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Radiotherapy of Head and Neck Cancer Patients: Small Safety Margins with Daily Imaging or Larger Safety Margins?

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Keywords

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Abstract

Objective: To evaluate differences of intensity-modulated radiotherapy (IMRT) with helical tomotherapy in head and neck cancer for two clinical scenarios: irradiation with a small safety margin (SM) and daily imaging, or irradiation with a larger safety margin in combination with less frequent imaging.

Materials and methods: Retrospective analysis of irradiation plannings of 10 head and neck patients with two different safety margins (3 mm (SPTV)/ 7 mm (LPTV)) from CTV to PTV. Additionally for the SPTV daily imaging control was calculated. PTVs, conformity (CI) and homogeneity index (HI) and especially applied dose to organs at risk (OAR) were compared.

Results: As expected a difference was found regarding PTV volumes, while CI and HI showed no statistically significant differences. The exposure of the OARs external, parotids and mandible is up to 3.5 Gy lower for SPTV plans in combination with daily image control. Concerning the myelon, the difference is much smaller and shows slight advantages for the LPTV plans.

Conclusions: With SPTV including daily imaging and LPTV without imaging, comparable plans can be calculated in terms of HI and CI. With regard to OAR exposure, there are clear advantages for irradiation with small SM in combination with daily imaging.

ABBREVIATIONS

IMRT: Intensity-Modulated Radiotherapy; IGRT: Image-Guided Radiotherapy; SM: Safety Margin; CI: Conformity Index; HI: Homogeneity Index; CTV: Clinical Target Volume; PTV: Planning Target Volume, MV-CT: Megavolt Computer Tomography

INTRODUCTION

Today, intensity-modulated radiotherapy (IMRT) is the absolute standard for both adjuvant and definitive irradiation of head and neck patients. Due to the steep dose gradients possible with this method, excellent target volume coverage is achieved in combination with good protection of organs at risk, which leads to a decreasing side effect rate [1]. Particularly well documented is the possibility of improved sparing of the parotids with resulting reduced dry mouth [2,3].

The combination of IMRT with image-guided radiotherapy (IGRT) makes it possible, among other things, to reduce the safety margins [4,5]. This leads to an additional dose reduction of the organs at risk and thus to further avoid or reduce side effects. Conversely, if no regular, in the best case daily, imaging is performed, the safety margins must be chosen larger [6,7].

However, daily imaging automatically means additional dose exposure for patients. At the same time, this makes irradiation more time-consuming. For irradiations with tomotherapy, the additional dose applied per MV-CT is given as 1-2 cGy [8,9]. The additional time required depends on the length of the CT and is up to 4 minutes.

This raises the question of what is better: irradiation with a small safety margin but then necessary daily imaging, or irradiation with a larger safety margin in combination with less frequent imaging.

In the retrospective study presented here, we analyzed irradiation plans of head and neck patients with regard to this question.

MATERIALS AND METHODS

Patients

Data were retrospectively collected from 10 patients undergoing radiotherapy (RT) on a Hi-Art II tomotherapy system (Accuray, Madison, Wisconsin, USA) for head and neck cancer.

Inclusion criteria were adjuvant radiotherapy for head and neck cancer and a target volume including the (former) tumour site as well as cervical lymph nodes.

Patients' characteristics are summarized in Table 1

Radiotherapy

The head and neck region of each patient was immobilized using a headrest and a thermoplastic mask which was fixed to the treatment couch.

The radiotherapy planning was based upon a kilovolt (kV) computed tomography (CT) scan as inverse planning using tomotherapy Hi-Art planning system (Accuray HIART Version 5.1.0). The pitch was set to 0.430 and the beam width to 2.5 cm.

The prescribed total dose to the (former) tumour site and the neck nodes at high risk was 60–66 Gy and 54 Gy for those at low risk, with single doses of 1.8–2.2 Gy. All patients were irradiated with 30 fractions with integrated plans.

