Aus der Klinik für Radioonkologie und Strahlentherapie
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DISSERTATION

Accelerated Intensity Modulated Radiotherapy using Simultaneous Integrated Boost (SIB-IMRT) versus Intensity Modulated Hyperfractionated Accelerated Radiotherapy using Sequential Field (HART-SEQ-IMRT) for Primary Treatment in Patients with Locally Advanced Head and Neck Squamous Cell Carcinoma

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Dedicated to .....

Egypt&

My family

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Abbreviations

AF	Altered fractionation
AFRT	Accelerated fractionation radiotherapy
AJCC	American Joint Committee on Cancer
BED	Biologically effective dose
CBCT	Cone Beam CT
CHART	Continuous Hyperfractionated accelerated radiotherapy
CI	Confidence interval
CR	Complete response
cSMG	Contralateral submandibular gland
CT	Computed tomography
CTH	Chemotherapy
CTV	Clinical target volume
$D_{2\ \%}$ =$D_{\text{near-max}}$	$D_{\text{near-maximum}}$
$D_{50\ \%}$	Median absorbed dose
D95	Dose received by ≥ 95% of the target volume
$D_{95\ \%}$	Minimum absorbed dose that covers 95 % of the volume of the PTV
$D_{98\ \%}$ = $D_{\text{near-min}}$	$D_{\text{near-minimum}}$
$D_{\text{difference}}$=D_{diff}	Differences between prescribed dose and the calculated mean absorbed dose
D_{max}	Maximum absorbed dose
D_{mean}	Mean absorbed Dose
D_{min}	Minimum absorbed Dose
DARS	Dysphagia/aspiration-related structures
DFS	Disease free survival
DMFS	Distant metastases-free survival
doIMRT	dysphagia-optimized IMRT
DRRs	Digitally reconstructed radiographs
DVH	Dose–volume histogram
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EPI	Electronic portal imaging
Fig.	Figure
5-FU	5-fluorouracil
GTV	Gross tumor volume
Gy	Gray
HART	Hyperfractionated accelerated radiotherapy
HART-SEQ-IMRT	Hyperfractionated accelerated radiotherapy using sequential field IMRT
HR	Hazard ratio
HFRT	Hyperfractionated radiotherapy
HNC	Head and neck cancer
HNCQOL	HNC–related QOL
HNSCC	Head and neck squamous cell carcinoma
ICRU	International Commission on Radiation Units and Measurement

IGRT	Imaging-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
i.v.	Intravenous
KM-PF	Reverse Kaplan-Meier method
KPS	Karnofsky performance status
LAHNSCC	Locally advanced Head and neck squamous cell carcinoma
LCR	Local control rate
LENT-SOMA	Late Effect in Normal Tissue-Subjective Objective Management Analytic
linacs	Linear accelerators
LRFS	Locoregional recurrence free survival
LRC	Locoregional control
LRF	locoregional failure
MLC	Multileaf collimators
MRI	Magnetic resonance imaging
MTD	Maximal tolerable dose
NPC	Nasopharyngeal carcinoma
NTD	Nominal total dose
OARs	Organs at risk
OR	Odds ratio
ORN	Osteoradionecrosis
OS	Overall survival
OTT	Overall treatment time
PD	Progressive disease
PEG	Percutaneous endoscopic gastrostomy
PF	Cisplatin–5-fluorouracil
PFS	Progression free survival
PR	Partial response
PRV	Planning organ at risk volume
PS	performance status
PTV	Planning target volume
QOL	Quality of life
RPFS	Regional progression-free survival
XRT	Radiation therapy
RTOG	Radiotherapy Oncology Group
SD	Stationary disease
±SD	± Standard deviation
SEQ-IMRT	Sequential field IMRT
SIB	Simultaneous integrated boost technique
SMART	Simultaneous modulated accelerated radiation therapy
SPFR	stimulated parotid flow rate
stIMRT	standard IMRT
TCP	Tumor control probability
TPF	Docetaxel–cisplatin–5-fluorouracil
TPS	Treatment planning system
2DRT	Two-dimensional radiation therapy
3DCRT	Three-dimensional conformal radiotherapy

3D-RTP	Three-dimensional radiation treatment planning
ULN	Upper limit of normal
V30	Mean volumes receiving 30 Gy
V50	volume receiving ≥50 Gy
V60	volume receiving ≥60 Gy
V65	volume receiving ≥65 Gy
VF	Videofluoroscopy
$V_{95\%}$	Target volume covered by 95% isodose level
WHO	World Health Organization

2. Purpose of this Study

IMRT is considered the most important advancement of XRT for HNC patients in the last decade; however few data are available regarding its combination with other important advances in HNC treatment such as altered fractionation, CTH, and targeting agents.

Budach et al (2005) published the final results of the radiotherapy cooperative clinical trials group of the German Cancer Society 95-06 prospective randomized trial, which proved that hyperfractionated accelerated chemoradiation with concurrent Fluorouracil-Mitomycin C is more effective than dose-escalated hyperfractionated accelerated XRT alone in LAHNSCC. Based on this trial, patients with LAHNSCC at Charité - Universitätsmedizin Berlin Campus Virchow-Klinikum and Campus Mitte, have been routinely offered hyperfractionated accelerated chemoradiation.

For HNSCC, values of 14 days to 30 days have been suggested for the lag time before the onset of accelerated tumor growth after the initiation of XRT (Withers et al., 1988; Maciejewski et al., 1989). Based on this background, hybrid fractionation with 6-weeks schedule using the sequential field IMRT technique (HART-SEQ-IMRT) has been used to treat patients; conventional 2 Gy single fractions in the first 3 weeks followed by HART with twice daily fractions (1.4 Gy per fraction) for the last 3 weeks. An exception is made only in the case of patients with NPC with infiltration visual structures at the base of the skull, or patients with tumors involving brachial plexus, in whom HART (twice daily fractions with small dose per fraction) is used during the whole course of treatment to avoid damage of late reacting neurologic structures.

Using sequential field reduction, the prescribed doses to different target volumes and the tolerance doses of OARs must be respected over the sum of the two or three plans, which is practically difficult to implement. Furthermore, to accomplish AF in the context of IMRT, adds further challenge to IMRT implementation.

SIB Technique is the most effective solution to overcome such limitations. The SIB concept was developed by Mohan et al. (2000) and it has already been clinically introduced in several institutes to accelerate OTT and to escalate the gross tumor radiation dose in HNC patients. However, clinical experience with such technique is limited and many radiotherapists are reluctant when prescribing unconventional fractionation schemes or calculating their

radiobiological equivalent doses. Furthermore, combining SIB technique with other systemic therapies adds further to this uncertainty.

Several studies have documented the dosimetric benefits from SIB-IMRT; nevertheless, there is still limited experience with its implementation in Charité - Universitätsmedizin Berlin in terms of clinical outcome and therapeutic benefit.

Furthermore, data about direct comparison between the two IMRT techniques (SEQ-IMRT and SIB-IMRT) are sparse, and most of these comparisons were conducted using direct planning comparison studies. To our knowledge, there is no study till present time compared between the two techniques as regards the clinical outcome. The purpose of this study is to compare differences in dosimetric, and clinical endpoints among patients with stage IV HNSCC treated using two accelerated IMRT techniques, HART-SEQ-IMRT and SIB-IMRT.

2.1. Primary Objective (safety assessment)

- Assessment and comparison of toxicity profiles in patients with stage IV HNSCC treated with HART-SEQ-IMRT and SIB-IMRT techniques.

2.2. Secondary objectives (efficacy assessment)

- To determine and to compare the tumor response rates in patients with stage IV HNSCC after treatment with HART-SEQ-IMRT and SIB-IMRT techniques.
- To determine and to compare the one-year PFS, locoregional recurrence-free survival (LRFS), DMFS, and OS in patients with stage IV HNSCC treated with HART-SEQ-IMRT and SIB-IMRT techniques
- To determine the pattern of relapse in patients with stage IV HNSCC within the first year following treatment with HART-SEQ-IMRT and SIB-IMRT techniques**.**
- To analyze LRC in patients with stage IV HNSCC treated with IMRT.

2.3. Tertiary objectives (dosimetric assessment)

- To compare the dose distributions generated by IMRT using SEQ field reduction technique and those generated by IMRT using SIB technique.
- To assess the potential patients, disease, and treatment characteristics together with potential dosimetric parameters to predict outcome in patients with stage IV HNSCC treated with IMRT.

3. Patients and Methods

3.1. Study design

This study was prospectively planned to compare two XRT dose escalation/acceleration schedules: HART-SEQ-IMRT technique and SIB-IMRT technique, in patients with stage IV HNSCC who were treated in Charité - Universitätsmedizin Berlin Campus Virchow-Klinikum and Campus Mitte in the period from May 2009 to June 2010.

Study design and endpoints: Prospective, interventional, non-randomized, two group parallel study to evaluate safety and efficacy.

Study title: Accelerated intensity modulated radiotherapy using simultaneous integrated boost (SIB-IMRT) versus intensity modulated hyperfractionated accelerated radiotherapy using sequential field (HART-SEQ-IMRT) for primary treatment in patients with locally advanced head and neck squamous cell carcinoma.

Table 2: Prescription of therapeutic interventions used in the study

Condition	Intervention
Stage IV HNSCC	**Radiotherapy** 1- HART-SEQ-IMRT 2- SIB-IMRT **Chemotherapy and targeting Therapy** 1- PF regimen (concurrent cisplatinum and 5- FU) 2-TPF regimen (neoadjuvant docetaxel, cisplatinum, and 5-FU) followed by XRT concurrent with cetuximab

3.2. Inclusion criteria: patients meeting the following criteria were included into the study;

- Age 18 years and above.
- Both genders.
- Stage IV (T1-T3, N2-N3; T4, N0-N3; M0) histologically proven HNSCC [Oral cavity, oropharynx, hypopharynx, and larynx] according to the AJCC Cancer Staging Manual, Sixth Edition (AJCC cancer staging, 2002).
- Patients in whom definitive XRT was the selected curative treatment.
- Patients who received neoadjuvant CTX with TPF.
- Patients without neoadjuvant CTX.
- Karnofsky performance status (KPS) $\geq$ 70%.
- Adequate bone marrow reserve in the form of: Total leukocyte count at least 3.5 X 10^9/L, neutrophil count at least 1.5 X 10^9/L, platelet count at least 100 X 10^9/L, and hemoglobin > 9g/dL.

- Adequate liver function in the form of: Serum bilirubin < 1.25 x the institutional ULN (upper limit of normal); and AST (aspartate transaminase)/ALT (alanine transaminase) < 2.5 x the institutional ULN.
- Adequate renal function as defined by: serum creatinine ≤ 1.5 x the institutional ULN or creatinine clearance ≥60 mL/min for patients with creatinine levels above the institutional ULN.

3.3. Exclusion criteria: patients meeting the following criteria were excluded from the study;

- Patients with prior therapy for the tumor, including XRT, immunotherapy, targeted therapy or any other investigational agents.
- Patients with extensive surgery (apart from surgical biopsy prior to beginning the study).
- No active second malignancy (patients are not considered to have an active second malignancy if they have completed therapy and are at less than 30% risk of relapse) or other concurrent CTX.
- Primary tumor location in nasopharynx, nasal cavity, paranasal sinuses, or salivary glands.
- Pregnant or breast-feeding women or fertile patients not willing to use effective contraception during treatment and for at least 6 months thereafter.

3.4. Pre-treatment evaluation: Every patient in the study was subjected to the following:

- History & physical examination: As institutional standard.
- Laboratory investigation: Complete blood count, bilirubin, ALT, AST, serum creatinine and creatinine clearance when indicated.
- Radiological studies: CT scans of the head and neck and/or MRI of head and neck, CT chest, abdominal ultrasonography.
- Direct flexible fiberoptic endoscopic examination.
- Audiogram.
- Echocardiography.

3.5. Treatment

All cases were evaluated at a multidisciplinary tumor board comprising head and neck surgeons, radiation oncologists, and medical oncologists. After pretreatment evaluation was completed and eligibility criteria were met, a total of 44 patients were selected for the study, 16 patients were enrolled in the SIB-IMRT arm, and 28 patients in the HART-SEQ-IMRT arm.

