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The impact of image guided radiotherapy in head and neck cancers: soft tissue changes, dosimetric consequences and adaptive radiotherapy

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THE IMPACT OF IMAGE GUIDED RADIOTHERAPY IN HEAD AND NECK CANCERS:

SOFT TISSUE CHANGES, DOSIMETRIC CONSEQUENCES AND ADAPTIVE RADIOTHERAPY

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List of abbreviations

95%CI	95% confidence interval
actSit	the actual situation on the day of replanning
adaptPlan	adapted radiotherapy plan
ART	adaptive radiotherapy
BMI	body mass index
BTV	boost target volume
cm	centimeters
CMD	cumulative median dose
CT	computed tomography
Dmax	maximum dose
Dmean	mean dose
Dmin	minimum dose
DVH	dose volume histogram
fx	fraction
GEE	generalized estimation equation approach
Gy	Gray
H&N	head and neck cancer
HT	helical tomotherapy
IGRT	image guided radiotherapy
IMRT	intensity modulated radiotherapy

inPlan	initial plan
kVCT	kilo-voltage computer tomography
Lx	larynx
mm	millimeters
MVCT	mega-voltage computer tomography
OAR	organs at risk
OC	oral cavity
PCT	planning computer tomography
PG	parotid gland
PTV	planning target volume
ROI	regions of interest
SC	spinal cord
SIB	simultaneous integrated boost
Vol<1Gy	volumes that were irradiated with less that 1.0 Gy per fraction
Vol>1.6Gy	volumes that were irradiated with more that 1.6 Gy per fraction

1. INTRODUCTION

Science may set limits to knowledge, but should not set limits to imagination.

Bertrand Russell

1.1 Head and Neck Tumors

The term head and neck cancer refers to a group of biologically similar cancers originating from the upper aerodigestive tract, including the lip, oral cavity, nasal cavity, paranasal sinuses, pharynx, and larynx. Clinical management of head and neck cancer is complex due to the multiple sites within the head and neck region, diagnosis, prognosis, treatment and its effects on quality of life.

1.1.1 Incidence and mortality

Squamous cell carcinoma of the head and neck remains a significant cause of morbidity and mortality, with approximately 540 000 new cases annually worldwide and 271 000 deaths per year [22] . Figure 1 offers an overview on the incidence and mortality for both sexes for all cancers and ages in Germany, in absolute numbers.

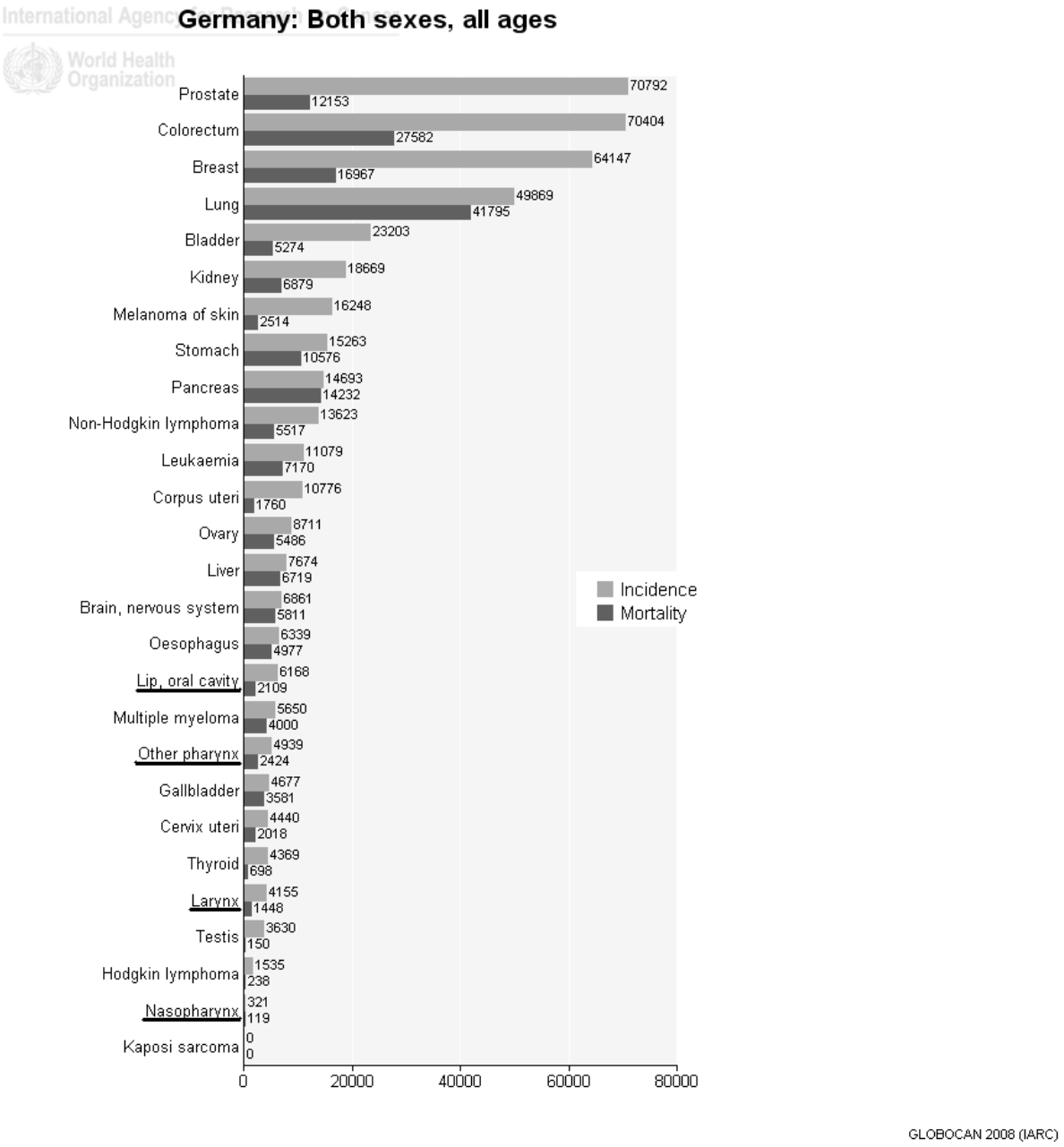


Figure 1. Incidence and mortality for both sexes for all cancers and ages in Germany, in absolute numbers.
Local incidence data and national mortality data from GLOBOCAN [23]: incidence was estimated by using incidence mortality ratios derived from recorded data in country-specific cancer registries; mortality rates are projected to 2008.
Underlined are the head and neck cases. When compared for e.g. with prostate cancer, it is obvious, that even if the incidence is significantly lower, the ratio of incidence to mortality in head and neck cancers is very poor. One of every four to one of every two patients diagnosed with head and neck tumors will probably die from the disease.

1.1.2 Histopathology and TNM Classification

Histologically about 90% of the H&N cancers are squamous cell carcinomas. Other types include adenocarcinoma, melanoma, lymphoma, sarcoma.

Squamous cell carcinoma originates from the mucosal epithelium of the head and neck. It arises from a premalignant progenitor followed by outgrowth of clonal populations. Cumulative genetic alterations and phenotypic progression lead to invasive malignancy.

Squamous cell head and neck cancer is currently graded according to morphological patterns: well-differentiated, moderately well-differentiated, and poorly differentiated. Patients with poorly differentiated tumors have a worse prognosis than those with well-differentiated tumors. However, this classification is frequently ineffective in predicting the biological behavior of these cancers, and therefore, molecular characteristics such as gene expression profiles could be considered as alternative classification approaches. Molecular studies and genomic arrays indicate that this cancer is a heterogeneous disease with complex molecular abnormalities; the genetic alterations result in inactivation of multiple tumor suppressor genes and activation of proto-oncogenes, including p16ink4A, p53, cyclin D1, p14ARF, FHIT, RASSF1A, epidermal growth factor receptor (EGFR), and Rb.

Further, head and neck cancers are staged according to size and site of the primary tumor (T), number and size of metastases to the cervical lymph nodes (N), and evidence of distant metastases (M). The classification is based either on clinical and radiological features (cTNM) or on the histopathological examination of the resected tumor (pTNM).

However the head and neck region comprises a variety of anatomic sites: tumors arising from the skin, nasal cavity and paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, salivary glands, soft-tissue tumors, bone sarcomas, and miscellaneous tumors such as neurogenic tumors and paragangliomas are all generically included in the head and neck region. More importantly, these tumors have diverse clinical behavior and outcomes. It is therefore literally impossible to generate a uniform staging system that would be relevant for all tumors arising in the

head and neck region. Therefore specific TNM classifications are available for H&N sub-sites. The subsequent classification is only a rough categorization of most H&N cancers.

TNM classification valid for a large part of head and neck tumors:

T:

- T1 ≤ 2 cm in greatest dimension;
- T2 = 2–4 cm or affects 2 areas within a specific site;
- T3 > 4 cm or affects 3 areas within a specific site;
- T4 = invades specific structures (4a is resectable and 4b is unresectable)

N:

- N0 = none;
- N1 = one node ≤ 3 cm;
- N2 = node between 3 and 6 cm or multiple nodes;
- N3 = node > 6 cm.

M:

- M0 = none;
- M1 = present.

Staging of cancer is the most important predictor of survival, and cancer treatment is primarily determined by staging. Table 1 illustrates the staging used in head and neck cancers.

Table 1.Staging of head and neck cancers

Stage	Tumor (Maximum Penetration)	Regional Lymph Node Metastasis	Distant Metastasis
I	T1	N0	M0
II	T2	N0	M0
III	T3 or	N0	M0
	T1-3	N1	M0
IVA	T1-3	N2	M0
	T4a	N0-2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

A further important classification used in head and neck cancers is the lymph nodes' level classification. The level system is used for describing the location of lymph nodes (important for

radiological staging, surgical dissection and radiation therapy treatment volumes delineations) (Figure2).

In 2003 and 2006 the major cooperative groups from Europe (DAHANCA, EORTC and GORTEC) and in North America (NCIC and RTOG) provided guidelines for defining lymph node levels for radiotherapeutic treatment in the node negative and in the node positive neck [27-28]. Briefly, level I encompasses the submental and submandibular lymphnodes; level II includes the upper jugular; level III, the middle jugular and level IV the lower jugular lymph nodes; Level V, posterior triangle group and Level VI, the anterior compartment.

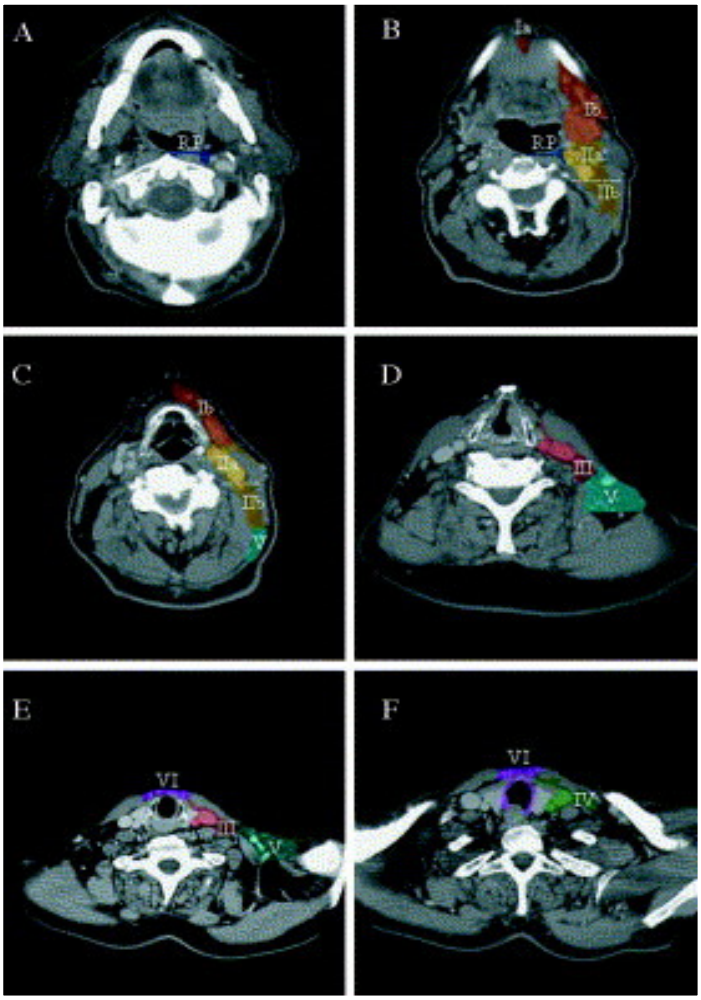


Figure 2. Lymph nodes levels as proposed by Gregoire et. al [28, 27]
Level I, submental and submandibular group; Level II, upper jugular group; Level III, middle jugular group; Level IV, lower jugular group; Level V, posterior triangle group; Level VI, anterior compartment

1.2 Therapy in Head and Neck Tumors

Improvements in diagnosis and local management, as well as in targeted therapies, have led to improvements in quality of life and survival for head and neck cancer patients. With appropriate treatment, 5-year survival can be as high as 90% for stage I, 75% to 80% for stage II, 45% to 75% for stage III, and up to 40% for stage IV [3] .

A phase III trial from the UK published in the late nineties demonstrated the benefit of a multidisciplinary approach. 350 T2 to T4 N0 to N2 oral cavity or oropharynx cancer patients were randomized to either receive surgery and postoperative irradiation or irradiation alone. The trial was closed early, as a significant difference in favor of the combined treatment arm was noted at 23 month for overall survival, cause-specific survival, and local control [55] .

More recently, two randomized trials (the EORTC 22391 and the RTOG 9501/ Intergroup) demonstrated the benefit of radiochemotherapy versus radiotherapy alone in high risk squamous cell carcinoma for the head and neck. However the combined treatment was associated with an increase in adverse effects [6, 15] .

Subsequently a short overview of treatment options of head and neck cancers by site.

1.2.1 Hypopharyngeal Cancers

Except for very early stage (T1) cancers of this region, treatment has primarily been surgery followed with postoperative radiation therapy. Some early stage (T1 and T2), low-volume, exophytic pyriform sinus carcinomas have been successfully treated with radiation alone . 26, 43, 50] Single-modality therapy of advanced-stage hypopharyngeal cancer, with either surgery or radiation therapy has resulted in consistently poor survival [4, 26, 35, 45].

Combined-modality (operation and radiotherapy or definitive combined radiochemotherapy) treatment should be considered for patients who present with stage III or stage IV disease [32, 36, 62]. Patients with stage III and stage IV cancer should be considered for a larynx preservation approach [4, 30, 37, 42, 45, 50].

1.2.2 Lip and Oral Cavity Cancer

Depending on the site and extent of the primary tumor and the status of the lymph nodes, the treatment of lip and oral cavity cancer may be by surgery alone, radiation therapy alone, or a combination of these. Surgery (wide local excision with or without neck dissection) is a common treatment for all stages of lip and oral cavity cancers. Early cancers (stage I and II) are highly curable by surgery or radiation therapy. Most patients with advanced cancers (stage III and IV) are candidates for treatment by a combination of surgery and (chemo)radiotherapy ; patients with small T3 lesions , no regional lymph node and no distant metastases or patients with lymph nodes no larger than 2 cm, may be treated by radiation alone or by surgery alone [4, 30, 45].

1.2.3 Oropharyngeal Cancer

On attempting to define the optimal therapeutic approach to the oropharynx, it becomes clear that no single therapeutic regimen offers a clear-cut superior survival over other regimens [4, 30, 45]. The results of 6400 patients concerning local control, local-regional control, 5-year absolute survival, 5-year cause specific survival were similar for patients who underwent surgery +/- RT or RT +/- neck dissection. Nonetheless severe or fatal treatment complications are significantly greater for the surgery+/- RT group[52]. For stage I and II surgery or radiation are equally successful in controlling the cancer. Radiation may be the preferred modality where the functional deficit will be great, such as the base of tongue or tonsil, as shown in the RTOG-9003 trial, for example [46]. Surgery may be the preferred modality where the functional deficit will be minimal, such as the tonsil pillar. The stage 3 of the tonsil cancer can be treated by radiation therapy alone [46]. Hyperfractionated radiation therapy yields a higher control rate than standard fractionated radiation therapy for patients with stage III cancer of the Oropharynx [33], but this has not resulted in an increase in overall survival [8]. A combination of surgery with postoperative radiation therapy or postoperative chemoradiation for selected high-risk patients [6, 17, 51, 59, 65].

For stage 4 resectable oropharyngeal cancer management is complex and requires multidisciplinary input to establish the optimal treatment.: a combination of surgery with postoperative radiation therapy

plus chemotherapy in high-risk patients[65], radiation therapy alone for patients with stage IVA cancer of the tonsil that does not deeply invade the tongue base[46, 44].

For stage 4 unresectable oropharyngeal cancer radiation therapy or chemoradiation therapy is mandatory [6, 17, 51].

1.2.4 Nasopharyngeal Cancer

Despite being potentially curable at an early stage, more than 50% of patients who have nasopharyngeal carcinoma present with advanced locoregional disease, which results in high rate of mortality [4, 30, 45].

Nasopharyngeal carcinoma is divided pathologically into three types: Type 1 or keratinizing squamous cell cancer; Type 2 or nonkeratinizing carcinoma; and type 3 or undifferentiated carcinoma. The presence of keratin has been associated with reduced local control and survival. The standard of care for patients with nasopharyngeal carcinoma staged T1-4 N2-3 M0 is cisplatin-based concurrent chemoradiation [4, 30, 45, 49]. Surgery is usually reserved for nodes that fail to regress after radiation therapy or for nodes that reappear following clinical complete response.

1.3 Radiotherapy Techniques

1.3.1 Treatment planning

Starting with the nineties intensity modulated radiotherapy (IMRT) found its way slowly into clinical routine.

As for 3D-CRT intensity modulated radiotherapy planning is based on a computer tomography of the region of interest of the patient. Before starting the treatment, the patient undergoes a CT scanning. The region that should be treated (Figure 3) and the normal tissue that should be spared (organs at risk – OAR) are contoured on this CT.

