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Head and neck radiotherapy

Sequentially delivered boost plans are superior to simultaneously delivered plans in head and neck cancer when the boost volume is located further away from the parotid glands

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ABSTRACT

Purpose: To find parameters that predict which head and neck patients benefit from a sequentially delivered boost treatment plan compared to a simultaneously delivered plan, with the aim to spare the salivary glands.

Methods and materials: We evaluated 50 recently treated head and neck cancer patients. Apart from the clinical plan with a sequentially (SEQ) given boost using an Intensity Modulated Radiotherapy Technique (IMRT), a simultaneous integrated boost (SIB) technique plan was constructed with the same beam set-up. The mean dose to the parotid glands was calculated and compared. The elective nodal areas were bilateral in all cases, with a boost on either one side or both sides of the neck.

Results: When the parotid gland volume and the Planning Target Volume (PTV) for the boost overlap there is on average a lower dose to the parotid gland with a SIB technique (−1.2 Gy), which is, however, not significant ($p = 0.08$).

For all parotid glands with no boost PTV overlap, there is a benefit from a SEQ technique compared to a SIB technique for the gland evaluated (on average a 2.5 Gy lower dose to the parotid gland, $p < 0.001$). When the distance between gland and PTV is 0–1 cm, this difference is on average 0.8 Gy, for 1–2 cm distance 2.9 Gy and for glands with a distance greater than 2 cm, 3.3 Gy. When the lymph nodes on the evaluated side are also included in the boost PTV, however, this relationship between the distance and the gain of a SEQ seems less clear.

Conclusions: A sequentially delivered boost technique results in a better treatment plan for most cases, compared to a simultaneous integrated boost IMRT technique, if the boost PTV is more than 1 cm away from at least one parotid gland.

Conventional radiotherapy regimens for head and neck cancer consist of an elective irradiation followed by reduced boost fields aiming at the high-risk area. With the introduction of Intensity Modulated Radiotherapy (IMRT), many institutes have switched to irradiate head and neck cancer patients with a Simultaneous Integrated Boost (SIB) technique. This concept uses the advantages of IMRT treatment planning by generating one single treatment plan. In conventional radiotherapy regimens the dose distributions of two treatment plans need to be summed. Modern techniques offer various possibilities, like dose escalation [1]. Therefore, there are a lot of different radiation doses and dose schedules known to be adequate for tumour. [4–6,11,13,17]. The "first report of RTOG 9003" by Fu et al. [8] reported that several fractionation schemes and acceleration schemes show no significant increase of late effects [7]. The conclusion of these findings is that SIB is the technique of choice in terms of dose conformality and side effects.

In standard, given elective dose (with a SEQ technique) in head and neck radiotherapy, usually around 50 Gy, is delivered to the elective nodal regions, followed by a dose of 20 Gy to the boost PTV all in 2 Gy per fraction. When the boost is given simultaneously the overall treatment time for the elective dose delivery is increased to 6–7 weeks. To compensate for this, the dose to the elective region needs to be increased, i.e. 46 Gy becomes 57.8 Gy.

With SIB the overall treatment time becomes longer for the elective node area (from 23 to 35 fractions). Analyses of clinical studies show that a longer overall treatment time leads to a loss of tumour control of approximately 1.4% per day [14]. To compensate for this loss a so called "recovery dose" is needed of approximately 0.7 Gy per day (Steel, 2002, page 138, table 13.3) [14,12].

In the linear quadratic (LQ) model several assumptions are used to come to a responsible choice for this adaptation. In general the α/β ratio for normal tissue is approximately 3 Gy (Steel, 2002).

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However, for late side effects to the parotid glands the α/β ratio is approximately 10 Gy [16]. In clinical practice, the mean dose of the parotid gland remains the best predictive factor. Investigators report that the tolerance dose (TD50) for mild xerostomia is 23 Gy in 2 Gy per fraction for bilateral irradiation and 45 Gy for unilateral irradiation [9,10,15].

Taking all these considerations into account, a dose scheme for a SIB treatment of 35 times 1.65 Gy for elective areas and 35 times 2 Gy for tumour volume seems comparable [2]. This scheme results in a higher physical dose of 12 Gy to the elective nodal area and is, therefore, likely to deliver a higher physical dose to the surrounding tissues, i.e. parotid glands.

One might question whether the superior dose distribution of SIB balances this higher physical dose. The aim of this study is to determine the superiority of the SIB or SEQ technique with respect to the geometrical relationship between the high dose region and the parotid glands.