3.5.1. Supportive measurement during therapy

- All patients underwent pre-treatment comprehensive primary dental care and assessment that included extractions, restorations, and prophylaxis by an appropriately experienced dental practitioner. All smoker patients received counseling about the importance of smoking cessation.
- All patients were advised on how to maintain good oral hygiene during and after XRT, and received supportive care throughout their treatment course, including pain management with narcotics, and topical treatment as required with benzydamine oral rinse (15 mls 4-8 times daily) in an attempt to reduce the frequency and severity of radiation-induced oral mucositis. Patients' mucosa was inspected regularly during treatment, and analgesia and antimicrobial/antifungal agents to treat mucositis were administered if necessary. Adequate patient hydration and nutrition were ensured by regular evaluation of dietary and fluid intake, including regular measurement of weight, and enteral nutritional supplementation with PEG. Out of 44 patients, 42 underwent PEG before the start of treatment, and only 2 patients who initially refused PEG eventually got it 2 weeks later.
- A moderate level of moisture on skin was maintained with the use of linimentum aquosum.

3.5.2. Systemic therapy

PF regimen concurrent with XRT was given to 30 patients, and TPF regimen followed by cetuximab concurrent with XRT was given to 14 patients.

3.5.2.1. Cisplatinum and 5 FU (PF) concurrent with XRT

PF regimen was given as institutional standard in the form of cisplatinum 30 mg/m² as 1-hour intravenous (i.v.) infusion weekly for 6 weeks, and 5-FU 600 mg/m²/24h administered by continuous i.v. infusion on days 1 to 5.

3.5.2.2. Neoadjuvant TPF followed by cetuximab concurrent with XRT

TPF regimen consisted of docetaxel at a dose of 75 mg/m^2, administered as a 1-hour i.v. infusion on day 1, followed by cisplatinum at a dose of 75 mg/m^2, administered as a 1-hour i.v. infusion on day 1, and 5 FU at a dose of 750 mg/m^2 /24h, administered by continuous i.v. infusion on days 1 to 4, repeated every 22 days for 3 Cycles. Patients who did not have progressive disease and who had adequate bone marrow function underwent XRT combined with cetuximab within 4-5 weeks after the completion of CTX. Cetuximab was administered at an initial dose of 400

mg/m^{2}given as a 2-hour i.v. infusion given one week before beginning of XRT, followed by subsequent weekly doses of 250 mg/m^2 given as a 1-hour i.v. intravenous infusion.

3.5.3. Radiotherapy

3.5.3.1. Patient fixation and immobilization

Patient fixation and immobilization was done using a Sinmed Posifix head and neck positioning system. The following procedure was used; First, all patients were positioned in the supine position on 3-D formed Posifix head support cushions. Each patient was immobilized into a five-point thermoplastic custom made head-shoulder mask (Sinmed Posifix®), resulting in a repositioning errors less than 2 mm. The mask was fixed to a Posifix® Radiotransparent carbon fiber baseplate, which is attached to both the head of CT simulator Couch and the head of an Exact Couch, enabling the patient's head and neck to extend beyond the treatment table for true 360-degree treatment. The carbon fiber baseplate was used also to facilitate higher image quality and to lower the surface dose by reducing radiation attenuation (Fig.3).

When needed, a bite block is used to separate the mandible and tongue from the upper oral cavity to facilitate a decrease in the irradiation dose delivered to these structures and hence to decrease side effects (Fig.3).

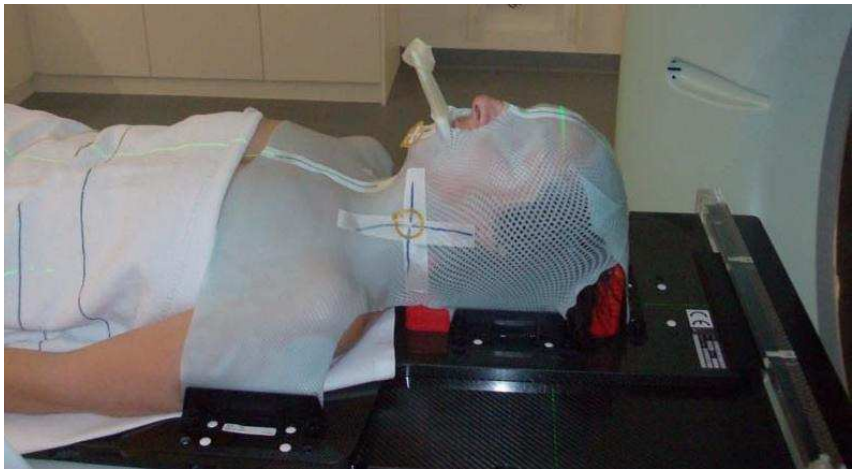


Fig. 3: Fixation and immobilization using a Sinmed Posifix® head and neck positioning system for one representative patient included in the study.

3.5.3.2. Delineation of target volumes

Each patient underwent a treatment planning CT scan with i.v. contrast (The Somatom Sensation Open 16-slice CT system from Siemens Medical Solutions (Malvern, PA)), that features an 82-cm gantry bore with an 82-cm extended field of view for improved patient accessibility and positioning. The CT scan covered the distance from the base of the skull to the carina with slice spacing of 2 mm.

CT slices were imported into the treatment planning software (Eclipse™ Version 8.6.15; Varian Medical Systems, Hansen Way, Palo Alto, CA, USA) through a DICOM network. Other imaging studies like [18F] fluorodeoxyglucose positron emission tomography (FDG-PET) scan, or MRI, were obtained with the patient in the treatment position (Fig.4). They are registered with the planning CT and used in GTV and OARs delineation. For the 14 patients who received neoadjuvant TPF, a pre-chemotherapy CT was registered with the planning CT, and GTV and CTVs were contoured according to the tumor status in the pre-chemotherapy CT (even if downstaging occurred).

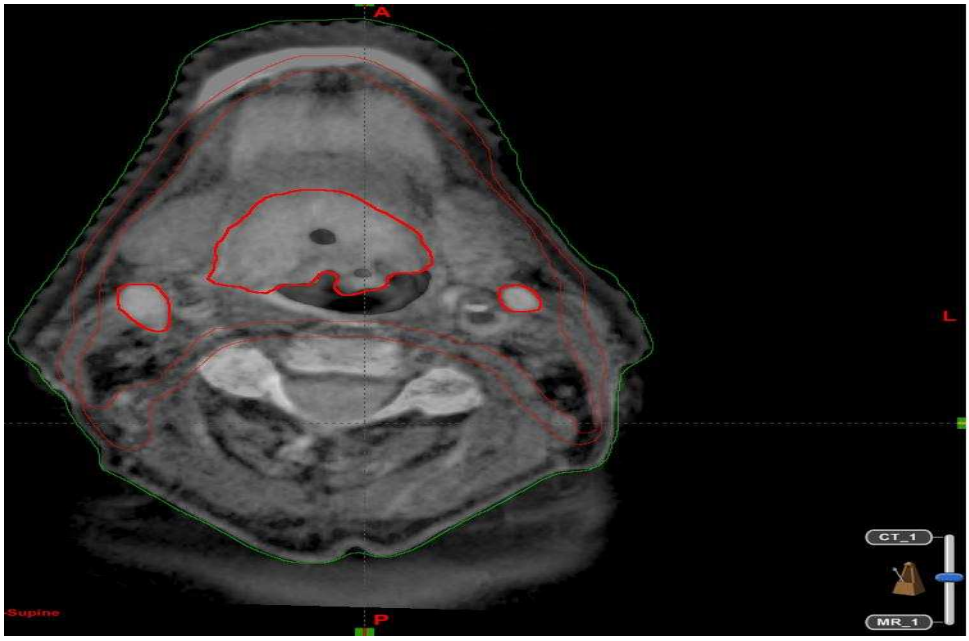


Fig. 4: CT–MRI image fusion: delineation of GTV (red line) could be determined by MRI and directly transferred to the treatment planning CT system: Image obtained for one representative patient (oropharyngeal cancer T4 N2c) included in the study.

According to the ICRU report 50 and ICRU report 62 recommendations, target volumes (GTV, CTVs, and PTVs) and OARs were contoured for each patient. GTV included all clinically and radiologically demonstrable tumors including the involved nodes. Lymph nodes were included in the GTV if they have any of the following radiologic features: (1) diameter >1 cm; (2) smaller than 1 cm with spherical rather than ellipsoidal shape; (3) contain inhomogeneities suggestive of necrotic centers; (4) FDG-PET positive (David and Eisbruch, 2007).

CTV included all potential areas at risk for microscopic tumor involvement by either direct extension or nodal spread. Elective lymph nodes volume definitions were carried according to the recommendations of Gregoire et al. (2000), Chao et al. (2002), Eisbruch et al. (2002), and David and Eisbruch (2007). The PTV defined as a geometric concept used for planning includes a margin necessary to account for setup variations, organ, and patient motion. It was defined to

select appropriate beam sizes and beam arrangements to ensure that the prescribed dose was actually delivered to the CTV.

Three clinical target volumes, CTVA, CTVB, and CTVC, were defined and outlined on each CT slice:

- CTVC $_{(\text{gross tumor})}$: was defined as GTV based on clinical and radiologic information (including primary tumor and involved lymph nodes), expanded with 10-mm margins in three dimensions. The CTVC was then manipulated to exclude uninvolved bone, air, and critical structures.
- CTVB $_{(\text{high-risk})}$: included the high-risk areas harboring microscopic disease. This included normal structures immediately surrounding the CTVC with high risk of local tumor invasion (primary tumor CTVB), and the high-risk lymphatic regions determined according to the primary site, T stage, and involved lymph nodes (lymphatic CTVB).
- CTVA $_{(\text{low-risk})}$: was defined as the low-risk lymphatic areas also determined according to the primary site, T stage, and involved lymph nodes.

The PTVs (PTVA $_{(\text{low-risk})}$, PTVB $_{(\text{high-risk})}$, and PTVC $_{(\text{gross tumor})}$) encompassed their corresponding CTVs with a border 5 mm in the three directions. Limiting the PTVs 3 mm within the external body contour was generally used except where bolus was indicated (suspected skin infiltration).

OARs were defined according to ICRU report 62, which introduced the concept of the planning organ at risk volume (PRV), in which a margin is added around the critical structure to compensate for that organ's geometric uncertainties (ICRU Report 62; McKenzie et al., 2002). The OARs delineated were, the spinal cord, brain stem, parotid glands, lips, and oral cavity, and brachial plexus;

- Contours of the spinal cord were expanded to include the whole spinal canal, and contours of brainstem were expanded by 0.5 cm radially on each CT slice. The expanded volume was used instead of the original organ volume for dose optimization in IMRT planning.
- Oral cavity mucosa contouring encompassed, the surfaces of the inner table of mandible, the surfaces of the inner lips, buccal mucosa, tongue, base of tongue, floor of mouth and palate as described by Eisbruch et al. (2001). The contouring of the noninvolved oral cavity was obtained by subtracting the PTVs from the oral cavity volume
- Parotid gland tissue was excluded from radiation (obtained by subtracting the PTVs from the parotid gland), especially in the neck side which had a lesser risk of metastases

(contralateral parotid). In patients with N2c, no attempt was made to exclude either ipsilateral or contralateral parotid glands from the radiation field.

- Brachial plexus contouring was done according to Hall et al. (2008).
- Lips contouring include both upper and lower lips.

3.5.3.3. Radiation dose prescription

3.5.3.3.1. SIB-IMRT arm

One Plan: All planning target volumes were treated simultaneously in 32 fractions with a 3 dose levels; a dose of 70.4 Gy (2.2 Gy/fraction), 60.8 Gy (1.9 Gy/fraction), and 54.4 Gy (1.7 Gy/fraction) was delivered to the $PTVC_{(gross\ tumor)}$, $PTVB_{(high\text{-}risk)}$, and $PTVA_{(low\text{-}risk)}$, respectively. Patients with N2c received radiation with 2 dose levels; a dose of 70.4 Gy (2.2 Gy/fraction), and one of 60.8 Gy (1.9 Gy/fraction) were delivered to the $PTVC_{(gross\ tumor\ +\ involved\ lymph\ nodes)}$, and $PTVA_{(low\text{-}risk)}$ + $PTVB_{(high\text{-}risk)}$, respectively.