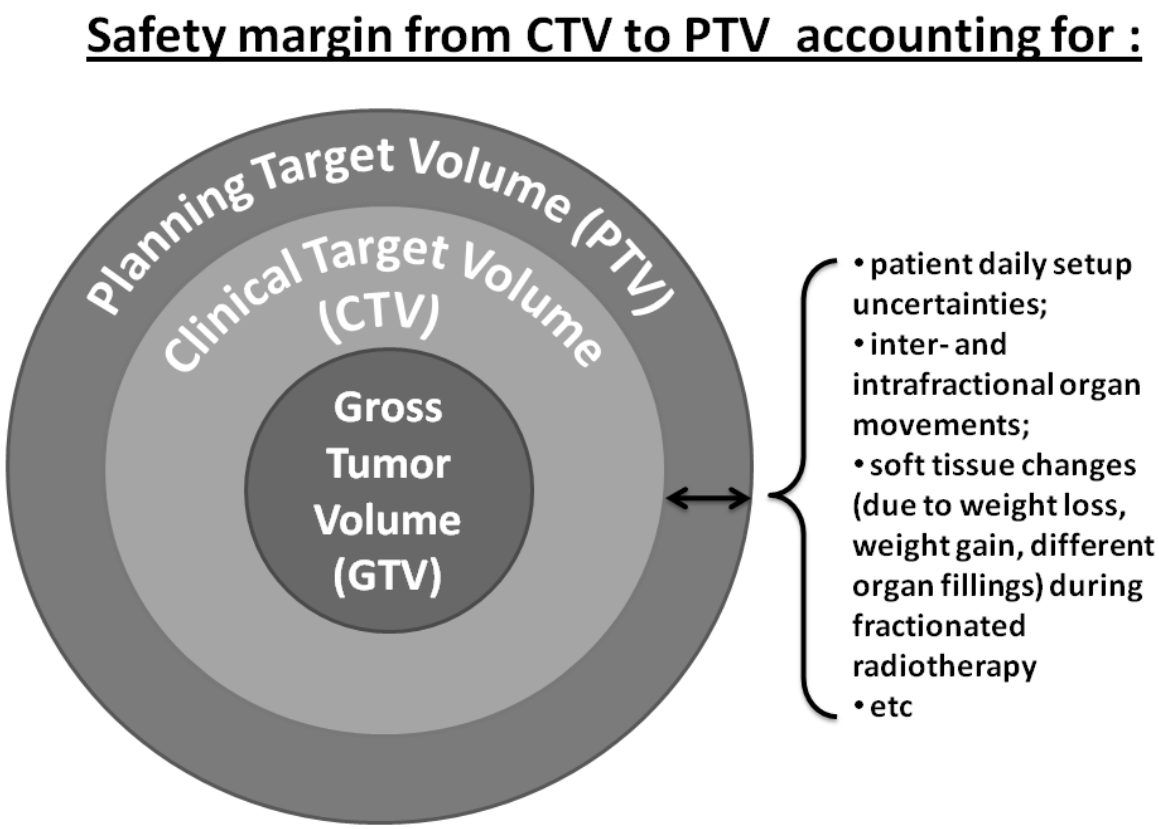
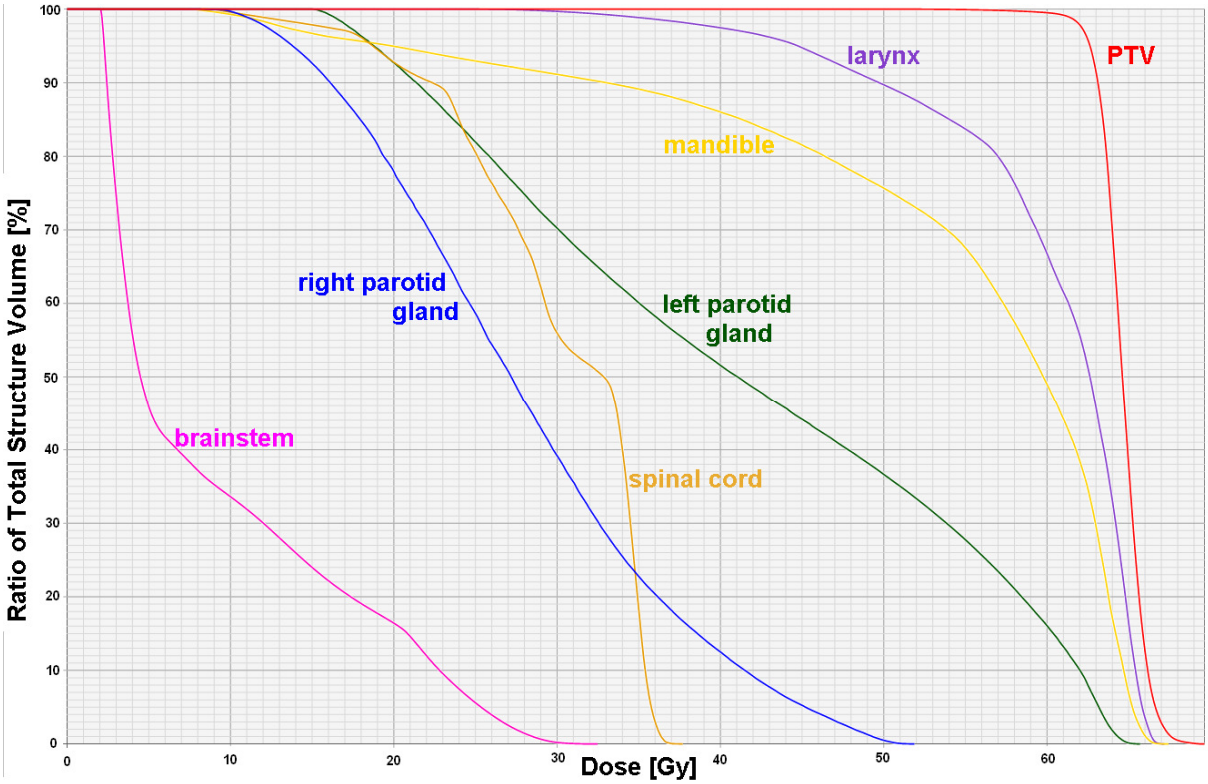


Figure 3. GTV, CTV and PTV concept according to the ICRU
The Gross Tumor Volume (GTV) is the visible tumor - for e.g. there is one GTV for the primary tumor and one GTV for each of the pathological lymph nodes. The Clinical Target Volume (CTV) is a tissue volume that contains the subclinical microscopic malignant disease. The Planning Target Volume (PTV) is a geometrical concept, and it is defined to select appropriate beam size and beam arrangements, taking into consideration the net effect off all possible geometrical variations and inaccuracies in order to ensure that the prescribed dose is actually absorbed in the CTV.

Afterwards a calculation of dose is performed, so that the prescribed radiation dose is delivered to the planning target volume and the normal organs are irradiated as little as possible.

In 3D-CRT treatment planning, the physicist defines the gantry angles and the size of the radiation fields. The radiation treatment planning computer calculates the dose to every organ for the defined gantry angles and the given radiation field size. This is depicted in a dose-volume histograms (DVH) (Figure 4).

Figure 4. Dose-volume histograms (DVHs) for a head and neck case



In contrast to conventional planning (i.e. 3D-CRT planning) in IMRT a so-called „inverse radiation treatment planning" is performed. In this process in a first step the physician defines dose constraints. These are dose limitations to the organs at risk (OARs) and the planning target volumes (PTVs). The planning system will try to match the DVH parameters to the constraints given. The process is an active one, during which the computer tries to further improve the solution previously found. Therefore it is still problematical to define a guideline for optimal DVH constraints to be taken into

account when doing the inverse planning and much is still dependent on the clinicians and physicists experience.

Another important innovation is that IMRT uses treatment beams of varying intensity. This is in contrast to the uniform doses within each 3D-CRT beam. Each IMRT radiation field is subdivided and the amount of radiation delivered to each of these subdivisions varies. There are several ways of delivering IMRT. Tomotherapy is one of them. As the name already states, the delivery of the radiation is done in slices ("tomos "= Greek for slice), whereas the radiation is delivered by a slit beam in a manner analogous to a helical CT scanner. The beam intensity is varied by interposing the leaves of the collimator in or out of the radiation beam path as the gantry rotates around the patient. The complete treatment is accomplished by delivering adjoining axial slices (Figure 5). Typically, tens of thousands of beamlets are included in a treatment fraction. A beamlet corresponds to the radiation emitted through a single open MLC leaf, with the gantry at any given angle during rotation.

The width of the fan-beam projected to the axis is 40 cm, and the maximum length the couch can transport the patient is 160 cm.

Tomotherapy can be integrated with mega voltage computer tomographies (MVCT), permitting image-guided radiotherapy (IGRT). By performing a CT before delivering radiation (image-guidance) radiation oncologists ensure that the patient is correctly aligned for radiation (setup correction). The mega voltage image of tomotherapy is completed in a manner analogous to a helical CT scanner. After the MVCT image is acquired and reconstructed, it is registered with the kV CT image to determine corrections to the patient's position in the lateral, longitudinal, vertical and roll direction. For the automatic registration the algorithm can be chosen by bone anatomy, bone and tissue anatomy or full image registration. The system allows applying manual shifts to the set-up after automatic registration. An automatic and manual couch shift to the indicated position by the matching of the CTs is done before applying the treatment.

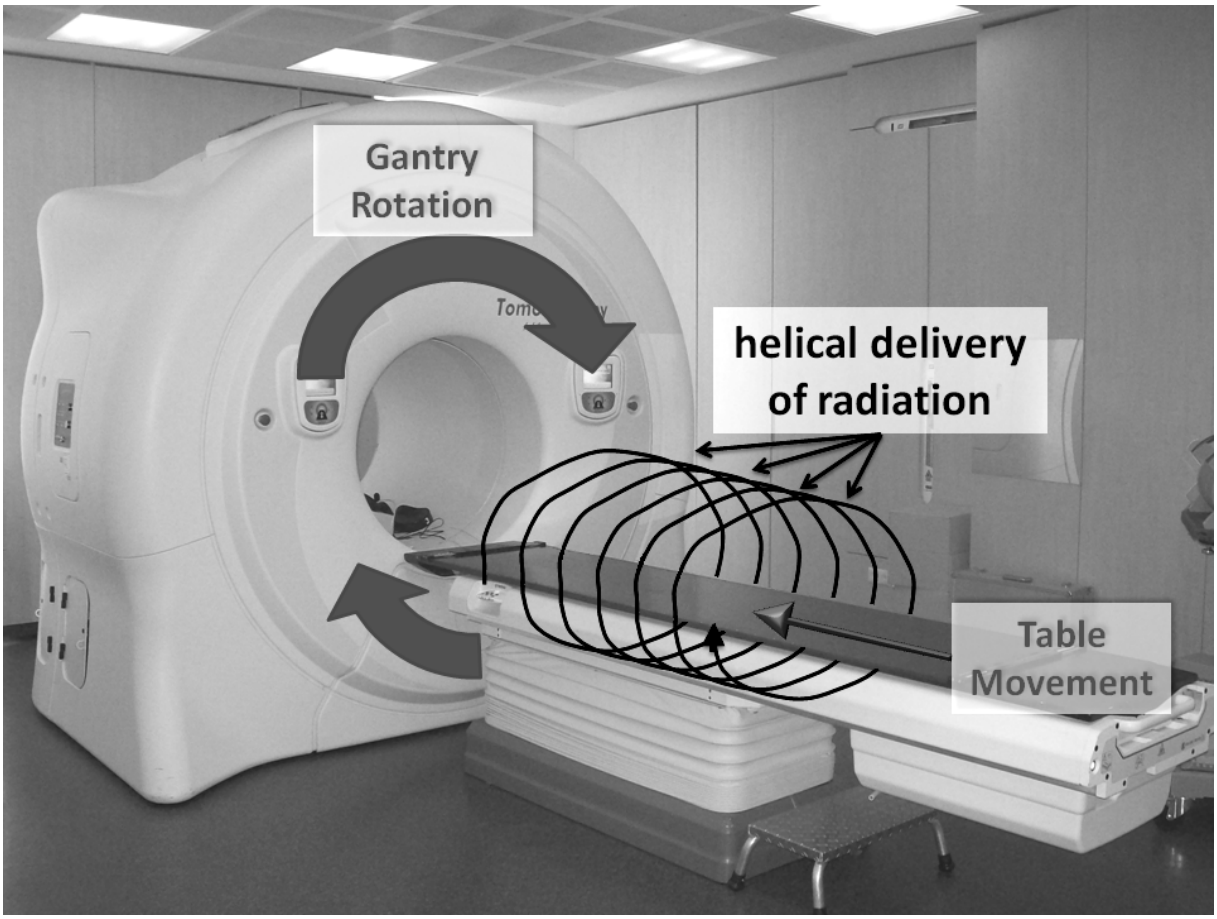


Figure 5. Helical IMRT exemplified for TomoTherapy
As the ring gantry rotates in simultaneous motion to the couch, helical fan-beam IMRT is continuously delivered from all angles around the patient

1.4 Setup uncertainties in relationship to delivered dose to the planning target volume and organs at risk

The setup uncertainties analyzed up to date can be roughly divided in data from bone alignment and data from soft tissue alignment. As the latter is more exact and this thesis is focused on patients treated with tomotherapy, we will present only data on CT matched setup uncertainties for tomotherapy [55].

Due to very complex registration programs assessment and correction of setup errors can be made nowadays for translational and rotational errors (Figure 6).

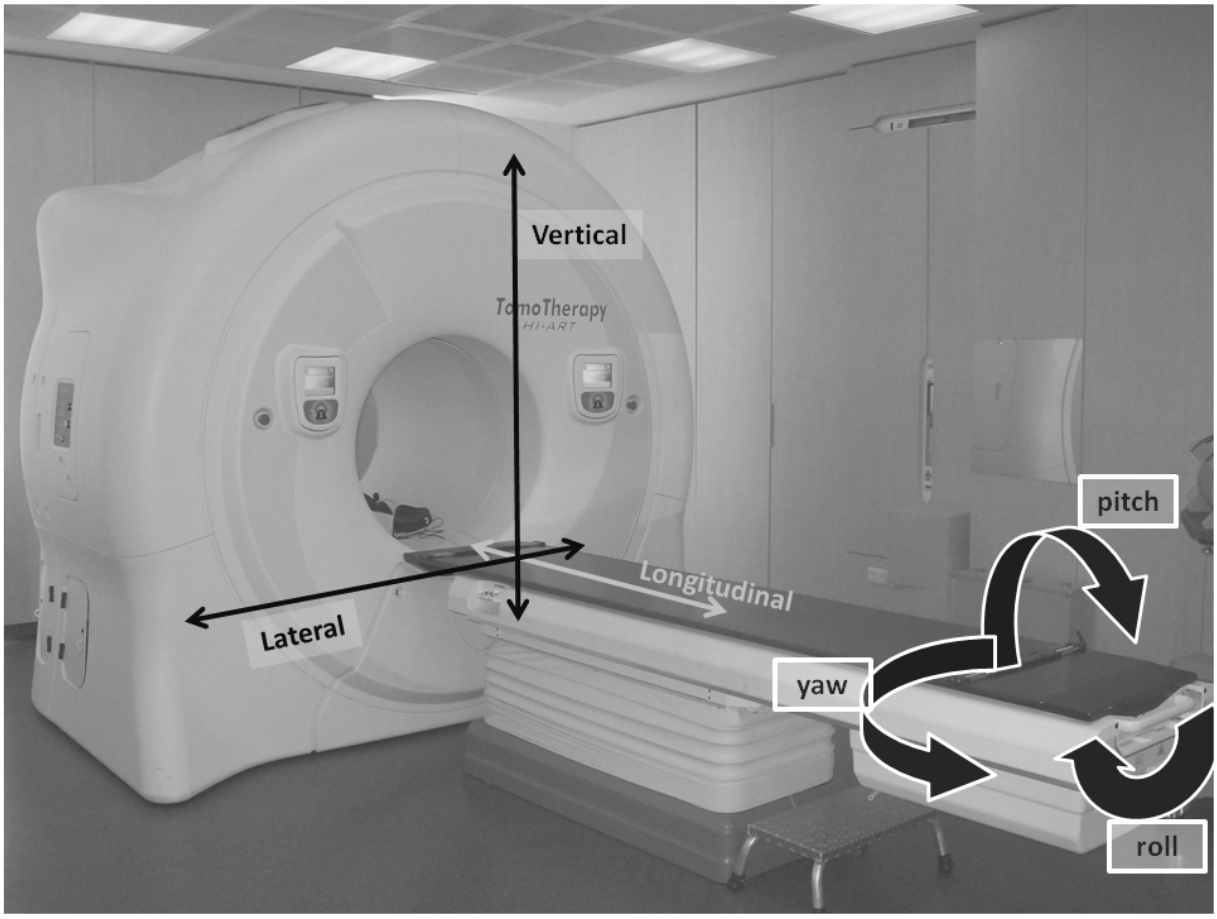


Figure 6. Translational (lateral, longitudinal and vertical) and rotational (roll, pitch, yaw) setup directions exemplified for tomotherapy.
The directions of the shifts are documented by plus or minus before the absolute values.
Lateral: (+) left, (-) right; longitudinal: (+) cranial, (-) caudal; vertical: (+) anterior, (-) posterior; roll: (+) clockwise, (-) anti-clockwise.

A comprehensive assessment is available on translational and rotational setup corrections, based on registration of daily MVCT to planning CT images for 1,179 brain and head and neck (H&N), 1,414 lung, and 1,274 prostate treatment fractions.

Table 2 depicts the setup errors for the different sites [55].

