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Scientific Article

Impact on quality of life of IMRT versus 3-D conformal radiation therapy in head and neck cancer patients: A case control study

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Abstract

Objective: The purpose of this study was to prospectively and longitudinally compare the health-related quality of life (HRQOL) outcomes between head and neck (HN) cancer patients treated with parotid-sparing intensity modulated radiation therapy (IMRT) and patients treated with 3-dimensional conventional radiation therapy (3D-CRT).

Methods and materials: Before and up to 12 months after treatment, HRQOL was recorded in patients with HN cancer who were referred to the Department of Oncology at Sahlgrenska University Hospital for curative IMRT. The study group's HRQOL was compared with a matched group of patients from previous descriptive HRQOL studies treated with 3D-CRT. Both groups' HRQOL was measured by the European Organization for Research and Treatment for Cancer QLQ-C30 and European Organization for Research and Treatment for Cancer QLQ-HN35 at 6 time points in the first year after diagnosis.

Results: Two hundred and seven patients were included, 111 treated with IMRT and 96 matched controls treated with 3D-CRT. Both groups' HRQOL deteriorated during and after treatment. Just after treatment, worse HRQOL scores were observed in the IMRT group regarding insomnia (38 vs 27; $P = .032$), appetite loss (64 vs 50; $P = .019$), senses (54 vs 41; $P = .017$), and coughing (39 vs 26, $P = .009$). At 12 months, however, significantly better HRQOL scores were observed in the

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Conflicts of interest: None.

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IMRT group regarding problems with dry mouth (72 vs 62; $P = .018$), pain (28 vs 20; $P = .018$), sexuality (37 vs 23; $P = .016$), social contacts (10 vs 6; $P = .026$), cognitive functioning (79 vs 87; $P = .0057$), and financial difficulties (12 vs 20; $P = .0019$).

Conclusions: This study further supports the hypothesis that the introduction of IMRT has improved the long-term quality of life of HN cancer patients who have been treated with radiation therapy, but might cause more acute side effects. Longer follow-up is needed to study late complications.

Introduction

External radiation therapy remains a standard modality for the treatment of advanced squamous cell carcinomas of the head and neck (SCCHN) as either single treatment or in combination with surgery and/or chemotherapy and results in a high overall survival rate.[1,2] Because of the increasing numbers of cancer survivors, long-term health-related quality of life (HRQOL) has become a crucial endpoint that requires study. Several well-known acute toxicities are related to chemoradiation, including mucositis, dysgeusia, and dermatitis, and temporarily affect the HRQOL but return to baseline values 1 year posttreatment[3]; however, xerostomia and dysphagia are common long-term side effects that significantly reduce the HRQOL of surviving patients.[4,5]

Intensity modulated radiation therapy (IMRT) has been introduced in the treatment of SCCHN to achieve the complex dose distributions needed for curative treatment of moderately radiosensitive SCCHNs in the vicinity of many radiosensitive vital organs at risk, such as the spinal cord, salivary glands, and pharyngeal constrictor musculature.[6-9] Specifically, parotid-sparing techniques seem to reduce the dose to an extent that the effects on HRQOL parameters are apparent.[10] The theoretical benefits regarding the exposure of critical organs at risk to lower radiation doses are obvious, but the long-term values of the technique as measured in terms of patient-experienced improvements in the quality of life and objectively measured improved organ functions have yet to be fully established. The main benefits of IMRT treatment seem to be improvements in HRQOL scores related to dryness of the mouth, swallowing, and pain, and improved global quality of life.[11-13] However, the majority of the relevant studies have either been retrospective, lack baseline values or control groups, or have not followed patients longitudinally, and some reports have demonstrated no significant long-term improvements.[14] As a result, the need for prospectively collected data to strengthen these findings is evident. The present study was designed to prospectively and longitudinally follow the quality of life for patients who received curative-intended IMRT for SCCHNs and to compare their HRQOL with matched controls treated with 3-dimensional conventional radiation therapy (3D-CRT).

