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REVIEW ARTICLE

A comparison of swallowing dysfunction after three-dimensional conformal and intensity-modulated radiotherapy

A systematic review by the Italian Head and Neck Radiotherapy Study Group

Stefano Ursino[1] · Elisa D'Angelo[2] · Rosario Mazzola[3] · Anna Merlotti[4] · Riccardo Morganti[1] · Agostino Cristaudo[1] · Fabiola Paiar[1] · Daniela Musio[5] · Daniela Alterio[6] · Almalina Bacigalupo[7] · Elvio Grazioso Russi[4] · Frank Lohr[2]

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Abstract

Purpose Dysphagia is one of the most important treatment-related side effects in head and neck cancer (HNC), as it can lead to severe life-threating complications such as aspiration pneumonia and malnutrition. Intensity-modulated radiotherapy (IMRT) could reduce swallowing dysfunction by producing a concave dose distribution and reducing doses to the swallowing-related organs at risk (SWOARs). The aim of this study was to review the current literature in order to compare swallowing outcomes between IMRT and three-dimensional conformal radiotherapy (3DCRT).

Methods A search was conducted in the PubMed and Embase databases to identify studies on swallowing outcomes, both clinically and/or instrumentally assessed, after 3DCRT and IMRT. Dysphagia-specific quality of life and objective instrumental data are summarized and discussed.

Results A total of 262 papers were retrieved from the searched databases. An additional 23 papers were retrieved by hand-searching the reference lists. Ultimately, 22 papers were identified which discussed swallowing outcomes after 3DCRT and IMRT for HNC. No outcomes from randomized trials were identified.

Conclusion Despite several methodological limitations, reports from the current literature seem to suggest better swallowing outcomes with IMRT compared to 3DCRT. Further improvements are likely to result from the increased use of IMRT plans optimized for SWOAR sparing.

✉ Stefano Ursino, MD
stefano.ursino@med.unipi.it

Elisa D'Angelo
e.dangelo@yahoo.it

Rosario Mazzola
rosariomazzola@hotmail.it

Anna Merlotti
annamerlotti@virgilio.it

Riccardo Morganti
r.morganti@ao-pisa.toscana.it

Agostino Cristaudo
agostino.cristaudo@gmail.com

Fabiola Paiar
fabiola.paiar@unipi.it

Daniela Musio
daniela.musio@libero.it

Daniela Alterio
daniela.alterio@ieo.it

Almalina Bacigalupo
almalina.bacigalupo@hsanmartino.it

Elvio Grazioso Russi
elviorussi@gmail.com

[1] Radiation Oncology, University Hospital S. Chiara, Via Roma 55, 56126 Pisa, Italy

[2] Radiation Oncology, University Hospital, Largo del Pozzo 74, 44125 Modena, Italy

[3] Radiation Oncology, Sacro Cuore-Don Calabria Cancer Care Center, Via Don Sempreboni 5, 37024 Negrar-Verona, Italy

[4] Radiation Oncology, S.Croce e Carle Hospital, Via M. Coppino 26, 12100 Cuneo, Italy

[5] Radiation Oncology, University Hospital La Sapienza, Viale del Policlinico 155, 00161 Roma, Italy

[6] Radiation Oncology, Advanced Radiotherapy Center, European Institute of Oncology, Via G. Ripamonti 435, 20141 Milan, Italy

[7] Radiation Oncology, AOU IRCCS San Martino – IST National Cancer Research Institute and University, Largo Rosanna Benzi 10, 16132 Genoa, Italy

Keywords Dysphagia · Chemotherapy · Quality of life · Organs at risk · Pneumonia, aspiration

Ein Vergleich von Schluckstörungen nach dreidimensionaler konformaler und intensitätsmodulierter Strahlentherapie

Ein systematischer Review der "Italian Head and Neck Radiotherapy Study Group"

Zusammenfassung

Hintergrund Dysphagie ist eine der wichtigsten Nebenwirkungen bei der Behandlung von Kopf-Hals-Tumoren (HNC), da sie zu lebensbedrohlichen Komplikationen wie Aspirationspneumonien und Mangelernährung führen kann. Durch Erzeugung konkaver Dosisverteilungen und durch die Reduzierung der Dosis an schluckrelevanten Strukturen (SWOAR) kann die IMRT Schluckstörungen möglicherweise vermindern. Ziel dieser Studie war es, die gegenwärtige Literaturlage hinsichtlich der Schluckfunktion nach IMRT und konformaler dreidimensionaler Strahlentherapie (3DCRT) systematisch zu überprüfen.

Material und Methoden Studien, die die Schluckfunktion nach 3DCRT und IMRT klinisch und/oder instrumentell untersuchten, wurden durch eine Datenbankrecherche in PubMed und Embase identifiziert. Schluckbezogene Lebensqualität und objektiv instrumentell erhobene Daten wurden zusammengefasst und diskutiert.

Ergebnisse Insgesamt wurden 262 Manuskripte aus den Datenbanken extrahiert. Weitere 23 Manuskripte wurden durch manuelle Suche in den Literaturlisten ermittelt. Schließlich wurden 22 Arbeiten identifiziert, welche die Schluckfunktion nach 3DCRT und IMRT zum Gegenstand hatten. Darunter waren keine randomisierten Studien.

Schlussfolgerung Trotz methodisch bedingter Einschränkungen der Aussagekraft dieser Analyse legt die gegenwärtige Literaturlage bessere Ergebnisse hinsichtlich der Schluckfunktion nach IMRT im Vergleich zu 3DCRT nahe. Weitere Verbesserungen werden wahrscheinlich durch die gezielte Optimierung von IMRT-Plänen hinsichtlich der SWOAR resultieren.