3.5.3.3.2. HART-SEQ-IMRT arm

The radiation dose was delivered in 2-Gy fractions/ day for 5 days/week for 3 weeks followed by 2 x 1.4-Gy fractions/day for 5 days/week for the next 3 weeks, with an interval of at least 8 h between the two daily fractions. A total dose of 72 Gy was delivered in 3 dose levels (49.4 Gy, 59.6 Gy, and 72 Gy), for a total of 30 fractions with OTT of 6 weeks, as follows:

First phase plan: Including $PTVA_{(low\text{-}risk)}$, $PTVB_{(high\text{-}risk)}$, and $PTVC_{(gross\ tumor)}$, treated with conventional fractionation with 2 Gy per fraction per day to a total dose of 30 Gy for 3 weeks,

followed by:

The same target volume treated with HART, with a dose of 1.4 Gy per fraction twice daily for a dose of 19.6 Gy to a total dose of 49.4 Gy.

Followed by first sequential field reduction:

Second phase plan: Including the $PTVC_{(gross\ tumor)}$, and $PTVB_{(high\text{-}risk)}$ treated with HART, with a dose of 1.4 Gy per fraction twice daily for a dose of 9.8 Gy to a total dose of 59.4 Gy.

Followed by second sequential field reduction:

Third phase plan: Including the $PTVC_{(gross\ tumor)}$ treated with HART, with a dose of 1.4 Gy per fraction twice daily for a dose of 12.6 Gy to a total dose of 72 Gy.

For patients with N2c, a total dose of 72 Gy was delivered in 2 dose levels (59.6 Gy, and 72 Gy) for a total of 30 fractions with OTT of 6 weeks, as follows:

First phase plan: Including PTVA $_{(low\text{-}risk)}$, PTVB $_{(high\text{-}risk)}$, and PTVC $_{(gross\ tumor)}$, treated with conventional fractionation with 2 Gy per fraction per day to a total dose of 30 Gy for 3 weeks.

Followed by:

The same target volume treated with HART, with a dose of 1.4 Gy per fraction twice daily for a dose of 29.4 Gy to a total dose of 59.4 Gy.

Followed by one sequential field reduction:

Second phase plan: Including the PTVC $_{(gross\ tumor\ +\ involved\ lymph\ nodes)}$ treated with HART, with a dose of 1.4 Gy per fraction twice daily for a dose of 12.6 Gy to a total dose of 72 Gy.

For those patients with multiple suspected lymph nodes ≤ 1 cm (cluster of 3 or more borderline nodes) that could not be included in the PTVC volume (because these lymph nodes either did not meet the radiological and clinical criteria of positive lymph nodes or the PTVC volume receiving 72 Gy would be too large if it included them), an intermediate dose of 66.4 Gy was prescribed. A total dose of 72 Gy was delivered in 3 dose levels (59.6 Gy, 66.4 Gy, and 72 Gy) for a total of 30 fractions with OTT of 6 weeks, as follows:

First phase plan: Including PTVA $_{(low\text{-}risk)}$, PTVB $_{(high\text{-}risk)}$, and PTVC $_{(gross\ tumor)}$, treated with conventional fractionation with 2 Gy per fraction per day to a total dose of 30 Gy for 3 weeks.

Followed by:

The same target volume treated with HART, with a dose of 1.4 Gy per fraction twice daily for a dose of 29.4 Gy to a total dose of 59.4 Gy.

Followed by first sequential field reduction:

Second phase plan: Including the PTVC $_{(gross\ tumor)}$, and PTVB $_{(high\text{-}risk)}$ (included the suspected lymph nodes) and treated with HART, with a dose of 1.4 Gy per fraction twice daily for a dose of 7 Gy to a total dose of 66.4 Gy.

Followed by second sequential field reduction:

Third phase plan: Including the PTVC $_{(gross\ tumor)}$ treated with HART, with a dose of 1.4 Gy per fraction twice daily for a dose of 5.6 Gy to a total dose of 72 Gy.

Table 3: The different dose fractionation schemes used in the study

XRT fractionation	**1st phase**	**2nd phase**	**3rd phase**
HART	PTVA+B+C 30Gy 2Gy/fx + 19.6Gy 1.4Gy/fx	PTVB+C 9.8 Gy 1.4Gy/fx	PTVC 12.6 Gy 1.4Gy/fx
Total prescribed dose	**49.6 Gy**	**59.4 Gy**	**72 Gy**
HART (N2C)	PTVA+B+C 30Gy 2Gy/fx + 29.4 Gy 1.4Gy/fx	PTVC 12.6 Gy 1.4Gy/fx	
Total prescribed dose	**59.4 Gy**	**72 Gy**	
HART (multiple lymph nodes <1cm)	PTVA+B+C 30Gy 2Gy/fx + 29.4Gy 1.4Gy/fx	PTVB+C 7 Gy 1.4Gy/fx	PTVC 5.6 Gy 1.4Gy/fx
Total prescribed dose	**59.4 Gy**	**66.4 Gy**	**72 Gy**
SIB-IMRT	PTVA 54.4Gy 1.7Gy/fx PTVB 60.8Gy 1.9Gy/fx PTVC 70.4Gy 2.2Gy/fx		
Total prescribed dose	**70.4 Gy**		
SIB-IMRT (N2C)	PTVA+B 60.8Gy 1.9Gy/fx PTVC 70.4Gy 2.2Gy/fx		
Total prescribed dose	**70.4 Gy**		

Table 4: Distribution of patients according to different XRT schedules

XRT schedule	**NO (%)**
HART-SEQ-IMRT (28 patients):	
HART (49.6, 59.4, 72 Gy)	13 (46.4%)
HART (59.4, 72 Gy)	6 (21.4%)
HART (59.4, 66.4, 72Gy)	8 (28.6%)
HART (49.6, 66.4, 72 Gy)	1 (3.6%)
SIB-IMRT (16 patients):	
SIB (54.4, 60.8, 70.4 Gy)	10 (62.5%)
SIB (60.8, 70.4 Gy)	5 (31.25%)
SIB (54.4, 70.4 Gy)	1 (6.25%)

3.5.3.4. Biologically equivalent dose (BED) comparison

For a more comprehensive treatment plan evaluation, and to compare the SIB regimen to the HART regimen in terms of radiobiological efficacy, we used the BED iso-effect formula (Fowler, 1989), without taking into account the amount of repopulation of the tumor cells.

$BED = D\ (d + \alpha/\beta)/2 + \alpha/\beta$

D = total dose

d = dose per fraction

Calculations were performed using a tumor and early reacting tissue α/β of 10 Gy, and late reacting tissue α/β of 2 Gy.

Table 5: Biologically effective dose calculated for different fractionation schemes used by the different irradiation schedules

	HART	α/β_{2}	α/β_{10}	SIB	α/β_{2}	α/β_{10}
PTVA	49.6	46.66	48.62	54.4	50.32	53.04
PTVB	59.4 66.4	54.99 60.94	57.93 64.58	60.8	59.28	60.29
PTVC	72	65.61	69.9	70.4	73.92	71.57

All doses are prescribed in Gy.

3.5.3.5. IMRT planning and optimization process

IMRT planning and optimization were performed using a commercial inverse planning system (Eclipse and Helios; VarianMedical Systems, Hansen Way, Palo Alto, CA). For all patients, 7-9 coplanar, equally distanced 6 MV photon beams were used. The optimization process was based on user-defined dose volume constraints and penalty factors. These constraints were used as initial guidelines before the start of the optimization process. During planning the highest priority was given to a satisfactory PTV coverage and secondarily to the OAR.

3.5.3.5.1. Dose specification for PTVs

95% of the prescribed dose should cover ≥ 95% of the respective PTVs and maximal dose received to PTVs should be ≤ 110% of the prescribed dose.

3.5.3.5.2. Dose constraints for OARs

- Spinal cord maximal dose ≤ 50 Gy (Emami et al., 1991; Habrand and Drouet , 2010).
- Brain stem maximal dose ≤ 54 Gy (Emami et al., 1991; Debus et al., 1999; Mayo et al., 2010).
- If possible, sparing of at least one parotid gland (mean dose ≤26 Gy) was attempted (sparing of the contralateral gland was given priority compared with the ipsilateral gland), No attempt of sparing was made in patients with N2c (Eisbruch et al., 1999).

- The noninvolved oral cavity mean dose ≤30 Gy (Ben-David et al., 2007).
- Brachial plexus maximal dose ≤ 66 Gy (Emami et al. 1991; Schierle and Winograd, 2004; McGary et al. 2007).
- Mandible mean dose ≤ 65 Gy (Murray et al., 1980; Emami et al., 1991; Studer et al., 2007; Ben-David et al., 2007).
- Lips mean dose ≤ 50 Gy (institutional standard).

Dose calculation was performed using the Varian Anisotropic Analytical Algorithm (AAA) with a calculation grid size of 2.5 mm. This calculation method improves the dose calculation accuracy especially in heterogeneous media, takes into account the lateral dispersion, and is almost as good as a Monte-Carlo calculation (Ono et al., 2010; Breitman et al., 2007; Van Esch et al., 2006).

3.5.3.6. Plan evaluation

Plans were optimized till desired objectives were met. Relative and absolute DVHs were calculated for optimized treatment plans and a slice-by-slice analysis of dose color wash displays was done. Plans were deemed acceptable by a senior staff member when normal tissue sparing was maximized without compromising target coverage (Fig.5).

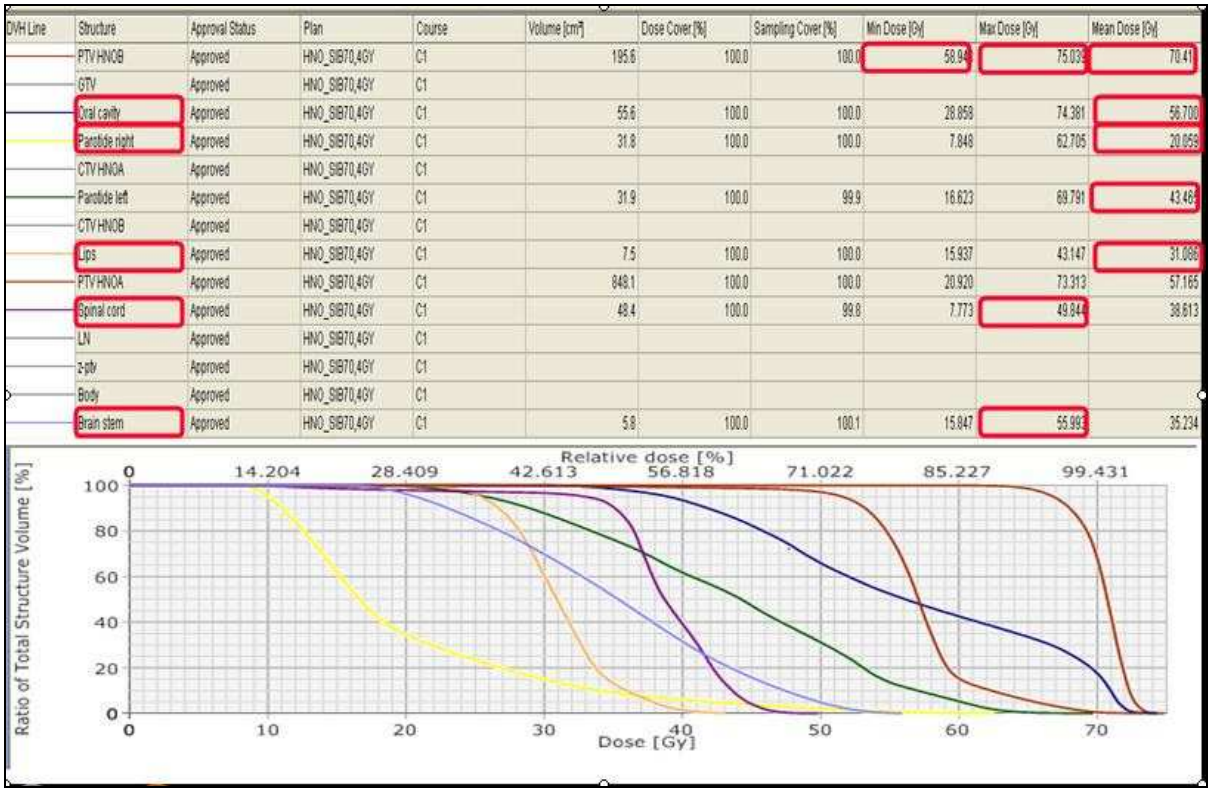


Fig. 5: Absolute and relative DVH showed dose received by target volumes and different OARs: SIB-IMRT plan obtained for one representative patient included in the study.