Methods

Study design

The study started when it was decided that IMRT will be used in clinical routine at the Department of Oncology, Sahlgrenska University Hospital. All patients with untreated, newly diagnosed oral or pharyngeal cancers in the Västra Götalands Region of Sweden with planned IMRT treatment with curative intent were invited to participate in the study. Patients were included after the multidisciplinary therapy conference for head and neck cancer patients at the Department of Otorhinolaryngology of Sahlgrenska University Hospital, Gothenburg, Sweden. At this conference, the patients were staged according to the UICC TNM Classification of malignant tumors (6th edition) and treatments were recommended. Depending on the tumor site and stage, the recommended treatments ranged from radiation therapy alone to radiation therapy combined with surgery and/or chemotherapy. HRQOL questionnaires were distributed at 6 time points during the first year after diagnosis, and clinical data were recorded regarding patient characteristics, treatment, and survival.

Patients with SCCHN and treated with 3D-CRT in the Västra Götalands region of Sweden who previously took part in descriptive prospective longitudinal HRQOL studies, using the same questionnaires and the same measurement points, were used as controls. The control group was matched to the study group in terms of tumor site, stage, sex, age, and other antitumor treatments.

The study was approved by the regional ethics committee in Gothenburg (Reference number: 076-08).

Study population

One hundred and thirty-two patients treated with IMRT were included between 2008 and 2011. Ten individuals were excluded for various reasons (ie, those who refused the intended treatments [n = 2] and those

who withdrew consent [n = 8]). Another 11 patients with nasopharyngeal cancer were excluded during data processing because of a lack of matching controls. It was possible to include 96 patients in the control group who fulfilled the matching criteria.

In total, the study contained 207 patients, 111 treated with IMRT (study group) and 96 patients treated with 3D-CRT (control group).

Radiation therapy

External radiation therapy was applied in full doses ranging from 64.6 to 68 Gy. The fractionation schedules varied because of the changes in the institution's treatment policy over time. Treatment planning was based on computed tomography imaging. For IMRT, 2 different schedules were used. Schedule 1 consisted of hyperfractionated accelerated split-course radiation therapy with 2 daily fractions of 1.7 Gy, 5 days a week, to a final dose of 64.6 Gy to the primary tumor volume and 40.8 Gy to adjuvant volumes. IMRT dose distribution plans (DDP) were used up to 40.8 Gy and 3D-CRT DDP for the remaining course up to 64.6 Gy. Schedule 2 was moderately accelerated radiation therapy given with concomitant boost technique with 2 Gy per fraction, 6 fractions per week to 68 Gy to involved tumor and 1.55 Gy per fraction to 52.7 Gy to adjuvant volumes. 3D-CRT was given exclusively with hyperfractionated accelerated split-course radiation therapy.

In both the study group and the control group, patients with T3-4 tumors in the base of tongue received an additional pulse-dose-rate brachytherapy boost of 10 to 12 Gy.

Sparing the parotid glands, aiming to reduce the dose to <25 Gy to the contralateral gland without compromising the dose to the PTV, was a priority during treatment planning.

Chemotherapy

Induction chemotherapy was applied to stage III-IV disease according to the local practice at that time with the preferred regimen of 2 courses of intravenous infusion of 100 mg/m^2 of cisplatin on day 1 and 1000 mg/m^2 of 5-fluorouracil daily as a continuous infusion on days 1 through 5.

Surgery

Surgical intervention for the primary tumors and involved lymph nodes were performed on patients with resectable primary tumors in the oral cavity before radiation therapy. Neck surgery was also performed on patients with lymph node metastases with unknown primaries before radiation therapy and as salvage treatments for persisting positive lymph nodes after chemoradiation for patients with oropharyngeal cancers.

