Videofluoroscopic Swallowing Outcomes in Patients with Locally Advanced Oropharyngeal Head and Neck Cancer: a Retrospective Cohort Study

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ABSTRACT

Title: Videofluoroscopic Swallowing Outcomes in Patients with Locally Advanced Oropharyngeal Head And Neck Cancer: a Retrospective Cohort Study.

Background: Patients with advanced oropharyngeal Cancer (OPC) often receive organ-preservation therapy, such as chemoradiotherapy with Cisplatin (CRT), or Cetuximab-irradiation (BioRT). It is unclear if there is a difference in objective swallowing function and patient-reported experiences in and between CRT and BioRT on swallowing function.

Aim: This study aims to retrospectively determine the experienced as well as observed swallowing function, measured with videofluoroscopy, pre- versus post-treatment, and between treatment types in patients with an advanced OPC treated with CRT or BioRT.

Method: Pre- and post-treatment videofluoroscopic recordings and patient-reported experiences were used. Two blinded raters scored 54 videofluoroscopy using the Dynamic Imaging Grade of Toxicity (DIGEST). Patient-reported experiences were dichotomized and compared with the outcomes of the DIGEST.

Results: Twenty-seven patients were included. Only the 'DIGEST safety' grade worsened statistically significant (P=0.043) of both groups, meaning that the number of patients with aspiration/penetration or the severity of dysphagia after treatment increased. Besides, objective DIGEST outcomes and patient-reported experiences did not always correspond. Videofluoroscopy showed more patients with swallowing disorders than there were patients who reported swallowing complaints, both pre - and post-treatment.

Conclusion: Patients' safety of swallowing decreased statistically significantly after both treatment types, resulting in more, or more severe, aspiration/penetration during the post-treament videofluoroscopic assessment. However, based on this study solely, it is not possible to assume that there is a difference between CRT or BioRT on swallowing function. A mismatch exists between videofluoroscopic outcomes and patient-reported experiences.

Implications: It is recommended to assess the pre- and post-treatment swallowing function with videofluoroscopy because aspiration/penetration might develop, and patients do not seem to notice this adequately.

Keywords: Videofluoroscopy, Oropharyngeal Neoplasms, Deglutition Disorders, Cetuximab, Chemotherapy

SAMENVATTING

Titel: Slikfunctie van Patiënten met een Vergevorderd Orofarynxcarcinoom Gemeten met Videofluoroscopie: een Retrospectieve Cohort Studie.

Achtergrond: Patiënten met een vergevorderd orofarynxcarcinoom kunnen in aanmerking komen voor orgaan-besparende behandelingen; zoals chemotherapie gecombineerd met Cisplatin (CRT) of bestraling met Cetuximab (BioRT). Momenteel is het onbekend of er een verschil is in de slikfunctie en de ervaringen van patiënten omtrent hun slikfunctie, tussen en binnen beide behandelopties.

Doel: Het doel betreft het in kaart brengen van de objectieve slikfunctie en de subjectieve ervaringen over de slikfunctie van patiënten met een vergevorderd orofarynxcarcinoom en deze gegevens te vergelijken voor-, na en tussen CRT en BioRT.

Methode: Twee geblindeerde onderzoekers analyseerden 54 videofluoroscopische slikvideo's met de Dynamic Imaging Grade of Toxicity (DIGEST). Ervaringen van patiënten werden gedichotomizeerd en vergeleken met de uitkomsten van de DIGEST.

Resultaten: Zevenentwintig patiënten werden geïncludeerd. Enkel de 'DIGEST safety' score verslechterde statistisch significant (P=0.043) over beide groepen, inhoudend dat er meer aspiratie of pentetratie optrad, of dat de ernst hiervan troenam na behandeling. Tevens werd een discrepantie gevonden tussen subjectieve patiënt-ervaringen en objectieve DIGEST uitkomsten. Videofluoroscopie identificeerde meer patiënten met slikproblemen dan dat er patiënten waren die slikklachten ervaarden, zowel voor- als na behandeling.

Conclusie: Patiënten slikten statistisch significant minder veilig na behandeling, ongeacht CRT of BioRT. Wat inhoud dat patiënten vaker of ernstiger aspireerden/penetreerden tijdens de videofluoroscopische opnames. Echter kan, enkel op basis van deze studie, niet worden aangenomen dat CRT en BioRT verschillende uitkomsten hebben op de slikfunctie. Daarnaast lijkt er een discrepantie te bestaan tussen de objectieve uitkomsten en de subjectieve evaringen van patiënten.

Aanbevelingen: Het dient tot aanbeveling om voor en na behandeling de slikfunctie van patiënten te onderzoeken middels videofluoroscopie, omdat de slikfunctie van patiënten verslechterd en zij dit niet goed aan lijken te geven.

Keywords: Videofluorocopie, Orofarynxcarcinoom, Dysfagie, Cetuximab, Chemotherapie

INTRODUCTION

Approximately 650 new patients a year are diagnosed with oropharyngeal cancer (OPC), and its incidence has been rising since 1980.[1] The most important risk factors for OPC are tobacco use, alcohol consumption, and Human Papilloma Virus infection (HPV).[2] Classification and staging of tumors are used for uniform reporting, treatment decision making, and to estimate disease prognosis.[3–5] Tumor classification ranges from I to IV, based on tumor size, nodal status, and the presence of distant metastasis.[3] Advanced tumor stages (III, IV) are associated with worse overall survival.[4] Management of OPC primary focusses on curative treatment.[5] Patients with OPC classified as stage I or II mostly receive single modality surgery or radiotherapy, whereas patients with advanced OPC receive multimodality treatment. This multimodality treatment consists of surgery combined with (chemo)radiation or organ-preservation treatment, such as Cisplatin/Carboplatin-based chemoradiotherapy (CRT) or irradiation with Cetuximab (BioRT).[5–7] Both treatment modalities have numerous reported side effects, including dysphagia.[5,8,9] Dysphagia may lead to (silent) aspiration, laryngeal penetration and residue, which can result in malnutrition, dehydration, aspiration pneumonia, and even death.[7,10–12]

To examine clinical swallowing function, the Fiberoptic Endoscopic Evaluation of Swallowing (FEES)[13,14] and the Videofluoroscopic Swallow Study (VFSS)[15] are both considered as the golden standard.[16] FEES is a video-endoscopic tool that is sensitive to detect residuals, laryngeal penetration and aspiration, without exposure to radiation.[17,18] Limitations are that this assessment does not show the oral phase, pharyngeal stripping, transit through the upper esophageal sphincter (UES), or the extent of aspiration.[13,15] VFSS examination, also known as the Modified Barium Swallow, shows the entire oropharyngeal swallow. It focusses on the structure and dynamics of the swallowing process and assesses the swallowing of radio-opaque thin and thick liquid, pastes, and solids.[10] Limitations of VFSS examination are that this is an expensive, highly skilled, and time-consuming assessment with radiation exposure.[19]

