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Morbidity of head and neck RT

Swallowing-sparing intensity-modulated radiotherapy for head and neck cancer patients: Treatment planning optimization and clinical introduction

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ABSTRACT

Purpose: To report on the potential benefits of swallowing-sparing intensity-modulated radiation therapy (SW-IMRT) in the first 100 SW-IMRT treated patients, as well as on the factors that influence the potential benefit of SW-IMRT relative to standard parotid sparing (ST)-IMRT.
Material and methods: One hundred consecutive head and neck cancer patients, scheduled for primary radiotherapy, were included in this prospective cohort study. For each patient, ST-IMRT and SW-IMRT treatment plans were created. All patients were eventually treated with SW-IMRT. Objectives for SW-IMRT were identical to those with ST-IMRT, with additional objectives to spare the swallowing organs at risk (SWOARs). After 20 patients, interim results were evaluated by a multidisciplinary committee.
Results: The mean gain of SW-IMRT relative to ST-IMRT in the first 20 patients was less than expected based on our previous planning comparative study. A critical review of all plans revealed that the results with SW-IMRT could be improved by: (1) gaining experience and attempting to reduce SWOAR dose as much as possible; (2) accepting a moderate shift of dose to unspecified tissues; (3) maximizing SWOAR sparing while keeping PTV coverage exactly according to protocol. In the additional 80 patients, the mean dose to the various SWOARs was further reduced significantly compared to ST-IMRT. Dose reductions with SW-IMRT were largest for patients who received neck irradiation, had a tumour located in the larynx, oropharynx, nasopharynx or oral cavity, and had <75% overlap between SWOARs and PTVs. The mean absolute reduction in predicted physician-rated RTOG grade 2–4 swallowing dysfunction for patients numbered 21–100 was 6.1%, ranging from 0.0% to 17.2%.
Conclusions: The benefit of SW-IMRT depends significantly on neck radiotherapy, tumour site and the amount of overlap between SWOARs and PTVs. Optimal clinical introduction requires a detailed evaluation and comparison between the standard (ST-IMRT) and new technique (SW-IMRT) in order to fully exploit the potential benefits.
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We recently reported on swallowing-sparing intensity-modulated radiotherapy (SW-IMRT) for head and neck cancer (HNC) and demonstrated that the dose in swallowing organs at risk (SWOARs) can be significantly reduced relative to standard IMRT (ST-IMRT), aiming at reducing the dose to the parotid glands only [1]. By integrating the results of in-silico planning comparative studies with multivariable predictive models for physician-rated and patient-rated swallowing dysfunction [2], the SWOAR dose reductions can be translated into potential clinical benefits [1]. In the development phase, we found that in a group of 30 HNC patients, the average normal tissue complication probability (NTCP) of physician-rated Radiation Therapy Oncology Group (RTOG) grade 2–4 swallowing dysfunction could be reduced from 42.3% with ST-IMRT to 33.4% on average with SW-IMRT [1]. An important observation was the large variation between individual patients, both with regard to the initial NTCP-values with ST-IMRT as with regard to the reductions that could be obtained with SW-IMRT [1,2]. Although the patient group was relatively small and the study had a descriptive design, it seemed that tumour location and nodal stage influenced the initial NTCP-values as well as the potential NTCP-reductions. However, it should be noted that the results described in that study were obtained under optimal conditions, i.e., all treatment plans were thoroughly optimized by a single experienced research dosimetrist (HPvdL) without the burden and pressure of daily practice. Moreover, treatment planning was accurately performed according to a predefined research protocol [1].

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Following the development phase, SW-IMRT was clinically implemented at our department in September 2010 and by November 2011, 100 patients had received SW-IMRT. As radiotherapy treatment planning for SW-IMRT is more complex and time consuming than for ST-IMRT, we felt that it was worthwhile to test if the potential gain of SW-IMRT showed similar results as obtained in the development phase when it was actually implemented in routine clinical practice under less ideal circumstances (e.g., various members of the team of dosimetrists with different levels of skills and experience with limited time available per patient). Therefore, a prospective evaluation of the quality of the created plans was started simultaneously with the clinical introduction of SW-IMRT.

Our main aim was to investigate whether translation of the results of in-silico planning comparative study into real clinical practice in terms of radiotherapy treatment planning was optimal and which factors could influence this.

