of the larynx with the risk of aspiration. Dysphagia is often associated with mucositis, loss of weight, and the necessity of hospitalization. This can lead to a serious impact on a patient's quality of life.

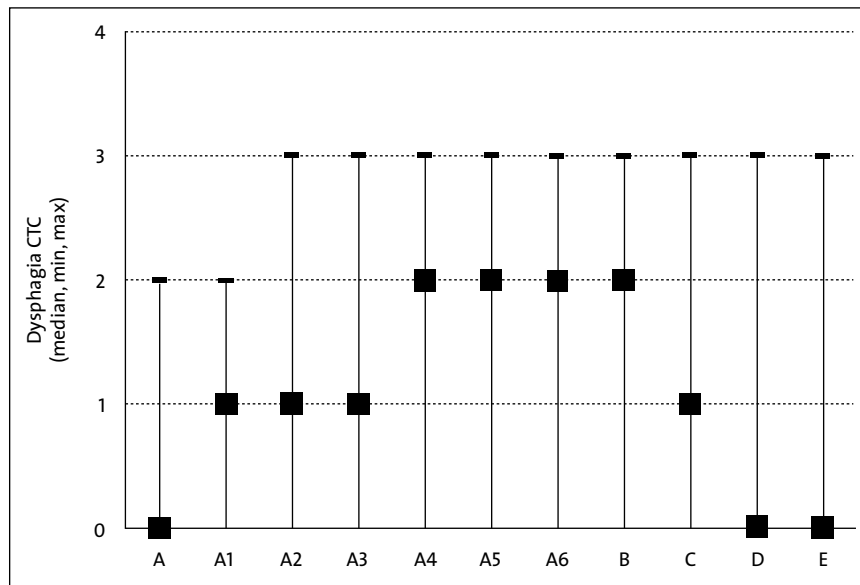


Figure 1. Dysphagia (CTC) – chronological change (median, minimum, maximum). A: before therapy, A1–A6: after weeks 1–6, B: end of therapy, C: follow-up at 6 weeks, D: follow-up at 6 months, E: follow-up at 12 months; 0 = CTC 0°, 1 = CTC I°, 2 = CTC II°, 3 = CTC III°/RTOG III°, 4 = CTC IV°/RTOG IV°.

Abbildung 1. Dysphagie (CTC) – Zeitverlauf (Median, Minimum, Maximum), A: Vor Therapiebeginn, A1–A6: Nach Woche 1–6, B: Bei Therapieabschluss, C: 6 Wochen nach Therapie, D: 6 Monate nach Therapie, E: 12 Monate nach Therapie; 0 = CTC 0°, 1 = CTC I°, 2 = CTC II°, 3 = CTC III°/RTOG III°, 4 = CTC IV°/RTOG IV°.

If oral feeding is not tolerated, a feeding tube can be used. Patients who receive radiochemotherapy lose approximately 10% of their body weight. More than a third of the patients use feeding tubes before, during, and also after the treatment [23].

Because of these well-known problems, the installation of a feeding tube was in many cases already recommended before starting therapy. In this study, the majority of patients used a feeding tube after therapy, and 6 months after therapy 40% of the patients were still using it. Gunn et al. [10] and Berger et al. [2] showed similar results with about 60% of the patients depending on the feeding tube over the long term.

Gunn et al. [10] described 96% of the patients having moderate to heavy dysphagia during therapy. Dirix et al. [5] showed that 6 months after the end of therapy, 65% of the patients suffered from dysphagia (48% moderately to severe). Logemann et al. [20] examined 30 patients with advanced oropharyngeal carcinoma who had been treated with radiochemotherapy: 70% of the patients described swallowing dysfunction 12 months after therapy. Overall, the incidence of dysphagia varies throughout the analyzed studies. In general the number of cases reporting dysphagia in the current literature is mostly slightly higher than in this survey showing dysphagia in about 50% of the cases after 6 and 12 months (15% moderate to severe) [23, 25, 28].

The data after radiochemotherapy reported by Berger et al. [2] basically resembles the present study: dysphagia occurred in 70% of the cases, while chronic moderate to heavy dysphagia lies at approximately 20–25%. Wolff et al. [37] reported less

acute dysphagia; 76% of their patients suffered from acute dysphagia after radiotherapy or radiochemotherapy (35% moderately to severe). However, only 70% of the patients in this study were simultaneously treated with chemotherapy.