Methods and materials

Patients

We selected 50 patients treated between 2007 and 2009. In the patient population studied, 71% had stage T2 or T3 tumours and 62% N2 disease. In clinical practice the selected patients were treated either with a SEQ technique or with a SIB technique. Several parameters were looked into to be able to predict the outcome, i.e. minimum distance between boost volume and each parotid gland, parotid gland volume, tumour stage, lymph node stage, location of the boost PTV and the position of the boost PTV relative to the parotids (Table 2). The minimum distance between the parotid gland and the boost PTV location was measured 2D in an axial, coronal and sagittal plane and stratified from inside the boost (overlap), per cm, up to more than 2 cm (Table 2). The location of the boost PTV was stratified in 6 areas: in the middle, in the middle and left or right side, single sided left or right and middle and both sides.

First, two regimens (one SIB and one SEQ) were chosen to deliver equivalent tumour and elective doses as well as with the same tolerance doses to the organs at risk (Table 1). Data of twenty randomly chosen patients were selected and a first analysis indicated that for those patients with a PTV at some distance from one or two parotid glands (i.e. more than 2–3 cm), a SEQ is always superior. Therefore, we changed the selection procedure slightly, by including another 30 patients with a larynx or oropharynx tumour for whom we expected distances around 1–2 cm for at least one parotid gland. The elective node areas were bilateral for all patients, with a boost on either one side, or both sides. In total, we evaluated 50 patients and 100 parotid glands in this study.

Radiation treatment

For each patient, two treatment plans were generated: one with SEQ and one with SIB technique. An axial CT-scan in treatment position was taken from the base of the frontal sinus to the lower neck. The slice thickness was 3 mm. Each patient was immobilized in a five-point fixation mask.

Table 1
Prescription doses for PTVs and tolerance doses for organs at risk used in this study.

Structures	Prescription dose	
	Sequential	SIB
PTVelective	46 Gy (23 × 2 Gy)	57.75 Gy (35 × 1.65 Gy)
PTVboost	24 Gy (12 × 2 Gy)	70 Gy (35 × 2 Gy)
Brainstem	Maximum dose < 56 Gy	
Spinal cord	Maximum dose < 50 Gy	
Parotid gland	Mean dose < 26 Gy	
Oral cavity	Mean dose < 26 Gy	

Table 2
Patient and tumour characteristics.

Characteristic	*N* (%)
T stage	
T1	6 (12)
T2	17 (34)
T3	19 (38)
T4	8 (16)
N stage	
0	14 (28)
1	5 (10)
2	31 (62)
Location	
Nasopharynx	3 (6)
Oropharynx	35 (70)
Larynx	12 (24)
Location boost	
Left	1 (2)
Right	3 (6)
Middle	10 (20)
Middle + left	9 (18)
Middle + right	6 (12)
Middle + left + right	21 (42)
Distance boost-parotid	
<0 cm	52 (52)
0–1 cm	12 (12)
1–2 cm	16 (16)
>2 cm	20 (20)
Volume parotid gland	26.1 (11.6–66.3)

All target volumes, CTV (high risk, i.e. primary tumour area) and CTV-ln (low risk, i.e. lymph nodes), were outlined, every 3 mm, on this treatment CT scan. The clinical target volume (CTV) was defined as the GTV plus a margin for potential microscopic spread, including the regional lymph node draining areas. The PTVs were defined as these CTVs plus 0.5 cm margin. The surrounding critical tissues, namely the brainstem, spinal cord, parotid glands, optic nerves, optic chiasm and the oral cavity were also outlined, but the volumes were not expanded.

Technique

The two techniques were calculated using the Pinnacle treatment-planning system (TPS) (software version 8.0 h, Philips, Best, The Netherlands). The treatment plans were developed for a 6 MV photon beam, using a Multi Leaf Collimator (MLC) with 1 cm leaf width (Elekta SL15 accelerator, Elekta, Crawley, UK).

The SEQ techniques evaluated in this study were the clinical treatment plans originally given. This first SEQ technique was a 6-field setup with gantry angles of 216, 288, 0, 72 and 144 degrees with a table rotation of 0 degrees and a 6th gantry angle of 330 degrees with a table rotation of 90 degrees to avoid the oral cavity. Small gantry angle adjustments were made to cover the PTVs while minimizing the dose to the surrounding tissue.