There are several tools available to evaluate VFSS recordings, such as the Dysphagia Outcome and Severity Scale (DOSS)[20], Penetration and Aspiration Scale (PAS)[21], Oropharyngeal Swallowing Efficiency (OPSE)[22], Modified Barium Swallow Impairment Profile (MBSimp)[23], and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST).[24]

Since dysphagia is a complex disorder with multiple factors, not only observer-rated outcomes are essential but also patient-reported outcome measures. In practice, sometimes there is a mismatch between the patients' experience and the objective swallowing function outcome. Van der Molen et al. (2009) found that 30% of patients with advanced head and neck cancer

who showed laryngeal penetration or aspirated on the baseline VFSS did not experience swallowing problems.[25] This finding makes it essential to explore patient-reported experiences and to compare them with the objectified VFSS swallowing outcomes. Within the Netherlands Cancer Institute (NCI), it is usual care to perform VFSS as a baseline clinical swallow function assessment in patients with advanced OPC. This assessment can expose deficits related to impaired bolus efficiency and airway protection.[26] Furthermore, baseline VFSS can be compared with post-treatment VFSS. Pre-treatment assessment allows for individualized swallowing-related treatment recommendations to optimize oral intake, establish appropriate patient-centered goals, and set realistic expectations for functional changes throughout cancer treatment.[26] Post-treatment assessment allows for evaluation of swallowing function and the effect of compensation techniques.

At this moment, it is unclear if there is a difference in the experienced as well as the observed swallowing function pre- versus post-treatment, and between CRT or BioRT in patients with advanced OPC. This information is needed to inform and prepare patients on what they may experience before, during, or after treatment and also help patients during the shared-decision making process. Therefore, this retrospective cohort study focusses on the difference between pre- and post swallowing function using VFSS in patients with advanced OPC who are treated with CRT or bioRT.

We hypothesized that patients treated with CRT have more severe and chronic swallowing problems than patients treated with BioRT because of the toxicity of Cisplatin/Carboplatin. The results of this study, hopefully, can be used in daily clinical practice to better inform patients about the possible side effects of the treatment related to their swallowing function.

AIM

This study aims to retrospectively determine the experienced as well as observed swallowing function, measured with VFSS, pre- versus post-treatment, and between treatment types in patients with an advanced OPC treated with CRT or BioRT.

MATERIALS AND METHODS

Design

A quantitative retrospective study was executed on data that have previously been collected between January 2015 and December 2018 at the department of head and neck surgery and oncology of the NCI. A retrospective design is the most appropriate design for this study since

this data is already available, and it enables the comparison of the swallowing function from the moment of diagnosis (pre-VFSS) until three months after treatment (post-VFSS).

Population and domain

Patients diagnosed with newly, locally advanced OPC who received curative CRT or BioRT treatment between January 2015 and December 2018 at the department of head and neck surgery and oncology of the NCI were eligible for inclusion. CRT consists of radiotherapy (5 times a week, a total dose of 70Gy in 35 fractions) concurrent with 100mg/m^2 of Cisplatin as a 40-min IV infusion on days 1, 22, and 43 over the seven weeks of radiation course. BioRT consists of radiotherapy (5 times a week, a total dose of 70Gy in 35 fractions) concurrent with Cetuximab (loading dose 400mg/m^2 in week -1, and 250mg/m^2 week 1-7). Included patients were referred for objective swallow evaluation and underwent VFSS before or in the first week of treatment and approximately 10 weeks after treatment. Patients who already underwent treatment or surgery in the head and neck area that can influence the swallowing function were excluded, as were those with more than one primary tumor, concurrent malignancy, a history of dysphagia, a tumor residue or a recurrence at six months after treatment, and patients with less than two VFSS recordings.

Figure 1 here

Data collection

Data on patient characteristics and reports of interviews that were conducted before the VFSS examination were extracted from an Electronic Patient File (EPF) partly by DATADESK and partly by the researcher. Data on characteristics of patients included age, gender, stage of Cancer, HPV status, treatment, Bodyweight, BMI, Diet, Functional Oral Intake Scale (FOIS), and (history of) pneumonia. VFSS recordings have been recorded at the radiology department of the NCI with a Philips CombiDiagnost R90 in 25 FPS. The VFSS recordings were processed and saved with Bandicam Software.[27] All VFSS recordings were stored together in the same folder on a secured computer in the NCI. Titles of VFSS recordings were coded by an independent SLP, who was the only non-blinded researcher with access to the coded document. The coded VFSS videos were watched on the computer of the NCI frame by frame and analyzed using digital score forms to score the DIGEST (Figure 2). DIGEST is a reliable, validated ordinal scoring tool of pharyngeal dysphagia, and very valuable to analyze swallowing function in patients treated with organ preservation regimens.[24] DIGEST uses a Safety Profile (DIGEST-S) and an Efficiency Profile (DIGEST-E) to quantify pharyngeal bolus transit.[24] Within the DIGEST, the Penetration Aspiration Scale (PAS; range 1-8 with 1: the

material does not enter the airway, to 8: material enters the airway, passes below the vocal cords, and no effort is made to eject)[21] is used to assess the DIGEST-S. The percentage of pharyngeal residue is selected as the primary measure of the DIGEST-E on an ordinale scale (<10%, 10%–49%, 50%–90%, and >90%).[24] The summary grade of the DIGEST (DIGEST-SUM) is based on the interaction of the safety and efficiency classification (grade 0 = no-, 1 = mild-, 2 = moderate-, 3 = severe-, and 4 = life-threatening pharyngeal dysphagia).[24] In this study, DIGEST-SUM was dichotomized with grade 2 or higher as moderate/severe dysphagia based on published data, suggesting that this is a meaningful split associated with diet and quality of life. DIGEST grade 2 or higher indicates at least intermittent high-grade penetration or aspiration (PAS≥5) or post-swallow residue of a 50% or greater bolus.[24,28,29]

Patient-Reported Outcome Measures

In the NCI, it is usual care for SLPs to have a short (non-standardized) interview with the patient before VFSS assessment. The SLP asks questions about the patients' experiences about their swallowing function, the modification of their diet, and other details. A short summary of this interview is reported in the EPF. Patient-reported experiences about aspiration, penetration or residue were dichotomous divided into 'complaints' or 'no complaints' and compared with the DIGEST grades.

Procedures

The previously collected VFSS recordings were recorded according to a standard VFSS guideline.[10] All patients were asked to swallow different Omnipaque™ (300 mg I/ml) based consistencies of varying amounts twice: 3cc thin liquid, 10cc thin liquid, 5cc thickened liquid, as well as a solid dice size Omnipaque™ coated piece of gingerbread.[10] When aspiration or penetration occurred, patient safety was guaranteed by providing compensation techniques or deviating from the protocol if patient safety was at risk. Recorded swallows of patients that used compensatory techniques were not included for analysis per DIGEST instructions. Included VFSS recordings were analyzed by two blinded SLPs separately, using the DIGEST. To ensure consistent scoring methodology, proper scoring tool usage was discussed. Practice scoring rounds were performed on VFSS videos of excluded patients. The SLPs were allowed to play the VFSS multiple times and in preferable speed (slow motion, normal, sped up).