3.5.3.7. Treatment verification and implementation

Thirty nine patients were treated on a Varian Clinac-2100C accelerator (Varian Medical Systems, Palo Alto, CA). The "sliding window" technique (80-leaf MLC) was used for the delivery of IMRT. Electronic portal images that localize the isocenter placement were acquired in two orthogonal projections (0° anteroposteriorly and 90° laterally) prior to treatment delivery, and compared with the corresponding digitally reconstructed radiographs (DRRs) of the same beams obtained by treatment planning system reconstruction. Deviations ≥3 mm in the isocenter position were immediately corrected. Subsequent electronic portal images were acquired two times per week and image off-line corrections were done when setup error ≥ 3 mm was found in any direction (Fig.6).

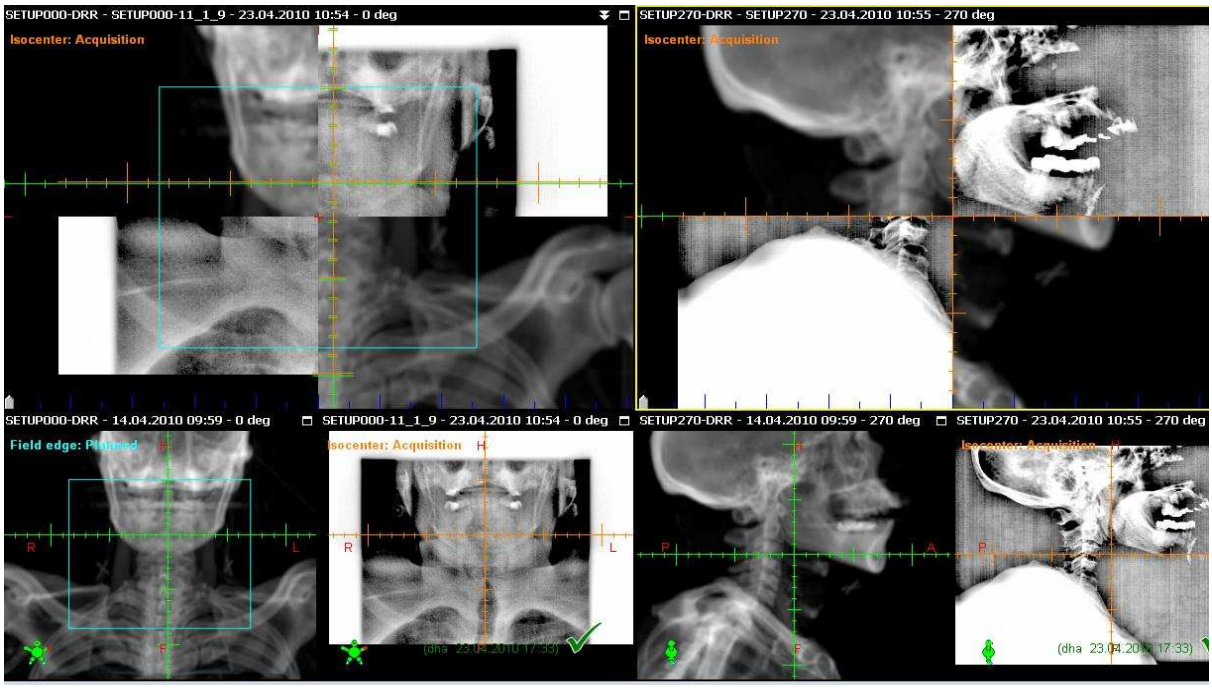


Fig. 6: Electronic portal images\DRRs image fusion: Image obtained for one representative patient included in the study.

Five patients were treated on a 2100 DHX Varian linear accelerator equipped with the On-Board Imager (OBI, Varian Medical Systems, Palo Alto, CA). The sliding window technique (120-leaf MLC Millenium) was used for the delivery of IMRT. Each patient underwent on-board image set for 2D positioning verification using orthogonal 2D kV radiographs, followed by on-board image set for 3D positioning verification using Cone Beam CT (CBCT) scans. The 3-D manual image registration using bony anatomy was used to match between the planning CT scan and verification CBCT. Registration was verified using the split view. CBCT was acquired after both initial setups, after any repositioning, and at least once a week (Fig.7).

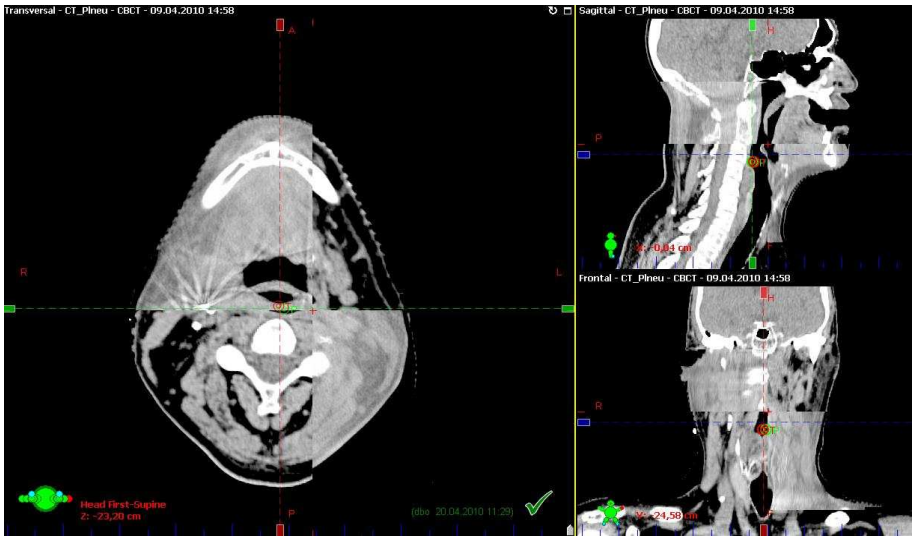


Fig. 7: CBCT\Planning CT Image Fusion: Image obtained for one representative patient included in the study.

Individual patient quality assurance was carried out using the commercially available software, VeriSoft (PTW-Freiburg, Germany), to ensure that the isodose distributions and relative doses calculated by the planning system match the doses delivered by the linear accelerator.

3.6. Follow-up

Patients were monitored at least weekly during XRT, and one week after completing XRT for signs of acute toxic effects, with appropriate adjustments in CTX, cetuximab, or XRT were made when necessary. Three months after completion of XRT, evaluation by physical examination, laboratory investigation and radiological studies including CT and/or MRI scans of the head and neck region was preformed with assessment of clinical tumor response.

Thereafter, patients were followed regularly at 3-month intervals for the first year. Evaluations consisted of history physical examination to assess late treatment toxicities. Direct flexible fiberoptic endoscopic examination alternating with CT and/or MRI scans of the head and neck region was done to detect local and/or regional recurrence. Chest CT and abdominal ultrasonography were done to detect metastases. Patients with residual, recurrent disease, or distant progression were referred for salvage therapy according to the status of each patient.

3.7. Outcomes and data analysis

3.7.1. Dosimetric analysis

DVHs—dose statistics based plan evaluation and comparison metrics for the 2 IMRT arms were done retrospectively using the following criteria (ICRU Report 83, 2010);

- For PTVA, PTVB, and PTVC: Mean (D_{mean}), minimum (D_{min}), and maximum dose (D_{max}), $D_{98\ \%}$ ($D_{near\text{-}min}$), $D_{95\ \%}$ (minimum absorbed dose that covers 95 % of the volume of the PTV), $D_{50\ \%}$ (median), and $D_{2\ \%}$ ($D_{near\text{-}max}$). Also, dose coverage was assessed by comparing the volume of each PTV that received 95% of the prescription dose ($V_{95\%}$).
- For CTVA, CTVB, and CTVC: D_{mean}, and $D_{50\ \%}$.
- Differences between prescribed dose and the calculated mean absorbed dose (D_{diff}) was also assessed for nodal target volumes (CTVA\PTVA$_{(low\text{-}risk)}$, and CTVB\PTVB$_{(high\text{-}risk)}$).
- For ipsilateral parotid, contralateral parotid glands, oral cavity, and lips: $D_{mean,\ and}\ D_{50\ \%}$.
- For spinal cord and brain stem: D_{max}.

3.7.2. Toxicity scoring

The primary endpoint of the study was to compare the toxicity profile of the 2 IMRT techniques. Acute and late toxicities were scored using version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events system developed by the NCI (NCI–CTCAE v3.0, 2006).

- Acute radiation-related toxicities were assessed including dysphagia, skin erythema (dermatitis), xerostomia, mucositis, dysgeusia, pain, weight loss, fatigue, and hoarseness of voice. The interruption of the XRT course due to severe toxicity of ≥ grade III was recorded and classified into interruption for a period ≤ one week, or > one week.
- Occurrence of early death within 3 months after completion of XRT was also reported. Death was further classified into death from malignant disease, death from treatment toxicity, or death due to other cause.
- Late radiation-related toxicity assessment started 3 months after completion of XRT including xerostomia, skin fibrosis, lymphoedema, ORN, hoarseness of voice, trismus, dysgeusia, pain, brachial plexopathy, and myelitis (L'hermittes syndrome).

3.7.3. Assessment of tumor response

The response to treatment was classified according to World Health Organization (WHO) criteria (Miller et al., 1981). Response criteria were defined as follows:

- Complete response (CR): was defined as complete disappearance of all known disease.
- Partial response (PR): was defined as a decrease of at least 50% in total tumor load.

- Stationary disease (SD): was defined as a decrease of less than 50%, or an increase of less than 25% in the tumor area of one or more measurable lesions.
- Progressive disease (PD): was defined as an increase of at least 25% in total tumor load, or appearance of at least one new lesion.

3.7.4. Assessment of treatment failure

Failures were recorded as local (at the primary site), regional (in the neck nodes), or distant failure (outside the treated volume). In-field (locoregional) failures were further classified according to the site of occurrence; in CTVC $_{(\text{gross tumor})}$, CTVB $_{(\text{high risk})}$, or CTVA $_{(\text{low risk})}$.

3.7.5. Statistical analysis

In the univariate descriptive analysis and for the comparison of percentages between groups cross-tables with Chi-square tests were used. Mann-Whitney U- and Kruskal-Wallis H- tests were used when appropriate to compare continuous data between groups non-parametrically. All results were described using mean ± standard deviation (± SD).

Survival times were calculated from the date radiation therapy was initiated, and the results were analyzed as of December 1, 2010.

Time to progression [PFS] was calculated from the date of the initiation of XRT up to the date of first progression of any type, or death from any cause. Time to loco-regional failure [LRF] was calculated from the date of the initiation of XRT up to the date of local and/or regional recurrence, or death from any cause. Time to distant metastases [DMFS] was calculated from the date of the initiation of XRT up to the date of distant metastases, or death from any cause. Overall survival [OS] was measured from the date of the initiation of XRT until death.

For all survival endpoints Kaplan-Meier estimates were calculated according to the product-limit method (Kaplan and Meier, 1958). Differences between the survival curves with respect to interesting groups of patients were assessed by the Log–Rank statistics.

For quantification of median follow-up, Schemper & Smith (1996) proved that the simple calculation of the median of observation times is not a valid method and can be misleading. Therefore, the reverse Kaplan-Meier method (KM-PF) which can be meaningfully interpreted was used to estimate the median follow-up time. KM-PF was calculated in the same way as the Kaplan-Meier estimate of the survival function, but with the meaning of the status indicator reversed (Altman, 1995 or Parmar & Machin, 1996).

Cox's proportional hazard regression analysis was used to identify risk factors for LRFS and OS multivariately (Cox, 1972). For numeric reasons (relative number of patients and number of variables), only variables with $p \leq 0.025$ in univariate analyses and confirmed in univariate Cox's regressions, together with other explanatory variables expected to have effect on LRF, were included in multivariate Cox's regression analysis. For the multivariate analysis, a stepwise backward feature selection procedure was used in order to find out the most relevant features. Hazard ratios (HR) with 95% confidence intervals (CI) and the corresponding p-values were given.