HRQOL assessment

The HRQOL data were collected using the European Organization for Research and Treatment for Cancer (EORTC) questionnaire QLQ-C30 and the EORTC Head and Neck cancer module.[15-17] The questionnaires were distributed to patients at inclusion and at 1, 2, 3, 6, and 12 months after the initiation of treatment as prespecified in the protocol. Nonresponders were reminded once.

Statistics

The data collected from the questionnaires were calculated according to the EORTC scoring manual, which yielded transformed scales in the range from 0 to 100.[18] High values on the global and functional scores represent better functioning, whereas increases in the symptom scales indicate the presence of symptoms. Nonparametric statistics were used because the HRQOL data were not normally distributed. Differences in scoring of 10 points were regarded as clinically relevant.[19] For the comparisons between groups, the Fisher exact test was applied to dichotomous variables, and the Mantel-Haenszel χ^2 exact test was applied to ordered categorical variables. The χ^2 exact test was used for nonordered categorical variables, and the Mann-Whitney U test was applied to continuous variables. A significance level of .05 was applied throughout.

Results

Patient characteristics

Patient characteristics are presented in Table 1. The majority was male, and the mean age was approximately 60 years. Oropharyngeal cancer was the most common tumor site, with 78 patients (70.3%) in the IMRT group and 60 patients (62.5%) in the 3D-CRT group. Most patients (85%) had an advanced clinical stage (stage III-IV) in both groups.

There were no significant differences in the distributions of sex, age, primary tumor size, clinical stage, 1-year survival rate, or treatment between the study and control groups.

HRQOL

Table 2 presents the proportions of patients who completed the questionnaires at each time point. At 12 months, 87 of the 104 patients who were still alive

Table 1 Patient characteristics

Characteristic	IMRT (n = 111)	3D-CRT (n = 96)	*P* value
Sex			
Female	26 (23.4%)	27 (28.1%)	
Male	85 (76.6%)	69 (71.9%)	.5392
Age (mean years)	60.7 (40.0-82.0)	59.2 (31.0-81.0)	.2591
Tumor site			
Pharynx[a]	85 (76.6%)	64 (66.7%)	
Oral	16 (14.4%)	23 (24.0%)	
Unknown primary	10 (9.0%)	9 (9.4%)	.2199
T-stage			
T 0-2	69 (62.2%)	54 (56.3%)	
T 3-4	42 (37.8%)	42 (43.8%)	.4703
Stage			
I-II	16 (14.4%)	14 (14.6%)	
III-IV	95 (85.6%)	82 (85.4%)	1.00
Additional treatment			
CT	71 (78.9%)	58 (66.7%)	
Surgery	13 (14.4%)	21 (24.1%)	
Surgery + CT	6 (6.7%)	8 (9.2%)	.1785
1-year survival			
Dead	7 (6.3%)	7 (7.3%)	
Alive	104 (93.7%)	89 (92.7%)	.9920

CT, chemotherapy; 3D-CRT, 3-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy.
Hypopharynx: 7/85 (8.2%); 4/64 (6.2%).
[a] Oropharynx: 78/85 (9.8%); 60/64 (93.8%).

(83.7%) in the study group and 74 of the 89 living patients (83.1%) in the control group responded.

The mean scores for all symptom scales at each time point that were collected from the questionnaires are presented in Table 3. At baseline, there were significant differences in the following items that favored the IMRT group: loss of appetite (25.0 vs 15.5; $P = .042$), problems with the teeth (18.7 vs 10.6; $P = .048$), and problems opening the mouth (18.8 vs 11.8; $P = .025$).

In the acute phase (ie, 2 and 3 months after the initiation of treatment), as expected, there was significant worsening in both groups. The deterioration was clinically significant for the majority of functions and symptoms. For both groups, the problems that increased the most were appetite loss, problems with swallowing, local pain, sticky saliva, dry mouth, fatigue, and decreased role functioning.