Data analysis

Descriptive statistics were used to calculate the mean and standard deviation of age and bodyweight. Median and quartiles of the FOIS were calculated. Percentages and numbers were used to analyze gender, stage of Cancer, HPV status, treatment, BMI, Diet, and (history

of) pneumonia. The swallowing function was assessed using VFSS recordings and analyzed using the DIGEST. Due to the ordinal outcome of the DIGEST, the data were summarized as median, quartiles, and minimum-maximum.[30] To compare the outcomes of the DIGEST pre- versus post-treatment in and between groups (BioRT and CRT), the nonparametric statistical Wilcoxon Signed-Rank Test was used. This test takes into account that data might not be normally distributed.[31,32] Because it is a nonparametric test, it does not require a particular probability distribution of the dependent variable in the analysis. With 27 evaluable patients, the study had 27.6% power to detect the effect size of 0.28 with two-sided α=0.05. Inter- and intraobserver reliability was calculated using Weighted Kappa, which takes the ordinal scale of the DIGEST into account. Interpretation of kappa includes; <0 no agreement , 0.0-0.20 slight agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, and 0.81-1.00 almost perfect agreement.[33]

Since the patient-reported experiences were not systematically obtained, no statistical analysis was possible. Descriptive statistics were used to analyze the patient-reported experiences.

The statistical analysis was performed using IBM SPSS Statistic version 26 (Corp. I. IBM, Armonk)[34], and power calculations using G*Power 3.1.9.4 (Heinrich- Heine Universitat Dusseldorf, Germany).[35] A P-value <0.05 was considered statistically significant.

Ethical Issue

This retrospective cohort study was approved following WMO regulations by the Institutional Review Board of the NCI (IRBd19165). This study was conducted according to the principles of the Declaration of Helsinki (64th WMA, 2013)[36] and in accordance with the Medical Research Involving Human Subjects Act. The NCI holds final responsibility for conforming to the regulations concerning the Medical Treatment Act (WGBO), the General Data Protection Regulation (AVG) and following the Code of Conduct for Health Research with regard to (anonymous) personal data as described by the Foundation Federation of Medical-Scientific Associations (FEDERA).[37] An opt-out procedure is used in the NCI, which means that by default, all residual tissue may be stored and used for research unless a patient explicitly refuses. The reviewers requested DATADESK for a list of suitable patients for this study. To ensure privacy, data were de-identified by using a pseudonym in lieu of the original data according to pseudonymization guidelines 2019.[38]

RESULTS

Between 2015 and 2018, 91 patients were treated for an advanced OPC and underwent a VFSS assessment. In total, 27 patients were included in this study (Figure 1). Sixty-four patients were excluded due to the presence of more than one primary tumor (N=2), missing pre- or post VFSS assessment (N=23), other tumor location (N=26), a residue or recurrence at six months post-treatment (N=9), dysphagia in medical history (N=2), or VFSS recordings missing in storage (N=2). All patients had a pre-treatment VFSS assessment and a post-VFSS assessment approximately 10 weeks after their last treatment (range 8-13; two outliers had the post-VFSS at 18 weeks post-treatment). Of these twenty-seven patients, 10 patients (seven males and three females, mean age: 62,8 years; range 47-72 years) were treated with CRT, and 17 patients (15 males and two females, mean age: 65,8; range 50-79 year) were treated with BioRT. All 10 patients treated with CRT started with Cisplatin; however, seven patients switched after one dose, and one patient switched after two doses of Cisplatin to Carboplatin due to kidney failures. Pre-treatment, 19 of 27 patients had a normal diet, versus 11 of 27 post-treatment. The number of patients with tube feeding increased from four to nine. The FOIS grade decreased from median grade 7 to 5. Demographic information of the included patients can be found in Table 1.

Table 1 here

The interrater reliability of DIGEST-S, DIGEST-E, and DIGEST-SUM scores were 0.684 (substantial), 0.505 (moderate), and 0.566 (moderate), respectively. In 20 VFSS, there were differences in scoring between the two raters. All these differences were discussed until consensus was reached. Ten of 54 VFSS recordings (19%) were scored again after three weeks by one researcher. The intrarater-reliability of DIGEST-S, DIGEST-E, and DIGEST-SUM scores were 0.773 (substantial), 0.531 (moderate), and 0.878 (almost perfect).

DIGEST

Table 2 here

Baseline VFSS found no or mild dysphagia (DIGEST≤1) in 22 of 27 patients (81%), and moderate/severe dysphagia (DIGEST≥2) in five patients (19%) (see Table 2). Pre-treatment the mean grades of the DIGEST-S, DIGEST-E, and DIGEST-SUM of all patients (N=27) were 0.592, 0.815, and 0.963. Post-treatment, they were 1.037, 0.997, and 1.259, respectively (see Table 3).

Overall DIGEST-S grade worsened statistically significant (P=0.043), indicating more severe problems with the safety of swallowing after treatment (see Table 3, Figure 3). However, within

the CRT and BioRT group, no statistically significant differences were found in DIGEST-S, DIGEST-E, and DIGEST-SUM scores before and after treatment (see Table 4).

Table 3 here.

In the CRT group (n=10), baseline VFSS found no to mild dysphagia (DIGEST-SUM≤1) in eight patients (80%), and moderate/severe dysphagia (DIGEST-SUM≥2) in two patients (20%). In three patients (30%), a DIGEST-SUM grade of 0 or 1 before CRT increased to a grade of 2 (20%) or 3 (10%) post-treatment. Compared with the pre-treatment DIGEST-SUM grade, three patients (30%) stayed equal, five patients (50%) were diagnosed with 1 or 2 grades worse, and two patients (20%) improved on the grade post-treatment (see Table 2).

Table 4 here

Within the BioRT group (n=17), pre-treatment, 14 patients (82%) were diagnosed with no to mild dysphagia, and three (18%) had moderate/severe dysphagia (DIGEST-SUM≥2). In three patients (18%), a DIGEST-SUM grade of 0 or 1 pre-treatment increased to a grade 2 (6%) or 3 (12%) post-treatment. Compared with pre-treatment DIGEST-SUM grade, six patients (35%) stayed equal, five patients (29%) worsened with 1 or 2 grades, and four patients (24%) improved on the grade post-treatment (see Table 2).

Figure 3 here

An overview of the DIGEST summary score at the patient level can be found in Table 5.

Table 5 here.

Patient-reported outcomes

Patients mentioned different types of complaints during the interview before the VFSS assessment, including aspiration or penetration (safety problems) and pharyngeal residue (efficiency problems). Pre-treatment, eight (30%) of 27 patients experienced complaints, of which seven included aspiration or penetration. Post-treatment, the number of patients that experienced complaints increased to 12 (44%), of which nine included aspiration or penetration.