The purpose of the current study was to analyse whether the SWOARs dose reductions and subsequent estimated NTCP-reductions for physician-rated and patient-rated swallowing dysfunction were optimal when SW-IMRT was introduced into real clinical practice. In addition, we aimed to describe the patient and treatment related factors that influenced the results with SW-IMRT in real clinical practice.

Materials and methods

Patients

The study population was composed of 100 consecutive patients scheduled to receive primary (chemo)radiotherapy for HNC (Table 1). Contrast-enhanced planning computed tomography (CT) scans were acquired in treatment position with a slice thickness and index of 2 mm. Radiotherapy treatment planning was performed in the clinical Pinnacle^3 treatment-planning system (version 8.0 h, Philips Radiation Oncology Systems, Fitchburg, WI, USA). The adaptive convolution algorithm was used for all dose calculations.

Table 1
Baseline patient, tumour and treatent characteristics.

n = 80 (patients #21-100) Factors	%
Gender	
Male	69
Female	31
Age, years	
18–65	60
>65	40
Neck radiotherapy	
Local RT	9
Unilateral neck RT	21
Bilateral neck RT	70
Concomitant chemotherapy	
No	66
Yes	34
Tumour location	
Larynx	31
Hypopharynx	11
Oral cavity	8
Oropharynx	29
Nasopharynx	4
Other (salivary glands, skin, etc.)	17
Overlap SWOAR-PTV[a]	
0–25%	28
26–50%	26
51–75%	25
>75%	21
T stage	
T0	1
T1	14
T2	32
T3	30
T4	20
Tx	3
N stage	
N0	38
N1	15
N2a	1
N2b	25
N2c	16
N3	4
Nx	1

Abbreviations: PCM, pharyngeal constrictor muscle; PTV, planning target volume; RT, radiotherapy; SWOAR, swallowing organ at risk.
[a] Overlap defined as the proportion of the combined superior PCM and supraglottic larynx overlapping with any PTV.

Regions of interest

The definition of the target volumes (PTV) was previously described in more detail [3–5]. All elective and high dose PTVs were restricted to 5 mm within the skin surface for the purpose of dose optimization and evaluation. Different dose levels were prescribed to the PTVs according to a simultaneous integrated boost fractionation schedule, i.e., treatment plans were created with a daily higher dose delivered to the high dose PTVs [1]. In some patients, only a high dose PTV was defined and in some patients another total dose was prescribed to the PTVs for medical reasons. The following OARs were delineated: the parotid glands, spinal cord, brainstem, optic nerves and optic chiasm. In addition, anatomical structures found to be related to swallowing dysfunction were delineated as well, including the superior and middle pharyngeal constrictor muscle (PCM), the supraglottic larynx and the oesophageal inlet muscle (EIM) [2]. Delineation was performed according to CT-based delineation protocols for OAR definition in the head and neck region developed at our department [6,7].

IMRT treatment planning

In all patients and for all plans, direct aperture optimization-based IMRT treatment plans were created. The technical aspects and the dose–volume objectives of the treatment plans have been described previously in more detail [1]. In brief, attempts were made to obtain adequate target coverage, while limiting the dose to structures outside the PTV for both ST-IMRT and SW-IMRT.

In all patients included in this study, a two-step approach was used. First, a ST-IMRT plan was created, aiming at optimal sparing of the parotid glands according to routine institutional procedures before the clinical introduction of SW-IMRT. By a trial-and-error adaptive adjustment of the objective values and weights, the dose plan was optimized such that a clinically acceptable plan was obtained. Second, the ST-IMRT plan was saved and copied. The copy was then used to create the SW-IMRT plan that was subsequently used for the actual treatment of the patients. In order to minimize the radiation dose to the SWOARs, objective values and weights were added for the SWOARs. The doses to the SWOARs were reduced according to the following order of priority: (1) minimizing mean dose to the superior PCM; (2) minimizing the mean dose to the supraglottic larynx; (3) minimizing the mean dose to the middle PCM; and (4) minimizing the proportion of the EIM receiving $\geqslant$60 Gy (EIM V60). This order of priorities was based on the outcome of the multivariable logistic regression analysis previously described [2]. The mean dose in the parotid glands was not allowed to be higher with SW-IMRT than with ST-IMRT.

Dose–volume data and complication probabilities

The volume in the patient receiving $\geqslant$95% of the dose prescribed to the elective PTV and the high dose PTV were determined

and relevant OAR and SWOAR dose–volume parameters were obtained from corresponding dose–volume histograms (DVH). To estimate NTCP-values for ST-IMRT and SW-IMRT with regard to endpoints related to swallowing dysfunction, we used the equation as previously described by Christianen et al. [2].