Schlüsselwörter Dysphagie · Chemotherapie · Lebensqualität · Risikoorgane · Aspirationspneumonie

In Western countries, head and neck cancer (HNC) accounts for about 5% of all tumors [1, 2].

Due to the tumor location at the aerodigestive crossroad, patients frequently suffer from swallowing dysfunction and its potentially life-threating complications (i. e., aspiration pneumonia and malnutrition), which are caused by both primary cancer (baseline dysphagia) and cancer therapies (treatment-related dysphagia) [3–5].

Over the past decades, several organ-preservation protocols using a combination of chemotherapy (CT) and radiotherapy (RT) have been investigated. These have shown comparable oncologic results to radical surgery (i. e., total laryngectomy) but are associated with a high rate of treatment-related dysphagia [6, 7]. In fact, the recent publication of 10-year results of the Radiation Therapy Oncology Group (RTOG) 91-11 trial [8, 9] has revealed that concomitant radio-chemotherapy (RTCT) results in better locoregional control and laryngeal preservation than induction chemotherapy followed by RT alone, despite being hampered by a relevant rate (17 to 24%) of swallowing dysfunction that compromises patient nutritional status and quality of life. Historically, RT has always been burdened by a high rate of radiation-related dysphagia occurring in more than 50% of patients and often leading to aspiration pneumonia, pharyngo-esophageal strictures, and malnutrition status with long-term percutaneous endoscopic gastrostomy (PEG) tube dependence [3, 10–12]. Compared to three-dimensional conformal RT (3DCRT), several studies have suggested that intensity-modulated RT (IMRT) reduces the probability of swallowing dysfunction due to the fact that it can produce concave dose distributions with better avoidance of several critical dose-limiting structures, such as swallowing organs at risk (SWOARs), which might lead to better functional outcomes [13–16]. Swallowing disorders can be both clinically and/or instrumentally assessed. In this regard, clinical evaluation is usually performed using patient-reported questionnaires such as the M.D. Anderson Dysphagia Inventory (MDADI)—the sole questionnaire validated to specifically assess oropharyngeal dysphagia (OPD) [17]—and/or observer-rated toxicity scales such as the Common Toxicity Criteria for Adverse Events (CTCAE) or RTOG scales [18, 19]. Finally, objective instrumental assessment is usually provided using the videofluoroscopic swallowing study (VFSS) and/or fiberoptic endoscopic evaluation of swallowing (FEES) [20].

Unfortunately, the current data are inhomogeneous in terms of swallowing outcome due to several methodological issues as well as the different radiation techniques used (3DCRT and IMRT). Thus, the aim of this study was to review the current literature on posttreatment swallowing function in order to compare outcomes between 3DCRT and IMRT. For this purpose, we distinguished clinical and instrumental swallowing outcomes to allow a more homogeneous comparison of results.

Methods

A search of the PubMed and Embase databases for original articles published between 2000 and 2016 was performed. The Medical Subject Headings (MeSH) terms used were

"head and neck cancer," "squamous cell carcinoma," "radiotherapy," "radio-chemotherapy," "intensity and modulated radiotherapy," "swallowing dysfunction," and "deglutition dysfunction." Additional search terms included swallowing function, deglutition function, and dysphagia. Only English-language articles were included. The review articles retrieved were not included in the study but the reference lists in these articles, as well as those from other papers, were hand-searched for additional relevant publications. Two investigators (SU and DM) reviewed all the titles and abstracts for inclusion into the study. The review was performed systematically according to the PICO questions-based methodology as follows: P (population) = squamous head and neck cancers; I (intervention) = RT, RTCT, or RT-biotherapy with IMRT; C (comparison) = 3DCRT; O (outcome) = swallowing dysfunction [21].

The inclusion criteria were 1) prospective (presence of a baseline swallowing assessment) or retrospective (absence of a baseline swallowing assessment) studies which evaluated dysphagia after RT in HNC; 2) nasophaynx, oropharynx, larynx, hypopharynx, and oral cavity as primary sites; 3) RT, RTCT, or RT plus cetuximab with curative intent (±induction chemotherapy); 4) 3DCRT or IMRT treatment techniques; 5) clinical swallowing evaluation using dysphagia-specific quality of life measures and/or "gold-standard" objective instrumental assessment (VFSS and/or FEES) both early (within 3 months) and/or late (over 3 months) after treatment.

Papers were excluded if 1) prospective or retrospective trials were focused exclusively on patients who complained of dysphagia after treatment; 2) primary sites were different from the inclusion criteria; 3) postoperative or palliative RT or RTCT was performed; 3) surrogate or composite endpoints to evaluate dysphagia were used; 4) two-dimensional radiotherapy (2DRT) or hadrontherapy was performed; 4) non-English language. We also considered studies that included patients treated with both 3DCRT and IMRT (mixed treatment population); subsequently, these papers were excluded if it was not possible to analyze them separately and compare the swallowing outcomes between the two different techniques. Papers dealing with both clinical and instrumental assessment of dysphagia were analyzed separately for the different endpoints. Finally, papers where the swallowing outcomes were incompletely or partially reported because they were part of a wider acute or late toxicity category or health-related quality of life study were not considered.

This review was performed using studies with the primary aim of specifically assessing the oropharyngeal swallowing function (both clinically and/or instrumentally) after 3DCRT and/or IMRT.