Because of the limited number of events, results of Cox' regressions for the other survival endpoints were only reported.

In order to investigate the influence of different clinical parameters on XRT interruption and grade III -toxicity (dysphagia, mucositis, and xerostomia), multivariate logistic regressions were conducted using the same variable selection scheme as before. Odds ratios (OR) with 95% confidence intervals and the corresponding p-values were calculated.

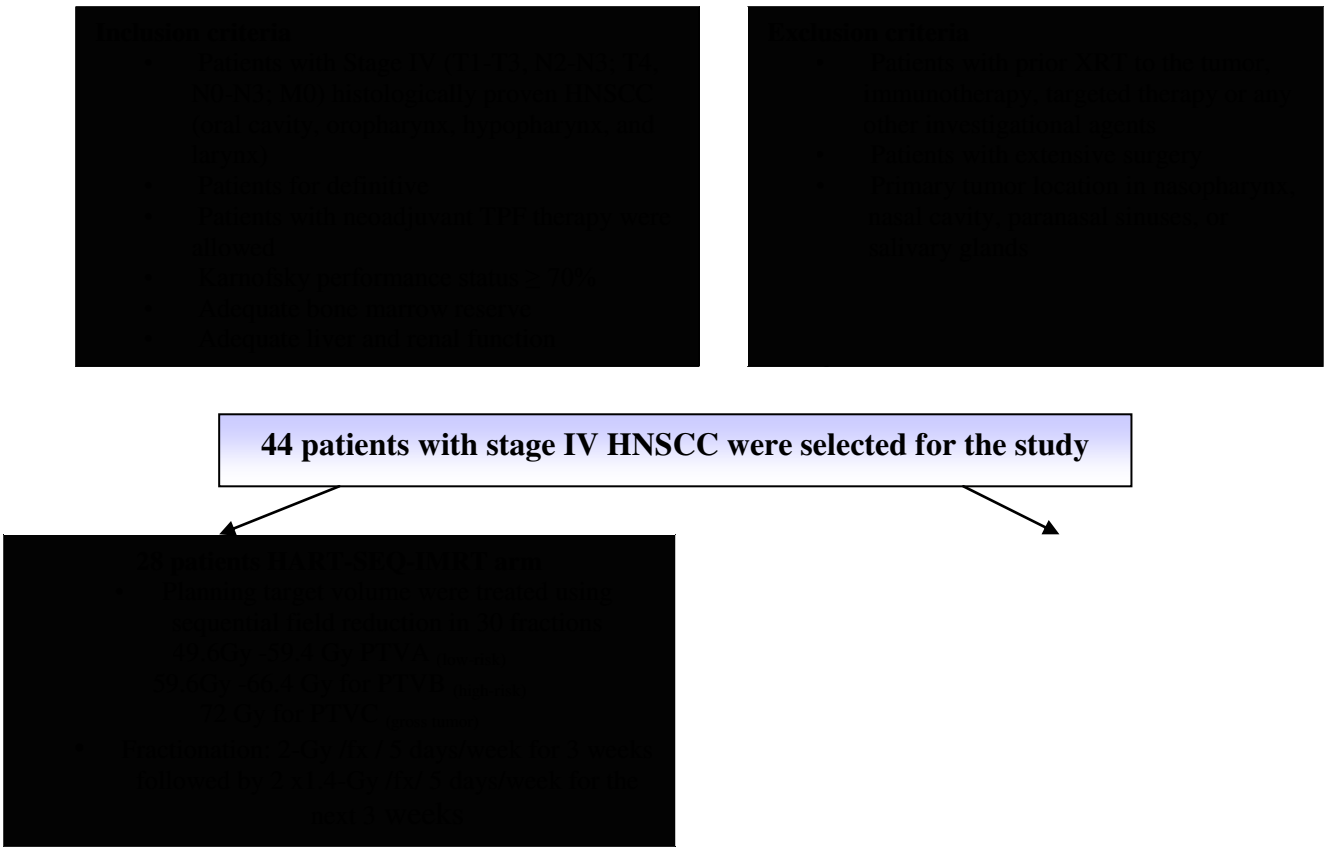
All analyses were performed using the Statistical Package for Social Sciences software PASW (version 18.0, SPSS, Chicago, IL). All statistical tests were two sided, and p=0.05 was used to indicate statistical significance.

3.7.6. Study limitations

One major limitation of this study is its design as a non-randomized trial. However, the strengths of the presented work include its prospective continuous assessment and monitoring of the patients. Moreover, we investigated statistically all possible confounders for their influence on the results and tested various subgroups accordingly. Also, it must be recognized that we enrolled only patients with very advanced stage HNSCC (stage IV).

Another limitation: a rather small number of patients which leads to a lack of power. Nevertheless, we thought that the descriptive data may be informative.

Other limitations include: short duration of follow-up, discrepancy in tumor characteristics regarding volume of GTV between the two study arms, and heterogeneous systemic therapy regimens. Given these heterogeneities between the two XRT arms in disease and treatment characteristics, it would not be possible to reach clear results and to compare the two XRT arms without bias. Therefore, we regarded various subgroups of patients for further analyses. In particular, three subgroups of patients were examined: patients with GTV ≤ 100 cm^3, PF group, and TPF group.


Inclusion criteria
Patients with Stage IV (CT: T3, N2-N3; T4, N0-N3; M0) histologically proven HNSCC (oral cavity, oropharynx, hypopharynx, and larynx)
Patients for definitive
Patients with neoadjuvant TPF therapy were allowed
Karnofsky performance status ≥ 70%
Adequate bone marrow reserve
Adequate liver and renal function
Exclusion criteria
Patients with prior XRT to the tumor, immunotherapy, targeted therapy or any other investigational agents
Patients with extensive surgery
Primary tumor location in nasopharynx, nasal cavity, paranasal sinuses, or salivary glands
44 patients with stage IV HNSCC were selected for the study
28 patients HART-SIBO-IMRT arm
Planning target volume were treated using sequential field reduction in 30 fractions
49.8Gy -59.4 Gy PTVA high risk
59.6Gy -60.4 Gy for PTVB high risk
72 Gy for PTVC low risk
Fractionation: 2 Gy/fx/5 days/week for 3 weeks, followed by 2.3/1.4 Gy/fx/3 days/week for the next 3 weeks

4. Results

4.1. Patients, disease, and treatment characteristics

From May 2009 to June 2010, a total of 44 patients were enrolled in this prospective nonrandomized study and treated with IMRT for stage IV HNSCC. There were 38 (86.4%) male and 6 (13.6%) female patients with a mean age of 57.93 ± SD 8.55 years (range 43 - 76 years). Thirty three (75%) patients were either current or former smokers while 11 (25%) non-smokers. Nineteen (43.2%) patients used alcohol and 25 (56.8 %) did not use alcohol. The primary tumor site was oropharynx in 16 (36.4%), hypopharynx in 8 (18.2%), oral cavity in 11 (25%), and larynx in 9 (20.5%) patients. Forty (90.9%) patients were diagnosed after incisional biopsy, and 4 (9.1%) after excisional biopsy. Regarding tumour grade, 8 (18.2%) patients had well differentiated, 25 (56.8%) had moderately differentiated, and 11 (25%) had poorly differentiated PECA. According to T stage distribution, only 3 (6.8%) patients presented with T2, 11 (25%) with T3, and 30 (68.2%) with T4. The N stage was N0 in only 2 (4.6%), N1 in 3 (6.8%), N2a\b in 13 (29.5%), N2c in 24 (54.5%), and N3 in 2 (4.6%) patients. Forty two (95.5%) patients had stage IVA, and only 2 (4.5%) patients had stage IVB. The GTV mean volume was 66.876 ± SD 47.75 cm^3 (range 3.22 - 188.3 cm^3). The body weight before starting XRT ranged from 48 – 100 kg (mean 70.78 ± SD 12.01 kg). Twenty (45.5%) patients had a baseline KPS of 90% at presentation, 18 (40.9%) had 80%, and 6 (13.6%) had 70%. All 44 patients were treated definitively, amongst these, 28 (63.6%) patients were enrolled in the HART-SEQ-IMRT arm and 16 (36.4%) in the SIB-IMRT arm. Thirty (68.2%) patients received PF regimen concurrent with XRT, while neoadjuvant TPF regimen followed by cetuximab concurrent with XRT was received by 14 (31.8%) patients (Table 6).

4.1.1. Patients, disease, and systemic therapy characteristics for each XRT technique

There were no statistically significant differences between the two treatment groups for patient, tumor, or treatment characteristics, except for volume of GTV and systemic therapy received. Patients who were enrolled in the SIB-IMRT arm had significantly smaller GTV mean volume of 39.54 ± SD 25.23 cm^3, compared to 82.49 ± SD 50.8 cm^3 for patients enrolled in the HART-SEQ-IMRT arm ($p = 0.003$). The systemic therapy received was also significantly different between the two groups. Out of 28 patients treated with the HART-SEQ-IMRT technique, 24 patients received PF regimen concurrent with XRT and only 4 patients received neoadjuvant TPF regimen followed by cetuximab concurrent with XRT, compared to 6 patients and 10 patients, respectively, treated with the SIB-IMRT technique ($p = 0.001$) (Table7).

To avoid bias in the subsequent analyses, in addition to the analyses for all patients, we examined the corresponding subgroups of GTV and systemic treatment.

Table 6: Patients, disease, and treatment characteristics for the 44 patients

Characteristic	**NO (%)*** **No =44**
Gender:	
Male	38 (86.4%)
Female	6 (13.6%)
Age:	
Range (Mean ± SD)	43 - 76 years (57.93± 8.55 years)
Smoking:	
Smoker (former and current)	33 (75%)
Non-smoker	11 (25%)
Alcoholic:	
Alcoholic	19 (43.2%)
Non-alcoholic	25 (56.8 %)
Primary site:	
Oropharynx	16 (36.4%)
Hypopharynx	8 (18.2%)
Oral cavity	11 (25%)
Larynx	9 (20.5%)
Type of biopsy:	
Incisional biopsy	40 (90.9%)
Excisional biopsy	4 (9.1%)
Histology:	
Well differentiated	8 (18.2%)
Moderately differentiated	25 (56.8%)
Poorly differentiated	11 (25%)
T stage:	
T2	3 (6.8%)
T3	11 (25%)
T4	30 (68.2%)
N stage:	
N0	2 (4.5%)
N1	3 (6.8%)
N2a\b	13 (29.5%)
N2c	24 (54.5%)
N3	2 (4.5%)
AJCC Staging:	
Stage IVA	42 (95.5%)
Stage IVB	2 (4.5%)
GTV:	
Range	3.22 - 188.3 cm^3
Mean ± SD	66.876 ± SD 47.75 cm^3
Baseline KPS:	
90%	20 (45.5%)
80%	18 (40.9%)
70%	6 (13.6%)
Baseline body weight:	
Range (Mean ± SD)	48 – 100 kg (70.78 ± 12.01 kg)
XRT arm:	
HART-SEQ-IMRT	28 (63.6%)
SIB-IMRT	16 (36.4%)
Systemic therapy:	
PF regimen concurrent with XRT	30 (68.2%)
Neoadjuvant TPF regimen + cetuximab concurrent with XRT	14 (31.8%)