To obtain a clinical deliverable plan the minimum segment area had to be 9 cm^2 with a minimum number of monitor units of 4. The first technique was then followed by a boost technique with an individual beam set-up based on the shape of the boost PTV. A 3-D dose calculation was performed for both techniques using the superposition-convolution algorithm of the TPS and a grid size of 3 mm. A composite plan was obtained; dose–volume histograms for the PTVs and the OARs were calculated.

Exactly the same beam set-up was used for the SIB technique with the difference that for the SIB plan different objectives and

dose schemes were used (Table 1). In this study we ensured that the beam set-up was consistent between SEQ and SIB to make sure that differences in dose were responsible for differences in outcome and not different techniques. The two techniques fulfilled the ICRU recommendations (ICRU report 50, 62, [19]) for target coverage and reporting the dose in the organs at risk (Table 1, Fig. 3). The focus was primarily on sparing the parotid glands and secondarily on the oral cavity.

The distance between the parotid gland and the boost PTV area, the parotid volume, the mean parotid gland dose and the mean oral cavity dose were calculated for both techniques. Tumour stage and the lymph node level were also scored.

Statistical analysis

Relative and absolute differences in physical dose between the SIB and SEQ treatment plan for each parotid gland were calculated. We used a linear regression model to analyse which clinical factors were related to this difference (univariate and multivariate). We choose percentage difference as an endpoint instead of absolute difference, because we regard a 2 Gy difference at for instance a 35 Gy level, different than a 2 Gy difference at a 20 Gy level. For comparison of differences between SIB and SEQ, a paired *T*-test was used. ©SPSS for Windows software was used for the analysis (release 15.0, SPSS Inc., Chicago, Illinois, USA).

Results

General

The minimum distance to the parotid gland measured for all 100 evaluated glands, varied between −3.4 cm (overlap) and +5.8 cm. Calculated differences in SIB and SEQ dose varied between −19 Gy and +14 Gy, with a median of +0.9 Gy.

From the studied parameters, the distance between the boost volume and the parotid glands; the lymph node levels treated and the location of the boost volume were significant (Table 4). The volume of the parotid gland, the tumour stage and the position of the boost to the parotid glands were found not to be significant. We plotted the mean dose to the parotid gland with a SEQ technique versus the dose with a SIB technique, indicating the distance parameter (Figs. 1A and 3 and Table 3) and the involvement of lymph nodes (Fig. 1B). When the parotid gland is partly inside the boost PTV, which gives a negative distance, there is a modest advantage for the mean parotid gland dose using the SIB technique for most patients (average −1.2 Gy, $p = 0.08$). A distance between 0 and 1 cm results mostly in comparable dose to the parotid gland with a slight advantage for the SEQ technique (Table 3). There is a benefit for the SEQ technique for almost every patient if the distance is more than 1 cm. The dose can be kept below 30 Gy for almost every case and below 26 Gy for the majority of cases when a SEQ technique is used, whereas this is not always possible with a SIB technique (Table 3).

There are, however, in the distance <0 cm group also patients who benefit from the SEQ technique, and the other way around, there are patients who do not benefit in the distance >1 cm group, as shown in Fig. 1. This might indicate that there are more parameters which influence the outcome.

The inclusion of the lymph nodes in the boost PTV is visible in Fig. 1B. The majority of the population concerns oropharyngeal cancer patients and the lymph node levels involved for most patients are level 2 and 3 [18]. These levels are located close to the parotid glands which can be of importance for the parotid dose.

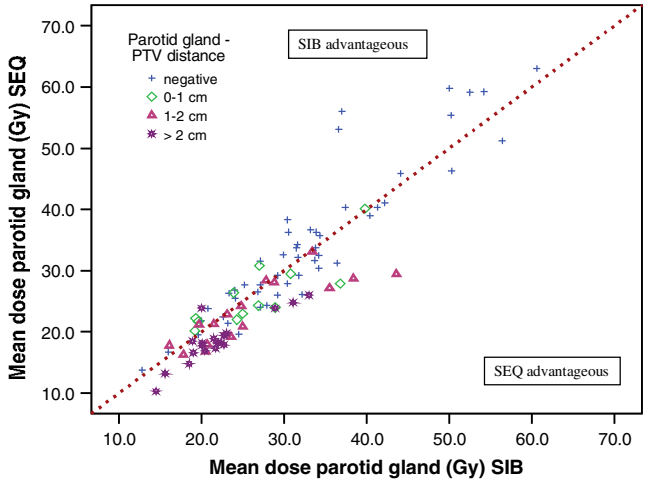

Fig. 1A. The mean dose to the parotid gland with a SEQ technique versus the mean dose with a SIB technique (Y). The dotted line indicates the situation with no difference between the SEQ and SIB technique. The parotid gland to PTV distance in categories. Diamonds (0–1 cm), triangles (1–2 cm) and circles (>2 cm).