Statistical analyses

For comparison of the DVH parameters and NTCP-values with ST-IMRT and SW-IMRT, the mean values were analysed with the paired-samples *t*-test. Linear regression analysis was performed to identify factors that were related to the NTCP gain of SW-IMRT relative to ST-IMRT. For comparison of the mean values in patient sub-groups, ANOVA or independent-samples *t*-tests were performed, depending on the number of patient sub-groups. All tests were two-tailed, and differences were considered statistically significant when the *p*-value was 0.05 or less.

Results

Results for first 20 patients

It appeared that the dose in the SWOARs in the SW-IMRT plans for the first 20 patients was only slightly lower than in the ST-IMRT plans, e.g., the mean dose to the superior PCM and the supraglottic larynx were reduced by 1.6 Gy and 2.2 Gy, on average, respectively. The calculated mean NTCP reduction for grade 2–4 RTOG swallowing dysfunction at 6 months with SW-IMRT was only 2.6%. This gain was less than expected on the basis of the results obtained in the development phase, in which the mean NTCP reduction was 8.9% [1]. Moderate gains were also observed with regard to the patient-rated complaints. The mean NTCP reduction of chocking when swallowing and problems with swallowing liquids, soft food and solid food were 0.5%, 0.6%, 0.9% and 2.4%, respectively. In order to distinguish whether this was due to variation in patient selection or to non-optimal treatment planning, we randomly selected the SW-IMRT plans from 6 patients that were subsequently re-planned by the same experienced research dosimetrist. After re-planning, a marked further reduction could be obtained to the SWOARs. This also resulted in larger reductions in the NTCP-values for swallowing dysfunction, e.g., the mean NTCP-reduction for RTOG grade 2–4 swallowing dysfunction with SW-IMRT increased from 2.0% to 6.2%.

In addition, the treatment plans of all first 20 patients were reviewed in the radiation oncology head and neck cancer treatment team in order to identify the possible reasons for the non-optimal SW-IMRT treatment plans of the first 20 patients. Based on this review, we were able to identify methods to improve the gain in the SW-IMRT plans.

First, we observed that larger gains were obtained by more experienced dosimetrists who had sufficient time available to maximize SWOAR sparing and really attempted to reduce the dose in the SWOARs as much as possible. Second, we found that in order to maximize SWOAR sparing we needed to accept a moderate shift of dose to unspecified tissues, such as the oral cavity and the neck muscles. Third, we found that SWOAR sparing could be improved by allowing the PTV coverage in the vicinity of the SWOARs to be exactly according to protocol, i.e., the SWOAR dose was decreased until exactly 98% of the PTVs volume received 95% of the prescribed dose. These findings were discussed and taken into account in all subsequent patients.

PTV coverage and irradiated volume

At least 98% of the PTVs volume received $\geqslant$95% of the prescribed dose in almost all patients. In 9 patients, a slight under-dosage to the PTV was accepted, because the PTV included air cavities or because the dose to the brainstem or spinal cord had to be limited. In other words, these under-dosages to the PTVs were not related to SW-IMRT. In all cases, PTV coverage obtained with ST-IMRT and SW-IMRT was comparable.

With SW-IMRT, the volume in the patient receiving $\geqslant$95% of the dose prescribed to the largest PTV (the elective PTV in most patients but the high dose PTV in the case of a single PTV) increased by 2.8% on average (Table 2).

Dose delivered to OARs and SWOARs

All dose plans complied with the maximum allowed doses to critical structures such as the brainstem and spinal cord. The mean dose delivered to the parotid glands was not increased as a result of SWOAR sparing (Table 2). The mean dose in the SWOARs was significantly lower with SW-IMRT. The EIM *V*60 was zero with both ST-IMRT and SW-IMRT in 80% of the patients.