Table 2. Results of setup error analysis showing patient-to-patient variations in systematic errors and magnitudes of random errors [55]

	Variation in systematic errors				Magnitude of random errors			
	Lateral (mm)	**Longitudinal (mm)**	**Vertical (mm)**	**Roll (°)**	**Lateral (mm)**	**Longitudinal (mm)**	**Vertical (mm)**	**Roll (°)**
Brain	1.8	2.6	2.1	0.8	1.8	1.7	2.0	0.9
H&N	2.3	1.9	1.6	0.8	1.8	1.9	1.9	1.2
Lung	4.3	5.2	5.2	0.7	3.9	6.1	5.9	1.0
Prostate	3.7	3.6	7.2	0.5	3.2	4.7	4.4	0.5

Abbreviation: **H&N - head and neck**

The data above are similar to other published studies. It should also be mentioned that the setup errors slightly differ depending on the mask system used or on the anatomical sub-regions the fusion was performed to (i.e. matching to the mandible, larynx, jugular notch, occiput bone, vertebrae C1-C3, C3-C5, and C5-C7, and the vertebrae caudal of C7) [20, 38, 66, 68].

In general the setup errors for H&N cases are small (within less than 5 mm in all studies) however the impact of these in IMRT plans could be important. The first studies which assessed the impact of setup uncertainties on the dose to the PTV and OARs for IMRT considered only the planning CT and shifted the isocenter [27, 39, 52, 60].

However, it is known that anatomical changes occur in almost all head and neck cancer (H&N) patients throughout the radiation therapy treatment course due to tumor shrinkage, body weight loss and soft tissue changes [37-39, 41, 47].

It is therefore obvious that the information on impact of setup uncertainties on dose is incomplete without taking the soft tissue changes occurring during fractionated radiotherapy into account.

1.5 Tolerance doses, soft tissue changes, actual delivered dose and adaptive radiotherapy (ART)

One of the best studied organs at risk in H&N radiotherapy is the parotid gland, as xerostomia is a very important late toxicity. It has various secondary effects. These include impairment of taste, mastication, swallowing, speech and sleep patterns. Furthermore, a reduction in saliva leads to diminished protection of the oral cavity against injuries to both, hard and soft tissues, alters microbial flora to a more pathogenic type, precipitates a dry ulcerated painful mucosa and affects the wearing of oral prostheses.

It is widely acknowledged that fully irradiated parotid glands receiving doses higher than 60 Gy undergo permanent salivary damage without recovery of function. It has also been confirmed that salivary flow is dramatically reduced in patients whose parotid glands receive doses of 30–50 Gy [13, 19, 40, 65]. The dose that can be delivered to the parotid glands and permits recovery of the salivary function is still under research. Data like those of Eisbruch et al. have shown a recovery of salivary function in most of the cases after mean parotid gland doses of 26 Gy in the initial plan [19].

Nevertheless, with the introduction of repeated CTs throughout the treatment course, the volumetric changes of the parotid glands during fractionated radiation therapy have become available for assessment for the first time. Significant volumetric shrinkage with increase in delivered dose was described [5, 25, 35, 53, 67].

Thus, the known tolerance data is flawed. Firstly because the dose-function relationship analyzed up to date is based on the initial DVHs of the planning CT scan. Secondly, as previously stated, interfractional setup uncertainties occur when no daily IGRT is performed and might have a further impact on the actual delivered dose to the parotid glands.

Regarding the gross tumor volume (GTV), CTV or PTV similar data are available. Tumor shrinkage occurs in almost all H&N cases during fractionated radiotherapy with an impact on the actual delivered dose to the PTV [5, 7, 25, 53].

Most studies concluded that replanning should be taken into consideration during the course of fractionated intensity modulated radiotherapy in order to maintain adequate PTV coverage and sparing of OARs.

Adaptive radiotherapy (ART) is the umbrella term given to repeated recalculations of treatment plans during fractionated radiotherapy adapted to the morphological changes that occur. There are several ways (some already commercial available, some available only as research tools) of performing adaptive radiotherapy:

1. offline ART: the adaptation/recontouring of the PTV and OARs and the recalculation of a new treatment plan is performed between treatment sessions.
2. online ART: the adaptation/recontouring of the PTV and OARs and the recalculation of a new treatment plan is performed "online", with the patient lying on the treatment table.

The second way to perform ART is still under intensive technical research in order to find the best software that would allow such quick changes of radiation treatment plans.

Even so, the optimal time when replanning should be performed and the exact dosimetric gain of adaptive radiotherapy (ART) is still not well defined [25, 72]. Furthermore, almost no data are available for H&N patients on the gain of routine adaptive radiotherapy triggered by anatomical changes observed on the daily setup CT during the course of radiotherapy [64].

2. PURPOSE

The scientist is not a person who gives the right answers; he's one who asks the right questions.

Claude Lévi-Strauss

The questions that were to be answered by this thesis were:

1. Can we trust the tolerance data known up to date?

   In particular to:

   a. quantify the soft tissue changes of the organs at risk (i.e. parotid glands) occurring during fractionated radiotherapy;
   b. quantify the impact of soft tissue changes on the delivered dose;
   c. assess whether the extreme scenario of complete lack of any IGRT during radiotherapy has a significantly different effect on the delivered dose to the parotid glands than daily IGRT.

2. Is adaptive radiotherapy (ART) the answer for organs at risk sparing and better planning target coverage in head and neck IMRT (i.e. helical tomotherapy)?

   In particular to:

   a. quantify how many of the head and neck patients undergo significant soft tissue changes on the daily mega-voltage setup CTs
   b. quantify the dosimetric benefit of ART for PTV and OAR for these patients
   c. assess whether soft tissue changes can be predicted.

3. WHAT IS THE IMPACT OF DAILY IMAGE GUIDANCE IN HEAD AND NECK THERAPY?

The most exciting phrase to hear in science, the one that heralds new discoveries, is not 'Eureka!' (I found it!) but,That's funny ...'

Isaac Asimov

3.1 Material and Methods

3.1.1 Patients Characteristics

We analyzed a group of ten head and neck cancer patients that were treated with helical TomoTherapy for head and neck cancers from October 2007 to June 2008 at our institution. Two patients received definitive radiotherapy and eight patients underwent postoperative, concomitant platinum based chemo-radiotherapy (Table 3).

3.1.2 Treatment planning and delivery

Each patient underwent a planning kVCT scan (PCT) before treatment (Siemens Somatom, Siemens Inc., Erlangen, Germany) with an axial slice thickness of 3 mm. A two layer thermoplastic head and shoulder mask (BrainLAB AG, Feldkirchen, Germany) was used for immobilization. The contouring of the PTV and the OARs was performed on the on the Oncentra MasterPlan (Nucletron B.V., Veenendaal, The Netherlands). The PTV for all patients encompassed the primary tumor region and the bilateral lymph node levels, including the supraclavicular lymph nodes. For postoperatively treated patients, the high risk PTV (boost target volume - BTV) comprised the former tumor site and involved lymph nodes. For definitively treated patients, the BTV was defined as the tumor region and involved lymph nodes.

Table 3. Patients' characteristics and target volumes dose prescriptions.

Patient no.	Age	Tumor Localization	TNM	Definitive/ adjuvant treatment	PTV Total Dose/ Dose per fraction (Gy)	PTV Number of fractions	BTV Cumulative Dose/ Dose per fraction (Gy)	BTV Number of fractions
1	57	Nasopharynx	cT2 cN2c cM0	definitive	50 / 2	25	70/2	10
2	43	Nasopharynx	cT1 cN1 cM0	definitive	50 / 2	30	70/2	10
3	40	Soft palate	pT2(m) pN2c cM0	adjuvant	50 / 2	30	64/2	7
4	67	Palate	pT4a pN2a cM0	adjuvant	50 / 2	25	64/2	7
5	59	Soft palate	pT1is pN2a cM0	adjuvant	50 / 2	30	64/2	7
6	54	Tonsil	pT3 pN1 cM0	adjuvant	50 / 2	25	64/2	7
7	55	Tonsil	pT3 pN1 cM0	adjuvant	50 / 2	25	64/2	7
8	50	Tonsil	pT1 pN1c M0	adjuvant	50 / 2	30	64/2	7
9	46	Tonsil	pT2 pN2a cM0	adjuvant	50 / 2	25	64/2	7
10	63	Tonsil	pT2a pN2a cM0	adjuvant	50 / 2	25	64/2	7

All patients were treated five times per week, with daily fractions of 2 Gy. Table 3 summarizes the patients' characteristics and target volumes dose prescriptions.

The treatment planning was carried out with the TomoTherapy treatment planning system (TomoTherapy Inc., Madison, WI, USA).

The medial part of the parotid glands and the PTV overlapped in all our patients. The dose prescription was set to the median of the PTV. The median dose constraints for the parotid glands were set at 25 Gy or less. The primary objective of the TomoTherapy dose optimization process was to achieve the best possible PTV coverage. Further, plan optimization was carried out in order to spare the lateral part of the parotid glands. The treatment process at the helical TomoTherapy treatment system was previously described [69].

3.1.3 Assessment of treatment setup errors and dose variations to the organs at risk

For the setup phase all patients were initially positioned guided by the mask/skin marks as accurate as possible and as if no daily image guidance would be done to optimize the setup. Daily pretreatment MVCTs were performed during the entire treatment. After acquisition and reconstruction, the MVCTs were automatically registered to the planning kVCT, by choosing the bone and tissue algorithm provided by TomoTherapy. To account for the best positioning of the patient, every automatic registration was corrected by staff members before treatment. The setup errors in the lateral (x), longitudinal (y), vertical (z) direction and roll rotations were documented (see Chapter 1.4.,Figure 6).

In our clinical practice only the translational errors and the roll are corrected before treatment. The translational errors are corrected by couch travels; the roll rotation is corrected by gantry movements. We do not perform a correction of the pitch or yaw as our TomoTherapy couch does not allow rotations.

The absolute values and the direction (minus and plus for translational and rotational errors) of the setup errors were recorded (Figure 6). In order to assess the reproducibility of patient setup, periodical examinations of the applied setup were performed by the physician in charge. Registration uncertainties, which have been shown to be generally less than 1 mm for a head-and-neck phantom, have not been taken into account when analyzing the setup uncertainties [7].

To determine a three dimensional vector (V) for the setup error, we used the following equation:

$$V=\sqrt{x^2+y^2+z^2} \quad (1)$$

where x, y and z are the previously mentioned errors in the lateral (x), longitudinal (y) and vertical (z) direction.

To reduce dimension of complexity within this analysis, every fifth fraction (1, 6, 11, 16, 21, and 25) out of the total number of 25 fractions for the PTV was considered for investigation.

Two scenarios were evaluated. The first scenario (IGRT-scenario) analyzed the actual delivered dose to the parotid glands with daily MVCT setup correction beforehand. A second scenario (non IGRT-scenario) was assessed for the same fractions in order to evaluate the impact of the lack of MVCT setup, including the implications of anatomical changes on the dose to the parotid gland. The setup correction by MVCT was reset for the analyzed fraction, as if no image guidance setup correction had been performed. The contouring of the regions of interest and the assessment of dose variations was carried out using the PlannedAdaptive® software (TomoTherapy Inc., Madison, WI, USA). The software automatically generates a duplication of the original structure set from the planning CT and rigidly transposes the structure set on the MVCT taking the setup correction performed during daily IGRT into account.

The regions of interest were thus recontoured by adapting the duplicated original planning CT contours, having the planning CT with the original contour as guidance (rigidly registered to the MVCT). Each parotid gland was recontoured separately on the corresponding MVCT for each fraction and each scenario.

To account for biases in contouring by interobserver variability, the parotid glands were all delineated by the same physician (M.N.D.). The actual delivered dose (IGRT-scenario) and the dose without image guidance (non-IGRT-scenario) for the parotid glands were recalculated for every analyzed MVCT and DVH data for the contoured structures was extracted. The dose calculation process on the MVCT has been described elsewhere [69].

The median dose, the overall volume and the volume that received less than 1 Gy per fraction, (Vol<1Gy) and more than 1.6 Gy per fraction (Vol>1.6Gy) for each fraction and each scenario were assessed separately (Figure 7). These doses were chosen considering reported parotid gland TD50 with an endpoint of stimulated saliva flow rates reduced to $\leq$ 25% of the pre-radiation therapy rate. The TD50 is the tolerance dose of an organ with a risk of 50% at 5 years for a given late toxicity to occur. 1 Gy per fraction e.g. a total dose of 25 Gy for all the 25 fractions is regarded as a dose where the chance of reduction of saliva flow is low, whereas a dose of 1.6 Gy per fraction e.g. 40 Gy for 25 fractions is considered to be associated with a high risk of saliva flow reduction [13, 19, 21, 56, 58]. For each scenario, the cumulative median doses of the parotid glands (CMD) dose were calculated as the sum of the median doses of each analyzed fraction. Therefore for each patient a CMD for the IGRT-scenario and a CMD for the non-IGRT-scenario was calculated.

Weight and body mass index (BMI) were assessed once a week for all patients.

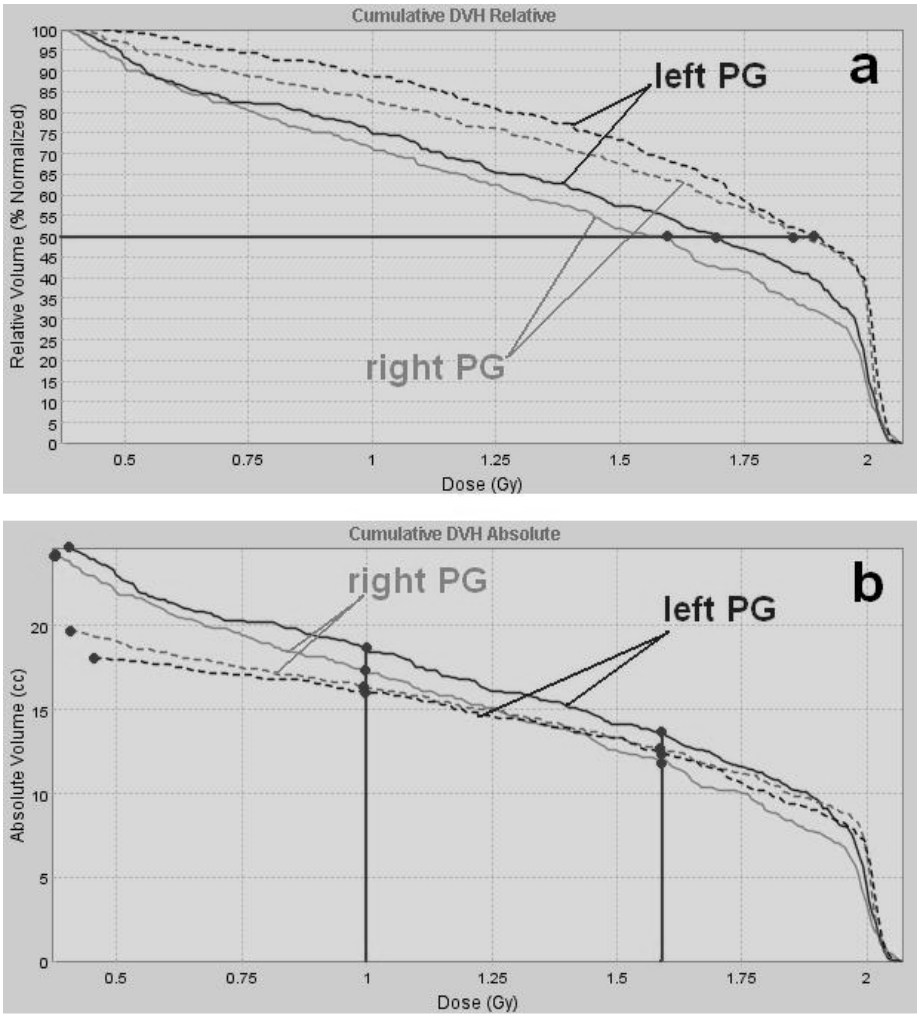


Figure 7. Relative and absloute DVHs of the parotid glands

Figure 7. a - relative DVH; Figure 7. b - absolute DVH of the parotid glands. Points on the DVH correspond to the analyzed values: in a. the median value; in b. the 1 Gy and 1.6 Gy volumes, as well as the absolute volumes. Solid lines – DVHs on the planning CT. Dashed Lines – recalculated DVHs on the MVCT

3.1.4 Statistical analyses

The statistical analyses were performed using SPSS Software for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were performed two-sided and a p-value <0.05 was considered to indicate statistical significance. No correction of alpha-error level was conducted within the course of multiple tests performed during data analysis.

The setup direction (plus or minus) was taken into account when evaluating the patient setup systematic error. The overall absolute values in each direction as well the three dimensional setup errors were also assessed.

To ensure representativeness and comparability of the fractions 1, 6, 11, 16, 21 and 25 to the remaining ones (2-5, 7-10, 12-15, 17-20, 22-24), the mean differences in setup displacements were reported with 95% confidence intervals (95%CI) from the generalized estimation equation (GEE) approach. The GEE approach reflects the structure of repeated data and takes correlation of measurements within the same subject into account.

The GEE approach was also applied to investigate the changes of cumulative median doses in a linear regression model framework. The cumulative median dose to the parotid glands was used to assess the differences in dose between the IGRT-scenario and non-IGRT-scenario and was compared to the expected cumulative median doses from the planning CT. The same approach was used to assess the changes of Vol<1Gy and Vol>1.6Gy of the parotid glands.

The effects of potential confounding , random or explanatory variables such as fraction, parotid volume, parotid side (left or right) and BMI change on the cumulative median doses, Vol<1Gy and Vol>1.6Gy were considered in the GEE model and estimates were reported with 95%CI.

3.2 Results

3.2.1 Setup uncertainties during fractionated radiotherapy

The absolute overall setup errors in all the analyzed directions as well as the absolute setup vector in space are presented in Table 4.

Table 4. Overall set up-error displacement

Parameter	Mean	95% CI
Lateral (mm)	1.8	(1.4 to 2.3)
Longitudinal (mm)	2.0	(1.4 to 2.6)
Vertical (mm)	1.9	(1.3 to 2.6)
Roll (°)	0.6	(0.3 to 0.8)
3D vector (mm)	4.1	(3.1 to 5.0)

Assessment of set-up errors when setup direction error was taken into account, revealed no statistically significant differences to the zero-position for longitudinal (mean difference: -0.09 mm; 95%CI: -1.0 to 0.95; p=0.85) and vertical (0.11 mm; 95%CI: -0.83 to 1.01; p=0.82) direction. Nevertheless, a minor deviation from zero was observed in the lateral direction (mean difference: -0.75 mm; 95%CI: -1.5 to -0.08, p=0.029), indicating a small systematic setup error with a mean shift of 0.75 mm to the right for the non-IGRT-scenario. Further, with a mean difference of 0.55° (95%CI: 0.26 to 0.83) the roll was significantly shifted from zero (p<0.001), indicating a small systematic error around the longitudinal axis with a mean rotation of 0.55° clockwise for the non-IGRT-scenario.