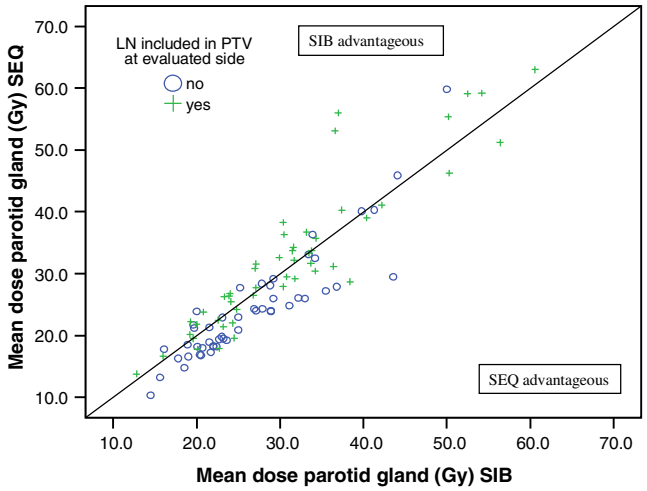

Fig. 1B. The mean dose to the parotid gland with a SEQ technique versus the mean dose with a SIB technique (Y). The dotted line indicates the situation with no difference between the SEQ and SIB technique. Lymph nodes included or not included in the PTV at the evaluated side.

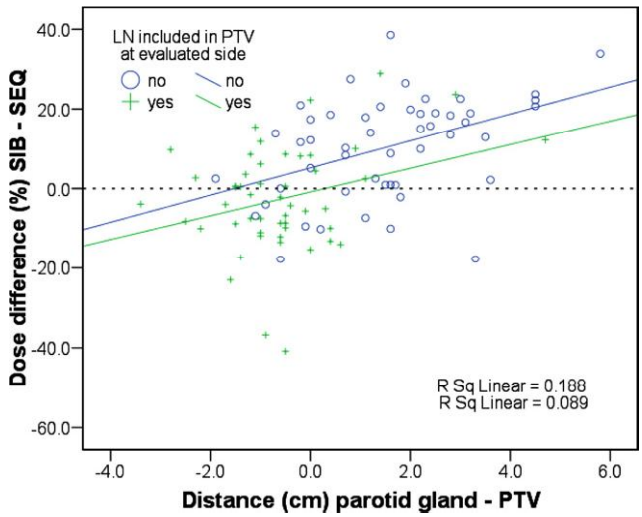

Fig. 2. The relative dose difference between the SIB and the SEQ technique versus the distance between the parotid gland and the boost PTV.