Of the seven patients with aspiration or penetration complaints before treatment, three were from the CRT-group. Two patients kept complaints, and the third patient was free of complaints after treatment. However, another patient developed complaints after treatment, meaning that the number of patients with complaints stayed equal after treatment (n=3). In the BioRT group, four patients complained about aspiration or penetration pre-treatment. One patient kept

complaints post-treatment, and three were free of complaints after treatment. However, five patients developed complaints after treatment. This resulted in an increased number of patients (n=6) with complaints after treatment (see Table 6).

We found that of the seven patients with complaints before treatment, baseline VFSS identified no- (n=1), mild- (n=4), and moderate/severe safety problems (n=2). Post-treatment VFSS evaluation identified no- (n=1), mild- (n=3) and moderate/severe safety problems (n=5) in the nine patients with complaints after treatment.

Table 6 here

Focussing on the outcomes of the DIGEST versus the patient-reported experiences, this study found that pre-treatment, 14 patients were diagnosed with mild dysphagia, of which 10 (71%) had no complaints. The four patients with complaints included one patient from the CRT group and three from the BioRT group. Post-treatment, eight patients were diagnosed with mild dysphagia, of which five (63%) had no complaints. The three patients with complaints included one patient from the CRT group and two from the BioRT group.

Five patients were diagnosed with moderate/severe dysphagia pre-treatment, of which three (60%) had no complaints. Post-treatment, 11 patients had moderate/severe dysphagia, of which five (45%) had no complaints. The six patients with complaints included three from the CRT group and three from the BioRT group (see Table 7).

Table 7 here

DISCUSSION

The objective of this study was to retrospectively determine the experienced as well as observed swallowing function, measured with VFSS, pre- versus post-treatment, and between treatment types in patients with an advanced OPC treated with CRT or BioRT.

At baseline, the characteristics of patients in both groups were comparable. Pre-treatment, 81% of all patients were diagnosed with no to mild dysphagia, and 19% with moderate/severe dysphagia. Post-treatment, these percentages were 59% and 41%, respectively. Focussing on treatment groups, this study found that 20% of patients in the CRT group started with moderate/severe dysphagia versus 18% in the BioRT group. Post-treatment, these percentages were 50% and 35%, respectively. These results suggest that there might be a trend in worsening safety and efficiency of swallowing and the severity of dysphagia.

Samuels et al. (2016) evaluated dysphagia in HPV positive OPC, a specific group in OPC, who were treated with CRT or BioRT. They found a significant worsening of swallowing function in the entire cohort, measured with VFSS and the PAS.[39] Although the inclusion criteria, sample size, and severity of dysphagia at baseline differed, the current study found a comparable result; the DIGEST-S score worsened statistically significant in all patients.

The current study also focussed on patient-reported experiences. We found that before treatment, 71% of patients diagnosed with mild dysphagia had no complaints about aspiration or penetration versus 63% of patients after treatment. Pre-treatment, 60% of patients diagnosed with moderate/severe dysphagia had no complaints about aspiration or penetration, versus 45% post-treatment. These percentages are higher than those reported by Van der Molen et al. (2009). They found that 30% of the patients diagnosed with aspiration or penetration did not experience swallowing problems.[25] The differences in inclusion criteria could explain the differences in percentages. The current study focusses on patients with an advanced oropharynx tumor, whereas van der Molen et al. (2009) included patients with various tumor locations, i.e., nasopharynx, oral cavity, and more.[25] Furthermore, the percentages of the current study could be distorted due to the small sample size per treatment group. However, both the current study as well as van der Molen's results seem to indicate a serious mismatch between the experiences of patients and the objective swallowing function evaluation.

This study has several strengths. First of all, as far as we know, this is the first retrospective cohort study that focusses on the determination of the swallowing function, measured with VFSS, pre- versus post-treatment in different types of advanced OPC treated with CRT or BioRT. Secondly, before the VFSS was scored, proper scoring tool usage was discussed. Practice scoring rounds were performed on the VFSS videos of excluded patients. Thirdly, both researchers scored the VFSS independently, and the interrater-reliability, calculated with the Weighted Cohens' kappa, was moderate to substantial. Differences in scoring between the raters were small. All VFSS were discussed until consensus was reached. Fourthly, the current study minimized the influence of tumor residue or recurrence on swallowing function by retrospectively excluding patients who were diagnosed with tumor residue or recurrence before 6 months after treatment. Finally, the current study used a small but unique dataset and combined objective with subjective data.

However, there are several limitations to this retrospective study. The power of twelve patients in each group was not achievable in the CRT group. With the 27 eligible patients, this study had 27.6% power to detect the effect size of 0.28. A larger cohort would provide more

representative and reliable outcomes. Some VFSS recordings were of poor quality, i.e., VFSS without sound or stuttering video. Furthermore, according to the DIGEST protocol, when a patient aspirate and uses compensation techniques, the swallow was excluded from scoring. Most DIGEST evaluations (43/54) were based on seven or six swallows. Another limitation is the difference in health status and comorbidity of patients in the different treatment groups. Cisplatin and Carboplatin are both highly toxic medicine, even more so than Cetuximab. Patients with worse health status and comorbidity more often receive Cetuximab treatment. Eight of 10 patients treated with Cisplatin switched to Carboplatin. Both medicines are platinum-based antineoplastics, which have comparable side effects. Finally, this study involved a small sample size; thus, findings can be based on coincidences, meaning that they cannot be generalized based on this research alone.

Conclusion

In conclusion, the results of the current study showed that patients have more severe problems with the safety of swallowing, resulting in more severe dysphagia after treatment. However, the hypothesis that patients treated with CRT have more severe and chronic swallowing problems could not be assumed based on this study solely. Furthermore, there seems to be a mismatch between patients' experience and objective swallowing function outcomes.

Recommendations

Recommendations for clinical practice would be to examine the pre- and post-treatment swallowing function with VFSS, even when patients do not experience swallowing problems. This is important because ignored disorders in swallowing function pre-treatment might influence the treatment process.

Future research should aim to investigate if the findings of the current study also appear in larger samples. We recommend to use the same VFSS protocol with the required swallows for proper DIGEST scoring and to use standardized questionnaires to explore patient experiences on swallowing function.