***** Except as otherwise stated.

Table 7: Distribution of patients, disease, and treatment characteristics for each XRT technique

variable	XRT Technique		p-value
	HART-SEQ-IMRT **NO = 28** **NO (%)***	**SIB- IMRT** **NO = 16** **NO (%)***	
Gender:			
Male	26 (92.9%)	12 (75%)	0.097
Female	2 (7.1%)	4 (25%)	
Age:			
Mean ± SD	56.93 ± 7.855 years	59.69 ± 9.659 years	0.309
Smoking:			
Smoker	22 (78.6%)	11 (68.8%)	0.469
Non-smoker	6 (21.4%)	5 (31.3%)	
Alcoholic:			
Alcoholic	13 (46.4%)	6 (37.5%)	0.565
Non-alcoholic	15 (53.6%)	10 (62.5%)	
Primary site:			
Oropharynx	8 (28.6%)	8 (50%)	0.203
Hypopharynx	6 (21.4%)	2 (12.5%)	
Oral cavity	6 (21.4%)	5 (31.3%)	
Larynx	8 (28.6%)	1 (6.3%)	
Histology:			
Well differentiated	4 (14.3%)	4 (25%)	0.595
Moderately differentiated	16 (57.1%)	9 (56.3%)	
Poorly differentiated	8 (28.6%)	3 (18.8%)	
T stage:			
T2	1 (3.6%)	2 (12.5%)	0.137
T3	5 (17.9%)	6 (37.5%)	
T4	22 (78.6%)	8 (50%)	
N stage:			
N0	1 (3.6%)	1 (6.3%)	0.612
N1	1 (3.6%)	2 (12.5%)	
N2a\b	9 (32.1%)	4 (25%)	
N2c	15 (53.6%)	9 (56.3%)	
N3	2 (7.1%)	0 (0%)	
AJCC Staging:			
Stage IVA	26 (92.9)	16 (100%)	0.274
Stage IVB	2 (7.1%)	0 (0%)	
GTV [1]:			
Mean ± SD	82.49 ± 50.8 cm^3	39.54 ± 25.23 cm^3	0.003
Baseline KPS:			
90%	13 (46.4%)	7 (43.8%)	0.956
80%	11 (39.3%)	7 (43.8%)	
70%	4 (14.3%)	2 (12.5%)	
Baseline body weight:			
Mean ± SD	71.39 ± 12.09 kg	69.75 ± 12.18 kg	0.668
Systemic therapy [2]:			
PF regimen concurrent with XRT	24 (85.7%)	6 (37.5%)	0.001
Neoadjuvant TPF regimen followed by cetuximab concurrent with XRT	4 (14.3%)	10 (62.5%)	

***** Except as otherwise stated.

[1)] Analysis of subgroup of patients with GTV ≤100cm^3 was done.

[2)] Analysis of corresponding subgroups of patients (PF patients, and TPF patients) was done.

4.2. Planning parameters

4.2.1. Dose Prescription

For all patients, the mean prescribed dose for the PTVA $_{(low\text{-}risk)}$ was 55.19 ± SD 4.46 Gy (range 49.6 - 60.8 Gy). The mean prescribed dose for the PTVB $_{(high\text{-}risk)}$ was 61.27 ± SD 2.89 Gy (range 54.4-66.4 Gy). The mean prescribed dose for the PTVC $_{(gross\ tumor)}$ was 71.42.± SD 0.78 Gy (range 70.4 -72 Gy).

4.2.2. Dosimetric parameters

4.2.2.1. Target volumes

4.2.2.1.1. HART-SEQ-IMRT plans

Results of dosimetric analyses for the different targets and dose levels treated with HART-SEQ-IMRT are presented in Table (8). The HART-SEQ-IMRT technique provided the requisite coverage for the target volumes and resulted in good OARs sparing. However, we observed that the sequential field plans resulted in higher doses delivered to all target volumes, and the difference between the prescribed dose for each target volume and the mean absorbed dose was significantly high.

4.2.2.1.2. SIB-IMRT plans

Results of dosimetric analyses for the different targets and dose levels treated with SIB-IMRT plans are given in Table (9). For 16 patients, acceptable SIB-IMRT plans were achieved without exceeding normal structure dose constraints or clinically compromising PTV coverage. No large difference between the prescribed doses and the mean absorbed dose for different target volumes could be recorded.

4.2.2.2. Organs at risk

Doses to important OARs generated from IMRT plans to all 44 patients are shown in table (10). Normal tissue constraints for contralateral parotid glands could be obtained in only 19 (43.2%) of all patients; ipsilateral parotid gland could be spared in only one patient, and normal tissue constraints for oral cavity could be achieved only in 10 (22.7%) of patients.

However, after maintaining PTV prescription for each target volume, all patients met constraints for cord and brain stem, also reduction in the mean and maximum doses to some OARs could be observed (Table 10).

Table 8: Dosimetric parameters for different dose target levels for 28 HART-SEQ-IMRT plans

Parameter	Range	Mean ± SD
CTV 49.6 Gy:		
D_{mean}	51.54 – 63.58	57.85 ± 3.57
$D_{difference}$	1.94 – 13.98	8.25 ± 3.57
$D_{50\ \%}$	49.85 – 63.9	57.27 ± 4.14
PTV 49.6 Gy:		
Volume	28.50 – 494.90	159.8 ± 123.32
D_{mean}	50.43 – 62.21	56.03 ± 3.32
$D_{difference}$	0.83 – 12.61	6.43 ± 3.32
D_{min}	30.43 – 47.85	39.63 ± 5.54
D_{max}	62.09 - 75,92	71.4 ± 3.98
$D_{98\ \%}$	45.99 – 54.96	48.89 ± 2.68
$D_{95\ \%}$	46.83 – 56.72	50.19 ± 2.95
$D_{50\ \%}$	49.25 – 62.51	55.71 ± 3.80
$D_{2\ \%}$	59.23 – 70.97	64.29 ± 3.96
$V_{95\%}$ (%)	93.92 – 100	98.48 ± 1.93
CTV 59.4 Gy:		
D_{mean}	62.55 – 68.78	66.32 ± 1.72
$D_{difference}$	3.15 – 9.38	6.92 ± 1.72
$D_{50\ \%}$	61.13 – 70.22	66.57 ± 2.89
PTV 59.4 Gy:		
Volume	140.2 – 976.7	472.96 ± 188.99
D_{mean}	61.01 – 65.98	64.12 ± 1.37
$D_{difference}$	1.61 – 6.85	4.72 ± 1.37
D_{min}	17.93 – 51.82	44.91 ± 8.8
D_{max}	70.42 – 77.72	75.31 ± 1.4
$D_{98\ \%}$	51.55 – 58.8	56.28 ± 1.39
$D_{95\ \%}$	55.95 – 59.97	57.7 ± 0.92
$D_{50\ \%}$	60.13 – 67.26	63.65 ± 1.99
$D_{2\ \%}$	68.34 – 73.8	72.23 ± 1.56
$V_{95\%}$ (%)	94.92 – 99.92	98.34 ± 1.22
CTV 66.4 Gy:		
D_{mean}	69.6 – 73.02	71.28 ± 1.12
$D_{difference}$	3.2 – 6.62	4.88 ± 1.12
$D_{50\ \%}$	69.94 – 73.15	71.52 ± 1.11
PTV 66.4 Gy:		
Volume	48.8 – 666.8	340.67 ± 173.13
D_{mean}	67.82 – 71.8	69.9 ± 1.23
$D_{difference}$	1.42 – 5.4	3.5 ± 1.23
D_{min}	31.86 – 60.33	55.05 ± 8.91
D_{max}	74.67 – 77.35	76.11 ± 0.78
$D_{98\ \%}$	61.67 – 66.48	64.58 ± 1.69
$D_{95\ \%}$	63.09 – 67.77	65.71 ± 1.59
$D_{50\ \%}$	67.9 – 72.17	70.08 ± 1.38
$D_{2\ \%}$	73.1 – 75.04	74.11 ± 0.59
$V_{95\%}$ (%)	95.38 - 99.96	98.89 ± 1.79
CTV 72 Gy:		
D_{mean}	71.82 – 73.83	72.98 ± 0.43
$D_{50\ \%}$	71.98 – 73.97	73.06 ± 0.43
PTV 72 Gy:		
Volume	133.9 – 949.4	380.9 ± 180.14
D_{mean}	71.37 – 73.29	72.65 ± 0.39
D_{min}	34.27 – 66.53	57.77 ± 7.89
D_{max}	74.19 – 78.23	76.57 ± 0.83
$D_{98\ \%}$	65.63 – 70.07	68.47 ± 0.91
$D_{95\ \%}$	67.46 – 71.36	70.04 ± 0.73
$D_{50\ \%}$	71.79 – 73.48	72.85 ± 0.38
$D_{2\ \%}$	73.41 – 76.25	75.02 ± 0.58
$V_{95\%}$ (%)	93.75 – 99.9	98.7 ± 1.15

Table 9: Dosimetric parameters for different dose target levels for 16 SIB-IMRT plans

Parameter	Range	Mean ± SD
CTV 54.4 Gy:		
D_{mean}	55.58 – 60.05	56.77 ± 1.41
$D_{difference}$	1.18 – 5.65	2.37 ± 1.41
$D_{50\ \%}$	54.49 – 58.4	56.24 ± 1.22
PTV 54.4 Gy:		
Volume	96.3 – 848.1	292.12 ± 228.37
D_{mean}	53.93 – 57.17	55.3 ± 1.01
$D_{difference}$	0.41 – 2.77	1.21 ± 0.86
D_{min}	18.16 – 48.71	39.97 ± 10.47
D_{max}	60.23 – 73.31	65.45 ± 4.78
$D_{98\ \%}$	48.14 – 51.99	50.72 ± 1.12
$D_{95\ \%}$	51.03 – 52.98	51.93 ± 0.69
$D_{50\ \%}$	53.79 – 57.07	55.38 ± 1.01
$D_{2\ \%}$	57.63 – 67.93	59.91 ± 2.82
$V_{95\%}$ (%)	93.74 – 99.7	97.01 ± 2.08
CTV 60.8 Gy:		
D_{mean}	60.19 – 65.92	63.81 ± 1.24
$D_{difference}$	2.07 – 5.12	3.24 ± 0.74
$D_{50\ \%}$	60.45 – 65.27	62.96 ± 1.14
PTV 60.8 Gy:		
Volume	261.3 – 819.3	500.68 ± 167.66
D_{mean}	59.2 – 63.98	61.96 ± 1.31
$D_{difference}$	0.26 – 3.18	1.36 ± 0.87
D_{min}	24.91 – 50.91	38.43 ± 10.08
D_{max}	70.27 – 74.99	72.19 ± 1.41
$D_{98\ \%}$	47.83 – 58.97	55.77 ± 2.55
$D_{95\ \%}$	53.79 – 60.04	57.82 ± 1.4
$D_{50\ \%}$	59.72 – 64.13	62.0 ± 1.12
$D_{2\ \%}$	65.06 – 72.45	67.51 ± 1.66
$V_{95\%}$ (%)	80.82 – 99.87	95.38 ± 4.72
CTV 70.4 Gy:		
D_{mean}	70.95 – 72.07	71.32 ± 0.26
$D_{50\ \%}$	71.07 – 72.11	71.39 ± 0.28
PTV 70.4 Gy:		
Volume	48.3 – 482.0	208.34 ± 105.8
D_{mean}	70.40 – 70.43	70.41 ± 0.009
D_{min}	30.26 – 59.89	55.68 ± 7.25
D_{max}	73.82 – 77.65	75.22 ± 0.86
$D_{98\ \%}$	63.76 – 66.64	65.35 ± 0.69
$D_{95\ \%}$	65.63 – 67.54	66.71 ± 0.45
$D_{50\ \%}$	70.42 – 71.08	70.7 ± 0.18
$D_{2\ \%}$	72.53 – 74.71	73.49 ± 0.63
$V_{95\%}$ (%)	91.62 – 97.74	94.52 ± 1.44

Volume is prescribed in cm^3
Doses are prescribed in Gy
$D_{difference}$ = Difference between prescribed dose and mean absorbed dose.
D_{mean} = Mean Dose
D_{min} = Dose $_{minimum}$
D_{max} = Dose $_{maximum}$
$D_{98\ \%}$ = D $_{near\text{-}minimum}$
$D_{95\ \%}$ = minimum absorbed dose that covers 95 % of the volume of the PTV
$D_{50\ \%}$ = median dose
$D_{2\ \%}$ = D $_{near\text{-}maximum}$
$V_{95\%}$ = the volume of each PTV that received 95% of the prescription dose