The comparison of setup errors of the evaluated fractions (1, 6, 11, 16, 21, 25) to the not evaluated fractions showed a minor mean absolute difference in vertical position of 0.91mm (95%CI: 0.28 to 1.53; p=0.005). The mean difference of the analyzed fractions to the not evaluated fractions was 0.02° (95%CI: -0.34 to 0.08; p=0.274). The mean differences in the lateral and longitudinal direction were less than 0.22 mm and were statistically not significant (p=0.47 and p=0.69, respectively) (Figure 8).

These data indicate that the evaluated fractions were representative for the whole treatment with regard to the setup accuracy.

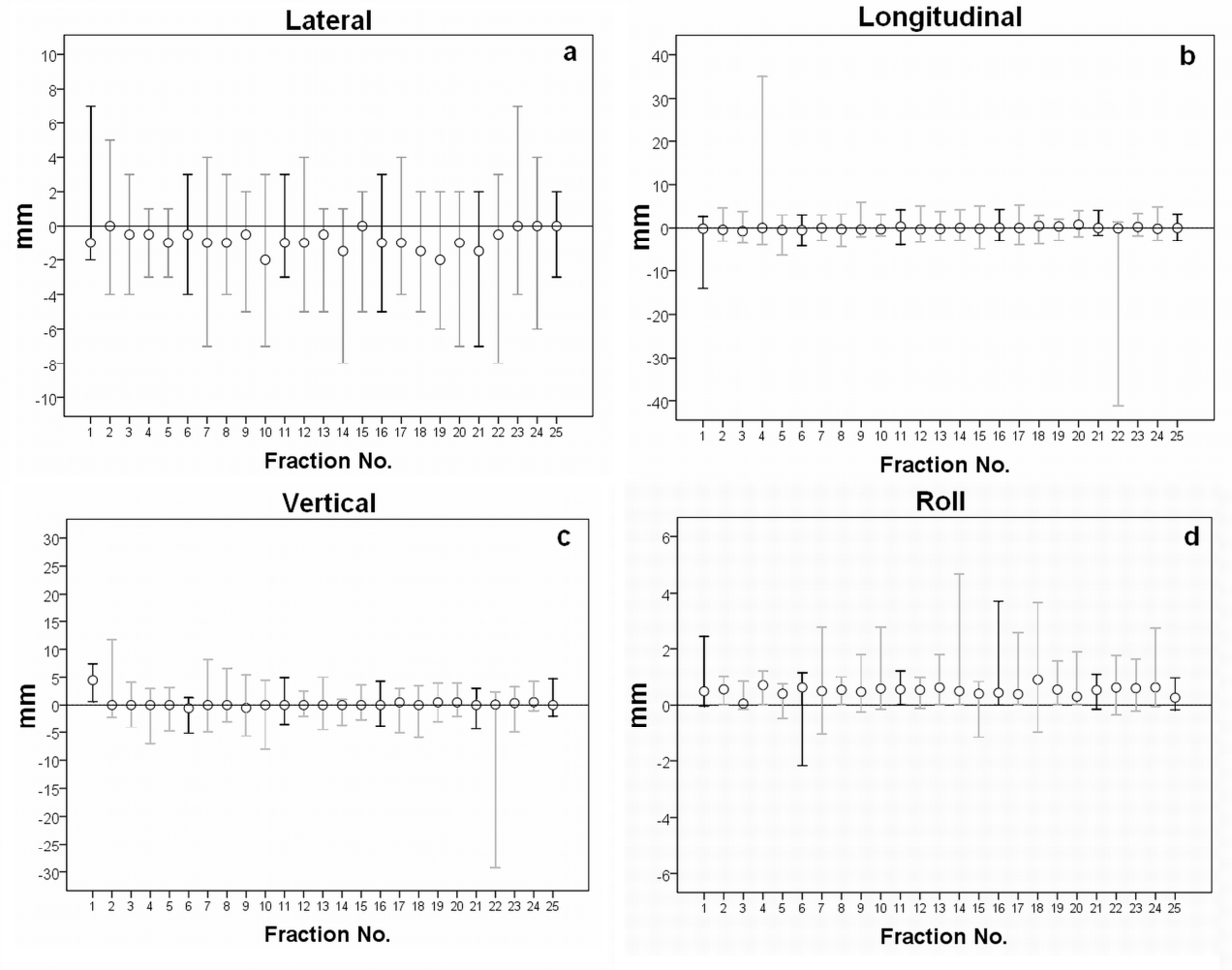


Figure 8. Overall setup errors for the 25 fractions
Depicted are the median setup errors with 95% intervals of the central data distribution in millimeters for the lateral (a), longitudinal (b), vertical (c) directions and in degrees for the roll rotation (d).

3.2.2 Soft tissue changes during fractionated radiotherapy

The mean weight and BMI loss at 50 Gy was: -5.1 kg and -1.85 kg/m^2 for females, and -5.4 kg and -1.7 kg/m^2, for males. A decrease of the volume of the parotid glands and a shifting into the PTV was observed in all patients. Overall, the mean decrease of the parotid gland volume was estimated to be -0.13 cm^3 per day (Figure 9). There was no considerable difference in volume decrease between the left and the right parotid gland (p=0.462). No significant association between the BMI and the change of volume (p=0.105) was noted.

We observed a significant association between the decrease of the parotid gland volumes and increasing number of fractions ($p<0.001$).

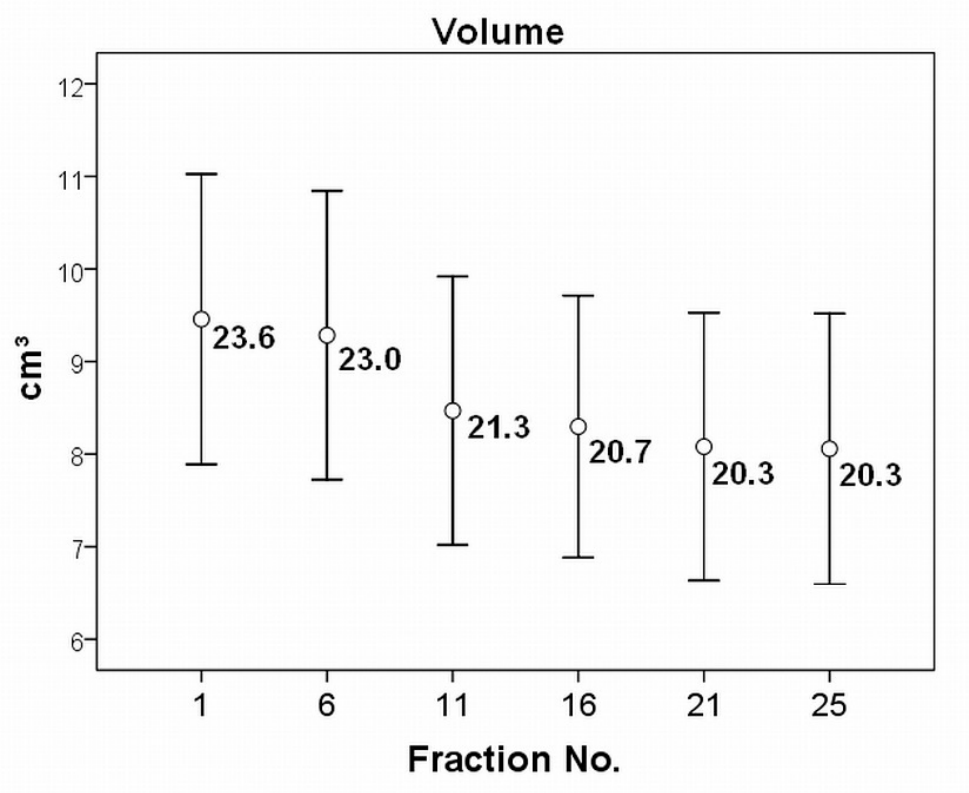


Figure 9 . Absolute volume changes of the parotid glands throughout the treatment course for the analyzed fractions
Depicted are the 95% confidence intervals with the mean absolute volume (in cm^3) for all patients. The most prominent changes of volume occur in the first 3 weeks of radiotherapy (fraction 1 to fraction 16).

3.2.3 Delivered doses to parotid glands: IGRT vs. non-IGRT

In the multivariable GEE-regression analysis adjusted for fraction number, side (right vs. left) and parotid gland volume, significantly lower values of the volumes that were irradiated with less that 1.0 Gy per fraction (Vol<1Gy) were detected for the IGRT-scenario compared to the planning CT (mean difference: 1.36 cm^3; 95%CI: 0.44 to 2.28; p=0.004), as well as for the non-IGRT-scenario as compared to the planning CT (mean difference: 1.35 cm^3; 95%CI: 0.44 to 2.25; p=0.003).

No significant difference was observed when comparing the Vol<1Gy in the IGRT-scenario to the non-IGRT-scenario (mean difference: -0.02 cm^3; 95%CI: -0.22 to 0.19; p=0.896).

A significant decrease of Vol<1 Gy was noted with increasing fraction number (p<0.001).

Similar associations were noted for the volumes that were irradiated with more that 1.6 Gy per fraction (Vol>1.6Gy). There was a significant increase of the Vol>1.6 Gy in both scenarios when compared with the Vol>1.6Gy on the planning CT. For the IGRT-scenario the mean increase as compared to the planning CT was of 1.14 cm^3 (95%CI: 0.25 to 2.02; p=0.01); for the non-IGRT-scenario the mean increase was of 1.16 cm^3 (95%CI: 0.327 to 1.991; p=0.006).

There was no significant difference between the two scenarios regarding Vol>1.6Gy changes (mean difference: -0.02 cm^3; 95%CI: -0.23 to 0.17; p=0.855). A significant increase of Vol>1.6Gy with fraction number was noted (p<0.001).

A large initial parotid gland volume predicted for a large decrease of the Vol<1Gy (p=0.002) and for a large increase of the Vol>1.6Gy (p<0.001) with increasing fraction number.

There was a significantly higher cumulative median dose for the analyzed IGRT-scenario than for the initial predicted cumulative dose (mean difference: 1.13 Gy; 95%CI: 0.67 to 1.59; p<0.001), as well as for the non-IGRT-scenario (mean difference: 0.96 Gy; 95%CI: 0.57 to 1.36; p<0.001). No statistically significant difference was detectable between IGRT and non-IGRT cumulative median doses (mean difference 0.17 Gy; 95%CI: 0.03 to 0.36; p=0.095) (Figure 10).

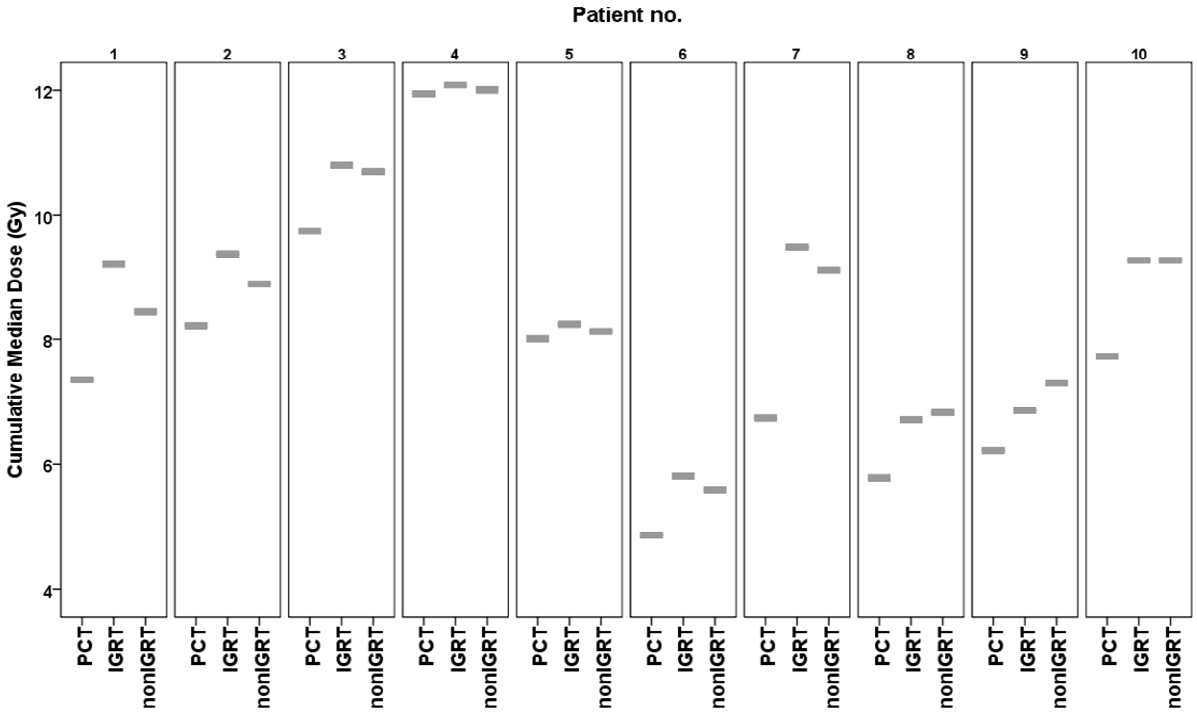


Figure 10. Absolute values of cumulative median doses for each patient (columns) and each scenario
The first bar in each column is the expected absolute value of the cumulative median dose by analyzing the planning kVCT DVH data (PCT).
The second bar depicts the actual delivered cumulative median doses for the IGRT-scenario (IGRT) and the third bar depicts the CMD that would have been delivered without image guidance (non-IGRT).

3.3 Discussion

IMRT provides a higher conformality in dose distributions. As the dose fall-off to the normal tissue is steep in IMRT plans, the accuracy of the daily setup of patients is essential. This is especially important in the head and neck patients, where many sensitive structures lie in the proximity of the PTV and a substantial setup uncertainty might lead to a significant overdosage of the organs at risk. In addition, morphological changes occur in almost all H&N patients throughout radiation therapy due to tumor shrinkage, body weight loss and soft tissue changes. Wang et al. associated weight loss with setup errors [68]. Therefore surveillance of setup uncertainties and anatomical changes, with their implications on dose distribution throughout the treatment course seems to be fundamental.

3.3.1 Setup errors

The overall magnitude of the 3D-vector of our study was of 4 mm, which is within the known setup uncertainties of 2 to 5 mm of head and neck immobilization masks used in radiation therapy [25, 29, 35, 63]. Further, our data are within the previously reported setup errors of head and neck tomotherapy ranging from 1 mm to 3 mm for the translational errors and from 0.8° to 1.5° for the roll rotation[57, 61].

There was no statistical difference in the vertical and longitudinal direction to the zero position; therefore no systematic errors in the positioning of the patient were present in those directions. Nevertheless, a slight overall systematic setup error seemed to be present in the lateral direction and roll rotation, but in both cases the mean displacements were small, of approximately 1 mm and of 0.5°, respectively.

When comparing the setup errors for the analyzed fractions (1,6,11,16,21,25) to the other fractions (2-5, 7-10, 12-15, 17-20, 22-24) no significant difference was found, except a minor mean absolute difference in the vertical position of less than 1 mm. Because of the similarity of the analyzed fraction setup and the overall setup of the patient, the presented results should be a good approximation of the overall implication of setup on actual delivered dose.

3.3.2 Volumetric changes of the parotid glands

The calculated overall parotid volume decrease was of 0.13 cm³/day. Other studies show a change in the volume of the parotid gland s of 0.19-0.21 cm³/day [5, 11, 31, 54].

Barker et al. [5] assessed 14 patients. Eligible patients had to have a pathologic diagnosis of head-and-neck cancer, be treated with definitive external beam RT, and had have gross primary and/or cervical nodal disease measuring at least 4 cm in maximal diameter. Barker et al. found shrinkage of parotid glands of median 0.19 cm³/day and an inner shifting (median, 3.1 mm; range, 0-9.9 mm). The medial displacement of the parotid glands correlated highly with the weight loss that occurred during treatment.

Robar et al. [54] assessed 15 head and neck cancer patients. The parotid glands showed a medial translation of 0.85 mm/week, and glands shrank by 4.9%/week.

Castadot et al. [11] assessed 10 patients. The parotid glands were redelineated during treatment by deformable image registration. The ipsilateral and contralateral parotid glands showed a mean decrease of 0.9% and 1.0% per treatment day, respectively.