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TABLES AND FIGURES

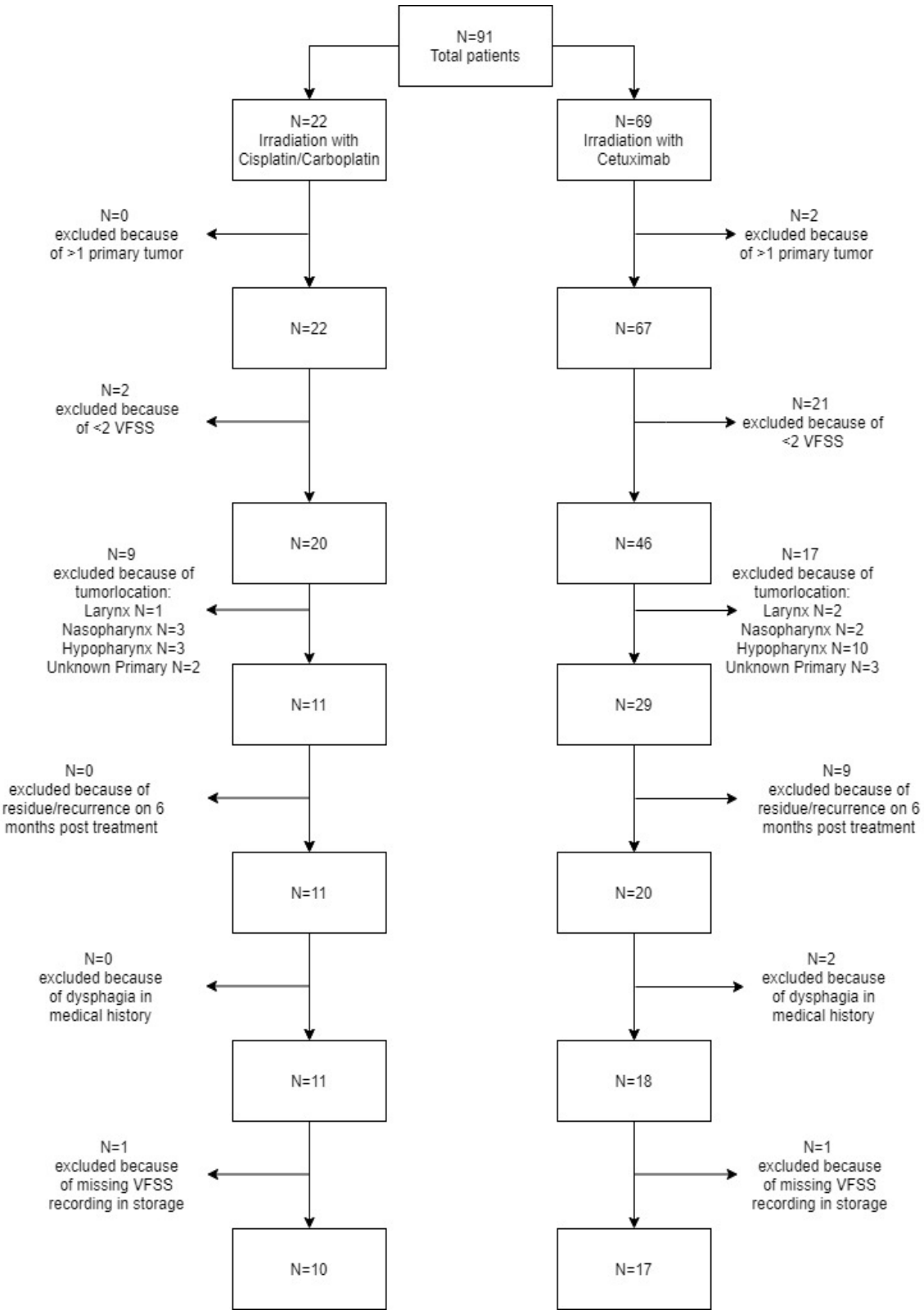
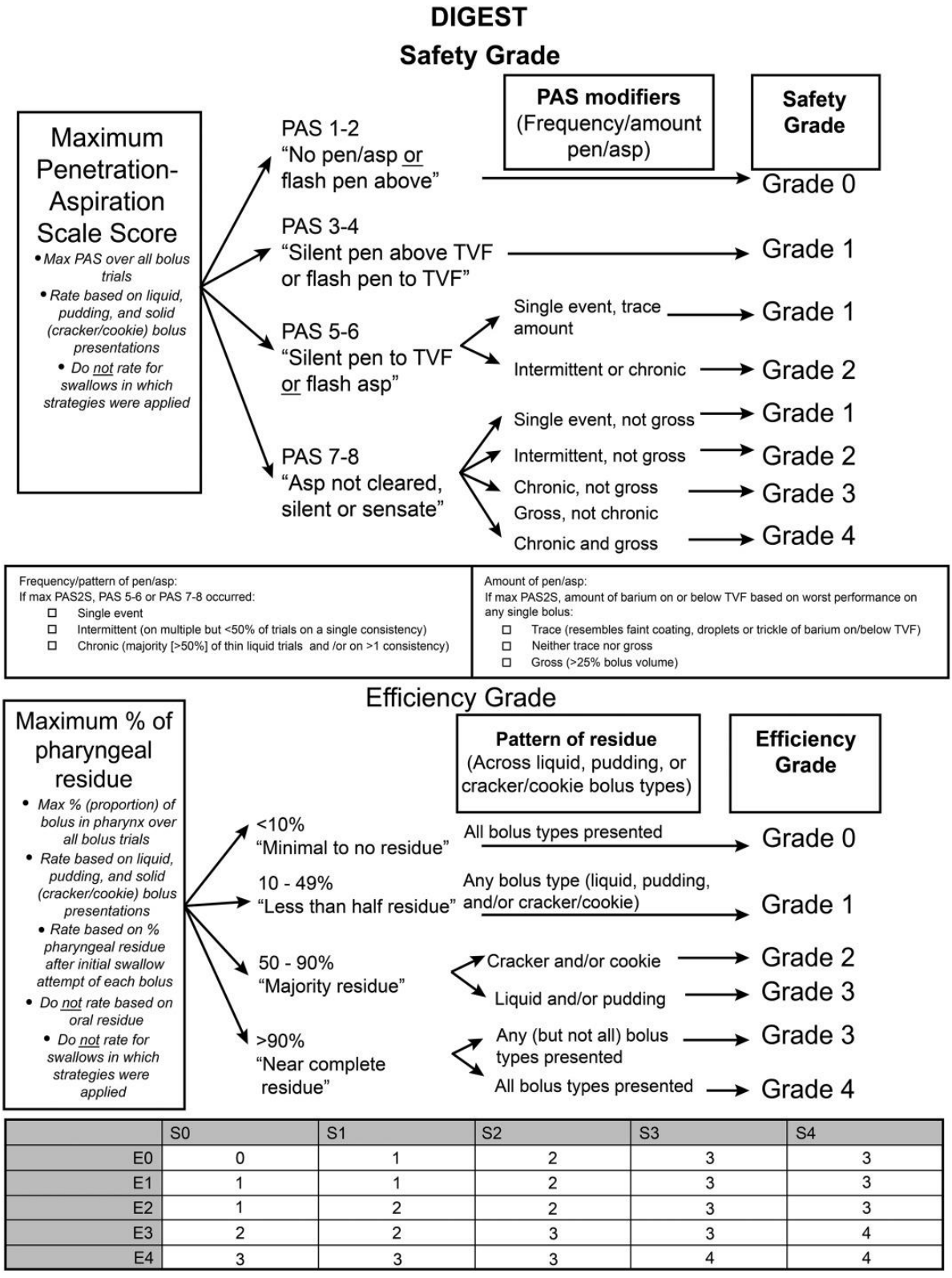


Figure 1 | Flowchart of included patients. VFSS: videofluoroscopic swallow study.