The clinical target volumes (CTVs) for all patients were defined on the basis of the (preoperative) CT- and/or PET-CT images and/or magnetic resonance imaging.

Table 1: Patients' Characteristics

patients	10
Age [years]	
Median	61.6
range	39 - 73
Gender	
Female	1
male	9
Tumour site	
Oropharynx	3
Parotid gland	2
Tonsil	2
Larynx	1
Hypopharynx	1
Mandible	1
Histology	
Squamous cell carcinoma	8
Adenocarcinoma	1
Mucoepidermoid carcinoma	1
TNM	
T1	1
T2	5
T3	2
T4	2
N0	2
N+	8
M0	10
Resection status	
R0	8
R1	2

The CTV was expanded by 3 mm to obtain the planning target volume (PTV).

A standardized megavolt CT scan (MV-CT) was performed frequently before the radiotherapy sessions to check patient positioning. Based upon the kV-CT from RT planning, the patient position was adjusted manually.

The patients then underwent radiotherapy (Hi-Art II tomotherapy system, 6MV photons) with a total of 300 fractions administered. All treatments were completed within the allotted time.

Comparison of 3 mm versus 7 mm plans

Retrospectively, for the study presented here, the CTVs were extended by an additional 7 mm to obtain a new PTV with a larger safety margin. A comparison plan was generated for this larger PTV (LPTV, CTV + 7 mm) using the identical planning method as for the smaller, irradiated PTV (SPTV, CTV + 3 mm).

A comparison was done between the SPTV- and the LPTV-plans in terms of volume of PTV, conformity index (CI), homogeneity index (HI) and dose applied to organs of risk.

For the target volumes of the integrated plans, the PTV with the highest prescribed dose was defined as PTV 1 (66 Gy or 63 Gy), and the target volumes with the lower dose prescriptions were defined as PTV 2 (60 Gy) and PTV 3 (54 Gy), respectively.

The CI was calculated for this work according to the formula

CI = TVPIV / TV

(PI = prescribed dose, PIV= PI Volume, TV = Target Volume and their intersection TVPIV)

However, due to errors in reading back the data, the CI could only be reliably determined for 9 patients.

The HI was calculated for all 10 patients according to the formula

(D98-D2) / D50

(D2: dose in 2% of the target volume (Max Dose), D50: mean dose in the target volume (DMean). D98: dose in 98 % of the PTV (Min Dose)).

The organs at risk selected for this study were the external, the whole body, the parotids, the mandible and the myelon. For the parotids, fewer values were available for evaluation (n = 8) because in some cases the tumor region was located in the area of a parotid gland.

The volumes for the external and the myelon were subsequently edited, since they are only partially in the range of direct irradiation. For this purpose, a structure was created in the 7 mm plan (1 cm cranial and caudal oft he largest PTV) in order to restrict the observation to the relevant area only. This "new" structure was copied into the 3 mm plan to generate a

comparably sized volume and the Dmean values for the external and myelon were read. Unfortunately, there were problems with reading back the planning data for one patient, so that the evaluation in relation to the organs at risk could only be carried out for 9 of the patients.

After ensuring via the parameters PTV coverage, OAR-dosage, CI and HI that the SPTV plans and the LPTV plans were clinically equivalent plans that met all criteria for radiotherapy treatment planning, the comparison was made with respect to the applied dose of PTV and organs at risk.

For the organs at risk, the comparison was made on the basis of the Dmean.

To gain a comparison of the applied PTV- / and OAR- dose from IMRT and IG-IMRT, the doses from daily MVCT were added to the doses for the SPTV-plans.

For the calculations used in this study, we assume a value of 1.5 cGy per MV-CT performed. For 30 fractions of an IG-IMRT, the exposures caused by the MV-CT add up to 0.45 Gy in the treatment volume.