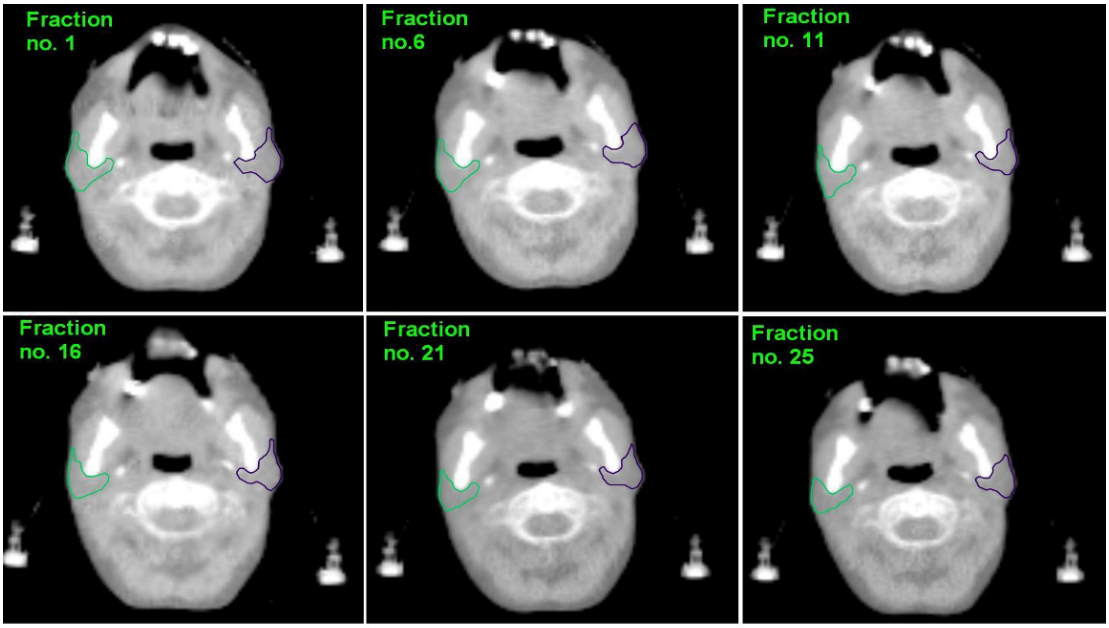
In our patient group, the mean weight and BMI loss at 50 Gy was: -5.1 kg and -1.85 kg/m² for the female and -5.4 kg and -1.7 kg/m² for the male patients. No significant association between the change of volume of the parotid glands and the changes of the BMI could be demonstrated. Probably the effect of weight loss is more important in patients above a certain weight loss threshold as stated by Lee et al.[41], which was not reached by the analyzed patients in our group. Thus, it is not entirely ruled out that the overall changes in the body weight of a patient might play a role in trying to predict the shrinkage of the parotid gland volume, but probably further factors should be taken into account.

Our study disclosed a significant association of the volume decrease with increasing number of fractions. Therefore events that take place during radiation in the parotid glands, like an immediate death of the serous cells, might play a role in parotid gland shrinkage [38, 47, 67]. This is consistent with other reports.

Vasquez Osorio et al. [67] reported a significant difference in the volume reduction, shape and position changes between the non irradiated major salivary glands and the irradiated glands in patients treated unilaterally. The study showed that irradiated and spared parotid glands had a volume loss of 17 ± 7% and 5 ± 4%, respectively. The authors concluded that the planned mean dose was significantly related to the parotid gland volume reduction.

3.3.3 Dosimetric implications of parotid glands shrinkage

The volume shrinkage and the shift of the parotid glands into the PTV led to a decrease of the absolute low-dose parotid gland volume (Vol<1Gy) and an increase of the absolute high-dose parotid gland volume (Vol>1.6Gy) with increasing fraction number. These changes in dose volume parameter over time are independent of the use IGRT for setup correction (Figure 10). An overall higher initial parotid gland volume was associated with a higher decrease of the low-dose parotid gland volume and a larger increase of the high-dose parotid gland volume. Therefore patients with higher initial volumes of the parotid glands might be candidates for repeated CTs during the treatment course and adaptive planning. Further, our study disclosed that the parotid glands typically shrink in the first 3 weeks of treatment (Figure 9). Combined with the knowledge that larger parotid glands shrink more, further studies are necessary to evaluate whether adaptive planning in the third week of treatment is helpful in reducing the dose to the parotid glands while maintaining adequate PTV coverage.



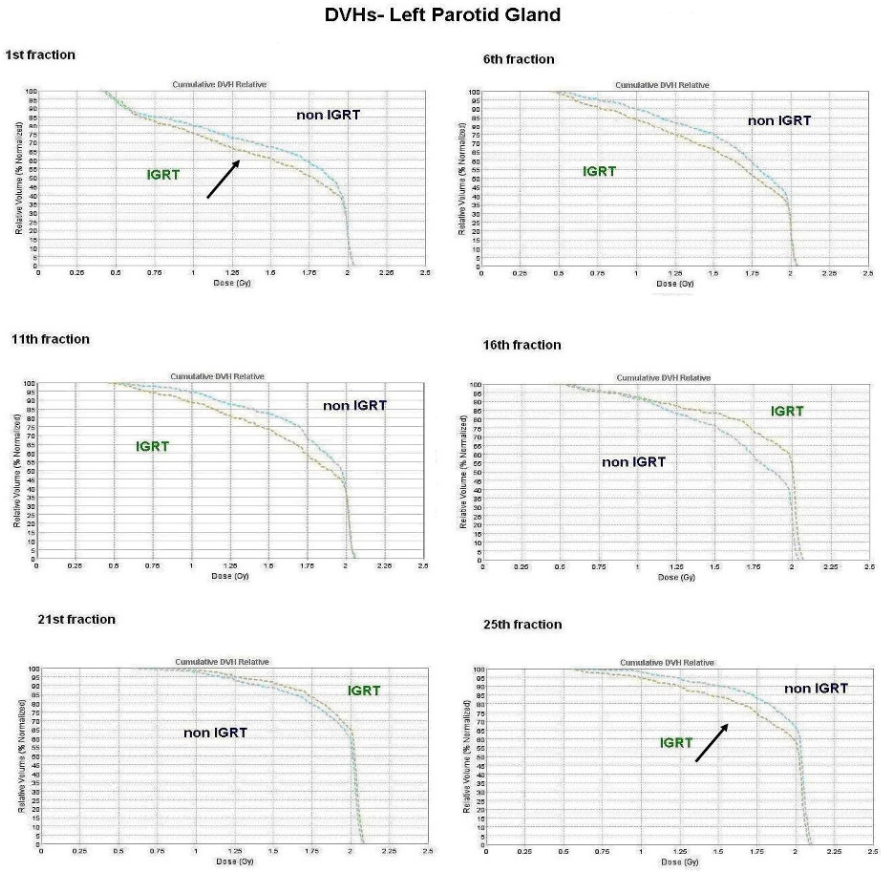


Figure 11. Parotid gland changes over time for patient no. 3 and the implication of these changes on the DVHs of the left parotid gland (PG) for both scenarios
The upper left panel contains the parotid glands for the 1st fraction, followed by the 6th, 11th, 16th, 21st and 25th fraction in the low right panel.
Below, the DVH data for the IGRT and non-IGRT-scenario. Shown are the DVH for the 1st (left upper panel), 6th, 11th , 16th, 21st and 25th fraction (right lower panel). The pronounced deterioration of the DVH (arrow) correlates with the shrinkage of the parotid gland.

3.3.4 Implications of daily image guided radiotherapy on the delivered dose to the parotid glands

Information regarding the implication of CT guided setup on the dose to the parotid glands is scarce. A paper from O'Daniel et al. [48] reviewed the question whether planned and delivered dose to the parotid glands was different if radioopaque markers alignment or bone alignment by CT were used. Eleven definitive treated patients were recruited in the O'Daniel's study. The radioopaque markers were used to align the patients for treatment. A simulated bone alignment by CT, based on the position of the second cervical vertebra was used solely for data analysis. Different radiotherapy techniques, based on the physician's clinical judgment, were used: either comprehensive nodal IMRT or a split field technique (the tumor and the upper neck were treated with IMRT; the lower neck was treated with an anterio-posterior supraclavicular field), followed by mid-neck boosts and electron boosts, if necessary. The authors concluded that daily bone alignment reduced the parotid dose compared with radioopaque markers alignment.

A comparison to our data is difficult due to several reasons. Most patients in our study are postoperative treated patients with a symmetrical change of soft tissue. The implications of asymmetrical soft tissue changes on the patient setup inside the immobilization mask and thus on the position of the parotid glands with regard to the PTV in the study of O'Daniel are expected to be different from the implications of symmetrical soft tissue changes we observed in our study. Further, all patients in our study were treated with daily IGRT by MVCT beforehand. For image registration bone and soft tissue information was used, whereas the O'Daniel study used only bone alignment for the IGRT-scenario.

In our study, the mentioned parotid gland volume shrinkage led to an increase of the mean cumulative median dose for 6 fractions of 1.13 Gy for the IGRT-scenario and of 0.96 Gy for the non-IGRT-scenario. There was no statistical significant difference between the two scenarios. One explanation might be that the random errors of the analyzed group of patients of approximately 2 millimeter are too small in comparison to the dose gradients of 4 mm (95% isodose to the 80% isodose) and of almost 30 mm (80% isodose to the 20% isodose) in our TomoTherapy plans. However, setup

verification and correction should be systematically performed in H&N IMRT, as the magnitude of setup errors, the exact OAR localization and the PTV coverage are interrelated and not all of them are taken into account in the present study.

Nevertheless all the data published up to date regarding the correlation of parotid gland dose and preservation of function, are based on the initial DVH of the planning CT [14, 19, 24, 43, 66]. Setup uncertainties and soft tissue changes during fractionated radiotherapy were not taken into account. Even if the setup uncertainties do not seem to play a crucial role as demonstrated by our study, the parotid glands received higher doses than predicted by the planning CT DVH data due to anatomical changes during the course of treatment. As it is known that H&N patients undergo soft tissue changes during fractionated radiotherapy, the actual tolerance dose of the parotid glands could be higher than expected by analyzing only the planning DVH data. We therefore believe that the actual tolerance doses of these organs should be established and taken into account when delivering IGRT. In our opinion IGRT should be also used as a tool for assessing soft tissue changes and establishing thresholds for adapting radiotherapy plans when the actual tolerance doses during radiotherapy is reached.

4. WHAT IS THE IMPACT OF ADAPTIVE RADIOTHERAPY?

All science is either physics or stamp collecting.
Ernest Rutherford

4.1 Material an Methods

4.1.1 Patients characteristics

Since April 2008 we routinely carried out adaptive radiotherapy [ART] (see also Chapter 1.5) based on the MVCT during the course of helical tomotherapy [HT] (TomoTherapy Inc., Madison, WI, USA). Adaptive radiotherapy was initiated when the daily MVCT showed substantial morphological changes that precluded precise image fusion with the planning kVCT or when the immobilization devices (masks) became loose (Figure 12).

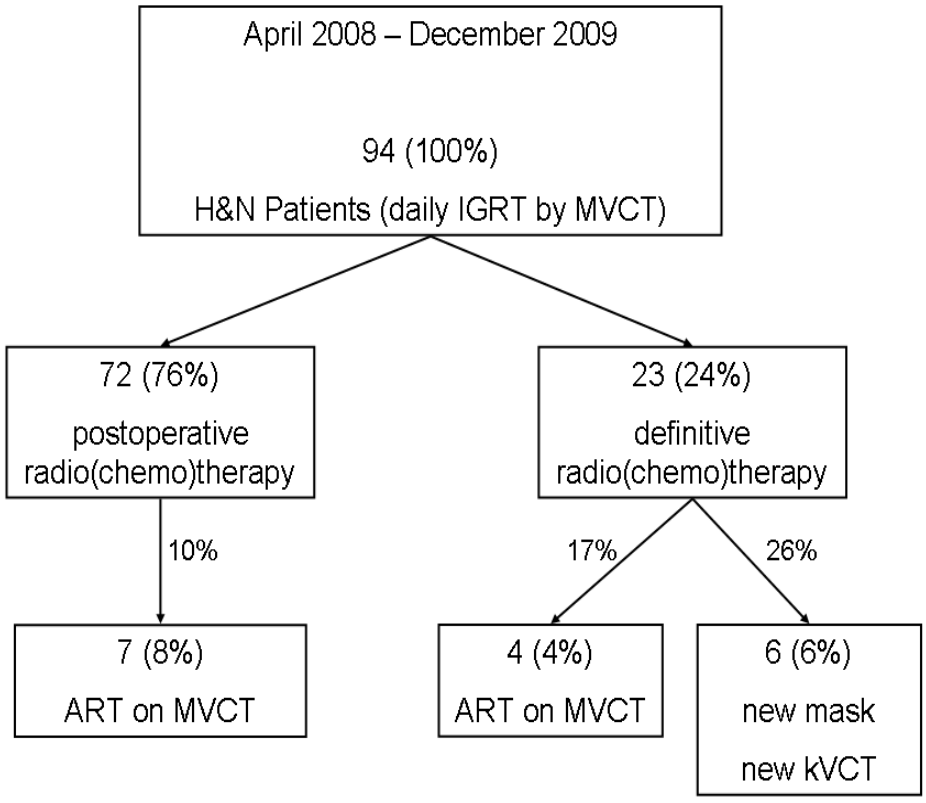


Figure 12. Head and neck patient cohort treated with tomotherapy between April 2008 and December 2009
Seventeen out of 94 H&N patients treated with TomoTherapy from April 2008 to December 2009 received ART. Six patients underwent a complete replanning with modeling of a new head and shoulder mask and a new planning kVCT. They are not the subject of this thesis. Eleven patients underwent replanning based on the MVCT.

We routinely performed ART for H&N patients either when : 1.) a change is clinically revealed by inspection or palpation and the mask is loose or 2.) the IGRT-CT shows a soft tissue change >0.5 cm (overall change in the body diameter >1cm) (Figure 13) .

Before starting with routine adaptive radiotherapy we performed some retrospective analyses by recalculating the actual delivered doses on the MVCT. If the soft tissue changes were only slightly visible (e.g. 2 to 4 mm) the changes in delivered doses were not considered relevant and the routine workload would have been huge for minimal expected benefits. We therefore proposed an internal guideline of a soft tissue change >0.5 cm at one side for replanning.

We do not present data on the patients that underwent adaptive radiotherapy on a new planning kVCT because of a loose mask. Several papers are available on this topic [10, 31, 70]. We focus on patients with less obvious soft tissue changes, which were difficult to recognize without IGRT: patients with a tight mask for whom ART was initiated exclusively by a soft tissue shrinkage noted on the MVCT– i.e. who would not have had an adaptive replanning if IGRT would not have been performed.

4.1.2 Treatment planning and delivery

The patient treatment planning was previously described (Chapter 3.1.2). The contouring of the PTV and the OARs was performed on the iPlan Net system (BrainLAB AG, Feldkirchen, Germany).Table 5 summarizes the ART patients' characteristics and the dose prescription to the PTV and boost target volume. All patients were treated five times per week. All patients except one (patient no.7) received concomitant platinum based chemo-radiotherapy (day 1-5, 29-33). The objective of the dose optimization process was to deliver the prescribed dose to the median of the PTV and boost target volume. The treatment process at the HT treatment system was previously described (see also Chapter 3.1.3) [69].

Patient No.	Age	Tumor Localization	TNM	Definitive/ adjuvant treatment	PTV Total Dose / Dose per fraction (Gy)	PTV Number of fractions	BTV Cumulative Dose/ Dose per fraction (Gy)	BTV Number of fractions
1	62	Oropharynx	pT3 pN2b(2/67) cM0 G3 R1	adjuvant	50 / 2	25	64 / 2	7
2	57	Oropharynx	pT2 pN2b (3/20) cM0 G2 R0	adjuvant	54 / 1.8	30	64.2 / 2.14	30 (SIB)
3	42	Oropharynx	pT1 pN1 (1/13) cM0 G3 R0	adjuvant	54 / 1.8	30	64.2 / 2.14	30 (SIB)
4	50	Nasopharynx	cT2 cN3b cM0 G4	definitive	50 / 2	25	70/2	10
5	57	Oropharynx	pT1 pN3 (1/26) cM0 G3 R0	adjuvant	54 / 1.8	30	64.2 / 2.14	30 (SIB)
6	63	Hypopharynx	pT4a pN2a (1/54) cM0 G2 R0	adjuvant	50 / 2	25	64 / 2	7
7	69	Oral Cavity	cT3 cN2b cM0 G2	definitive	50 / 2	25	70 / 2	10
8	55	Oropharynx	pT2 pN2b (2/15) cM0 G3 R0	adjuvant	54 / 1.8	30	64.2 / 2.14	30 (SIB)
9	77	Oropharynx	cT4 cN2c cM0 G2	definitive	50 / 2	25	70 / 2	10
10	66	Hypopharynx	pT2 pN3 (1/31) cM0 R0	adjuvant	50 / 2	25	60 / 2	5
11	45	Nasopharynx	cT1 cN2b cM0	definitive	54.4 / 1.7	33	70.4 / 2.2	33 (SIB)

Table 5. Patients' characteristics and target volumes dose prescriptions for the patients that underwent ART on the MVCT.

The patient numbering was performed alphabetical, not chronological.

PTV-planning target volume, BTV-boost target volume, SIB-simultaneous integrated boost

4.1.3 Soft tissue changes, dose variations to the organs at risk and initiation of adaptive radiotherapy on the MVCT

Adaptive radiotherapy on the MVCT was initiated when the daily setup MVCT showed a difference >0.5 cm in the body contours (Figure 13) and the patient still had more than two weeks of treatment.

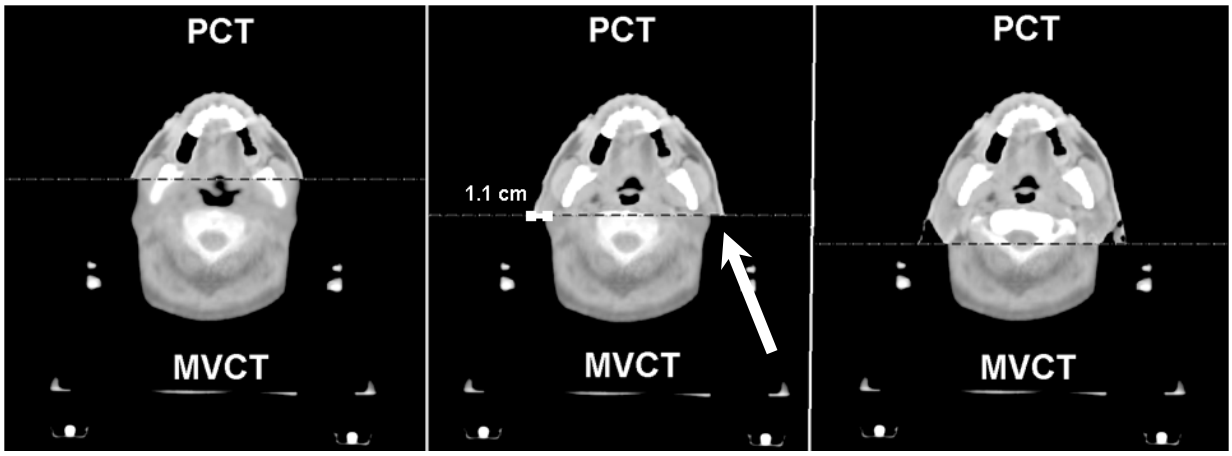


Figure 13. Example of soft tissue changes for patient no. 6 noted when fusing the MVCT to the planning kVCT (PCT) on the day when replanning was decided.
Substantial soft tissue changes are visible in the region of the parotid glands.