Table 2 Numbers of patients who completed the questionnaires at each time point

Timepoint	IMRT (n = 111)	3D-CRT (n = 96)
Inclusion	111	95
1 mo	76	86
2 mo	84	85
3 mo	85	82
6 mo	85	80
12 mo	87	74

Timepoints represent time after initiation of treatment. See Table 1 for abbreviations.

Significant differences between the groups, just after treatment, were found for the items regarding social functioning, nausea/vomiting, diarrhea, loss of appetite, senses (taste), coughing, and insomnia; all of these differences were related to worse outcomes in the IMRT group (Fig 1). Six months after treatment initiation, however, these differences vanished, and significant differences favoring the IMRT group appeared in the problems with teeth item (24.1 vs 14.5; $P = .033$) and the cognitive functioning scale (75.5 vs 83.5; $P = .024$).

At the 12-month follow-up, 161 of the 174 living patients completed the questionnaires. Significant differences favoring the IMRT group were observed in the QLQ-HN35 items related to problems with dry mouth (72.1 vs 62.8; $P = .018$), pain (28.3 vs 20.4; $P = .018$), decreased sexuality (36.9 vs 22.9; $P = .016$), and trouble with social contacts (9.77 vs 5.59; $P = .026$). The QLQ-C30 cognitive functioning scale results (78.6 vs 86.8; $P = .0057$) and the economy item (12.3 vs 20.3; $P = .0019$) also exhibited significant differences. These items and their respective changes over time are represented in Figure 2.

The global quality of life scale results exhibited similar changes over time in both groups that involved a decline during and shortly after treatment and a recovery to baseline or even slightly improved levels at 12 month of follow-up. The same pattern was observed for the majority of the items and scales, with the exception of the dry mouth item, which remained at significantly worse levels in both groups relative to the levels before treatment.

Parotid gland doses

Based on the DDPs of the IMRT patients, the mean ipsilateral and contralateral parotid doses were 44.5 Gy (standard deviation, 12.8) and 28.2 Gy (standard deviation, 8.5), respectively. For the cases treated with 3D-CRT, the available parotid gland dose data were insufficient for comparison.

Discussion

This study aimed to compare the patient-reported HRQOL between patients who were treated for SCCHNs with IMRT and those treated with 3D-CRT. Other clinical factors that could possibly have affected the outcome were adjusted for to highlight our focus on the radiation treatment technique. We believe the longitudinal