Statistics

Statistical analysis was performed using a two-tailed T-test for connected samples. The null hypothesis was that there were no differences between the two groups and the alternative hypothesis was that there were differences. The significance level was set at a p-value of 0.025.

RESULTS

PTV-volume

Table 2 shows the differences between SPTV and LPTV for the absolute volume of all PTV's.

The differences of the mean values range between 30 ml (PTV1) and 223 ml (PTV3).

Table 3 summarizes the differences between SPTV and LPTV of the 3 volumes (PTV 1,2 and 3).

Table 2: Volume changes of PTV 1-3

PTV	Mean [ml]	Standard deviation [ml]	Min [ml]	Max [ml]
SPTV1	55,98	23,13	22,55	111,68
LPTV1	85,95	29,72	39,69	149,42
SPTV2	126,74	105,67	23,70	326,09
LPTV2	197,93	154,82	38,59	463,04
SPTV3	458,47	194,22	128,29	742,60
LPTV3	681,40	283.59	189,44	1113,03

Table 3: Differences between SPTV and LPTV for PTV 1 - 3

				t-statistic	
Volume	Number of targetvolumes	Mean difference[ml]	Standard deviation [ml]	t-statistic (abs)	p value
PTV1	10	29,97	7,98	11,8717	8,4E-07
PTV 2	7	71,19	51,02	3,6922	1,0E-02
PTV3	10	222,93	91,07	7,7410	2,9E-05

Looking at this volume difference, there is a statistically significant difference between the SPTV and LPTV volumes.

Conformity and homogenity index

Also, the CI and HI were calculated separately for PTVs 1,2 and 3 for both SPTVs and LPTVs.

Table 4 summarizes the differences between the SPTvs and LPTVs regarding the CI and HI.

The differences of CI and HI show no statistically significant differences.

Dmean of OAR

For the organs at risk (external, myelon, parotid glands and mandible), the respective Dmean was first determined for the SPTVs and the LPTVs without taking into account the daily imaging.

Table 5 summarizes the results: For the myelon there is a very small dose difference of 0.15 Gy on average. The other OARs receive a dose more than 2 Gy higher by irradiation with the LPTV plan. In our collective, the largest difference is found in the area of the mandible (4 Gy).

Dose comparison taking into account daily imaging

For this comparison, the dose exposure of one MV-CT per fraction was added to the SPTV dose values of the plans. Subsequently, the difference to the LPTV dose values (without addition of an MV-CT) was calculated:

difference = dose LPTV - dose SPTV incl. MV-CT.

For the organs at risk, the Dmean were compared, and the differences between LPTV and SPTV + MV-CT were recorded. The summary shows Table 6.

Table 4: Differences regarding HI and CI

volume	mean	Standard deviation	t-statistic (abs)	P
HI PTV1	0,0026	0,0062	1,280	2,4E-01
HI PTV2	-0,0100	0,0205	1,203	2,8E-01
HI PTV3	-0,0069	0,0347	0,599	5,7E-01
CI PTV1	-0,006	0,012	1,455	1,8E-01
CI PTV2	-0,001	0,012	0,273	8,0E-01
CI PTV3	-0,001	0,009	0,406	7,0E-01

Table 5: Dmean of the organs at risk for SPTV and LPTV plans (without taking into account the daily imaging)

Organ	SPTV dose [Gy]	LPTV dose [Gy]	difference [Gy]	volume [cc]
External	26,509 ± 4,155	28,736 ± 4,315	2.228	4926,39 ± 1917,5
Myelon	18,844± 2,574	18,989 ± 2,677	0.145	46,31 ± 9,06
Parotid gland right	20,659 ± 5.67	24,49 ± 7,89	3.83	19,46 ± 8,71
Parotid gland left	20,53 ± 4.13	23,98 ± 6,18	3.45	20,73 ± 7,30
Mandible	38,46 ± 9,59	42,45 ± 9,6	3.98	53,20 ± 10,00