Table 2
Dose–volume data and normal tissue complication probabilities.

n = 80 (patients #21-100)	ST-IMRT	SW-IMRT	*p*-Value
Integral irradiated volume (cm^3)	871 (68–1911)	895 (63–1911)	<0.001
V95% PTV1			
Parotid glands mean dose (Gy)			
Ipsilateral	33.9 (0–69.9)	33.8 (0–69.9)	0.175
Contralateral	23.3 (0–53.4)	22.5 (0–54.2)	<0.001
SWOAR mean dose (Gy)			
Superior PCM	49.4 (1.6–70.4)	44.6 (1.5–69.6)	<0.001
Middle PCM	53.4 (9.2–71.9)	48.1 (4.2–70.3)	<0.001
Supraglottic larynx	55.8 (4.0–71.0)	51.0 (2.8–70.2)	<0.001
Volume receiving $\geqslant$60 Gy (%)			
EIM	6.8 (0–92)	3.9 (0–58)	0.011
NTCP swallowing dysfunction (%)			
RTOG grade 2–4	29.6 (1.1–61.7)	23.5 (0.6–59.7)	<0.001
Problems swallowing solid food	25.0 (0.5–63.3)	19.5 (0.2–61.4)	<0.001
Problems swallowing soft food	10.3 (0.3–47.7)	8.6 (0.2–45.3)	<0.001
Problems swallowing liquid food	6.4 (0.1–12.7)	5.3 (0.1–12.0)	<0.001
Choking when swallowing	5.9 (0.1–36.8)	4.3 (0.1–16.9)	<0.001

Values are means with ranges in parentheses.
Abbreviations: EIM, oesophageal inlet muscle; NTCP, normal tissue complication probability; PCM, pharyngeal constrictor muscle; PTV1, largest planning target volume; RTOG, (physicianrated) Radiation Therapy Oncology Group; ST-IMRT, standard intensity modulated radiation therapy; SW-IMRT, swallowing sparing intensity modulated radiation therapy; V95% PTV1, the volume in the patient receiving 95% of the dose prescribed to PTV1 (the largest PTV).

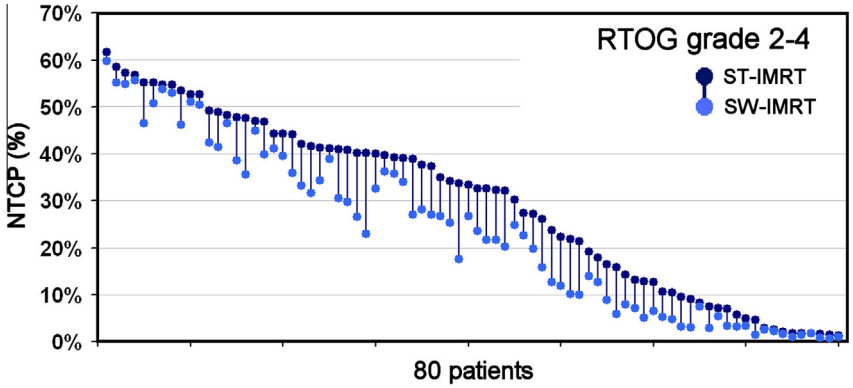

Fig. 1. Normal tissue complication probabilities (NTCP) of physician-rated Radiation Therapy Oncology Group (RTOG) grade 2–4 swallowing dysfunction with Standard Intensity Modulation Radiation Therapy (ST-IMRT) and Swallowing Sparing IMRT (SW-IMRT) in patients #21-100 (re-sorted by the NTCP values with ST-IMRT).

NTCP of swallowing dysfunction

Using the predictive models of Christianen et al. [2], we calculated the potential NTCP-reductions with SW-IMRT for patients #21–100. For all swallowing dysfunction endpoints, the NTCP-values were significantly lower with SW-IMRT (Table 2). The mean NTCP-reduction for physician-rated RTOG grade 2–4 swallowing dysfunction with SW-IMRT was 6.1% (range: 0.0–17.2%). This reduction was 7.3% (range: 1.0–17.2%) in a subgroup of 56 patients who received bilateral neck irradiation. In our previous study all patients received bilateral neck irradiation and the mean NTCP-reduction was 8.9% (range: 3.0–20.0%) [1]. The mean NTCP-reductions with SW-IMRT of patient-rated moderate-to-severe swallowing complaints for patients #21–100 were: 5.5% (range 0.0–17.3%) for solid food, 1.6% (range 0.0–6.4%) for soft food, 1.1% (range 0.0–3.4%) for liquid food, and 1.6% (range 0.0–26.1%) for choking when swallowing, respectively. When we limited the analysis to the subgroup of 56 patients with bilateral neck irradiation and compared these to the results of our previous study we found the following NTCP reductions: 6.7% and 7.9% for solid food, 1.9% and 2.3% for soft food, 1.3% and 1.4% for liquid food and 2.0% and 0.9% for chocking when swallowing, respectively. As shown in Fig. 1, the absolute NTCP values for ST-IMRT and SW-IMRT, as well as the NTCP-value reductions varied widely across individual patients. The proportions of patients and the corresponding gains that could be obtained with SW-IMRT relative to ST-IMRT in the first 20 patients, the subsequent 80 patients, and the 30 patients in our previous study are depicted in Fig. 2.