	S0	S1	S2	S3	S4
E0	0	1	2	3	3
E1	1	1	2	3	3
E2	1	2	2	3	3
E3	2	2	3	3	4
E4	3	3	3	4	4

*Figure 2 | Dynamic Imaging Grade of Swallowing Toxicity (*DIGEST). Obtained from "Dynamic Imaging Grade of Swallowing Toxicity (DIGEST): Scale development and validation" by Hutcheson KA, Barrow MP, Barringer DA, Knott JK, Lin HY, Weber RS, et al., 2017, *cancer, 123(1):62–70.*[24]

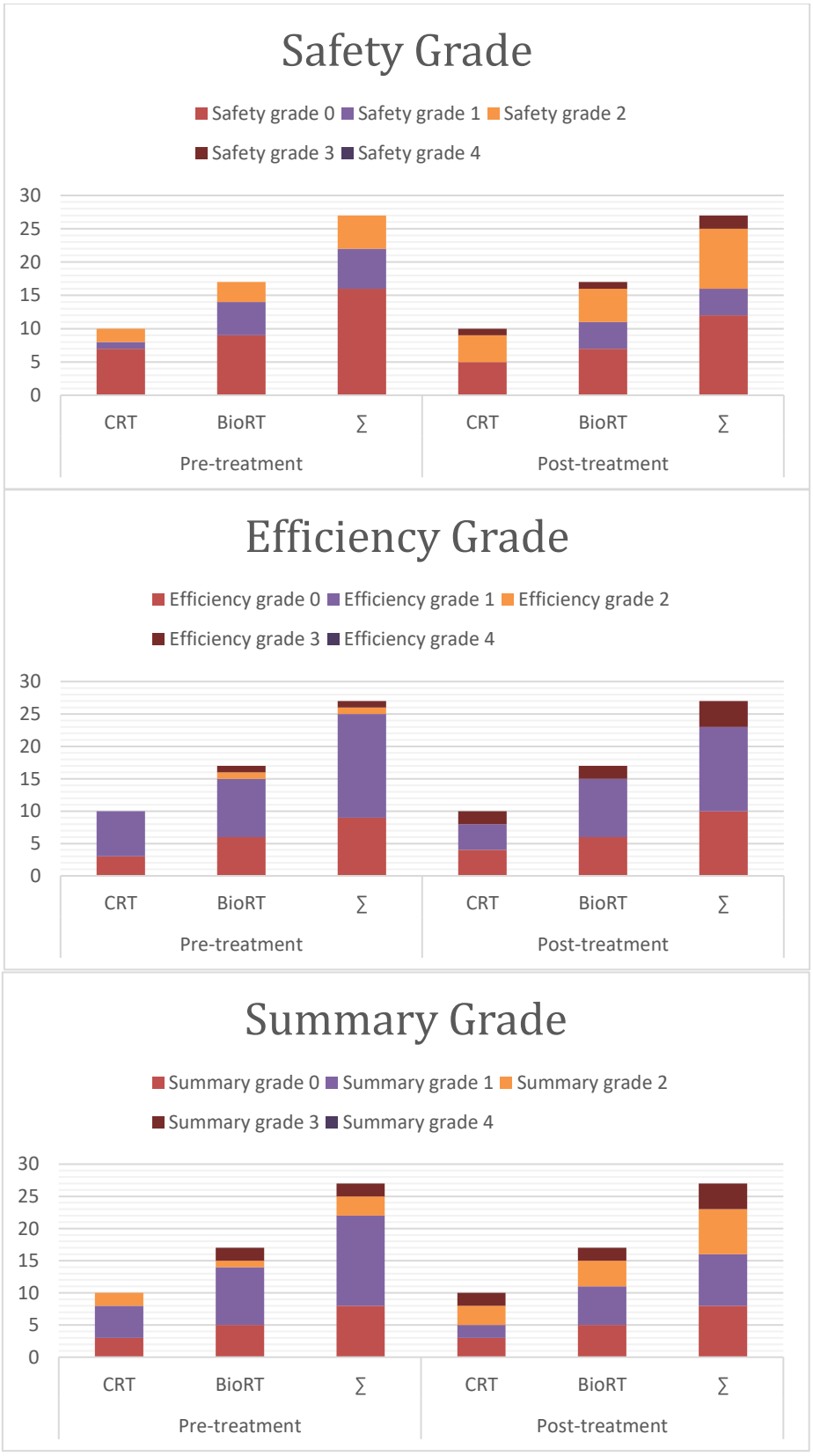


Figure 3 | Videofluoroscopy DIGEST grades among N=27 patients pre- and post-treatment, and among CRT (n=10) and BioRT (n=17). Dynamic Imaging Grade of Swallowing Toxiciy (DIGEST) worsened significantly in the Safety classification (P=0.043, upper), but did not statistically significant change in the efficiency grade (P=0.622, middle) and summary grade (P=0.115, lower).

Table 1 | Patient Characteristics

Characteristic	Total N (%)	CRT-Group n (%)	BioRT-Group n (%)
N	27 (100)	10 (37)	17 (63)
Age in years			
Mean (sd) (min-max)	64.7 (7.5) (47-79)	62.8 (6.8) (47-72)	65.8 (7.8) (50-79)
Gender			
Male	22 (81)	7 (70)	15 (88)
Female	5 (19)	3 (30)	2 (12)
Stage			
III	4 (15)	1 (10)	3 (18)
IV	23 (85)	9 (90)	14 (82)
HPV			
Positive	6 (22)	2 (20)	4 (24)
Negative	21 (78)	8 (80)	13 (76)
Treatment			
Cisplatin	2 (7)	2 (20)	
Cisplatin switch to Carboplatin	8 (30)	8 (80)	
Cetuximab	17 (63)		17 (100)
Bodyweight in kilograms			
Pre mean (sd) (min-max)	84.0 (20.7) (59.0-147.3)	80.9 (20.9) (60.4-136.5)	85.8 (21.1) (59.0-147.3)
Post mean (sd) (min-max)	77.1 (15.9) (54.0-117.0)	72.4 (15.5) (56.0-107.0)	79.9 (16.0) (54.0-117.0)
BMI			
<25	11 (41)	5 (50)	6 (35)
25-29.9	11 (41)	4 (40)	7 (41)
≥30	5 (18)	1 (10)	4 (24)
Diet before treatment			
Normal	19 (70)	8 (80)	11 (65)
Supplementary feeding	4 (15)	2 (20)	2 (12)
Tube feeding	4 (15)		4 (24)
Diet after treatment			
Normal	11 (41)	5 (50)	6 (35)
Supplementary feeding	7 (26)	2 (20)	5 (29)
Tube feeding	9 (33)	3 (30)	6 (36)
FOIS			
Pre median (Q_1-Q_3) (min-max)	7 (5-7) (2-7)	7 (5.8-7) (4-7)	5 (4-7) (2-7)
Post median (Q_1-Q_3) (min-max)	5 (3-6) (2-7)	5 (4-7) (2-7)	5 (3-6) (2-7)
Pneumonia			
None	26 (96)	10 (100)	16 (94)
Before treatment	0	0	0
During treatment	1 (4)	0	1 (6)
After treatment	0	0	0