Table 10: Dosimetric parameters for OARs for the 44 patients

Parameter	Range	Mean ± SD
Ipsilateral parotid:		
D_{mean}	24.77 – 69.60	52.46 ± 10.55
$D_{50\ \%}$	21.55 – 72.24	54.56 ± 11.95
Contralateral parotid (spared+unspared):		
D_{mean}	19.70 – 62.06	39.73 ± 15.36
$D_{50\ \%}$	12.91 – 65.75	37.89 ± 19.29
Contralateral spared parotid:		
D_{mean}	19.7 – 32.2	24.35 ± 2.78
$D_{50\ \%}$	12.91 – 24.33	18.1 ± 2.75
Contralateral Non-spared parotid :		
D_{mean}	29.18 – 62.06	51.41 ± 9.34
$D_{50\ \%}$	26.86 – 65.75	52.93 ± 10.72
Whole oral cavity:		
D_{mean}	22.24 – 73.05	56.22 ± 13.79
Oral cavity sub from PTVs:		
D_{mean}	21.1 – 64.54	48.11 ± 11.05
$D_{50\ \%}$	17.56 – 65.89	48.32 ± 12.44
Lips:		
D_{mean}	3.9 – 70.67	33.05 ± 16.87
$D_{50\ \%}$	2.79 – 73.15	33.25 ± 18.23
Spinal cord:		
D_{max}	41.39 – 51.41	46.87 ± 2.55
Brain stem:		
D_{max}	17.63 – 61.95	48.88 ± 8.78

All doses are prescribed in Gy

4.2.3. Comparison of dosimetric parameters of target volumes according to the XRT arm (all patients)

No statistically significant difference was found between the two treatment arms as regards the mean prescribed dose to different target volumes. For HART-SEQ-IMRT arm, the mean prescribed dose for $PTVA_{(low\text{-}risk)}$ was 54.5 ± 4.99 Gy vs. 56.4 ± 3.06 Gy for the SIB-IMRT arm (p=0.075), and for $PTVB_{(high\text{-}risk)}$ 61.65 ± 3.33 Gy vs. 60.6 ± 1.84 Gy, respectively, (p=0.112). For $PTVC_{(gross\ tumor)}$, all patients in the HART-SEQ-IMRT arm received 72 Gy, and for the SIB-IMRT arm all patients received 70.4 Gy (Table 11).

4.2.3.1. Target volumes

The HART-SEQ-IMRT technique resulted in higher values of most dosimetric target volume parameters for $CTV\backslash PTV_{(low\text{-}risk)}$, $CTV\backslash PTV_{(high\text{-}risk)}$, and $CTV\backslash PTVC_{(gross\ tumor)}$ when compared to the SIB-IMRT technique (Table 11).

4.2.3.2. Organs at risk

Both techniques were able to keep the doses to OARs within acceptable tolerance limits. There were no statistical differences between the two XRT techniques regarding the dose received by OARs except for brain stem maximal received dose, which was significantly higher for SIB-

IMRT plans compared to HART-SEQ-IMRT plans ((52.4 ± 5.57 Gy vs. 46.86 ± 9.69 Gy, respectively, p=0.045) (Table 12).

Table 11: Comparison of dosimetric parameters of target volumes according to the XRT technique

Parameter	XRT Technique		p-value
	HART-SEQ-IMRT NO = 28 Mean ± SD	SIB-IMRT NO = 16 Mean ± SD	
CTVA (low-risk):			
D_{mean}	61.72 ± 4.81	58.85 ± 3.39	0.026
$D_{difference}$	7.22 ± 2.94	2.45 ± 1.17	<0.001
$D_{50\ \%}$	61.37 ± 5.36	58.17 ± 3.14	0.014
PTVA (low-risk):			
Volume	321.67 ± 243.74	405.84 ± 266.24	0.354
Dose (pres)	54.5 ± 4. 99	56.4 ± 3.06	0.075
D_{mean}	59.82 ± 4.62	57.20 ± 3.02	0.023
$D_{difference}$	5.32 ± 2.77	0.98 ± 0.76	<0.001
D_{min}	44.41 ± 6.44	41.26 ± 9.79	0.29
D_{max}	73.24 ± 3.55	67.21 ± 4.75	<0.001
$D_{98\ \%}$	52.74 ± 4.39	52.33 ± 2.76	1.0
$D_{95\ \%}$	53.93 ± 4.39	53.70 ± 2.78	0.845
$D_{50\ \%}$	59.43 ± 4.86	57.23 ± 2.96	0.045
$D_{2\ \%}$	67.91 ± 4.77	62.11 ± 4.09	<0.001
$V_{95\%}$ (%)	98.48 ± 1.55	96.73 ± 2.47	0.017
CTVB (high-risk):			
D_{mean}	68.05 ± 2.62	63.81 ± 1.24	<0.001
$D_{difference}$	6.65 ± 1.83	3.23 ± 0.74	<0.001
$D_{50\ \%}$	68.43 ± 3.35	62.96 ± 1.14	<0.001
PTVB (high-risk):			
Volume	456.9 ± 203.35	500.68 ± 167.63	0.491
Dose (pres)	61.65 ± 3.33	60.6 ± 1.84	0.112
D_{mean}	65.99 ± 2.89	61.96 ± 1.13	<0.001
$D_{difference}$	4.59 ± 1.41	1.36 ± 0.86	<0.001
D_{min}	46.38 ± 10.76	38.43 ± 10.08	0.017
D_{max}	75.76 ± 0.99	72.19 ± 1.41	<0.001
$D_{98\ \%}$	58.39 ± 4.19	55.77 ± 2.55	0.103
$D_{95\ \%}$	59.90 ± 3.92	57.82 ± 1.40	0.491
$D_{50\ \%}$	65.69 ± 3.51	62.00 ± 1.12	0.001
$D_{2\ \%}$	73.19 ± 1.13	67.51 ± 1.65	<0.001
$V_{95\%}$ (%)	98.36 ± 1.48	95.38 ± 4.72	0.012
CTVC (gross tumor):			
D_{mean}	72.98 ± 0.43	71.32 ± 0.26	<0.001
$D_{50\ \%}$	73.06 ± 0.43	71.39 ± 0.27	<0.001
PTVC (gross tumor):			
Volume	380.9 ± 180.14	208.34 ± 105.8	0.001
D_{mean}	72.65 ± 0.39	70.406 ± 0.01	<0.001
D_{min}	57.77 ± 7.89	55.68 ± 7.25	0.038
D_{max}	76.57 ± 0.83	75.22 ± 0.86	<0.001
$D_{98\ \%}$	68.74 ± 0.91	65.35 ± 0.69	<0.001
$D_{95\ \%}$	70.04 ± 0.73	66.71 ± 0.45	<0.001
$D_{50\ \%}$	72.85 ± 0.38	70.70 ± 0.18	<0.001
$D_{2\ \%}$	75.02 ± 0.58	73.49 ± 0.63	<0.001
$V_{95\%}$ (%)	98.70 ± 1.15	94.52 ± 1.44	<0.001

Volume is prescribed in cm^3 and doses are prescribed in Gy

Table 12: Comparison of dosimetric parameters of OARs according to the XRT technique

Parameter	XRT Technique		p-value
	HART-SEQ-IMRT NO = 28 Mean ± SD	SIB-IMRT NO = 16 Mean ± SD	
Ipsilateral parotid:			
D_{mean}	54.04 ± 11.79	49.67 ± 7.46	0.097
$D_{50\ \%}$	56.33 ± 13.41	51.45 ± 8.31	0.054
Contralateral parotid:			
D_{mean}	42.74 ± 16.15	34.44 ± 12.64	0.083
$D_{50\ \%}$	41.52 ± 20.05	31.55 ± 16.58	0.088
Whole oral cavity:			
D_{mean}	54.29 ± 16.49	59.58 ± 6.03	0.884
Oral cavity outside PTVs:			
D_{mean}	47.12 ± 12.77	49. 86 ± 7.17	0.643
$D_{50\ \%}$	46.91 ± 14.45	50.78 ± 7.61	0.435
Lips:			
D_{mean}	31.95 ± 18.26	34.96 ± 14.44	0.464
$D_{50\ \%}$	31.86 ± 19.06	35.68 ± 17.01	0.495
Spinal cord:			
D_{max}	46.97 ± 2.4	46.69 ± 9.69	0.714
Brain stem:			
D_{max}	46.86 ± 9.69	52.4 ± 5.57	0.045

Doses are prescribed in Gy

4.2.4. Comparison of Dosimetric Parameters of target volumes for 33 patients with GTV of ≤ 100 cm^3 according to the XRT technique

All patients who were enrolled in the SIB-IMRT arm had GTV ≤ 100 cm^3; subsequently we conducted a further dosimetric analysis and comparison from IMRT plans generated for a subgroup of patients with GTV ≤ 100 cm^3 (33 patients, 17 HART-SEQ-IMRT, and 16 SIB-IMRT).

4.2.4.1. Target volumes

HART-SEQ-IMRT plans resulted in higher $D_{difference}$ for $PTVA_{(low\text{-}risk)}$ of 5.24 ± 2.95 Gy compared to 0.98 ± 0.76 Gy for SIB-IMRT plans (p<0.001), and 4.58 ± 1.54 Gy for $PTVB_{(high\text{-}risk)}$ compared to 1.36 ± 0.86 Gy, respectively, (p<0.001). For HART-SEQ-IMRT plans, the D_{mean} for $PTVB_{(high\text{-}risk)}$ was 65.21 ± 2.49 Gy compared to 61.96 ± 1.13 Gy for SIB-IMRT plans (p<0.001), for $PTVC_{(gross\ tumor)}$ 72.62 ± 0.44 Gy compared to 70.406 ± 0.01 Gy, respectively (p<0.001). Also, HART-SEQ-IMRT resulted in better $V_{95\%}$ for $PTVA_{(low\text{-}risk)}$ of 98.36 ± 1.79% compared to 96.73 ± 2.47 % for SIB-IMRT (p=0.041), 98.32 ± 1.53 % for $PTVB_{(high\text{-}risk)}$ compared to 95.38 ± 4.72 %, respectively, (p=0.037), and 98.72 ± 1.38 % for $PTVC_{(gross\ tumor)}$ compared to 94.52 ± 1.44 %, respectively, (p<0.001). Moreover, for $PTVC_{(gross\ tumor)}$, HART-SEQ-IMRT plans resulted in higher values compared to SIB-IMRT plans regarding $D_{near\text{-}min}$ (p<0.001), D_{max} (p<0.001), $D_{near\text{-}max}$ (p<0.001), and $D_{95\%}$ (p<0.001) (Table 13).

4.2.4.2. Organs at Risk

The statistically significant increase of the maximum dose received by brain stem with the SIB-IMRT technique in comparison to the HART-SEQ-IMRT technique was magnified (52.4 ± 5.57 Gy vs. 43.54 ± 10.09 Gy, respectively, p= 0.007) (Table 14).