Results

A total of 262 papers were retrieved from the search database. Of these, 172 papers were excluded based on their abstract and title. All 90 remaining full-text papers were retrieved and an additional 23 papers were retrieved by hand-searching relevant review articles. Thereafter, 91 papers were excluded based on the inclusion criteria and a total of 22 papers (eight 3DCRT, 11 IMRT, and three mixed 3DCRT/IMRT) were included in the final analysis (Fig. 1). All the included studies were published between 2000 and 2016. No randomized controlled trials were identified. All the reported trials were single-center experiences. Only three studies [22–24] focusing on a mixed-treatment population (3DCRT/IMRT) were included because it was possible to analyze the data separately and compare results on swallowing outcomes. Among the 22 studies included for the purpose of this review, 11 used only the instrumental swallowing assessment [25–35], three used only the clinical swallowing assessment [24, 36, 37], and eight combined clinical and instrumental assessments [22, 38–44]. Indeed, four of the 11 instrumental studies provided a combined clinical and instrumental swallowing assessment [29, 31, 32, 34], but their data on clinical evaluation were not considered for the purpose of this review because the questionnaires were inadequate in their reporting or inconsistent with our inclusion criteria. Of the 19 studies that provided an instrumental evaluation (both exclusively or combined with clinical questionnaires), all used VFSS except for three studies that used only FEES [38–40] and one study that combined VFSS and FEES [35].

Patient demographics

The total number of patients, patient age, gender, overall stage according to the American Joint Committee on Cancer, and swallowing evaluation method were extracted from the papers, where available, and are summarized in Table 1.

Median sample size was 24.5 patients (range 7–112; mean 38) for 3DCRT studies and 55 patients (range 7–300; mean 71) for IMRT; this difference was statistically significant ($p < 0.0001$).

Subjective clinical outcomes (intervention vs. comparison)

Among the 11 studies that reported a clinical assessment of OPD, four performed 3DCRT, five performed IMRT, and two performed mixed 3DCRT/IMRT treatments. Three out of the four 3DCRT studies (75%) as well as four out of the five IMRT studies (80%) provided a prospective evaluation of swallowing function; therefore, in both groups, only one study reported results on retrospective evaluation. A to-

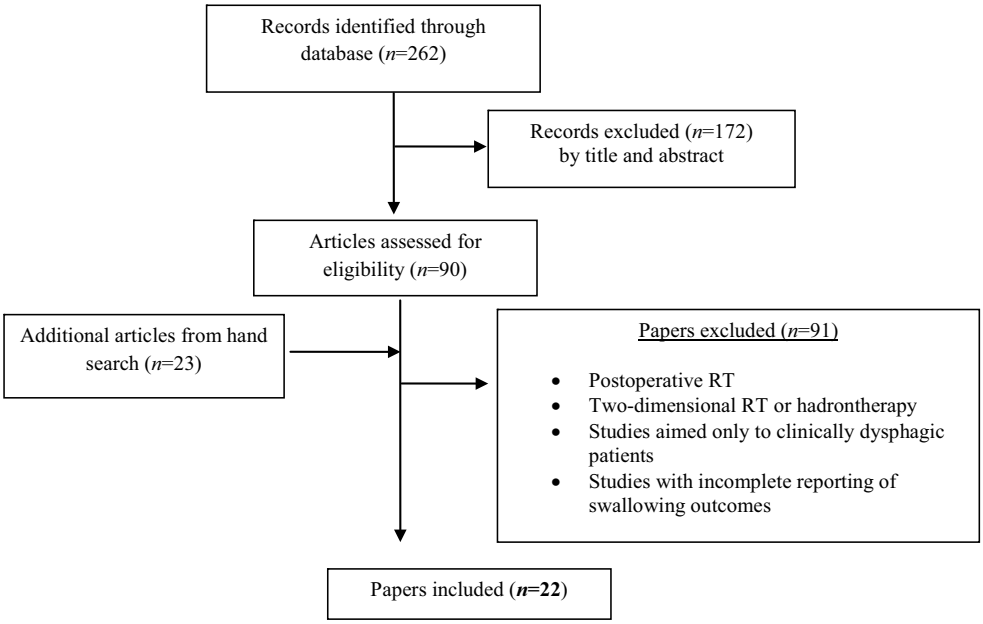

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included studies. *RT* radiotherapy

tal of 143 patients (mean: 36; range: 14–71) were accrued in 3DCRT studies compared to 267 patients (mean: 53.4; range: 18–116) in IMRT studies. None of the 3DCRT studies were focused on a specific subsite, whereas four of the five IMRT studies were focused on a single subsite; overall, the oropharynx was the most frequently investigated subsite as it was included in eight out of the nine studies (89%). The MDADI was the most frequently used questionnaire, as it was employed in five of the nine studies with clinical assessment of OPD (two in the 3DCRT and three in the IMRT studies); in the other four studies, the use of dysphagia-reported questionnaires was extremely variable.

Results of the clinical swallowing assessment studies for 3DCRT are reported in Table 2.

A significant reduction of the MDADI composite score from pretreatment to 3 months posttreatment (76.6 vs. 59.4; $p < 0.01$) without a subsequent improvement from 3 months to 6 and 12 months was reported by Patterson et al. [39].