BMI: Body Mass Index, FOIS: Functional Oral intake Scale, Pre: pre-treatment, post: post-treatment, sd: Standard deviation, min: minimum, max: maximum, Q1: first quartile, Q3: third quartile, CRT: chemoradiationtherapy in combination with Cisplatin or Carboplatin, BioRT: irradiation with Cetuximab

Table 2 | DIGEST Scores Pre- and Post-treatment. Number of patients in Each Box

		Pre-treatment			Post-treatment		
		CRT (n = 10)	**BioRT (n = 17)**	**∑ (N = 27)**	**CRT (n = 10)**	**BioRT (n = 17)**	**∑ (N = 27)**
Safety grade	**0**	7	9	16	5	7	12
	1	1	5	6	0	4	4
	2	2	3	5	4	5	9
	3	0	0	0	1	1	2
	4	0	0	0	0	0	0
Efficiency grade	**0**	3	6	9	4	6	10
	1	7	9	16	4	9	13
	2	0	0	0	0	0	0
	3	0	2	2	2	2	4
	4	0	0	0	0	0	0
Summary grade	**0**	3	5	8	3	5	8
	1	5	9	14	2	6	8
	2	2	1	3	3	4	7
	3	0	2	2	2	2	4
	4	0	0	0	0	0	0

DIGEST: Dynamic Imaging Grade of Swallowing Toxicity, DIGEST-SUM: Summary Grade of the DIGEST: severity of pharyngeal-phase dysphagia based on the safety and efficiency of bolues clearance. DIGEST-S: safety profile based on penetration-aspiration scale[21]; DIGEST-E: efficiency profile based on penetration-aspiration scale (using estimation of the percentage of pharyngeal residue);

Table 3 | Statistics DIGEST Pre- and Post-treatment in all patients (N=27)

		Pre-treatment		Post-treatment			
	N	Mean	Std. Deviation	Mean	Std. Deviation	Difference means	Exact Sig. (2-tailed)
DIGEST-S	27	0.5926	0.79707	1.0370	1.05544	0.4444	0.043
DIGEST-E	27	0.8148	0.78628	0.9259	0.99715	0.1111	0.622
DIGEST-SUM	27	0.9630	0.85402	1.2593	1.05948	0.2963	0.115

DIGEST: Dynamic Imaging Grade of Swallowing Toxicity, DIGEST-SUM: Summary Grade of the DIGEST: severity of pharyngeal-phase dysphagia based on the safety and efficiency of bolues clearance. DIGEST-S: safety profile based on penetration-aspiration scale[21]; DIGEST-E: efficiency profile based on penetration-aspiration scale (using estimation of the percentage of pharyngeal residue); Std. Deviation: Standard deviation.

WILCOXON SIGNED-RANK TEST: Ranks in all patients (N=27)

		N	Mean Rank	Sum of Ranks
DIGEST_S_POST - DIGEST_S_PRE	Negative Ranks	2[a]	3,50	7,00
	Positive Ranks	8[b]	6,00	48,00
	Ties	17[c]		
	Total	27		
DIGEST_E_POST - DIGEST_E_PRE	Negative Ranks	7[d]	7,14	50,00
	Positive Ranks	8[e]	8,75	70,00
	Ties	12[f]		
	Total	27		
DIGEST_SUM_POST - DIGEST_SUM_PRE	Negative Ranks	6[g]	6,50	39,00
	Positive Ranks	10[h]	9,70	97,00
	Ties	11[i]		
	Total	27		

a. DIGEST_SAF_POST < DIGEST_SAF_PRE, b. DIGEST_SAF_POST > DIGEST_SAF_PRE, c. DIGEST_SAF_POST = DIGEST_SAF_PRE, d. DIGEST_EFF_POST < DIGEST_EFF_PRE, e. DIGEST_EFF_POST > DIGEST_EFF_PRE, f. DIGEST_EFF_POST = DIGEST_EFF_PRE, g. DIGEST_SUM_POST < DIGEST_SUM_PRE, h. DIGEST_SUM_POST > DIGEST_SUM_PRE, i. DIGEST_SUM_POST = DIGEST_SUM_PRE

DIGEST-SUM: Summary Grade of the DIGEST: severity of pharyngeal-phase dysphagia based on the safety and efficiency of bolues clearance. DIGEST-S: safety profile based on penetration-aspiration scale[21]; DIGEST-E: efficiency profile based on penetration-aspiration scale (using estimation of the percentage of pharyngeal residue); PRE: pre-treatment, POST: post-treatment.

Table 4 | Statistics DIGEST Pre- and Post-treatment in CRT (n=10) and BioRT Group (n=17)

			Pre-treatment		Post-treatment			
TREATMENT		N	Mean	Std. Deviation	Mean	Std. Deviation	Difference in means	Exact Sig. (2-tailed)
CRT	DIGEST-S	10	.5000	.84984	1.1000	1.19722	+0.6	0.250
	DIGEST-E	10	.7000	.48305	1.0000	1.15470	+0.3	0.437
	DIGEST-SUM	10	.9000	.73786	1.4000	1.17379	+0.5	0.250
BioRT	DIGEST-S	17	.6471	.78591	1.0000	1.00000	+0.4	0.188
	DIGEST-E	17	.8824	.92752	.8824	.92752	0	1.000
	DIGEST-SUM	17	1.0000	.93541	1.1765	1.01460	+0.2	0.449

CRT: chemoradiationtherapy in combination with Cisplatin or Carboplatin; BioRT: Irradiation with Cetuximab; DIGEST: Dynamic Imaging Grade of Swallowing Toxicity, DIGEST-SUM: Summary Grade of the DIGEST: severity of pharyngeal-phase dysphagia based on the safety and efficiency of bolues clearance. DIGEST-S: safety profile based on penetration-aspiration scale[21]; DIGEST-E: efficiency profile based on penetration-aspiration scale (using estimation of the percentage of pharyngeal residue); Std. Deviation: Standard deviation.

WILCOXON SIGNED-RANK TEST: Ranks per treatment group

TREATMENT			N	Mean Rank	Sum of Ranks
CRT	DIGEST_S_POST - DIGEST_S_PRE	Negative Ranks	1[a]	1.00	1.00
		Positive Ranks	3[b]	3.00	9.00
		Ties	6[c]		
		Total	10		
	DIGEST_E_POST - DIGEST_E_PRE	Negative Ranks	2[d]	2.00	4.00
		Positive Ranks	3[e]	3.67	11.00
		Ties	5[f]		
		Total	10		
	DIGEST_SUM_POST - DIGEST_SUM_PRE	Negative Ranks	2[g]	3.00	6.00
		Positive Ranks	5[h]	4.40	22.00
		Ties	3[i]		
		Total	10		
BIORT	DIGEST_S_POST - DIGEST_S_PRE	Negative Ranks	1[a]	3.00	3.00
		Positive Ranks	5[b]	3.60	18.00
		Ties	11[c]		
		Total	17		
	DIGEST_E_POST - DIGEST_E_PRE	Negative Ranks	5[d]	5.50	27.50
		Positive Ranks	5[e]	5.50	27.50
		Ties	7[f]		
		Total	17		
	DIGEST_SUM_POST - DIGEST_SUM_PRE	Negative Ranks	4[g]	4.00	16.00
		Positive Ranks	5[h]	5.80	29.00
		Ties	8[i]		
		Total	17		

a. DIGEST_SAF_POST < DIGEST_SAF_PRE, b. DIGEST_SAF_POST > DIGEST_SAF_PRE, c. DIGEST_SAF_POST = DIGEST_SAF_PRE, d. DIGEST_EFF_POST < DIGEST_EFF_PRE, e. DIGEST_EFF_POST > DIGEST_EFF_PRE, f. DIGEST_EFF_POST = DIGEST_EFF_PRE, g. DIGEST_SUM_POST < DIGEST_SUM_PRE, h. DIGEST_SUM_POST > DIGEST_SUM_PRE, i. DIGEST_SUM_POST = DIGEST_SUM_PRE,