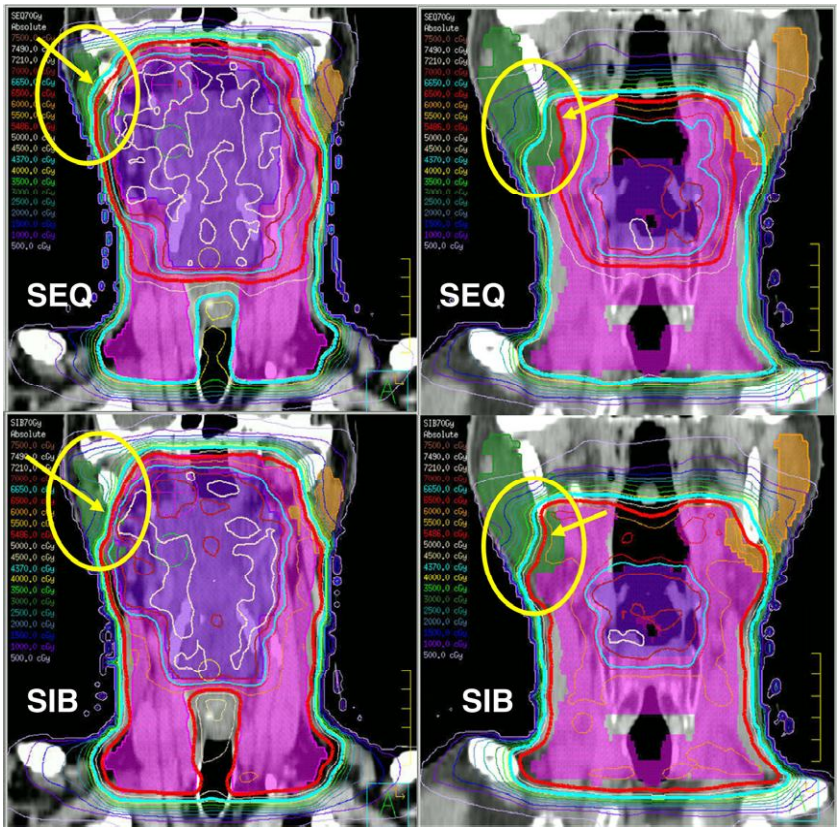

Fig. 3. Isodose distributions for a SEQ (left) and a SIB (right) treatment. In purple the boost PTV area and in pink the elective PTV. The red line indicates 95% of the SIB dose of 57.75 Gy. The thick light blue line indicates 95% of the SEQ dose of 46 Gy.

Table 3
Dose characteristics of the parotid gland stratified per cm distance between the parotid gland and the boost PTV. The volume parotid gland receiving dose increases with the distance.

Criterion	Overlap (n = 52)		0–1 cm (n = 12)		1–2 cm (n = 16)		>2 cm (n = 20)	
	SIB	SEQ	SIB	SEQ	SIB	SEQ	SIB	SEQ
Mean dose (Gy)	33.0	34.2	26.8	26.0	26.3	23.4	21.9	18.6
Median dose (Gy)	31.7	32.0	26.0	24.2	24.2	22.1	21.6	18.1
Range (Gy)	13–61	14–63	19–40	20–40	16–44	16–33	15–33	10–26
% $\leqslant$ 30 Gy	40	42	75	83	75	94	90	100
% $\leqslant$ 26 Gy	25	25	50	58	63	63	85	100

When the lymph node regions are not included in the boost PTV, most patients benefit from a SEQ technique (difference of 2.3 Gy, $p < 0.001$). When they are included there is a small difference between the SEQ and the SIB technique in favour of the SIB technique (−1.1 Gy, $p = 0.1$).

Both findings are combined in Fig. 2. If the distance between the parotid gland and the high dose PTV becomes larger and the lymph node region on the evaluated side is not included, the relative dose difference between the SIB and the SEQ becomes larger. If the distance is more than 2 cm this difference increases up to 20%.

Linear regression model

Results of the linear regression are shown in Table 4. In the univariate analysis most of the parameters are significant, but in the multivariate analysis only the distance between the parotid gland, boost PTV and the lymph node involved at the evaluated side remain predictive factors. The distance between the boost PTV and parotid gland is related to many of the parameters tested (N stage, T stage), therefore this multivariate result is to be expected.

Discussion

We studied the mean dose to the parotid gland in patients planned with a SIB and SEQ technique. We were able to identify a subgroup for which the SEQ technique was for almost every case a clinically superior plan: patients where the distance between the parotid gland and the PTV of the boost was larger than 2 cm. This was also true for patients where the distance was between 1 and 2 cm. However, the advantage (difference in mean dose to the parotid gland) was on average smaller.

The planned dose to the elective region was 46 Gy for the SEQ technique and 57.75 Gy for the SIB technique. The SEQ technique did, however, not always lead to a lower mean physical dose compared to the SIB technique. In our dataset we also had patients for whom the mean dose was lower with the SIB technique. No subgroups could be identified, however, for which the mean dose delivered by SIB was significantly lower. However, in cases where SEQ is not to be expected to be better than SIB, SIB is preferable because it gives lower workload and more conformal dose distributions.

Table 4
Results of linear regression. Outcome is difference (%) between SIB and SEQ technique in planned dose to the parotid gland (50 patients, 100 evaluated parotid glands). At multivariate analysis, "LN at evaluated side" is the only parameter that remains significant ($p < 0.05$) in a model together with the variable "PTV-parotid gland distance".

Variable	*B*	*p*
Univariate		
PTV-parotid gland distance	4.2	<0.0001
T stage	−3.0	0.004
N stage	−5.2	0.001
LN involved at evaluated side (L or R), yes versus no	−13.0	<0.0001
L3 involved at evaluated side	−6.5	0.067
L2 involved at evaluated side	−12.4	<0.0001
Volume parotid gland	−0.05	0.7
Multivariate		
PTV-parotid gland distance	3.2	<0.0001
LN at evaluated side	−6.1	0.04

B = regression coefficient.