Contrastingly, data reported by Cartmill et al. [44] revealed a significant reduction of global and functional MDADI domain scores soon after treatment (4–6 weeks), followed by a subsequent significant improvement by 6 months in the global domain ($p = 0.03$). A similar pattern, although not statistically significant ($p = 0.08$), was reported for the other domains (especially for the functional and physical domains); no statistically significant difference resulted between baseline and 6-months posttreatment scores. The study by Goguen et al. [43] reported an overall reduction in mean score for the swallowing-related questions of the FACT-H&N questionnaire. The retrospective data by Jensen et al. [40] on 35 patients reported an overall 83% pattern of some degree of dysphagia using European Organization Radiation Treatment Cancer (EORTC) H&N35 swallowing questionnaires.

Results of the clinical swallowing assessment studies for IMRT are reported in Table 3.

As shown in the study by Goepfert et al. [37], a significant reduction in the MDADI composite score was reported from baseline to 6 months posttreatment (from 88.3 to 73.8; $p < 0.0001$), followed by a slight subsequent improvement at 12 (73.8 vs. 78.6; $p = 0.006$) and 24 months (78.6 vs. 83.3; $p < 0.0001$), although at 2 years the score remained significantly decreased compared to baseline ($p < 0.001$). In addition, the authors reported a similar trend for MDADI subscale scores, which remained statistically reduced at 24 months compared to baseline values (emotional $p = 0.008$, functional $p = 0.006$, physical $p < 0.001$). In the prospective study by Lazaurus et al. [36], an overall significant worsening of swallowing function using MDADI, Eating Assessment Tool-10 (EAT-10), EORTC H&N, and Performance Status Scale for Head & Neck Cancer Patients (PSS-HN) questionnaires was reported. Similar to results reported by previous studies, the MDADI scores were found

Table 1 Comparison of patient demographics in included papers

Characteristics	3DCRT (*N*)	IMRT (*N*)	*p*-value
Total patients	382	929	<0.0001
Age (years)	57.2	57.3	>0.05
Male	280	735	<0.0001
Stage I–II	38	20	0.002
Stage III–IV	62	80	<0.0001
Clinical evaluation	6	7	0.987
Instrumental evaluation	10	11	0.961

3DCRT three-dimensional conformal radiotherapy, *IMRT* Intensity-modulated radiotherapy

Table 2 Clinical swallowing evaluation after 3DCRT

Investigator	Type of study	Sample size	Primary site	Questionnaire	Time of evaluation	Mean score difference (baseline – post-RT)
Patterson (2014) [39]	P	71	Oropharynx/ hypopharynx	MDADI composite	3 months 6 months 12 months	Δ: –16.2 Stable Stable
Cartmill (2012) [44]	P	14	Oropharynx/ larynx	MDADI subscale	4–6 weeks 6 months	Δ:–26.1 (G); –9.2 (E); –15.7 (F);–17.9 (P) Δ: –9.2 (G); –5.9 (E); –6.5 (F); –7.2 (P)
Goguen (2006) [43]	P	23	≥2 sites	FACT-H&N swallowing subscale	6 months	Δ: –1.2
						Mean score post-RT
Jensen (2007) [40]	R	35	≥2 sites	EORTC H&N 35	–	25

3DCRT three-dimensional conformal radiotherapy, *P* prospective, *R* retrospective, Δ variation, *MDADI* M.D. Anderson Dysphagia Inventory (Score 20 to 100; Δ+ improvement score, Δ-worsening score), *G* global, *E* emotional, *F* functional, *P* physical, *FACT-H&N* Functional Assessment of Cancer Therapy-Head and Neck Scale for swallowing-related questions (score 0–4; Δ+ improvement score; Δ-worsening score; 0 = not at all satisfied; 1 = a little bit satisfied; 2 = somewhat satisfied; 3 = quite a bit satisfied; 4 = very much satisfied), *EORTC QLQ-H&N35* European Organization Radiation Treatment Cancer for swallowing-related questions; scores are normalized to a number between 0 and 100 (high numbers, worse symptoms)

Table 3 Clinical swallowing evaluation after IMRT

Investigator	Type of study	Sample size	Primary site	Questionnaire	Time of evaluation	Mean score difference (baseline – post-RT)
Feng (2010) [41]	P	73	Oropharynx	HNQOL (eating domain)	1, 3, 6, 12, 18, 24 months	Δ: +33; +26; +23; +14; +14; +12
				UWQOL (swallowing question)		Δ: +31;+19;+11;+10;+10; +9
Schwartz (2010) [42]	P	31	Oropharynx	MDADI composite score	6, 12, 24 months	Δ: –13.5; –7.6; –6.7
				MDADI global score		Δ: –13.2; –7.1; –4.9
				PSS-HN normalcy of diet		Δ: –21.9; –16.1; –5.8
Lazaurus (2014) [36]	P	29	≥2 sites	EAT-10	3, 6 months	Δ: +6.79; +2.79
				MDADI		Δ: –7.22; –2.61
				EORTC H&N35		Δ: +9.56; +4.48
				PSS-HN normalcy of diet		Δ: –17; –13
				PSS-HN eating in public		Δ: –7; –6
Patterson (2014) [38]	R	18	Nasopharynx	AusTOMs	Mean 27 months (6–42 months)	16% (grade 5) 56% (grade 4) 28% (grade 3)
						Mean score post-RT
Goepfert (2016) [37]	P	116	Oropharynx	MDADI composite score MDADI subscale scores	6, 12, 24 months	Δ: –14.5; –9.7; –5 Δ: –10.3; –6.7; –2.1 (E) Δ: –12.1; –7.7; –2.6 (F) Δ: –19.7; 13.8; –8.9 (P)