Table 3 Mean HRQOL score for each item at the measured time points

	Baseline			1 mo			2 mo			3 mo			6 mo			12 mo		
	IMRT	3D-CRT	P value	IMRT	3D-CRT	P value	IMRT	3D-CRT	P value	IMRT	3D-CRT	P value	IMRT	3D-CRT	P value	IMRT	3D-CRT	P value
QLQ C-30																		
Physical functioning	89	91	NS	70	75	NS	69	70	NS	67	71	NS	79	77	NS	88	84	NS
Role functioning	76	70	NS	35	45	NS	39	40	NS	41	39	NS	62	60	NS	79	75	NS
Emotional functioning	69	68	NS	74	68	NS	71	70	NS	71	70	NS	78	73	NS	81	77	NS
Cognitive functioning	85	79	NS	76	73	NS	73	69	NS	73	70	NS	84	76	.020	87	79	.006
Social functioning	82	78	NS	55	65	.013	56	62	NS	55	60	NS	75	70	NS	83	79	NS
Global HRQOL	65	62	NS	50	51	NS	47	49	NS	46	51	NS	60	67	NS	69	67	NS
Fatigue	25	30	NS	55	49	NS	57	53	NS	59	53	NS	40	41	NS	25	32	NS
Nausea/vomiting	4	7	NS	27	19	.014	23	20	NS	24	17	NS	7	12	NS	3	6	NS
Pain	31	28	NS	42	35	NS	52	46	NS	51	47	NS	27	31	NS	18	23	NS
Dyspnea	20	18	NS	26	27	NS	37	34	NS	33	32	NS	28	29	NS	18	21	NS
Insomnia	30	29	NS	35	34	NS	33	26	NS	38	27	.032	29	23	NS	21	23	NS
Appetite loss	16	25	.042	52	41	NS	64	50	.019	66	55	NS	38	34	NS	17	23	NS
Constipation	9	13	NS	32	26	NS	31	30	NS	33	32	NS	15	20	NS	8	10	NS
Diarrhea	8	9	NS	20	11	.004	17	14	NS	13	15	NS	9	8	NS	6	5	NS
Financial difficulties	19	18	NS	24	21	NS	26	26	NS	23	29	NS	25	26	NS	12	20	.019
EORTC HN-35																		
Pain	26	30	NS	36	36	NS	56	52	NS	54	56	NS	31	35	NS	20	28	.018
Swallowing	20	23	NS	31	30	NS	58	49	NS	62	55	NS	32	30	NS	19	22	NS
Senses	12	8	NS	38	33	NS	54	41	.017	52	43	.017	33	32	NS	30	26	NS
Speech	13	16	NS	22	20	NS	34	27	NS	37	30	NS	24	21	NS	14	16	NS
Social eating	17	20	NS	39	37	NS	49	46	NS	53	50	NS	37	35	NS	22	26	NS
Social contacts	6	9	NS	17	16	NS	14	18	NS	19	21	NS	11	13	NS	6	10	.026
Sexuality	24	34	NS	55	59	NS	61	59	NS	61	54	NS	43	48	NS	23	37	.016
Dry mouth	21	20	NS	36	40	NS	60	61	NS	68	63	NS	75	76	NS	63	72	.018
Coughing	22	21	NS	20	17	NS	35	26	.024	39	26	.009	27	21	NS	21	20	NS
Teeth	11	19	.048	13	17	NS	16	17	NS	15	23	NS	14	24	.029	18	28	NS
Opening mouth	12	19	.025	21	30	NS	35	35	NS	31	37	NS	24	32	NS	22	30	NS
Sticky saliva	20	24	NS	43	45	NS	76	70	NS	78	74	NS	60	60	NS	48	54	NS
Feeling ill	20	23	NS	41	36	NS	41	39	NS	45	37	NS	22	27	NS	13	20	NS

NS, not significant. See Table 1 for other abbreviations.
High scores on a function and global quality of life scale imply high function. High scores on a symptom scale imply a high level of problems.

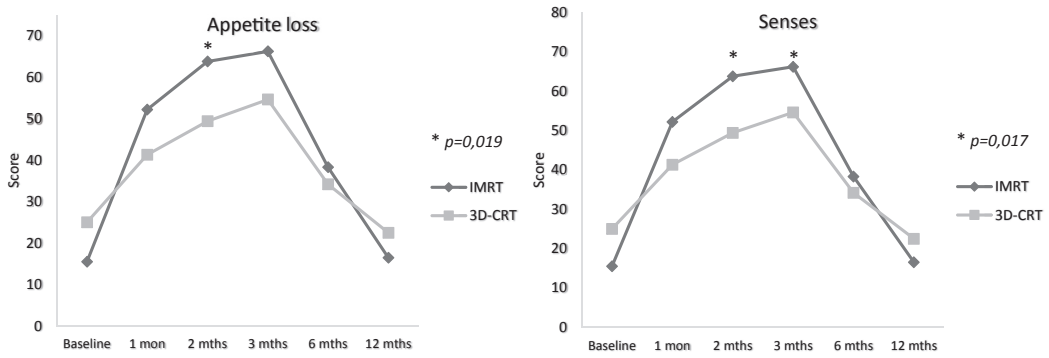

Figure 1 Mean health-related quality of life scores plotted over time for items with significant differences between the intensity modulated radiation therapy (IMRT) and 3-dimensional conformal radiation therapy (3D-CRT) groups just after treatment. High scores on the function and global quality of life scale imply high function. High scores on a symptom scale imply a high level of problems.

design coupled with a high rate of completed questionnaires (more than 80% at 12 months) strengthens the outcome. The results support the beneficial long-term role of IMRT relative to 3D-CRT in several HRQOL domains, such as dryness of the mouth, pain, trouble with social contacts, decreased sexuality, cognitive functioning, and economy, which demonstrated significant improvements at 12 months posttreatment.