Table 6: Dose difference OARs (LPTV - dose SPTV incl. MV-CT)

Structure	difference Dmean [Gy]	Sigma[Gy]	p
External	1.78	0.35	3.73E-7
Myelon	-0.30	0.54	1.31-E1
Parotid gland left	3.00	2.46	1.09E-2
Parotid gland right	3.38	2.77	1.07E-2
Mandible	3.53	1.50	7.97E-4

Overall, the comparison of the absolute dose values of the OARs shows that the exposure of the external, the parotids and the mandible is up to 3.5 Gy lower for the SPTV plans including daily position control

Regarding the myelon, the difference is much smaller with a slight advantage for the LPTV plans.

DISCUSSION

With modern radiotherapeutic techniques, especially IMRT, excellent target volume coverage can be achieved while sparing organs at risk (OARs). In order to achieve such good protection of the OARs, it makes sense to work with the smallest possible safety margin [7,10].

Based on the data known from the literature, for irradiation with such a small safety margin, e.g. 3 - 5 mm, a daily image control is necessary, which can be at least partially omitted with a greater safety distance [10,11].

Implementation of an “every day image control” however is time consuming, and also the applied radiation dose from the CT is discussed controversially [12-14]. Ding et al., calculated additional dose exposures to organs at risk of up to 300 cGy for daily kV CBCTs throughout treatment [15]. For tomotherapy an additional dose of 1-2 cGy is received by the OARs by every MV-CT [8,9].

The additional time needed for a standard head and neck volume with included lymphatic pathways, is for the pure CT time 180-240 seconds in our departement. In addition, there is the time required to compare the MV-CT and the planning CT and the resulting position correction. Thus, you can assume 4-5 additional minutes that are needed for the daily image control. With 30 irradiations, this means a time factor of more than 2 hours. However, this is only true if the entire PTV volume is visualized in the MV-CT. The possibility of shortening the MV-CT is also a possibility that can be discussed in this regard [7].

This raises the question of what is the better solution. Either irradiation with a smaller SM but daily position control or the choice of a larger SM to reduce the number of position controls. This is the question we have addressed in this paper.

Without daily imaging, the safety distance must be increased up to 10 mm [7]. For this work, we opted for a moderate magnification to 7 mm SM. Thus, the differences shown here could also be larger if even larger distances were used.

We compared the calculated SPTV and LPTV plans with respect to several points.

Before considering sparing of OARs, it is important to ensure that the therapy goal is achieved in terms of covering the target volume.

The analysis of our plans shows that clinically equivalent plans were calculated with both SMs (SPTV, LPTV) so that in this respect there is no advantage for one of the approaches.

As expected, the addition of 4 mm significantly increases the volume of the PTVs clearly. The largest differences logically arise in the largest volumes, the PTV3s, which cover the entire range of lymph nodes. On average, an enlargement of more than 200 ml is found here which illustrates that the increase in SM leads to a significant increase in the irradiated volume, thus increasing the applied integral dose. Similar could be seen from Al-Mamgani et al., who describe a reduction of the irradiated PTV by a median of 28.1% by reducing the SM by 6 mm [16]. Considering this aspect in isolation, this would speak in favor of irradiation with a lower SM.

Considering the dose calculated for the OARs without addressing the dose of additional image controls, the exposure from the LPTV plans is larger (up to 4 Gy), as expected. The difference inevitably depends on the localization of the organ at risk. The myelon, which has the farthest distance to the target volume due to its location, shows a very small dose difference of 0.15 Gy on average. In the area of the parotids, which are directly adjacent to the target volume during irradiation of cervical lymph nodes, there is accordingly a significantly greater difference.

Thus, these facts seem at first to clearly argue for a reduction of the safety distances from CTV to PTV, as is also recommended in the literature [10,16].

Our question was whether the inclusion of the additional dose from the required daily MV-CT position control compensates for this.