IMRT intensity-modulated radiotherapy, *P* prospective, *R* retrospective, Δ variation, *MDADI* M.D. Anderson Dysphagia Inventory (score 20 to 100; Δ+ improvement score, Δ-worsening score), *G* global, *E* emotional, *F* functional, *P* physical, *EAT-10* Eating Assessment Tool-10 (score 0–40; Δ+ worsening score, Δ-improvement score), *EORTC H&N35* European Organization Radiation Treatment Cancer for swallowing-related questions (scores 0–100; Δ+ worsening score, Δ-improvement score), PSS-HN= Performance Status Scale for Head & Neck Cancer Patients (score 0–100; Δ+ improvement score, Δ-worsening score), *HNQOL* Head and Neck Quality of Life Questionnaire (score 0–100; Δ+ worsening score, Δ-improvement score), *UWQOL* University Washington Head and Neck Quality of Life Questionnaire (score 0–100; Δ+ worsening score, Δ-improvement score), *AusTOMs* Australian Therapy Outcomes Measures (score 0–5; 0 = profound; 1 = severe; 2 = moderate/severe; 3 = moderate; 4 = mild; 5 = no)

to be significantly reduced at 3 months (81.9 vs. 74.67), followed by a subsequent slight recovery at 6 months (74.67 vs. 79.28). Moreover, also for the EAT-10 questionnaire was the score found to be significantly higher at 3 months compared to pretreatment (4.39 vs. 11.18; $p < 0.001$), with a subsequent slight reduction at 6 months (11.18 vs. 7.18; $p = 0.011$), as it was for EORTC H&N scores (from 11.36 at baseline to 20.92 and 15.84 at 3 and 6 months, respectively; $p = 0.057$). For PSS-HN, there was an approximately 18 ($p < 0.001$) and 14% ($p = 0.002$) reduction in normalcy of diet domain from baseline to 3 and 6 months, respectively, whereas for the eating in public domain there was not a statistically significant difference at any of the time points ($p = 0.270$ and $p = 0.326$, respectively). Similarly, Schwartz et al. [42] reported significantly lower MDADI composite and global scores from baseline to all posttreatment intervals ($p < 0.001$), showing a significant reduction of values at 6 months (89.7 vs. 76.5 and 89.1 vs. 75.6, respectively), a slight recovery at 12 months (76.5 vs. 82.6 and 75.6 vs. 81.5, respectively), and an approximate stabilization at 24 months (82.6 vs. 84.8 and 81.5 vs. 82.4, respectively). Likewise, a similar trend was observed for the PSS-HN normalcy of diet subscale. Feng et al. [41] reported an acute worsening at 1 month posttreatment both for the Head and Neck Quality of Life Questionnaire (HNQOL) eating domain and University Washington Head and Neck Quality of Life Questionnaire (UWQOL) swallowing scores (10 vs. 43 and 8 vs. 39, respectively; $p < 0.001$), followed by a significant improvement over time at 6–12 months ($p < 0.001$) and then a stabilization at 24 months ($p = 0.57$). Finally, in the retrospective study by Patterson et al. [38], moderate swallowing impairment or activity restriction was reported in 27.8 and 11.1% of patients, respectively.

Data resulting from the 3DCRT/IMRT mixed population studies are shown in Table 4.

In the study by Kraaijenga et al. [22], patients treated with IMRT showed a significantly better swallowing function compared to 3DCRT for Swallowing Quality of Life Questionnaire (SWAL-QOL) scores, especially on the domains of food selection ($p = 0.043$), eating desire ($p = 0.050$), communication ($p = 0.014$), mental health ($p = 0.014$), and social function ($p = 0.017$). Similar results were reported by Kerr et al. [24] for PSS-HN scores, showing a significant difference in favor of IMRT and predicting no restriction vs. any restriction (100 vs. <75; odds ratio, OR, 0.164; $p < 0.001$). Regarding the eating in public domain at 12 and 24 months, 83 and 82% of IMRT survivors had no restrictions compared to 49 and 64% of 3DCRT survivors, respectively, whereas for the normalcy of diet domain, a difference in favor of IMRT was observed at 12 and 24 months, with 22 and 25% in the IMRT group without restriction compared to 7 and 5% in the 3DCRT group, respectively.

Objective instrumental outcomes (intervention vs. comparison)

Results of the instrumental swallowing assessment studies for the different radiation treatment techniques are reported in Table 5 and 6. Among the 19 studies that reported an instrumental assessment of OPD, eight performed 3DCRT, nine IMRT, and two mixed 3DCRT/IMRT treatments. Seven out of the eight 3DCRT studies (87.5%) provided a prospective evaluation of the swallowing function compared to five out of the nine IMRT studies (55.5%). A total of 214 patients (mean: 26.75; range: 12–71) were accrued in 3DCRT studies compared with a total of 707 patients (mean: 74.5; range: 14–300) in IMRT studies. In the 3DCRT studies, the oropharynx was the most frequently investigated subsite as it was enrolled in six out of eight studies (75%), followed by the hypopharynx and larynx that were enrolled in five studies (62.5%), and the nasopharynx and oral cavity in three studies (37.5%). In the IMRT studies, the oropharynx was the most frequently investigated subsite as it was enrolled in nine out of 11 studies (82%), followed by the nasopharynx and oral cavity in four studies (36%), and larynx and hypopharynx in three studies (27%).

Only one study [44] in both groups reported differentiated swallowing outcomes at different times of evaluation or for administration of different bolus consistencies.