It was also noted, however, that the study group had worse HRQOL at the 2 and 3 months follow-up (ie, at the acute phase). This has to be considered when taking care of the patients' side effects. The patients probably need improved nutritional support during this period. One could speculate if the larger low-dose volumes distributed within the target area in the IMRT dose planning could contribute to the increased temporary problems after finishing treatment.

Several primarily retrospective studies have previously suggested the same advantages of using IMRT.[11,20-23] Vergeer et al published a relatively large prospective cohort study that used a standardized follow-up program that included HRQOL questionnaires and found

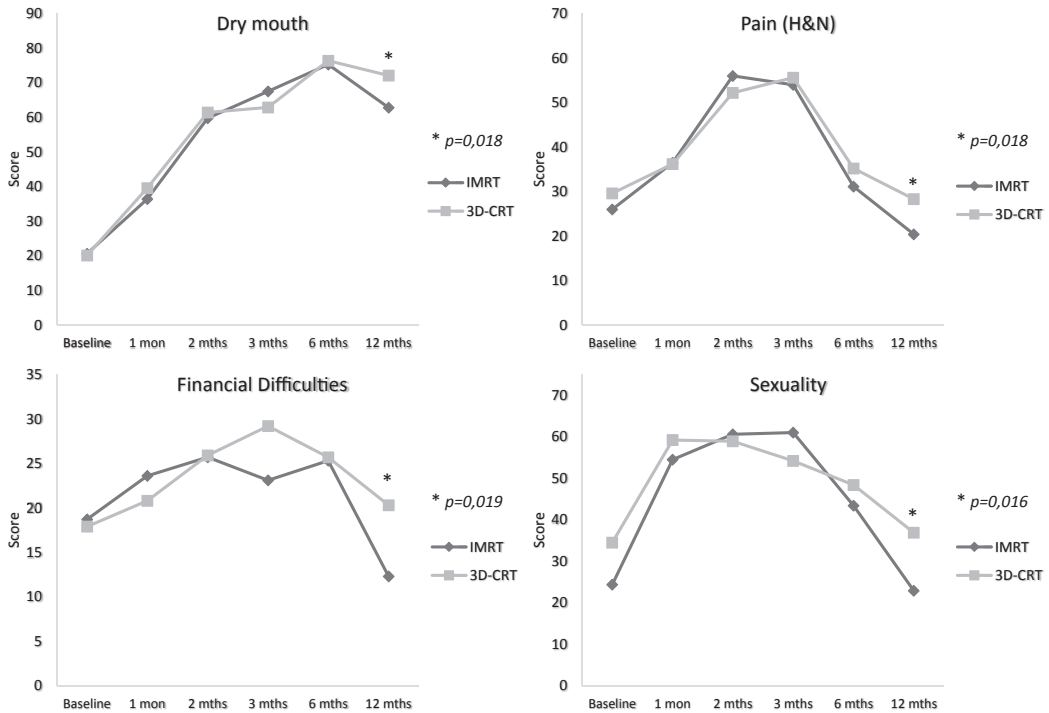

Figure 2 Mean health-related quality of life scores plotted over time for items with significant differences between the intensity modulated radiation therapy (IMRT) and 3-dimensional conformal radiation therapy (3D-CRT) groups at 12 months. High scores on the function and global quality of life scale imply high function. High scores on a symptom scale imply a high level of problems.