The contouring of the regions of interest [ROIs] (i.e. PTV and OAR) and the assessment of the actual delivered dose was carried out using the PlannedAdaptive® software as previously described (Chapter 3.1.3).

A new plan for the remaining fractions was generated on the MVCT using the adapted regions of interest [ROI] (organs at risk and PTV) with the tomotherapy treatment planning system. The dose calculation process on the MVCT has been described previously[69].

The replanning stretched for all patients over 24 hours. On the first day, after treatment, the ROIs were recontoured and the actual delivered dose was assessed (Figure 14). The planning, the quality assurance and the irradiation with the new plan was performed on the second day. All adaptPlans were evaluated and accepted by a radiation oncologist before treatment.

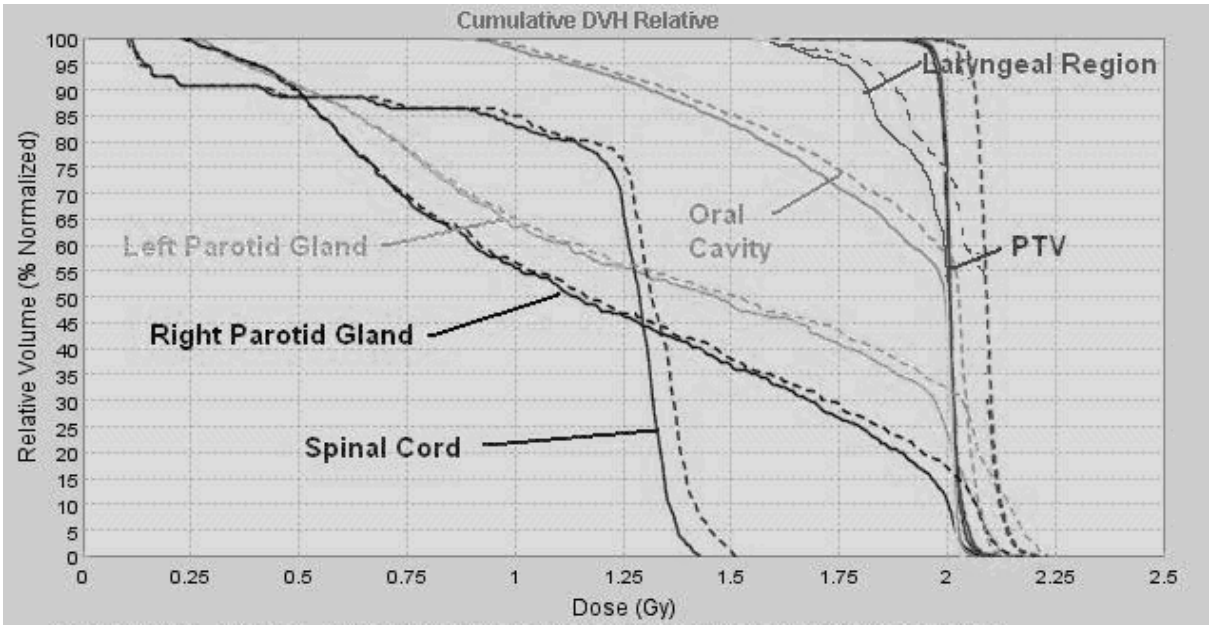


Figure 14. Example of differences in DVHs as recalculated with the PlannedAdaptive software on the day when soft tissue changes were noted and replanning was decided.
Solid DVH - DVHs of the OAR and PTV on the planning CT, dashed DVHs – DVHs of the OAR and PTV recalculated on the MVCT

Because the PlannedAdaptive ® software does not include DVH statistics so that the Dmean could be read out, all data were imported as DICOM files into CERR (Computational Environment for Radiotherapy Research, available at http://radium.wustl.edu/CERR) [16].

For the PTV we analyzed the mean dose (Dmean), maximum dose (Dmax) and the minimum dose (Dmin) per fraction normalized to the prescribed dose.

In the case of SIB treatment plans the dose assessment of the PTV dose was performed on a new generated PTV that did not encompass the voxels of the simultaneous integrated boost target volume. The new PTV was generated by subtracting a 0.5 cm enlarged simultaneous integrated boost target volume from the PTV (Figure 15).

In order to assess the dose conformity to the PTV, we generated a structure that encompassed the normal tissue outside the PTV, by subtracting the PTV from the body-contour. The delineation of the body-contour started 4 slices above the first CT slice where the PTV delineation began and ended 4 slices below the last CT slice where the PTV delineation ended. The volume of normal tissue outside

the PTV receiving equal to, or more than 95% of the prescribed dose to the PTV was evaluated (Figure 15).

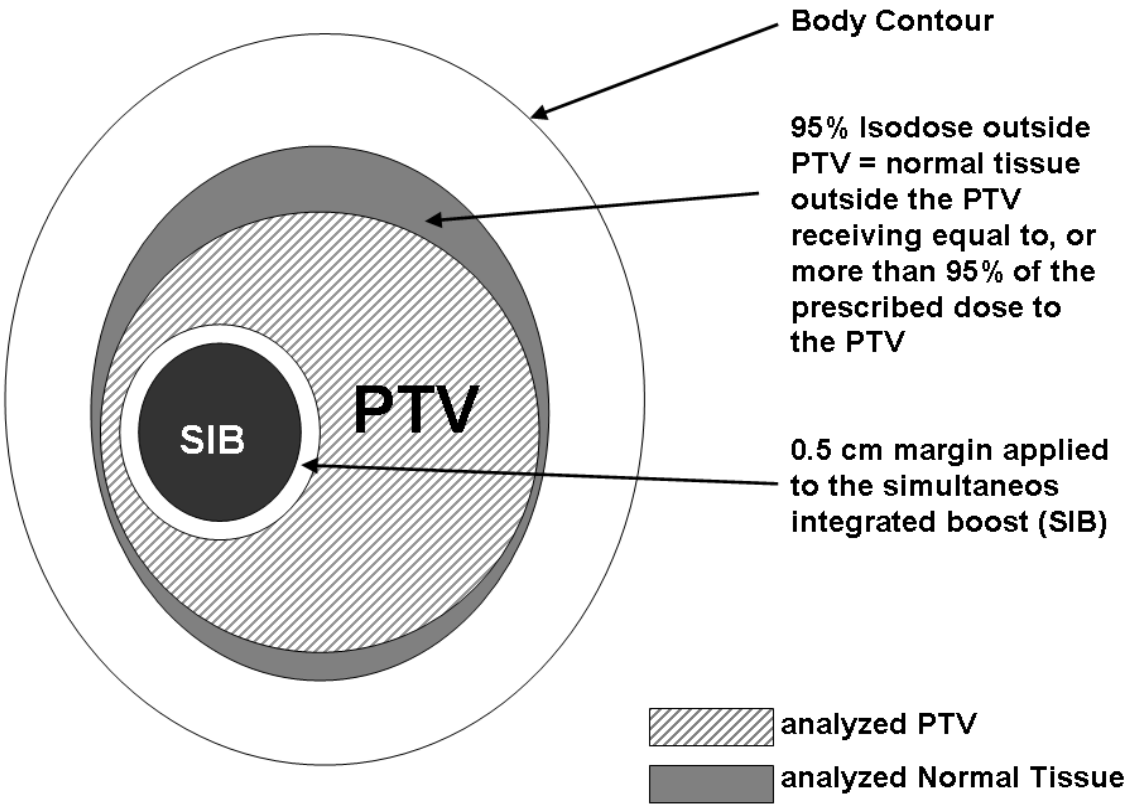


Figure 15. Schematic drawing of the analyzed PTV for simultaneous integrated boost treatments and the normal tissue outside the PTV (assessed in order to quantify the dose conformity to the PTV)

For the spinal cord (SC) the Dmax/fx; for the parotid glands (PGs), the larynx (Lx) and for the oral cavity (OC) the Dmean/fx were extracted.

All dosimetric analyses were performed for three situations: for the initial plan (inPlan), for the actual situation on the day of replanning (actSit) and for the adapted plan (adaptPlan).

In order to identify if clinical data correlate with the soft tissue changes observed on the MVCT we further assessed: i) changes in the weight of the patient at the moment of replanning; ii) days passed between surgery and the planning CT; iii) days passed between the dental extraction (if one performed) and the planning CT; iv) days passed between the moment of replanning and

chemotherapy; v) the initial volumes and the adapted volumes of the OAR and PTV/SIB; vi) the volume of the body-contour, on the planning CT as well as on the MVCT.

4.1.4 Statistical Analysis

The statistical analyses were performed using SPSS Software for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were performed two-sided and a p-value <0.05 was considered to indicate statistical significance. The Wilcoxon signed-rank test was used to assess changes in quantitative parameters. To assess bivariate relationship of quantitative data the Spearman correlation coefficient (rho) was used.

4.2 Results

4.2.1 Patient characteristics

17 of 94 patients (18%) needed adaptive radiotherapy ; 11 (12%) underwent adaptive radiotherapy on the MVCT (Figure 12). All following results refer to these 11 patients (median values and range in brackets).

Patients were treated with the new plan for 19 fractions (9 to 24 fractions). The weight loss at the moment of replanning was -2.3 kg (0 to -10.7 kg). 40 days (30 to 50 days) passed between surgery and the planning CT scan. Five patients underwent a dental extraction before radiotherapy: 11 days (3 to 13 days) passed between the dental extraction and the planning CT scan. No replanning was performed during a chemotherapy cycle. The time elapse between the last day of the first chemotherapy cycle and the replanning was on median 12 days (6 to 20 days).

4.2.2 Soft tissue changes and volumetric and dosimetric consequences

Table 6 Volumetric changes of the regions of interest as median values (range).

Organ	Volume (cm^3)		Decrease in percent of the initial volume
	inPlan	actSit	
PTV	1138 (575-1648)	1081 (537-1489)	6.6% (3.8-13.4)
BTV	203 (140-398)	188 (136-356)	7.2% (3.3-12.0)
Body-Contour	6523 (4357-8311)	5868 (3937-7417)	8.8% (3.7-16.9)
Left parotid gland	28.9 (18.9-54.8)	28.4 (17.2-48.0)	11.2% (0.2-40.0)
Right parotid gland	32.3 (20.5-52.8)	26.5 (15.1-50.4)	13.5% (1.5-45.7)

PTV-planning target volume, BTV-boost target volume

Table 6 summarizes the volumetric changes of the regions of interest. There was no evidence of a considerable relation between volumetric changes and weight loss (rho < 0.20 for all volumetric parameters). Further no significant correlation was noted between the volume changes of the ROIs to each other. The only exception was a strong positive correlation of the shrinkage of the left parotid with the shrinkage of the right parotid (rho= +0.77, p=0.005).

4.2.2.1 Planning target volume doses: maximum doses, minimum doses and maximum doses

In the actSit the Dmax (10 out of 11 patients), Dmin (8 out of 11 patients) and the Dmean (all patients) to the PTV increased when compared to the inPlan. By ART the Dmax (10 out of 11 patients, in 1 patient it remained unchanged), the Dmin (8 out of 11 patients) and the Dmean (all patients) to the PTV decreased when compared to the actSit.

4.2.2.2 Dose to the normal tissue outside the planning target volume

The normal tissue volume that received a dose higher than the 95% of the prescribed dose was median 256 cm³ on the planning CT (see also Figure 15). This volume increased in the actSit by median +56 cm³ and decreased by median -58 cm³ in the adaptPlan.

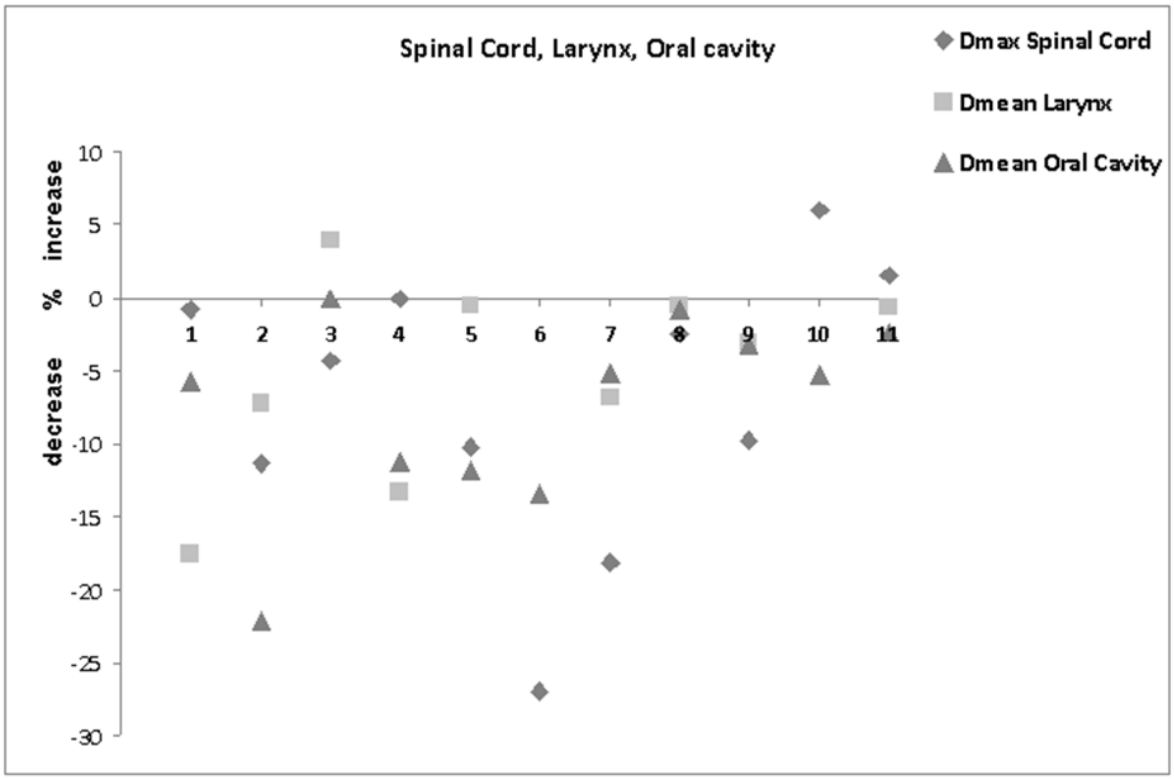
The dose in actSit was statistically significant higher for all OARs ($p<0.05$). With ART we achieved a statistical significant improvement for the Lx, OC and SC. No statistical improvement was noted by ART for either of the parotid glands (p=0.722). Figure 16 depicts the decrease or increase (percent normalized dose to the dose on the MVCT) achieved by ART for the OARs.

Table 7 illustrates the absolute doses for the PTV and the OARs.

Table 7. Doses per fraction for the PTV and the organs at risk

Organ	inPlan	actSit	adaptPlan
PTV (Dmax)	115% (105-120)	116% (108-123)	111% (93-121)
PTV (Dmin)	95% (91-99)	97% (93-101)	95% (81-98)
PTV (Dmean)	100% (97%-104)	103% (101-108)	100% (85-101)
Left parotid gland	1.23 Gy (0.97-1.75)	1.28 Gy (1.04-1.99)	1.36 Gy (0.9-1.90)
Right parotid gland	1.26 Gy (1.0-1.7)	1.38 Gy (1.02-1.71)	1.34 Gy (1.08-1.71)
Spinal Cord	1.31 Gy (0.98-1.63)	1.33 Gy (0.98-1.63)	1.19 Gy (0.88-1.43)
Larynx	1.70 Gy (1.49-1.88)	1.74 Gy (1.53-1.95)	1.66 Gy (1.5-1.9)
Oral Cavity	1.33 Gy (1.14-1.90)	1.36 Gy (1.14-1.94)	1.24 Gy (1.08-1.84)

Depicted are the median values (range) of the PTV´s normalized dose; the Dmean for the parotid glands; the Dmean for the larynx; the Dmean for the oral cavity and of the Dmax for the spinal cord.



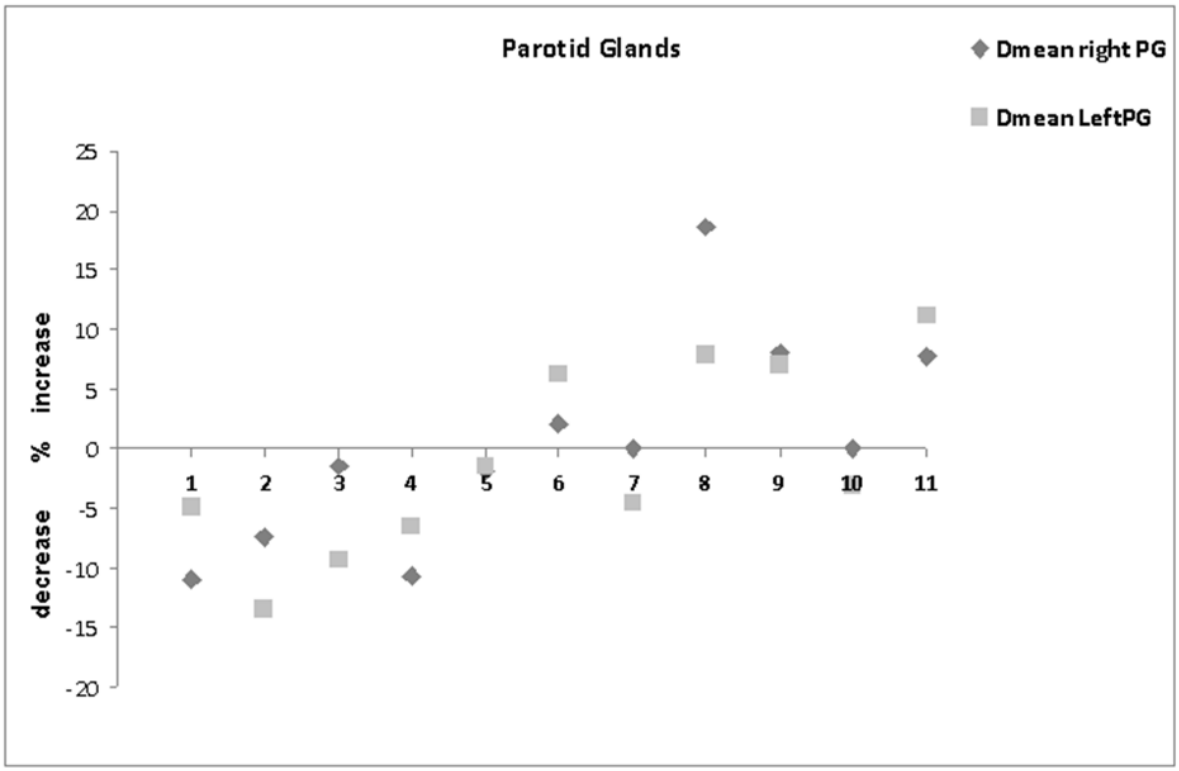


Figure 16.Dose differences in the adaptPlan in percent (decrease or increase) normalized to the actSit dose.
On the x axis are the patients' numbers as presented in table 2. The patient numbering was performed alphabetical, not chronological.