DIGEST-SUM: Summary Grade of the DIGEST: severity of pharyngeal-phase dysphagia based on the safety and efficiency of bolues clearance. DIGEST-S: safety profile based on penetration-aspiration scale[21]; DIGEST-E: efficiency profile based on penetration-aspiration scale (using estimation of the percentage of pharyngeal residue); PRE: pre-treatment, POST: post-treatment.

Table 5 | Overview of DIGEST-SUM Grade on patient level

Treatment group		**DIGEST-SUM Grade**	
	Case	*Pre-treatment*	*Post-treatment*
CRT (n = 10)	1.	0 (None)	2 (Moderate)
	2.	1 (Mild)	1 (Mild)
	3.	2 (Moderate)	3 (Severe)
	4.	1 (Mild)	0 (None)
	5.	2 (Moderate)	2 (Moderate)
	6.	0 (None)	0 (None)
	7.	0 (None)	1 (Mild)
	8.	1 (Mild)	2 (Moderate)
	9.	1 (Mild)	0 (None)
	10.	1 (Mild)	3 (Severe)
BioRT (n = 17)	11.	1 (Mild)	3 (Severe)
	12.	0 (None)	0 (None)
	13.	0 (None)	1 (Mild)
	14.	1 (Mild)	0 (None)
	15.	1 (Mild)	1 (Mild)
	16.	3 (Severe)	2 (Moderate)
	17.	2 (Moderate)	2 (Moderate)
	18.	0 (None)	0 (None)
	19.	1 (Mild)	2 (Moderate)
	20.	1 (Mild)	1 (Mild)
	21.	1 (Mild)	1 (Mild)
	22.	3 (Severe)	2 (Moderate)
	23.	0 (None)	0 (None)
	24.	1 (Mild)	3 (Severe)
	25.	1 (Mild)	1 (Mild)
	26.	1 (Mild)	0 (None)
	27.	0 (None)	1 (Mild)

DIGEST: Dynamic Imaging Grade of Swallowing Toxicity, DIGEST-SUM: Summary Grade of the DIGEST: severity of pharyngeal-phase dysphagia based on the safety and efficiency of bolues clearance. CRT: chemoradiationtherapy in combination with Cisplatin or Carboplatin; BioRT: Irradiation with Cetuximab

Table 6 | Overview of DIGEST-SUM grades and patient-reported experiences on patient level

		Pre-treatment				Post-treatment			
		Objective	Subjective: Complaints			Objective	Subjective: Complaints		
	Case	*DIGEST-SUM*	*None*	*Saf*	*Eff*	*DIGEST-SUM*	*None*	*Saf*	*Eff*
CRT (n=10)	1.	0		X	X	2		X	
	2.	1		X	X	1		X	
	3.	2	X			3	X		
	4.	1	X			0	X		
	5.	2		X		2	X		
	6.	0	X			0	X		
	7.	0	X			1	X		
	8.	1	X			2			X
	9.	1	X			0			X
	10.	1	X			3		X	
BioRT (n=17)	11.	1	X			3		X	
	12.	0			X	0	X		
	13.	0	X			1			X
	14.	1	X			0	X		
	15.	1	X			1	X		
	16.	3		X		2	X		
	17.	2	X			2	X		
	18.	0	X			0	X		
	19.	1	X			2	X		
	20.	1	X			1		X	
	21.	1	X			1		X	
	22.	3	X			2		X	X
	23.	0	X			0		X	
	24.	1		X	X	3		X	
	25.	1		X		1	X		
	26.	1		X		0	X		
	27.	0	X			1	X		

CRT: chemoradiationtherapy in combination with Cisplatin or Carboplatin; BioRT: Irradiation with Cetuximab; DIGEST: Dynamic Imaging Grade of Swallowing Toxicity; DIGEST-SUM: Summary Grade of the DIGEST: severity of pharyngeal-phase dysphagia based on the safety and efficiency of bolues clearance; DIGEST-SUM scores: 0 (no dysphagia), 1 (mild dysphagia), 2 (moderate dysphagia), 3 (severe dysphagia); None: No complaints; Saf: Including complaints about aspiration/penetration; Eff: Including complaints about residue.

Table 7 | Type of complaints the patients experience at different DIGEST-SUM grades. Numer of patients in each box.

		Pre-treatment					Post-treatment				
	DIGEST-SUM	*No*	*Saf*	*Eff*	*Both*	**Total**	*No*	*Saf*	*Eff*	*Both*	**Total**
CRT (n = 10)	*0*	2			1	**3**	2		1		**3**
	1	4			1	**5**	1	1			**2**
	2	1	1			**2**	1	1	1		**3**
	3						1	1			**2**
	4										
	Total	**7**	**1**		**2**	**10**	**5**	**3**	**2**		**10**
BioRT (n = 17)	*0*	4		1		**5**	4	1			**5**
	1	6	2		1	**9**	3	2	1		**6**
	2	1				**1**	3			1	**4**
	3	1	1			**2**		2			**2**
	4										
	Total	**12**	**3**	**1**	**1**	**17**	**10**	**5**	**1**		**17**
All patients (N = 27)	*0*	6		1	1	**8**	**6**	**1**	**1**		**8**
	1	10	2		2	**14**	**4**	**3**	**1**		**8**
	2	2	1			**3**	**4**	**1**	**1**	**1**	**7**
	3	1	1			**2**	**1**	**3**			**4**
	4										
	Total	**19**	**4**	**1**	**3**	**27**	**15**	**8**	**3**	**1**	**27**

CRT: chemoradiationtherapy in combination with Cisplatin or Carboplatin; BioRT: Irradiation with Cetuximab; DIGEST: Dynamic Imaging Grade of Swallowing Toxicity; DIGEST-SUM: Summary Grade of the DIGEST: severity of pharyngeal-phase dysphagia based on the safety and efficiency of bolues clearance; DIGEST-SUM scores: 0 (no dysphagia), 1 (mild dysphagia), 2 (moderate dysphagia), 3 (severe dysphagia), 4 (life-treathening dysphagia); N: No complaints; Saf: Including complaints about aspiration/penetration; Eff: Including complaints about residue; Both: complaints about Safety and Efficiency as well.