In our analysis, we calculated mean parotid dose without adjusting for the delivered dose per fraction to the gland. Many authors report physical mean dose as the best predictor for a deteriorated production of saliva and for xerostomia complaints [9,10]. However, some authors do report different estimations of α/β ratios. Estimations found in the literature range from 3 Gy to 10 Gy. For instance, 9.6 Gy was reported by Franzen et al. and 4.5 Gy by Blanco et al. [3]. If we should take this into account, results will change since the SEQ scheme will differ from the SIB scheme with regard to the dose per fraction. When we adjust the mean dose to the parotid gland, the estimated differences between SIB and SEQ will become somewhat smaller, since the dose per fraction to the parotid gland will be higher during the first 5 weeks of treatment (and lower during the last 2 weeks of treatment). For example, if the mean physical dose to a parotid gland is 20 Gy with SIB and 18 Gy with SEQ, and it is assumed that 90% of the dose is given in the first 5 weeks and 10% in the last 2 weeks for the SEQ technique, the adjusted mean dose (using an α/β ratio of 9.6 Gy) becomes 17.6 Gy and 15.9 Gy, respectively. So the difference of 2 Gy (10% of 20 Gy) in physical dose becomes a difference of 1.7 Gy (9.7% of 17.6 Gy with SIB) in effective dose with an α/β ratio of 9.6 Gy. In case of an α/β ratio of 4.5 Gy, the adjusted difference is 1.5 Gy (9.6% of 15.6 Gy with SIB). So the results show a smaller difference in absolute values and a stable difference in relative values, for the SEQ technique. Therefore, the benefit of the SEQ technique would hold when fractionation and α/β ratios are taken into account. Based on the literature on this subject as a whole, we think, however that physical dose is the best measure to report here.

If the 57.75 Gy isodose line and the 46 Gy isodose line are not very close and the dose gradient is located partly in the gland, this leads to a benefit of the SEQ technique (Fig. 3). When we look at dose distributions around the parotid gland, when the boost PTV is close to the organ at risk, we notice that the dose gradient for the SIB technique is higher, which explains why SIB is not inferior to a SEQ technique, or even better (Fig. 3).

The advantage of the SIB technique is that the dose gradient around the boost PTV is higher. The advantage of the SEQ technique is that the (prescribed) dose around the boost PTV (in the elective region) is 46 Gy whereas it is 57.75 Gy for the SIB technique. The more the dose to the salivary gland is determined by the elective dose, the less likely it is that SIB offers an advantage for mean dose to the salivary gland The first effect, a higher dose gradient, is predominant in case the boost PTV and parotid gland are close, the second effect, the increased dose, has more effect with larger distances.

Another issue here is the shrinkage of the parotid gland. For a number of patients, it will shrink towards the high dose region. This implies that delivered dose to the parotid gland in the second half of the radiotherapy treatment will affect a relatively larger part of the gland. This negative effect has more impact in case of a SIB technique because in this scenario dose to the elective area is delivered throughout the whole treatment.

Parameters

The results show that in a significant number of head and neck cancer cases, one shouldn't just assume that a SIB technique is at least equivalent to a SEQ technique. Although this saves time and the treatment is easier, some patients are potentially at a disadvantage, especially patients with parotid glands further away from the boost PTV. The gain for the parotid gland dose is mainly seen in the range between 25 and 35 Gy (Fig. 1) Therefore, a strategic choice between SEQ and SIB is relevant to the clinical outcome and xerostomia risk. Larynx carcinoma patients staged T2-3N0 will in almost all cases benefit from a SEQ technique, since the primary tumour boost is located far away from the parotid glands. On the basis of the location of the boost (tumour location and lymph node level) it is possible to make a global estimation of the optimal technique choice. In our series four N0 larynx carcinoma patients had an improved dose distribution with the SEQ technique. The distance between boost PTV and parotid gland varied from 1.4 to 5.8 cm. The gain in terms of reduction of mean parotid dose was between 1.5 and 4.4 Gy in favour of the SEQ technique. For patients with oropharyngeal cancer it is more difficult to generalize about the optimal technique. Although it can be difficult to make the right choice between a SEQ or a SIB technique, there are parameters to guide which choice to make. A boost distance of more than 2 cm from a parotid gland is in almost every case beneficial for parotid gland sparing. In this case a sequentially delivered technique is the treatment of choice. In the cases where it is not clear, direct comparison of the two techniques for the individual patient before start of treatment will aid in the right choice.

Conclusion

Primary IMRT for head and neck cancer with a sequential delivered boost technique results in less dose to the parotid glands for most patients compared to simultaneous integrated boost IMRT technique if the high dose region is more than 1 cm away from the parotid gland.

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