Almost all the studies reported the postradiation swallowing outcome as the pattern of penetration and/or aspiration. Several also reported the percentage of pharyngeal residue [27, 28, 30, 35, 38, 40], whereas only few studies [34, 41–43] reported data on OPSE or SPSS videofluoroscopy-based scores. An overall range of 5–78% and 7–75% was reported for aspiration and penetration, respectively, in the 3DCRT studies, compared to a range of 2.6–26% and 11–35%, respectively, in the IMRT studies. Moreover, a rate of 2–88% of pharyngeal residue was reported after 3DCRT compared to 10–63% after IMRT. Finally, only four studies (one on 3DCRT and three on IMRT) reported data on specific swallowing rating tools such as SPSS or OPSE. As shown in Table 5 and 6, in the 3DCRT study [43], a mean SPSS score of 5 (indicating moderate dysfunction that required a modified diet and swallowing precautions to minimize risk of aspiration) was reported, compared to a score of 4 (indicating mild/moderate dysfunction) or 78% of patients with an SPSS score <3 (indicating normal swallowing or mild dysfunction) in the IMRT studies [34, 41, 43]. Additionally, the only study that used OPSE reported a reduction of 13.2 points after IMRT [42].

Data resulting from the mixed 3DCRT/IMRT population are presented in Table 4. As shown in the prospective study by Paulosky et al. [26], a statistically significant better swallowing outcome measured using the OPSE score was reported with IMRT compared to 3DCRT, both after liq-

Table 4 Instrumental and clinical swallowing evaluation in the mixed 3DCRT/IMRT population

Investigator	Type of study	Sample size	Primary site	RT technique	Method of evaluation	Type of bolus	Time of post-RT evaluation	Swallowing outcome
Pauloski (2015) [26]	P	14	≥2 sites	3DCRT	VFSS	3–10 mL thin liquid barium 3 mL barium paste	3, 6 months	13% residue 80 OPSE (liquid bolus) 64 OPSE (paste bolus)
				IMRT	VFSS	3–10 mL thin liquid barium 3 mL barium paste	3, 6 months	3.5% residue 103 OPSE (liquid bolus) 81 OPSE (paste bolus)
Kraaijenga (2015) [22]	R	22	≥2 sites	3DCRT	VFSS	1–3–5–10 mL thin liquid barium 3–5 mL paste barium Iohexol-coated cake	≥10 years	83% aspiration
				IMRT	VFSS	1–3–5–10 mL thin liquid barium 3–5 mL paste barium Iohexol-coated cake	≥10 years	30% aspiration
								Mean absolute scores (3DCRT vs. IMRT)
Kraaijenga (2015) [22]	R	22	≥2 sites	3DCRT/IMRT	SWAL-QoL Food selection Eating desire Communication Mental health Social function	–	≥10 years	16 vs. 6 17 vs. 31 18 vs. 47 10 vs. 28 13 vs. 31
Kerr (2015) [24]	P	200	Oropharynx	3DCRT/IMRT	PSS-HN Eating in public PSS-HN Normalcy of diet	–	12 months	51 vs. 27% ≤75 93 vs. 78% ≤75

3DCRT three-dimensional conformal radiotherapy, *IMRT* Intensity-modulated radiotherapy, *P* prospective, *R* retrospective,
3DCRT three-dimensional conformal radiotherapy, *IMRT* Intensity and modulated radiotherapy, *VFSS* videofluoroscopy swallowing study, *OPSE* oropharyngeal swallowing efficiency (higher score, better function), *SWAL-QOL* Swallowing Quality of Life Questionnaire (score 0–100; Δ+ worsening score, Δ-improvement score), *PSS-HN* Performance Status Scale for Head & Neck Cancer Patients (score ≥75 normal function, <75 any restriction)

uid and paste bolus administration ($p = 0.0003$ and 0.018, respectively), as well as in terms of the percentage of pharyngeal residue ($p = 0.005$). Similarly, a lower pattern of aspirations (30 vs. 83%) was observed after IMRT compared with 3DCRT in the retrospective study by Kraaijenga et al. [22].

Discussion

This systematic review aimed to establish what evidence is currently available on better swallowing outcomes using IMRT rather than 3DCRT as part of a multidisciplinary organ-preservation treatment strategy in HNC patients. To our knowledge, this is the only review specifically focused on comparing the swallowing outcomes of these two treatment techniques. Previous reviews only aimed at exploring the potential effects of IMRT on swallowing performance and some concluded that there is limited evidence on this topic [45, 46].

Nevertheless, the rationale for using IMRT as a strategy to reduce posttreatment dysphagia has been well acknowledged based on the relationship between swallowing functional status and the pattern of radiation dose received