4.3 Discussion

4.3.1 Weight loss and soft tissue shrinkage

No significant correlation was observed between the weight loss of the patients and the volume reductions of the ROIs on the MVCT. Further, the volume decrease of the PTV, boost target volumes, parotid glands or of the body-contour did not correlate to each other. The only exception was a correlated shrinkage of the left and right parotid gland. This is consistent with literature [67] and with our own data (see also Chapter 3.2). As every organ has different reaction to weight loss and specific radiation sensitivity we believe that an assessment of one region of interest volume might not be able to predict another's region of interest volume change. This is further underlined in our study by the strong correlation of the shrinkage of the parotid glands to each other ("same organs react the same").

In patients treated without daily IGRT, different studies indicate that a major weight loss is an indicator for adaptive replanning. However the loss in percent of the initial body weight that is considered noteworthy is very different from study to study and lies somewhere above 6% [1, 41, 40]. In our study the weight loss at the moment of replanning was -2.6% of the initial weight. In order to assess if the measurement of the weight loss was underestimated due to the weight gain by saline volume expansion during chemotherapy administration, we assessed if adaptive radiotherapy was performed during the chemotherapy weeks. We found out that on median 12 day had passed since the chemotherapy and the adaptive replanning.

As the saline volume expansion hypothesis could not be confirmed and no striking weight loss was observed for most patients, we further made the assumption that a decrease of postoperative or post-dental-extraction edema could lead to soft tissue changes. Hence, we tested if the planning CT was performed soon after surgery or dental extraction [60].

However in this group of patients none of the hypotheses could be verified. In 9 out of 11 patients (one patient lost 10% weight and one patient underwent planning CT scanning 3 days after dental extraction) adaptive replanning could not have been predicted by the clinical judgment. Daily imaging by MVCT was the only way to detect soft tissue changes in these patients.

It is highly probable, that patients with a major weight loss need adaptive radiotherapy, but in our experience even patients with no weight loss undergo soft tissue changes. However, as only a subgroup of patients undergoes soft tissue changes, a routine replanning for all H&N patients at predefined times during fractionated radiotherapy is in our experience a superfluous workload.

4.3.2 Impact of soft tissue shrinkage and adaptive radiotherapy on the planning target volume

We performed adaptive radiotherapy on the premises that soft tissue shrinkage of more than 0.5 cm to each side has a significant dosimetric role in helical IMRT. The Dmean to the PTV increased by median +3% because of the soft tissue changes and decreased by replanning by median -3%. As the soft tissue changes noted in our patients are not circular (Figure 17) and the helical approach uses a 360-degree pattern, the dose to the PTV may not be severely changed as a substantial proportion of beamlets still go through unchanged soft tissue.

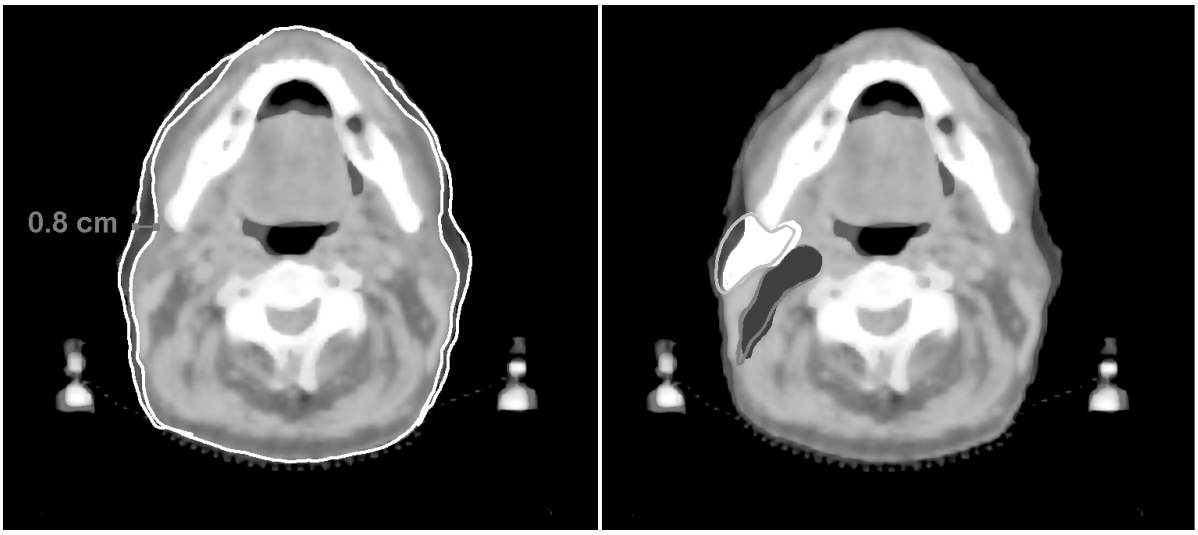


Figure 17. Soft tissue changes on the MVCT compared to the planning CT
The external contour is delineated on the planning CT and on the MVCT. The difference between the 2 contours is >0.5 cm at the height of the parotid glands. Further the changes in the CTV (Level 2) and the changes in the right parotid gland are depicted. The outer contour corresponds to the ROI delineated on the planning CT; the inner contour corresponds to the ROI delineated on the MVCT. The shrinkage and inner shifting of the parotid glands is not correlated to the deformation in the CTV.

4.3.3 Impact of soft tissue shrinkage and adaptive radiotherapy on the normal tissue outside the planning target volume

The ratio of normal tissue outside the PTV that receives the prescribed dose increased by one fifth. The normal tissue volume that received a dose higher than the 95% of the prescribed dose was median 256 cm³ on the planning CT (see also Figure 15). This volume increased in the actSit by median 56 cm³ and decreased by median 58 cm³ in the adaptPlan.

4.3.3.1 Parotid glands

In order to compensate the dose increase to the parotid glands because of soft tissue change during fractionated radiotherapy different replanning strategies are reported. Studies are available for one or more replans (up to six) and/or with different safety margins to the CTV.

Kuo et al. [39] performed a replanning at 45 Gy on 10 patients with enlarged neck lymph nodes. He reported a mean reduction of 2.95±1.10 Gy to the left and 3.23±1.37 Gy to the right parotid gland if replanning was performed for the last 21 Gy.

Eleven H&N patients, each with one planning and six weekly helical CTs were included in a study of Wu et al. [70]. Replanning was performed with different margins (0, 3, 5 mm) and either at midcourse (one replan), or every other week (two replans) or every week (six replans). One replanning during midcourse improved the sparing of the parotid glands by 3%, two replannings by 5%, and six replannings by 6% normalized to the cumulative doses without replanning.

Hansen et al. [31] retrospectively chose 13 H&N patients who had repeat CT imaging and replanning during the course of radiotherapy. The average number of radiation fractions delivered before the second CT scan was 19 fractions (out of 33 fractions). They found no significant improvement of the Dmean by replanning to the left parotid gland.

Castadot et.al [11] performed a preliminary analysis of the dose to the OAR target volumes on 10 H&N patients with re-optimization performed at mean doses of 14, 25, 35 and 45 Gy. No difference in

the Dmean to the parotid gland between the re-optimized plans and the actual delivered dose was detected.

As the replanning strategies are very different, it is hard to elucidate the reasons of these differences' in sparing. In our study we achieved no significant reduction of the dose to the parotid glands by ART. The inner shifting and decrease of Level II and IB [28, 27] at the height of the parotid glands were not correlated to the changes of the parotid glands (Figure 17). Further, in order to adequately cover the PTV at these levels and due to the relatively poor soft tissue contrast on the MVCT, we decided to perform a minor adaptation of the PTV in these regions. Thus a higher ratio of the total volume of the parotid glands was inside the PTV in the adaptPlan as compared to the inPlan. An improvement of the Dmean to the parotid glands was thus difficult to achieve by adaptive radiotherapy in our clinic.

4.3.3.2 Spinal cord

The reported improvements in the delivered dose to the spinal cord by ART are as well contradictory. Either no improvement or improvements up to 15 Gy are reported [2, 31, 70].

Hansen et al. [31] reported an increase in the Dmax to the spinal cord with a range of 0.2-15.4 Gy without replanning. Wu et al. [70] reported on the other hand stable doses to the spinal cord during radiotherapy.

The median increase for our patients was approximately 4 % normalized the initial Dmax. The increase in actSit dose was not only due to the soft tissue changes, but also to the different setup of the patient within the mask. In our experience, even in patients with a tight mask a different curvature of the cervical spinal cord can be noted on the MVCT. These different curvatures were daily reproducible on the MVCTs. The replanning on the MVCT compensated not only the soft tissue changes, but also the difference in spinal cord position (Figure 18). We will perform further studies to quantify these differences and their impact on delivered dose.

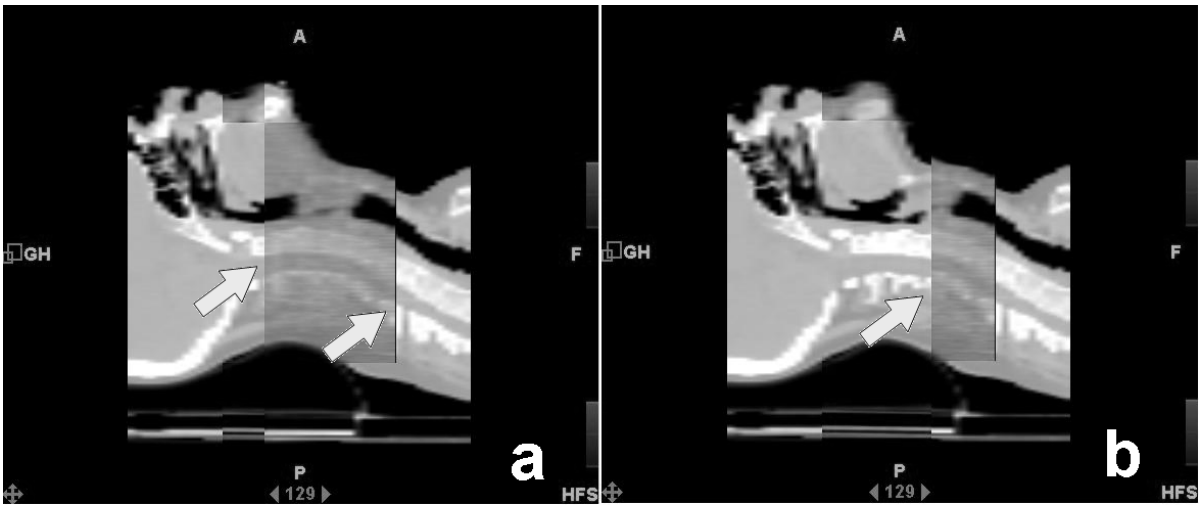


Figure 18. MVCT (dark grey) fused to the planning CT (light grey).
Figure 18a: the arrows mark the perfect fusion of the superior cervical spinal cord and the inferior cervical spinal cord
Figure 18b: the arrow marks the difference in the curvature of the middle cervical spinal cord

In most of our patients the dose reduction of -4% of the Dmax to the spinal cord by ART would not be clinically significant. However, one patient had a decrease of -27% and four patients of over -10%. In cases when the plan delivers doses close to the tolerance doses, especially correlated with a lack of daily image guidance, such a dose decrease could be important.

4.3.3.3 Larynx and oral cavity

Late dysphagia and aspiration is still one important issue in IMRT of the head and neck [53]. It is widely acknowledged that the dose to the larynx and pharyngeal musculature is associated with risk of long-term dysphagia [9, 12, 20, 34]. Caudell et al.[12] also demonstrated a significant correlation of the doses to the larynx and inferior pharyngeal constrictor with percutaneous endoscopic gastrostomy (PEG) tube dependence. It is recommended that the percentage of larynx volume receiving ≥50 Gy should be ≤27% and the mean laryngeal dose should be ≤44 Gy in order to minimize the risks of laryngeal edema [53].

Eisbruch et al. [18] showed that the Dmean to the oral cavity, representing the effect of radiotherapy on the minor salivary glands, is an independent predictor of xerostomia. In addition to the major

salivary glands, sparing the non-involved oral cavity should be considered as a planning objective to further reduce xerostomia.

Sparse data is available on the dosimetric changes in these organs due to soft tissue changes during fractionated radiotherapy. A preliminary study regarding the benefit of ART on the larynx and oral cavity is available from Castadot et al. [10]. By adaptive radiotherapy the delivered dose to the oral cavity could be decreased. No difference was observed for the larynx in Castadot's study. No further data were available from other groups regarding the delivered doses or the improvement by adaptive radiotherapy to the oral cavity or larynx during fractionated radiotherapy. In our analyzed group of patients, the decrease of the Dmean to the larynx achieved by ART was of approximately -5%. The reduction of the Dmean to the oral cavity was of approximately -9%. A dose reduction of 5% or 10% might be beneficial for the patients, especially if the reduction occurs on the steeper part of the dose effect curve [21].

5. CONCLUSION

Science is always wrong. It never solves a problem without creating ten more.

George Bernard Shaw

In all the analyzed patients the parotid gland shrunk during fractionated radiotherapy. Because of the volume change, the delivered dose was higher than expected from the planning CT DVH data. Thus, due to delivering higher doses than initially believed, the actual tolerance dose of the parotid glands could be higher than assumed up to date. Studies on the actual tolerance data with xerostomia as primary endpoint are needed. Nevertheless, if an accurate daily positioning of the patient by mask/skin marks is performed, the actual delivered dose in the parotid glands did not differ significantly between an image-guided and a non-image guided approach. Thus, in our opinion IGRT by MVCT performed for setup purposes is not a tool in itself to spare the parotid glands.

Adaptive radiotherapy because of soft tissue changes has been carried out in 10% of the patients on the MVCT. Soft tissue shrinkage >0.5 cm could not be predicted by the usual evaluations: i.e. measuring weight loss or assessment of the volume change of one organ as a predictor for the volume change of another organ during radiotherapy. The morphological changes had a dosimetric impact on the PTV as well as on the organs at risk. The impact of adaptive radiotherapy on the PTV and parotid glands was small. Adaptive radiotherapy reduced the delivered dose to the spinal cord, the larynx and the oral cavity. The effects for the entire group were small, nevertheless the gain by ART in individual patients could be substantial – especially in patients who receive doses close to the known tolerance doses of the organs at risk.

Further studies should focus on IGRT as a tool for assessing soft tissue changes and actual tolerance doses of organs at risk with the intent to establish thresholds for adaptive radiotherapy. The thresholds should be the actual tolerance doses of organs at risk.

6. SUMMARY

Purpose:

Radiotherapy is a very important part of the treatment in head and neck cancers (H&N). Intensity modulated radiotherapy (IMRT) - i.e. helical tomotherapy - is a newer approach that allows a higher conformality in dose distribution and a sharp dose fall-off to the normal tissue when compared to 3D-conformal radiotherapy.

In order to assure a reproducible setup of patients during radiotherapy – daily CTs can be performed while the patient lies on the treatment table (image guided radiotherapy – IGRT). Whether image guidance is used weekly, twice a week, or daily highly depends on the current clinical practice of the institution. The first part of the thesis assesses the impact of daily image guidance in H&N radiotherapy.

Further, it is documented that morphological changes occur during the six to seven weeks of radiotherapy treatment. This might have an important impact on dose distribution of IMRT plans. The second part of the thesis deals with the necessity, due to soft tissue changes, of recalculating a new treatment plan during radiotherapy treatment (adaptive radiotherapy).

Material and methods:

For the first part of the thesis we assessed two scenarios for ten head-and-neck cancer patients, treated with helical TomoTherapy (TomoTherapy Inc., Madison, WI). The IGRT scenario reviewed the dose that was actually delivered to the parotid glands with setup correction by CT beforehand. The non-IGRT scenario assessed the dose to the parotid glands without setup correction. The initial dose–volume histograms derived from the planning computed tomography scan and 120 recalculated dose–volume histograms of the parotid glands of each scenario and of corresponding fractions were compared. Setup errors, cumulative median doses for 6 fractions, overall volumes of the parotid glands, and volumes that received less than 1 Gy or more than 1.6 Gy per fraction were analyzed.

In the second part of the thesis we present the results of eleven H&N patients that underwent adaptive radiotherapy on the daily setup CT. The dose volume-histograms (DVHs) derived from the initial planning kVCT (inPlan), the recalculated DVHs of the fraction when replanning was decided (actSit), as well as the DVHs of the new plan (adaptPlan) were compared. We analyzed the conformity and homogeneity index of the planning target volume (PTV), the mean dose (Dmean) to the parotid glands, oral cavity and larynx and the maximum dose (Dmax) to the spinal cord.