significantly better outcomes regarding patient-observed xerostomia.[13] Two randomized studies with patient selections (ie, non-nasopharyngeal cancers) similar to that of the present study have been performed. The first and largest was the Parotid-Sparing Intensity Modulated versus Conventional Radiotherapy in Head and Neck Cancer (PARSPORT) multicenter study that included 47 patients in each arm. The late effects in normal tissues subjective, objective and management analytic scales and the Radiation Therapy Oncology Group scorings for xerostomia were significantly worse in the 3D-CRT arm; however, this effect was possibly due to an insufficient number of subjects. Moreover, the head and neck cancer module dry mouth scores did not differ significantly between the groups at 12 months.[12] A trial by Rathod et al included 60 patients. Although the primary endpoint of the study was acute salivary gland toxicity, several symptom scales, such as dry mouth and opening mouth, were significantly improved at 12 months in the IMRT arm.[24] As the authors themselves suggested, given the limited return rate of the HRQOL questionnaires (just over one-third of the patients completed all of the questionnaires), the statistical robustness was questionable.

There are few previous reports on effects over longer periods than 12 months after treatment. Chen et al published a study that demonstrated that IMRT was superior in specific domains, such as xerostomia, in addition to the global HRQOL, and that the effects lasted for at least 24 months.[11] Graff et al also reported a significant improvement in the IMRT patients at approximately 24 months.[21] These studies, however, report only retrospective data and lack baseline values. The PARSPORT trial demonstrated significant improvements in the clinical grade of xerostomia in the patients who were treated with IMRT both after 12 and 24 months. As mentioned previously, the difference in the HRQOL scores was not significant at either time point.[12] Recently, Huang et al reported long-term (>5 years) HRQOL data from patients with nasopharyngeal carcinomas who were treated either with conventional radiation therapy or IMRT and demonstrated improvements in a multitude of head and neck–specific HRQOL items.[25] Whether these findings can be translated to patients with other primary tumors in the head and neck area remains to be proven.

The importance of parotid-sparing treatment using IMRT and inverse treatment planning has been reported in several studies that linked this treatment with improvements in measured saliva production, Radiation Therapy Oncology Group/late effects in normal tissues subjective, objective and management analytic scales scores, and patient-experienced xerostomia.[10,13,20,23,26] In our present study, the mean dose to the ipsilateral parotid gland in the IMRT group was 28.2 Gy, which approaches the recommended threshold doses reported by both the Quantitative Analysis of Normal Tissue effects in the Clinic review and a separate analysis from the PARSPORT trial.[27,28] Further DDP optimization and improvements in delineation methods using advanced imaging technologies (eg, magnetic resonance imaging, positron emission tomography, computed tomography) could possibly yield even better outcomes in terms of various HRQOL parameters; however, even if we lack comparable parotid doses from the 3D-CRT group, the dose levels that we have achieved seem adequate.

Apart from dry mouth, the significant differences found in pain, social contacts, and sexuality are possibly linked with each other in that a decrease in oral health may negatively affect the patients' social lives. The differences in cognitive functioning and financial difficulties are nearly unique to this study. Apart from Vergeer et al, who reported a significant difference in cognitive functioning at 6 months, we have been unable to find any similar results in the literature.[13] Whether these findings are clinically relevant is a matter for further investigation.

The relatively low amount of longer term data (ie, >1 year) reveals an area in which we would like to expand into in ongoing studies. Another area worthy of investigation is the effect of the most recently introduced radiation therapy techniques, such as volumetric arc therapy and proton therapy, on HRQOL.

Limitations

In this study, matched controls were used because IMRT was implemented as clinical routine shortly after its introduction at the department; therefore, it was not possible to perform a randomized study, which would have been ideal. Another limitation was that we had to exclude patients with nasopharyngeal cancer because we could not provide any matched controls.

Conclusions

This study adds to the growing evidence that IMRT in SCCHN improve HRQOL 1 year after treatment.

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