Table 5 Instrumental swallowing evaluation after 3DCRT

Investigator	Type of study	Sample size	Primary site	Type of evaluation	Type of bolus	Time of post-RT evaluation	Swallowing outcome
Eisbruch (2002) [30]	P	26	≥2 sites	VFSS	5–15 mL liquid bolus (barium diluted with water) Soft bolus (fruit mixed with barium) Solid bolus (shortbread cookie coated with barium)	1–3 months 6–12 months	75% pharyngeal residue 25% penetration 65% aspiration 77% pharyngeal residue 23% penetration 62% aspiration
Kotz (2004) [27]	P	12	≥2 sites	VFSS	3–5–10 mL liquid barium 3–5 mL paste barium Single cookie bolus impregnated with barium	1–14 weeks (mean 8 weeks)	33–50% pharyngeal residue 75% penetration 33% aspiration
Goguen (2006) [43]	P	23	≥2 sites	VFSS	Liquid barium, barium paste and barium-coated cookie	Median 3.5 months (1 week–13.5 months)	78% aspiration (35% silent aspiration) SPSS mean score 5
Ku (2007) [29]	P	20	Nasopharynx	VFSS	5–10 mL liquid barium, paste barium, barium-coated cookie	6, 12 months	25–35% laryngeal penetration 0–5% aspiration
Jensen (2007) [40]	R	35	≥2 sites	FEES	Saliva/mash/fluid/solid	–	88% residue 59% penetration 18% aspiration
Cartmill (2012) [44]	P	14	Oropharynx/larynx	VFSS	Liquid barium (50% barium and 50% water) Thickened liquid barium (extremely, moderately, and mildly thick) Biscuit, diced fruit and marshmallow coated barium	4–6 weeks 6 months	21–23% penetration for liquids and solids 7–8% aspiration for liquids and solids 7–29% penetration for liquids and solids 7–14% aspiration for liquids and solids
Maruo (2014) [28]	P	13	Larynx/hypopharynx	VFSS	–	1, 3 months, and 1 year	2–5.5% residue (no significant worsening of pharyngeal residue and aspirations)
Patterson (2014) [39]	P	71	Oropharynx/hypopharynx	FEES	10 mL blue-dyed milk	3, 6, 12 months	28% aspiration (9% silent aspiration)

3DCRT three-dimensional conformal radiotherapy, *P* prospective, *R* retrospective, *VFSS* videofluoroscopy swallowing study, *FEES* fiberoptic evaluation of swallowing, *SPSS* Swallow Performance Status Score, *OPSE* oropharyngeal swallowing efficiency (higher score, better function)

Table 6 Instrumental swallowing evaluation after IMRT

Investigator	Type of study	Sample size	Primary site	Method of evaluation	Type of bolus	Time of post-RT evaluation	Swallowing outcome
Feng (2010) [41]	P	73	Oropharynx	VFSS	Not specified	3,12, 24 months	26, 20, 16% penetration/aspiration SPSS mean score 4
Schwarts (2010) [42]	P	31	Oropharynx	VFSS	Liquid, pudding, and cracker	6, 12, 24 months	OPSE Δ:–13.2 4–6% aspiration
Van Der Molen (2013) [32]	P	46	≥2 sites	VFSS	Not specified	10 weeks	2.6% aspiration 18% penetration
						1 year	2.6% aspiration 11% penetration
Mortensen (2013) [34]	R	65	≥2 sites	VFSS	3–5–10 mL liquid barium Barium-coated carrot gratin	–	63% retention 78% SPSS score<3 31% penetration 6% aspiration
Starmer (2014) [31]	R	72	Oropharynx	VFSS	Not specified	–	45% penetration/aspiration
Kumar (2014) [33]	P	46	Oropharynx	VFSS	Not specified	6–24 months	35% penetration and/or aspiration
Patterson (2014) [38]	R	18	Nasopharynx	FESS	Blue-dyed water bolus 14 g of diced drained fruit Dry biscuit	–	44% severe pharyngeal retention
Dale (2015) [25]	R	300	Oropharynx	VFSS	Not specified	≥12 months	7% aspiration
Ursino (2016) [35]	P	20	Nasopharynx and Oropharynx	FEES VFSS	Liquid bolus (5 mL water marked with methylene blue) Semisolid bolus (5 mL spoon of marmalade) Liquid bolus (barium diluted in 65 mL of water) Semisolid bolus (barium diluted in 30 mL of water)	1 month	10–30% moderate or severe pharyngeal retention 5% aspiration

IMRT Intensity-modulated radiotherapy, *P* prospective, *R* retrospective, Δ variation, *VFSS* videofluoroscopy swallowing study, *FEES* fiberoptic endoscopic evaluation of swallowing, *SPSS* Swallowing Performance Status Scale, *OPSE* Oropharyngeal swallowing efficiency (higher score, better function)

by the swallowing related structures (SWOARs) such as pharyngeal constrictor muscles (superior, medium, and inferior), supraglottic and glottis larynx, and the esophageal inlet [47–50]. In addition, several authors [13, 51] have already discussed the potential for significant dosimetric improvements when SWOARs are explicitly considered in the IMRT plan optimization process (SWOAR-sparing IMRT) compared to standard IMRT, in order to maximally reduce irradiation of these structures and to achieve better swallowing outcomes. In this regard, computed tomography (CT)-based guidelines for delineation of the main swallowing structures have recently been published by Christianen et al. [52], to assist radiation oncologists in clinical practice as well as to facilitate comparison of results between different clinical studies. Therefore, we identified 22 papers (for a total of 1311 patients), heterogeneously in favor of IMRT but homogeneous in terms of the method of evaluation, which were relevant according to our inclusion criteria.

In almost all prospective clinical evaluation studies analyzed in this review, an overall worsening of the swallowing function from baseline to after treatment was shown, regardless of the RT techniques and questionnaires used. In the IMRT studies, a greater number of evaluation steps were performed compared to the situation with 3DCRT. These evaluation steps reported a significant swallowing impairment soon after treatment (between 1 to 3 months), followed by an improvement or stabilization (6 months), and a subsequent gradual recovery (between 12 to 24 months), although there was a persistence of values at levels lower than baseline. Indeed, a statistically significant benefit in favor of IMRT emerged from a direct comparison in the two mixed population studies, highlighting its ameliorative role in reducing subjectively reported swallowing impairment compared to standard techniques.

Regarding the instrumental evaluation studies, the results were extremely variable and difficult to compare, mainly due to the lack of well-defined and standardized score parameters, which made it difficult to draw firm conclusions.