Results:

The mean decrease in the parotid gland volume was 0.13cm³/d. There was a significantly higher cumulative median dose than initially predicted (mean increase over 6 fractions, 1.13 Gy for IGRT and 0.96 Gy for non-IGRT). The volume that received less than 1 Gy per fraction decreased (mean difference to the planning CT: 1.36 cm3 for IGRT [p = 0.003] and 1.35 cm³ for non- IGRT [p = 0.003]). The volume that received more than 1.6 Gy per fraction increased with increasing fraction number (mean difference to the planning CT: 1.14 cm³ for IGRT [p = 0.01] and 1.16 cm³ for non-IGRT [p = 0.006]). There was no statistically significant difference between the two scenarios .

The conformity and homogeneity of the PTV significantly decreased in the actual situation (actSit). The PTV was however still treated with the prescribed dose to ≥ 95% volume in all cases. The homogeneity improved significantly by adaptive radiotherapy (improvement in 7 out of 11 patients, p=0.041) - i.e. by creating a new plan on the actual patient anatomy during fractionated radiotherapy-

All analyzed organs at risk received significantly higher doses in the actual situation (e.g. the respective analyzed fraction). This could be counteracted by adaptive radiotherapy. No statistical significant decrease of the Dmean of the parotid glands was achieved by adaptive radiotherapy (right and left parotid gland: p=0.722).The overall median decrease in Dmean to the left parotid gland was 0.76 Gy (range -3.10 to 2.43) and of 0.09 Gy (-2.61 to 1.98) to the right parotid gland, respectively. The Dmax to the spinal cord and the Dmean to the larynx and oral cavity improved significantly by adaptive radiotherapy. The overall median decrease in Dmax was for the spinal cord 1.05 Gy (-1.7 to 9.61). The overall median decrease in Dmean was for the larynx 1.17 Gy (-1.25 to 3.74), for the oral cavity 1.26 Gy (-0.11 to 5.56).

Conclusion:

The morphological changes had a dosimetric impact on the PTV as well as on the organs at risk. However, as the parotid glands shrank into the PTV, the actual delivered dose to the parotid glands did not differ significantly between an image-guided and a non-image guided approach. Further, as the change of the PTV is smaller than the change of parotid glands and large volumes of the parotid glands are inside the PTV, the impact of adaptive replanning on the PTV and parotid glands is small. Adaptive replanning reduced the delivered dose to the spinal cord, the larynx and the oral cavity. The gain by adaptive radiotherapy in individual patients could be substantial – especially in patients who receive doses close to the known tolerance doses of the organs at risk.

References

1. Ahamad A, Dong L, Zhang L, Ang K, O'Daniel J, Theriot L, Asper J, Chambers M, Palla S, Garden A. 181: Is There a Trigger Point for Adaptive Replanning During Head & Neck IMRT? Int J Radiat Oncol Biol Phys 2006;66:S100-S101.

2. Ahn PH, Chen CC, Ahn AI, Hong L, Scripes PG, Shen J, Lee CC, Miller E, Kalnicki S, Garg M. Adaptive Planning in Intensity-modulated Radiation Therapy for Head and Neck Cancers: Single-institution Experience and Clinical Implications. Int J Radiat Oncol Biol Phys 2010. epub

3. Al-Sarraf M. Treatment of locally advanced head and neck cancer: historical and critical review. Cancer Control 2002;9:387-399.

4. Bamberg M, Molls M, Sack H. Radioonkologie, Grundlagen und Klinik second edition ed. München: Zuckschwerdt; 2009.

5. Barker JL, Jr., Garden AS, Ang KK, O'Daniel JC, Wang H, Court LE, Morrison WH, Rosenthal DI, Chao KS, Tucker SL, Mohan R, Dong L. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. Int J Radiat Oncol Biol Phys 2004;59:960-970.

6. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945-1952.

7. Boswell S, Tome W, Jeraj R, Jaradat H, Mackie TR. Automatic registration of megavoltage to kilovoltage CT images in helical tomotherapy: an evaluation of the setup verification process for the special case of a rigid head phantom. Med Phys 2006;33:4395-4404.

8. Bourhis J, Lapeyre M, Tortochaux J, Rives M, Aghili M, Bourdin S, Lesaunier F, Benassi T, Lemanski C, Geoffrois L, Lusinchi A, Verrelle P, Bardet E, Julieron M, Wibault P, Luboinski M, Benhamou E. Phase III randomized trial of very accelerated radiation therapy compared with conventional radiation therapy in squamous cell head and neck cancer: a GORTEC trial. J Clin Oncol 2006;24:2873-2878.

9. Caglar HB, Tishler RB, Othus M, Burke E, Li Y, Goguen L, Wirth LJ, Haddad RI, Norris CM, Court LE, Aninno DJ, Posner MR, Allen AM. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2008;72:1110-1118.

10. Castadot P, Lee JA, Geets X, Gregoire V. Adaptive radiotherapy of head and neck cancer. Semin Radiat Oncol 2010;20:84-93.

11. Castadot P, Geets X, Lee JA, Christian N, Gregoire V. Assessment by a deformable registration method of the volumetric and positional changes of target volumes and organs at risk in pharyngo-laryngeal tumors treated with concomitant chemo-radiation. Radiother Oncol 2010;95:209-217.

12. Caudell JJ, Schaner PE, Desmond RA, Meredith RF, Spencer SA, Bonner JA. Dosimetric factors associated with long-term dysphagia after definitive radiotherapy for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2010;76:403-409.

13. Chao KS, Deasy JO, Markman J, Haynie J, Perez CA, Purdy JA, Low DA. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys 2001;49:907-916.

14. Cheng VS, Downs J, Herbert D, Aramany M. The function of the parotid gland following radiation therapy for head and neck cancer. Int J Radiat Oncol Biol Phys 1981;7:253-258.

15. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N, Fu KK. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-1944.

16. Deasy JO, Blanco AI, Clark VH. CERR: a computational environment for radiotherapy research. Med Phys 2003;30:979-985.

17. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Calais G. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial

comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69-76.

18. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;50:695-704.

19. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45:577-587.

20. Eisbruch A, Schwartz M, Rasch C, Vineberg K, Damen E, Van As CJ, Marsh R, Pameijer FA, Balm AJ. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys 2004;60:1425-1439.

21. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109-122.

22. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010.

23. Ferlay J SH, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. In: Lyon, France: International Agency for Research on Cancer; 2010.

24. Franzen L, Funegard U, Ericson T, Henriksson R. Parotid gland function during and following radiotherapy of malignancies in the head and neck. A consecutive study of salivary flow and patient discomfort. Eur J Cancer 1992;28:457-462.

25. Gilbeau L, Octave-Prignot M, Loncol T, Renard L, Scalliet P, Gregoire V. Comparison of setup accuracy of three different thermoplastic masks for the treatment of brain and head and neck tumors. Radiother Oncol 2001;58:155-162.

26. Godballe C, Jorgensen K, Hansen O, Bastholt L. Hypopharyngeal cancer: results of treatment based on radiation therapy and salvage surgery. Laryngoscope 2002;112:834-838.

27. Gregoire V, Levendag P, Ang KK, Bernier J, Braaksma M, Budach V, Chao C, Coche E, Cooper JS, Cosnard G, Eisbruch A, El-Sayed S, Emami B, Grau C, Hamoir M, Lee N, Maingon P, Muller K, Reychler H. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC,RTOG consensus guidelines. Radiother Oncol 2003;69:227-236.

28. Gregoire V, Eisbruch A, Hamoir M, Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. Radiother Oncol 2006;79:15-20.

29. Gupta T, Chopra S, Kadam A, Agarwal JP, Devi PR, Ghosh-Laskar S, Dinshaw KA. Assessment of three-dimensional set-up errors in conventional head and neck radiotherapy using electronic portal imaging device. Radiat Oncol 2007;2:44.

30. Halperin EC, Perez CA, Brady LF. Principles and Practice of Radiation Oncology. fifth edition ed. Philadelphia: Lippincott Williams & Wilkins; 2007.

31. Hansen EK, Bucci MK, Quivey JM, Weinberg V, Xia P. Repeat CT imaging and replanning during the course of IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2006;64:355-362.

32. Hinerman RW, Amdur RJ, Mendenhall WM, Villaret DB, Robbins KT. Hypopharyngeal carcinoma. Curr Treat Options Oncol 2002;3:41-49.

33. Horiot JC, Le Fur R, N'Guyen T, Chenal C, Schraub S, Alfonsi S, Gardani G, Van Den Bogaert W, Danczak S, Bolla M, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 1992;25:231-241.

34. Jensen K, Lambertsen K, Grau C. Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: frequency, intensity and correlation with dose and volume parameters. Radiother Oncol 2007;85:74-82.

35. Johansen LV, Grau C, Overgaard J. Hypopharyngeal squamous cell carcinoma--treatment results in 138 consecutively admitted patients. Acta Oncol 2000;39:529-536.

36. Jones AS, Stell PM. Squamous carcinoma of the posterior pharyngeal wall. Clin Otolaryngol Allied Sci 1991;16:462-465.

37. Kim S, Wu HG, Heo DS, Kim KH, Sung MW, Park CI. Advanced hypopharyngeal carcinoma treatment results according to treatment modalities. Head Neck 2001;23:713-717.

38. Konings AW, Coppes RP, Vissink A. On the mechanism of salivary gland radiosensitivity. Int J Radiat Oncol Biol Phys 2005;62:1187-1194.

39. Kuo YC, Wu TH, Chung TS, Huang KW, Chao KS, Su WC, Chiou JF. Effect of regression of enlarged neck lymph nodes on radiation doses received by parotid glands during intensity-modulated radiotherapy for head and neck cancer. Am J Clin Oncol 2006;29:600-605.

40. Lee C, Langen KM, Lu W, Haimerl J, Schnarr E, Ruchala KJ, Olivera GH, Meeks SL, Kupelian PA, Shellenberger TD, Manon RR. Assessment of parotid gland dose changes during head and neck cancer radiotherapy using daily megavoltage computed tomography and deformable image registration. Int J Radiat Oncol Biol Phys 2008;71:1563-1571.

41. Lee C, Langen KM, Lu W, Haimerl J, Schnarr E, Ruchala KJ, Olivera GH, Meeks SL, Kupelian PA, Shellenberger TD, Manon RR. Evaluation of geometric changes of parotid glands during head and neck cancer radiotherapy using daily MVCT and automatic deformable registration. Radiother Oncol 2008;89:81-88.

42. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890-899.

43. Marks JE, Davis CC, Gottsman VL, Purdy JE, Lee F. The effects of radiation of parotid salivary function. Int J Radiat Oncol Biol Phys 1981;7:1013-1019.

44. Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Werning JW, Villaret DB. Definitive radiotherapy for squamous cell carcinoma of the base of tongue. Am J Clin Oncol 2006;29:32-39.

45. Mendenhall WM, Riggs CEJ, Cassisi NJ. Treatment of head and neck cancers. In: DeVita VTJ, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. seventh ed. Philadelphia: Lippincott Williams & Wilkins; 2005:662-732.

46. Mendenhall WM, Amdur RJ, Stringer SP, Villaret DB, Cassisi NJ. Radiation therapy for squamous cell carcinoma of the tonsillar region: a preferred alternative to surgery? J Clin Oncol 2000;18:2219-2225.

47. Nagler RM. The enigmatic mechanism of irradiation-induced damage to the major salivary glands. Oral Dis 2002;8:141-146.

48. O'Daniel JC, Garden AS, Schwartz DL, Wang H, Ang KK, Ahamad A, Rosenthal DI, Morrison WH, Asper JA, Zhang L, Tung SM, Mohan R, Dong L. Parotid gland dose in intensity-modulated radiotherapy for head and neck cancer: is what you plan what you get? Int J Radiat Oncol Biol Phys 2007;69:1290-1296.

49. O'Meara WP, Lee N. Advances in nasopharyngeal carcinoma. Curr Opin Oncol 2005;17:225-230.

50. Okamoto M, Takahashi H, Yao K, Inagi K, Nakayama M, Nagai H. Clinical impact of using chemoradiotherapy as a primary treatment for hypopharyngeal cancer. Acta Otolaryngol Suppl 2002:11-14.

51. Olmi P, Crispino S, Fallai C, Torri V, Rossi F, Bolner A, Amichetti M, Signor M, Taino R, Squadrelli M, Colombo A, Ardizzoia A, Ponticelli P, Franchin G, Minatel E, Gobitti C, Atzeni G, Gava A, Flann M, Marsoni S. Locoregionally advanced carcinoma of the oropharynx: conventional radiotherapy vs. accelerated hyperfractionated radiotherapy vs. concomitant radiotherapy and chemotherapy--a multicenter randomized trial. Int J Radiat Oncol Biol Phys 2003;55:78-92.

52. Parsons JT, Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Villaret DB, Moore-Higgs GJ, Greene BD, Speer TW, Cassisi NJ, Million RR. Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. Cancer 2002;94:2967-2980.

53. Rancati T, Schwarz M, Allen AM, Feng F, Popovtzer A, Mittal B, Eisbruch A. Radiation dose-volume effects in the larynx and pharynx. Int J Radiat Oncol Biol Phys 2010;76:S64-69.

54. Robar JL, Day A, Clancey J, Kelly R, Yewondwossen M, Hollenhorst H, Rajaraman M, Wilke D. Spatial and dosimetric variability of organs at risk in head-and-neck intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2007;68:1121-1130.

55. Robertson AG, Soutar DS, Paul J, Webster M, Leonard AG, Moore KP, McManners J, Yosef HM, Canney P, Errington RD, Hammersley N, Singh R, Vaughan D. Early closure of a randomized trial: surgery and postoperative radiotherapy versus radiotherapy in the management of intra-oral tumours. Clin Oncol (R Coll Radiol) 1998;10:155-160.

56. Roesink JM, Moerland MA, Battermann JJ, Hordijk GJ, Terhaard CH. Quantitative dose-volume response analysis of changes in parotid gland function after radiotherapy in the head-and-neck region. Int J Radiat Oncol Biol Phys 2001;51:938-946.

57. Schubert LK, Westerly DC, Tome WA, Mehta MP, Soisson ET, Mackie TR, Ritter MA, Khuntia D, Harari PM, Paliwal BR. A comprehensive assessment by tumor site of patient setup using daily MVCT imaging from more than 3,800 helical tomotherapy treatments. Int J Radiat Oncol Biol Phys 2009;73:1260-1269.

58. Scrimger RA, Stavrev P, Parliament MB, Field C, Thompson H, Stavreva N, Fallone BG. Phenomenologic model describing flow reduction for parotid gland irradiation with intensity-modulated radiotherapy: evidence of significant recovery effect. Int J Radiat Oncol Biol Phys 2004;60:178-185.

59. Semrau R, Mueller RP, Stuetzer H, Staar S, Schroeder U, Guntinas-Lichius O, Kocher M, Eich HT, Dietz A, Flentje M, Rudat V, Volling P, Schroeder M, Eckel HE. Efficacy of intensified hyperfractionated and accelerated radiotherapy and concurrent chemotherapy with carboplatin and 5-fluorouracil: updated results of a randomized multicentric trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2006;64:1308-1316.

60. Shaw MJ, Kumar ND, Duggal M, Fiske J, Lewis DA, Kinsella T, Nisbet T. Oral management of patients following oncology treatment: literature review. Br J Oral Maxillofac Surg 2000;38:519-524.

61. Sheng K, Chow MC, Hunter G, Larner JM, Read PW. Is daily CT image guidance necessary for nasal cavity and nasopharyngeal radiotherapy: an investigation based on helical tomotherapy. J Appl Clin Med Phys 2008;9:2686.

62. Spector JG, Sessions DG, Emami B, Simpson J, Haughey B, Harvey J, Fredrickson JM. Squamous cell carcinoma of the pyriform sinus: a nonrandomized comparison of therapeutic modalities and long-term results. Laryngoscope 1995;105:397-406.

63. Suzuki M, Nishimura Y, Nakamatsu K, Okumura M, Hashiba H, Koike R, Kanamori S, Shibata T. Analysis of interfractional set-up errors and intrafractional organ motions during IMRT for head and neck tumors to define an appropriate planning target volume (PTV)- and planning organs at risk volume (PRV)-margins. Radiother Oncol 2006;78:283-290.

64. Tanyi JA, Fuss MH. Volumetric image-guidance: does routine usage prompt adaptive re-planning? An institutional review. Acta Oncol 2008;47:1444-1453.

65. Tupchong L, Scott CB, Blitzer PH, Marcial VA, Lowry LD, Jacobs JR, Stetz J, Davis LW, Snow JB, Chandler R, et al. Randomized study of preoperative versus postoperative radiation therapy in advanced head and neck carcinoma: long-term follow-up of RTOG study 73-03. Int J Radiat Oncol Biol Phys 1991;20:21-28.

66. Valdez IH, Atkinson JC, Ship JA, Fox PC. Major salivary gland function in patients with radiation-induced xerostomia: flow rates and sialochemistry. Int J Radiat Oncol Biol Phys 1993;25:41-47.

67. Vasquez Osorio EM, Hoogeman MS, Al-Mamgani A, Teguh DN, Levendag PC, Heijmen BJ. Local anatomic changes in parotid and submandibular glands during radiotherapy for oropharynx cancer and correlation with dose, studied in detail with nonrigid registration. Int J Radiat Oncol Biol Phys 2008;70:875-882.

68. Wang C, Chong F, Wu J, Lai M, Cheng J. Body Weight Loss Associates With Set-up Error in Nasopharyngeal Cancer Patients Undergoing Image Guided Radiotherapy. International Journal of Radiation Oncology*Biology*Physics 2007;69:S203-S203.

69. Welsh JS, Lock M, Harari PM, Tome WA, Fowler J, Mackie TR, Ritter M, Kapatoes J, Forrest L, Chappell R, Paliwal B, Mehta MP. Clinical implementation of adaptive helical tomotherapy: a unique approach to image-guided intensity modulated radiotherapy. Technol Cancer Res Treat 2006;5:465-479.

70. Wu Q, Chi Y, Chen PY, Krauss DJ, Yan D, Martinez A. Adaptive replanning strategies accounting for shrinkage in head and neck IMRT. Int J Radiat Oncol Biol Phys 2009;75:924-932.

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Always acknowledge a fault. This will throw those in authority off their guard and give you an opportunity to commit more.

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