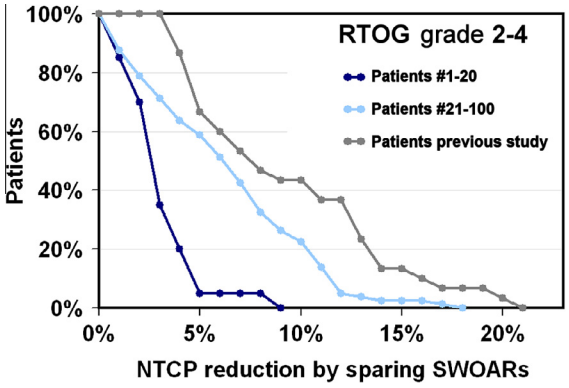

Fig. 2. Cumulative proportion of responders analysis, showing the proportion of patients and corresponding potential reductions in the normal tissue complication probability (NTCP) of physician-rated RTOG grade 2–4 swallowing dysfunction as achieved by reducing the dose in the swallowing organs at risk (SWOARs) in three groups of patients: (1) the first 20 patients in the present study; (2) the subsequent 80 patients in the present study; and (3) the 30 patients in our previous study.

Patient, tumour and treatment characteristics

Univariable and multivariable linear regression statistics indicated that neck radiotherapy (unilateral or bilateral neck irradiation versus local irradiation), the degree of overlap between the most important SWOARs (superior PCM and supraglottic larynx) and the PTVs (<25%, 25–49%, 50–74% or ⩾75% of these SWOARs overlapping with any PTV), and tumour site were significantly associated with NTCP reductions of physician-rated RTOG grade 2–4 swallowing dysfunction with SW-IMRT. In fact, we found that in patients who received neck irradiation, who had <75% overlap between the SWOARs and the PTV, and who had a tumour located in the larynx, oropharynx, oral cavity or nasopharynx, the potential gain with regard to the NTCP of physician-rated RTOG grade 2–4 swallowing dysfunction was on average 8.6% ('high'), while in the other patients this was on average 3.1% ('low') (Table 3).

Discussion

Our main purpose was to analyse whether the estimated NTCP-reductions for different swallowing dysfunction endpoints obtained with SW-IMRT in the development phase (our previous study) were similar when introduced in routine daily practice in the first 100 patients actually treated with SW-IMRT (the present study). We found that in the first 20 patients treated with SW-IMRT the SWOARs were spared only slightly better than with the reference back up ST-IMRT plans made for each patient, resulting in a potential gain with regard to the NTCP of RTOG grade 2–4 swallowing dysfunction of only 2.3%, while this was 8.9% in the development phase [1]. We observed the same effect with regard to the patient-rated swallowing complaints (figures not shown). After a critical multidisciplinary evaluation of the ST-IMRT and SW-IMRT plans of the first 20 patients we found a number of factors that could improve the gain of SW-IMRT in clinical practice (discussed below). These measures were taken into account in the subsequent 80 patients and resulted in an increased gain with SW-IMRT that were closer to the results obtained in the development phase. In our previous study we already discussed the methods and potential gains with SW-IMRT in more detail and compared our results with SW-IMRT to that of others [8–18].

The results of the present study demonstrate that the actual gain with SW-IMRT depends on a number of factors. In the first 20 patients, for example, only a minimal gain was obtained because certain decisions were made during treatment plan

Table 3
Sub-group values for reduced swallowing dysfunction when sparing SWOARs.

		Mean NTCP reduction by sparing SWOARs with SW-IMRT relative to ST-IMRT (SD)	ANOVA or *t*-test
n = 80	*n*	RTOG grade 2–4	*p*-Value
Neck radiotherapy			<0.001
Local RT[a]	7	0.3% (0.3%)	
Unilateral neck RT	17	4.3% (2.7%)	
Bilateral neck RT	56	7.3% (3.9%)	
Tumour location			0.001
Larynx	25	6.6% (5.2%)	
Hypopharynx[a]	9	2.3% (0.9%)	
Oral cavity	6	8.3% (3.3%)	
Oropharynx	23	7.6% (3.3%)	
Nasopharynx	3	8.0% (0.5%)	
Salivary-skin-other[a]	14	3.7% (2.5%)	
Overlap SWOAR-PTV[b]			<0.001
0–25%	22	4.4% (3.3%)	
26–50%	21	7.8% (4.1%)	
51–75%	20	8.4% (3.0%)	
>75%[b]	17	3.4% (3.9%)	
High and low potential gain			<0.001
Low potential gain[a]	37	3.1% (3.2%)	
High potential gain	43	8.6% (2.8%)	
Total	80	6.1% (4.1%)	