Penetration and aspiration were the most frequently used parameters to measure the severity of posttreatment dysphagia, although results were rarely reported according to the standardized penetration-aspiration scale (PAS) [53]. Sometimes the authors did not distinguish between these occurrences (i. e., reporting a global rate of penetration/aspiration), making it difficult to interpret the data as their clinical relevance is different ("ab ingestis" pneumonia is associated with the occurrence of aspiration rather than penetration). Even so, the pattern of aspiration seemed to be significantly lower after IMRT than after 3DCRT, as most papers specifically reported a rate of 2.6–7% from IMRT compared to 7–78% after 3DCRT. Some studies reported results using pharyngeal residue, although the absence of standardized scores to quantify the amount of bolus retained in the pharynx limited the possibility to compare the effects of the two different techniques. In this regard, we do believe that pharyngeal residue, if properly quantified and combined with the pattern of aspiration, is a useful tool to assess postradiation dysphagia. It has been well recognized by previous authors [4, 54] that the greater the amount of bolus retention in the pharynx after the swallowing act (post-swallowing residue), the higher the probability of aspiration (post-swallowing aspiration). Nevertheless, similar to clinical studies, a significant benefit in favor of IMRT clearly emerged from the direct comparison of the two different techniques, both in terms of aspiration and pharyngeal residue, and in terms of functional parameters such as OPSE.

Overall, despite our strict inclusion criteria, the heterogeneity of the population studied (many studies focused on more than two HNC subsites), the different clinical swallowing questionnaires used, and the lack of standardized objective instrumental parameter scores, as well as the lack of standardization of the amount and consistency of the bolus administered and the high variability in the timings of the evaluations, were the major limitations for the comparison of the results. However, a considerable benefit of IMRT in preserving the swallowing function emerged in this review and we believe that its positive impact is likely to increase as radiation oncologists will be more and more encouraged to optimize treatment plans for the swallowing-related structures in their clinical practice.

Among the 13 IMRT studies that we considered for the intent of this review, seven performed only parotid-sparing [22, 26, 34, 38, 42], whereas six performed SWOAR-sparing IMRT [25, 31–33, 35, 41], though only few [33, 35, 41] clearly reported dosimetric constraints for swallowing-related structures in their protocol study. In this regard, authors mostly referred to previous studies [3, 49, 55] that retrospectively correlated the dose to SWOARs to the occurrence of life-threating dysphagia-related complications (i. e., aspiration pneumonia), and generally suggested mean doses to the constrictor muscles below 55 Gy and to the larynx below 48 Gy.

In our opinion, the study by the University of Michigan [41] best investigated the impact of an "intent-SWOAR-sparing IMRT," albeit in a highly selected population (oropharyngeal cancers without infiltration of posterior pharyngeal wall and without lateral retropharyngeal node involvement), in terms of locoregional recurrence rates and functional preservation. These authors reported the safety of dose reduction to these structures together with a mild to moderate dysfunction (SPSS score 4) at 12 months after treatment. In this study, dosimetric goals for the swallowing structures were arbitrarily set at a maximum dose of 50 Gy outside the planning target volume (PTV) [47]. Hereafter, the subsequent dosimetric analysis on the same

population by Eisbruch et al. [56] found a significant correlation between the dose received by the SWOARs and the occurrence of VFS-based aspirations, reporting a 50 and 25% risk for doses of 63 Gy and 56 Gy to the pharyngeal constrictors, and for doses of 56 Gy and 39 Gy to the supraglottic and glottic larynx, respectively.

From these studies, a recent group analysis on long-term (median follow-up 6.5 years) health-related quality of life in 40 oropharyngeal cancer patients (97.5% human papillomavirus, HPV, positive) reported no significant change of patient-reported dysphagia measured by both HNQOL and UWQOL swallowing questions compared with the assessment at 24 months after treatment [57]. Thus, further potential improvements are warranted and likely to be achieved with more rigorous application of the published CT SWOAR delineation guidelines by Christianen et al. [52].

Conclusion

The maximum benefit of IMRT in swallowing function preservation has still to be thoroughly investigated, such that well-designed prospective trials specifically focused on this relevant endpoint are strongly encouraged by a panel of experts [58]. These trials should provide a good RT quality control protocol for dose reduction to SWOARs and homogeneous clinical inclusion criteria based on the tumor subsite (i. e., in the superiorly sited tumors, the upper and middle constrictor muscles receive higher doses, whereas larynx and inferior muscle are more exposed to higher doses in the inferiorly sited tumors), together with an accurate dysphagia assessment protocol providing a clinical and/or uniform standardized instrumental evaluation itemizing the different consistencies and the amount of the bolus used in order to facilitate comparison of results.

As far as we know, the DARS trial [59] is the only ongoing multicenter randomized controlled trial to determine whether SWOAR-sparing IMRT will led to an improvement in long-term swallowing function compared with standard IMRT in locally advanced oropharyngeal cancers after RTCT, using the difference in mean MDADI composite score as the primary endpoint of the study.

In the meantime, we suggest taking the SWAORs into consideration in the plan optimization process, to maximally reduce irradiation without compromising target coverage, and to refer patients (mostly HPV-positive patients who are candidates for a RTCT curative treatment with a bilateral neck irradiation) to deglutologists for management and prevention of swallowing dysfunction, as recommended by current guidelines [60–62].

Conflict of interest S. Ursino, E. D'Angelo, R. Mazzola, A. Merlotti, R. Morganti, A. Cristaudo, F. Paiar, D. Musio, D. Alterio, A. Bacigalupo, and E.G. FRussiand. Lohr declare that they have no competing interests.

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