For our calculations, we assumed a daily MV-CT check for the SPTV plans. No imaging was added for the LPTV plans.

The differences of the applied dose were particularly clear in the parotid region. The average difference in Dmean here is 3.0 Gy (left) respective 3.38 Gy (right). Thus both plans meet the generally accepted dose limit of 25 Gy, which was already elicited as a limit dose by Eisbruch et al in 1999 [17]. Also, Deqasy et al., evaluated that severe xerostomia (defined as long-term salivary function of <25% of baseline) is usually avoided if at least one parotid gland is spared to a mean dose of less than approximately 20 Gy or if both glands are spared to less than approximately 25 Gy (mean dose) [18]. Other studies additionally suggest an exponential relationship between the reduction in salivary flow and the mean parotid dose for each gland. Chao et al. found that the stimulated saliva flow at 6 months after treatment is reduced exponentially, for each gland independently, at a rate of

approximately 4% per Gy of mean parotid dose [19]. Thus, any reduction in dose applied to the parotid would be a benefit to the patient and SPTV plans with an average of 3 Gy or more less would be preferred.

Significant differences are also seen for the mandible, which is often very close to the target volume in head and neck irradiations. The Dmean decreases on average by 3.53 Gy. However, the average Dmean of both plans is in a noncritical range for the prevention of osteoradionecrosis. To avoid osteoradionecrosis, especially the avoidance of higher doses (above 50 / 60 Gy) seems reasonable [20]. However, since the dose applied to the mandible also allows indirect conclusions to be drawn about the applied dose to the mucosa in this area, a dose reduction of 3.5 Gy nevertheless appears desirable.

When comparing the dose applied to the external, there is again a benefit, albeit somewhat smaller, for the SPTV plans with daily imaging (difference 1.78 Gy).

Considering the organ at risk "myelon", the maximum applied dose is of particular interest. Kirkpatrick et al,. found that using conventional fractionation of 1.8–2 Gy/fraction to the full-thickness cord, the estimated risk of myelopathy is < 1% and < 10% at 54 Gy and 61 Gy [21]. Considering the dose levels applied by a usual head and neck irradiation, they should not come close to this limits (or higher). This is also confirmed in the irradiation plans evaluated here. In addition, since the dose differences between the both planings are only 0.3 Gy on average, there is no clinical advantage to be seen for one of the plans with regard to the myelon. This will be due to the greater distance of the myelon to the PTVs compared to other OARs and also fits with the findings of Noble et al. This study group found that during the course of therapy, sufficient protection of the myelon is provided even in the presence of changes in target volume due to, for example, weight loss or anatomical changes [22].

As described above for our calculations, we assumed a daily MV-CT check for the SPTV plans and no imaging was added for the LPTV plans. This, of course, does not correspond to reality, since even with a larger safety margin, positioning checks must be carried out, albeit at greater intervals. Especially during the first irradiation or if there are changes in the patient's anatomy, e.g. due to weight compression or similar. However, the differences in applied dose to the organs at risk will additionally increase with any imaging performed for the LPTV plans, as MV-CT dose must then added. Thus, it can be said that the calculated differences are smaller than they really are and the advantage of SPTV + MV-CT irradiation is even somewhat larger.

The small number of cases is certainly a weakness of the planning study presented here. Nevertheless, due to the fact that the results are consistent in all patients, we consider the results to be generally transferable. However, a further review is useful. In addition, our planning-only study lacks clinical data. It would be desirable to prove the demonstrated benefits of the plans in clinical practice by reducing side effects.

CONCLUSION

In summary, our results show that the doses applied to organs at risk are smaller with irradiation with a smaller safety margin and daily imaging than with irradiation of a larger safety margin and less frequent imaging. This, in our opinion, argues for the use of smaller safety margins in combination with daily imaging. However, a significant additional time expenditure has to be accepted.

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Conflict of Interest

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