In the literature, various factors (e.g., concomitant chemotherapy) exert considerable influence on dysphagia and quality of life [20]. Thus, in some studies – in particular the ones with concomitant chemotherapy – a higher incidence and gravity of the acute – in particular mucositis – and chronic side effects were shown. More aggressive chemotherapy patterns mostly cause severe side effects [3, 20, 33–35]. In the present paper, those patients who had simultaneously received especially platin-based chemotherapy suffered from much stronger discomfort in terms of dysphagia, i.e., painful food intake. These results also appeared in another study in which dysphagia also correlated with simultaneous chemotherapy [5]. Lee et al. [18] presented results similar to this survey

in a retrospective study about the treatment of larynx and hypopharynx carcinoma with concomitant platinum-based chemotherapy and IMRT with 31 patients, measuring the acute and late side effects by means of CTC criteria. One year after treatment, 23% of the patients showed dysphagia degree 3 and still depended on a feeding tube at that time. These data are in agreement with our results. The incidence and gravity of the side effects induced by chemotherapy, strongly depend on the given substances and therapy patterns. Thus, especially in the long run, the impairment of swallowing function continues, as Balermipas et al. [1] showed. However, for dysphagia – other than for the mucositis, which tends to be highly distinctive – no effective therapy methods exist. Therefore, the control of dysphagia is of great importance.

In the past, xerostomia was viewed as the most important factor of the quality of life after radiotherapy of the head and neck region [8, 11, 31]. Even in some other studies the focus was on further parameters for example dysphagia influencing quality of life. Since the implementation of IMRT has led to a decrease of ray-induced xerostomia, dysphagia has become one of the most important clinical side effects of radiotherapy in the head and neck region [15]. Dysphagia can affect quality of life by causing fear and depression [24]. In 50 patients with nasopharyngeal carcinoma, Hughes et al. [11] found dysphagia in 76% of the patients after radiotherapy and absence of the swallowing reflex in 78%. They identified subjective and objective difficulties in swallowing as very frequent complications

of the radiotherapy. A study of Langendijk et al. [17] showed the following results: the quality of life according to the reports given by the patients was mostly influenced by xerostomia and the difficulty in swallowing. Although the incidence of xerostomia was higher, quality of life was mostly influenced by the difficulty in swallowing during the first 18 months. Similar results were also found by Jensen et al. [13]. With 116 head and neck patients, the correlation between xerostomia and the items of QLQ-C30 EORTC after radiotherapy was not as distinctive as between the other toxicities as dysphagia and hoarseness. Other studies [12, 26, 30] confirmed this influence of dysphagia on the quality of life.

A study of Kulbersh et al. [15] stressed the importance of sparing the organs involved in the swallowing act during radiation. They indicated that a deglutition-training before beginning therapy can both improve not only swallowing after treatment but also quality of life. Some studies have dealt with the sparing of the anatomical structures involved in the deglutition act. Eisbruch et al. [8] indicated that the constriction of the pharynx- and larynx-muscular system was the principal reason for dysphagia after radiotherapy. Using IMRT, it was possible to spare these structures in comparison to 3D conformal radiotherapy without having to accept compromises with regard to the planning target volume. Levendag et al. [19] reported on a cross-sectional study about 81 patients with oropharyngeal carcinoma who were treated with 3D conformal radiotherapy or IMRT. Difficulties in swallowing were significantly associated with the mean total dose in the upper and middle pharynx-constrictors. Also Jensen et al. [14] showed in a small prospective study that significant correlations exist between the objective and subjective difficulties in swallowing function and the dose-volume histogram parameters of the anatomical structures.

Conclusion

The findings of this study suggest that special emphasis should be placed on to structured clinical diagnostics, therapy, and rehabilitation of deglutition problems. A suggestion for further research includes the question of how to achieve the sparing of the structures which appear to have a positive impact on deglutition.

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Address for Correspondence

Dr. Julia Maurer
Department of Radiotherapy
Regensburg University Medical Center
Franz-Josef-Strauss-Allee 11
93042 Regensburg
Germany
Phone (+49/941) 944-7610, Fax -7612
e-mail: julia.maurer@klinik.uni-regensburg.de