Values are means (SD).
Abbreviations: NTCP, normal tissue complication probability; PCM, pharyngeal constrictor muscle; PTV, planning target volume; RT, radiotherapy; RTOG, (physician-rated) Radiation Therapy Oncology Group (score); ST-IMRT, standard intensity-modulated radiotherapy; SW-IMRT, swallowing-sparing IMRT; SWOAR, swallowing organ at risk.
[a] Patients with local RT, a hypopharynx tumour, a tumour located outside the laryngo-pharyngeal axis or >75% overlap[b] were included in the low predicted gain group based on the regression analysis.
[b] Overlap was defined as the proportion of the combined superior PCM and supraglottic larynx overlapping with any PTV.

optimization that could be adjusted and in a random sample of 6 re-planned patients increased the sparing of SWOARs. It appeared that the gain of SW-IMRT was influenced by the level of experience of the involved dosimetrist and the time allocated for treatment planning. Physician-related factors also played an important role, such as the willingness to accept a moderate dose shift to unspecified structures or a locally slightly lower, yet acceptable, dose in the PTV as a means to provide additional SWOAR sparing. Other factors may also have an impact. For example, different institutes have different policies with regard to the use of specific treatment optimization methods. In the current study the objective values and weights were iteratively adjusted until finally a treatment plan was obtained in which the SWOAR dose was really as low as possible. In other institutions, fully automated or class solution approaches are often used. In that case, less additional efforts are made to spare an OAR and no further optimization is performed as soon as an acceptable plan is obtained [19]. RT treatment plans can fulfil all predefined requirements, but this does not mean that they cannot be further optimized. Other important factors that influence the potential gain of SW-IMRT cannot be altered so easily. In our previous studies, we showed that reductions in the NTCP-values of physician-rated grade 2–4 swallowing dysfunction can be obtained by reducing the mean dose in the superior PCM but also by reducing the mean dose in the supraglottic larynx [2]. Patients with laryngeal tumours often benefit from additional sparing of the superior PCM while on the other hand patients with oropharyngeal tumours are more likely to benefit from additional sparing of the supraglottic larynx. Tumour site also seems to have an indirect effect on the NTCP-reductions, because tumour site influences the degree of overlap between SWOARs and PTVs, which in turn has an influence on the potential reductions of the NTCP values with SW-IMRT. We found that the NTCP reductions were strongly related to the overlap between SWOARs and PTVs. The target volume (neck irradiation) also influenced the NTCP-reductions indirectly because patients receiving neck irradiation are more likely to have any degree of overlap between the SWOARs and the PTV. It appeared from the analysis that patients with intermediate overlap benefitted most from SW-IMRT, whereas patients with an almost complete overlap did not gain much from SW-IMRT, as only minor manipulation of the dose in the SWOARs is possible in such cases.

We are currently awaiting the follow-up results of the patients that were treated with SW-IMRT. We aim to compare the results in these patients to the results in a comparable cohort of patients who received ST-IMRT in the past and with whom swallowing dysfunction endpoints were prospectively scored in a similar way as in the current group of SW-IMRT treated patients.

Conclusions

The gain that can be obtained with SW-IMRT in clinical practice with regard to the reduction of swallowing dysfunction depends on a number of factors. Some of which can be manipulated, such as treatment planning methodology, experience of the involved personnel and institutional preferences, while other factors such as the administration of neck radiotherapy, the overlap between SWOARs and PTVs, and tumour site are patient or disease related and may either increase or limit the options of SW-IMRT to spare the SWOARs. Optimal clinical introduction of SW-IMRT requires a detailed evaluation and comparison between the standard (ST-IMRT) and new technique (SW-IMRT) in order to fully exploit the potential benefits. This study demonstrates that the introduction of new techniques aiming at avoiding additional organs at risk by adding new treatment planning objectives does not automatically translate into better dose distributions when introduced into clinical practice. Without optimal introduction there is no reason to expect better clinical outcome.

Conflict of interest

The authors state that the research presented in this manuscript is free of conflicts of interest.

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