Table 13: Comparison of dosimetric parameters of target volumes for 33 patients with GTV≤ 100 cm^3 according to the XRT technique

Parameter	XRT Technique		p-value
	HART-SEQ-IMRT NO = 17 Mean ± SD	SIB-IMRT NO = 16 Mean ± SD	
CTVA (low-risk):			
D_{mean}	60.17 ± 5.12	58.85 ± 3.39	0.368
$D_{difference}$	7.12 ± 3.16	2.45 ± 1.17	<0.001
$D_{50\ \%}$	59.64± 5.77	58.17 ± 3.14	0.292
PTVA (low-risk):			
Volume	284.32± 195.04	405.84 ± 266.24	0.204
D_{mean}	58.29 ± 4.81	57.20 ± 3.02	0.363
$D_{difference}$	5.24 ± 2.95	0.98 ± 0.76	<0.001
D_{min}	43.15 ± 5.86	41.26 ± 9.79	0.986
D_{max}	72.55 ± 4.15	67.21 ± 4.75	<0.001
$D_{98\ \%}$	51.35 ± 4.32	52.33 ± 2.76	0.204
$D_{95\ \%}$	52.49 ± 4.37	53.70 ± 2.78	0.146
$D_{50\ \%}$	57.75 ± 5.07	57.23 ± 2.96	0.631
$D_{2\ \%}$	66.86 ± 5.05	62.11 ± 4.09	0.003
$V_{95\%}$ (%)	98.36 ± 1.79	96.73 ± 2.47	0.041
CTVB (high-risk):			
D_{mean}	67.39 ± 2.41	63.81 ± 1.24	<0.001
$D_{difference}$	6.75 ± 1.93	3.23 ± 0.74	<0.001
$D_{50\ \%}$	67.71 ± 3.43	62.96 ± 1.14	0.001
PTVB (high-risk):			
Volume	457.59 ± 151.74	500.68 ± 167.63	0.682
D_{mean}	65.21 ± 2.49	61.96 ± 1.13	<0.001
$D_{difference}$	4.58 ± 1.54	1.36 ± 0.86	<0.001
D_{min}	43.95 ± 11.04	38.43 ± 10.08	0.097
D_{max}	75.62 ± 1.15	72.19 ± 1.41	<0.001
$D_{98\ \%}$	57.73 ± 3.29	55.77 ± 2.55	0.176
$D_{95\ \%}$	59.05 ± 3.19	57.82 ± 1.40	0.602
$D_{50\ \%}$	64.65 ± 3.15	62.00 ± 1.12	0.011
$D_{2\ \%}$	72.89 ± 1.27	67.51 ± 1.65	<0.001
$V_{95\%}$ (%)	98.32 ± 1.53	95.38 ± 4.72	0.037
CTVC (gross tumor):			
D_{mean}	72.96 ± 0.44	71.32 ± 0.26	<0.001
$D_{50\ \%}$	73.06 ± 0.44	71.39 ± 0.27	<0.001
PTVC (gross tumor):			
Volume	296.62 ± 129.98	208.34 ± 105.8	0.068
D_{mean}	72.62 ± 0.44	70.406 ± 0.01	<0.001
D_{min}	56.03 ± 9.64	55.68 ± 7.25	0.423
D_{max}	76.33 ± 0.85	75.22 ± 0.86	0.001
$D_{98\ \%}$	68.82 ± 1.06	65.35 ± 0.69	<0.001
$D_{95\ \%}$	70.11 ± 0.87	66.71 ± 0.45	<0.001
$D_{50\ \%}$	72.85 ± 0.42	70.70 ± 0.18	<0.001
$D_{2\ \%}$	74.84 ± 0.54	73.49 ± 0.63	<0.001
$V_{95\%}$ (%)	98.72 ± 1.38	94.52 ± 1.44	<0.001

Volume is prescribed in cm^3 and doses are prescribed in Gy

Table 14: Comparison of dosimetric parameters of OARs for 33 patients with GTV ≤ 100 cm^3 according to the XRT technique

Parameter	XRT Technique		p-value
	HART-SEQ-IMRT NO = 17 Mean ± SD	SIB-IMRT NO = 16 Mean ± SD	
Ipsilateral parotid:			
D_{mean}	49.84 ± 12.44	49.67 ± 7.46	0.488
$D_{50\ \%}$	52.23 ± 14.79	51.45 ± 8.31	0.817
Contralateral parotid:			
D_{mean}	38.94 ± 15.81	34.44 ± 12.64	0.423
$D_{50\ \%}$	37.23 ± 20.54	31.55 ± 16.58	0.488
Whole oral cavity:			
D_{mean}	54.02 ± 18.29	59.58 ± 6.03	0.845
Oral cavity outside PTVs:			
D_{mean}	47.48 ± 14.19	49. 86 ± 7.17	0.901
$D_{50\ \%}$	47.59 ± 15.66	50.78 ± 7.61	0.958
Lips:			
D_{mean}	33.47 ± 20.83	34.96 ± 14.44	0.873
$D_{50\ \%}$	33.45 ± 22.1	35.68 ± 17.01	0.817
Spinal cord:			
D_{max}	46.28 ± 2.41	46.69 ± 9.69	0.962
Brain stem:			
D_{max}	43.54 ± 10.09	52.4 ± 5.57	0.007

Doses are prescribed in Gy

4.3. Toxicity Assessment

4.3.1. Acute toxicities and XRT interruption

Acute toxicities were recorded for the 44 patients in table 15. No patient experienced grade IV toxicities. Thirty (68.2%) patients required no interruption of XRT. Because of acute toxicities experienced by the patients, the XRT course was interrupted for ≤ 3 days in 4 (9.1%) patients, and for > 3 days in 10 (22.7%) patients. Only 4 (9.1%) patients needed interruption of XRT for > one week. During XRT, 16 (36.4%) patients had grade 0 fatigue, 18 (40.9%) grade I, 8 (18.2%) grade II, and only 2 (4.5%) grade III. Weight loss of grade 0 was reported in 25 (56.8%), grade I in 8 (18.2%), grade II in 11 (25%) patients, and no patient complained of grade III. Dysphagia grade I was present in only 3 (6.8%) of patients, grade II in 21 (47.7%), and grade III in 20 (45.5%) of patients. Three (6.8%) patients had erythema grade I, 30 (68.2%) grade II and 11 (25%) grade III. Also, only 3 (6.8%) patients complained of mucositis grade I, 23 (52.3%) grade II, and 18 (40.9%) grade III. Grade 0 pain was present in 7 (15.9%) patients, grade I in 8 (18.2%), grade II in 25 (56.8%), and grade III in 4 (9.1%) patients. Three (6.8%) patients had grade I xerostomia, 21 (47.7%) grade II and 20 (45.5%) grade III. Salivary gland changes of grade 0 were reported in 12 (27.3%) of patients, grade I in 21 (47.7%), grade II in 11 (25%), and no patient had grade III. Grade I dysgeusia and taste alteration was present in 7 (15.9%) of patients, grade II in 16 (36.4%), and grade III in 21 (47.7%). Fifteen (34.1%) patients had grade 0 voice changes, 8 (18.2%) grade I, 19 (43.2%) grade II, and only 2 (4.5%) grade III.

Table 15: Distribution of acute toxicities among the 44 patients

Toxicity	**No = 44** **NO (%)**
XRT interruption for 3 days:	
No	30 (68.2%)
Less than 3 days	4 (9.1%)
More than 3 days	10 (22.7%)
XRT interruption for one week:	
No	30 (68.2%)
Less than one week	10 (22.7%)
More than one week	4 (9.1%)
fatigue:	
Grade 0	16 (36.4%)
Grade I	18 (40.9%)
Grade II	8 (18.2%)
Grade III	2 (4.5%)
Weight loss:	
Grade 0	25 (56.8%)
Grade I	8 (18.2%)
Grade II	11 (25%)
Grade III	0 (0%)
Dysphagia:	
Grade I	3 (6.8%)
Grade II	21 (47.7%)
Grade III	20 (45.5%)
Erythema:	
Grade I	3 (6.8%)
Grade II	30 (68.2%)
Grade III	11 (25%)
Mucositis:	
Grade I	3 (6.8%)
Grade II	23 (52.3%)
Grade III	18 (40.9)
Pain:	
Grade 0	7 (15.9%)
Grade I	8 (18.2%)
Grade II	25 (56.8%)
Grade III	4 (9.1%)
Xerostomia:	
Grade I	3 (6.8)
Grade II	21 (47.7%)
Grade III	20 (45.5%)
Salivary gland changes:	
Grade 0	12 (27.3%)
Grade I	21 (47.7%)
Grade II	11 (25%)
Grade III	0 (0%)
Dysgeusia & taste alteration:	
Grade I	7 (15.9%)
Grade II	16 (36.4%)
Grade III	21 (47.7)
Voice changes & dysarthria:	
Grade 0	15 (34.1%)
Grade I	8 (18.2%)
Grade II	19 (43.2%)
Grade III	2 (4.5%)

4.3.1.1. Acute toxicities and XRT interruption according to XRT technique (all patients)

Regarding acute toxicities and subsequent XRT course interruption, patients in the HART-SEQ-IMRT arm had more XRT course interruption than patients in the SIB-IMRT arm (p =0.038). Furthermore, HART-SEQ-IMRT arm patients experienced statistically significant higher grades of weight loss (p=0.045), dysphagia (p=0.019), and erythema (p=0.011) than SIB-IMRT arm patients (Table 16).

Table 16: Comparison of acute toxicities for 44 patients according to the XRT technique

Toxicity	XRT technique		p-value
	HART-SEQ-IMRT NO = 28 NO (%)	SIB-IMRT NO = 16 NO (%)	
XRT interruption:			
No	16 (57.1%)	14 (87.5%)	0.038
Yes	12 (42.9%)	2 (12.5%)	
fatigue:			
Grade 0	8 (28.6%)	8 (50%)	
Grade I	12 (42.9%)	6 (37.5%)	0.323
Grade II	7 (25%)	1 (6.3%)	
Grade III	1 (3.6%)	1 (6.3%)	
Weight loss:			
Grade 0	12 (42.9%)	13 (81.3%)	0.045
Grade I	7 (25%)	1 (6.3%)	
Grade II	9 (32.1%)	2 (12.5%)	
Dysphagia:			
Grade I	0 (0%)	3 (18.8%)	0.019
Grade II	12 (42.9%)	9 (56.3%)	
Grade III	16 (57.1%)	4 (25%)	
Erythema:			
Grade I	0 (0%)	3 (18.8%)	0.011
Grade II	18 (64.3%)	12 (75%)	
Grade III	10 (35.7%)	1 (6.3%)	
Mucositis:			
Grade I	1 (3.6%)	2 (12.5%)	0.197
Grade II	13 (46.4%)	10 (62.5%)	
Grade III	14 (50%)	4 (25%)	
Pain:			
Grade 0	4 (14.3%)	3 (18.8%)	
Grade I	3 (10.7%)	5 (31.3%)	0.325
Grade II	18 (64.3%)	7 (43.8%)	
Grade III	3 (10.7%)	1 (6.3%)	
Xerostomia:			
Grade I	2 (7.1%)	1 (6.3%)	0.320
Grade II	11 (39.3%)	10 (62.5%)	
Grade III	15 (53.6%)	5 (31.2%)	
Salivary gland changes:			
Grade 0	8 (28.6%)	4 (25%)	0.25
Grade I	11 (39.3%)	10 (62.5%)	
Grade II	9 (32.1%)	2 (12.5%)	
ysgeusia & taste alteration:			
Grade I	5 (17.9%)	2 (12.5%)	0.896
Grade II	10 (35.7%)	6 (37.5%)	
Grade III	13 (46.4%)	8 (50%)	
Voice changes & dysarthria:			
Grade 0	7 (25%)	8 (50%)	
Grade I	4 (14.3%)	4 (25%)	0.134
Grade II	15 (53.6%)	4 (25%)	
Grade III	2 (7.1%)	0 (0%)	

4.3.1.2. Acute toxicities and XRT interruption for 33 patients with GTV ≤ 100 cm^3 according to the XRT technique

By analysis of subgroup of patients with GTV ≤ 100 cm^3**,** there were no statistically significant differences between the two XRT techniques regarding percentages of different grades of acute toxicities, except for erythema. HART-SEQ-IMRT patients showed statistically significant higher grades of erythema than SIB-IMRT arm patients (p=0.037) (Table 17).

Table 17: Comparison of acute toxicities for 33 patients with GTV ≤ 100 cm^3 according to the XRT technique

Toxicity	XRT technique		p-value
	HART-SEQ-IMRT NO = 17 NO (%)	SIB-IMRT NO = 16 NO (%)	
XRT interruption			
No	12 (70.6%)	14 (87.5%)	0.235
Yes	5 (29.4%)	2 (12.5%)	
fatigue:			
Grade 0	4 (23.5%)	8 (50%)	
Grade I	8 (47.1%)	6 (37.5%)	0.335
Grade II	4 (23.5%)	1 (6.3%)	
Grade III	1 (5.9%)	1 (6.3%)	
Weight loss:			
Grade 0	8 (47.1%)	13 (81.3%)	0.106
Grade I	5 (29.4%)	1 (6.3%)	
Grade II	4 (23.5%)	2 (12.5%)	
Dysphagia:			
Grade I	0 (0%)	3 (18.8%)	0.173
Grade II	12 (70.6%)	9 (56.3%)	
Grade III	5 (29.4%)	4 (25%)	
Erythema:			
Grade I	0 (0%)	3 (18.8%)	0.037
Grade II	11 (64.7%)	12 (75%)	
Grade III	6 (35.3%)	1 (6.3%)	
Mucositis:			
Grade I	1 (5.9%)	2 (12.5%)	0.394
Grade II	8 (47.1%)	10 (62.5%)	
Grade III	8 (47.1%)	4 (25%)	
Pain:			
Grade 0	4 (23.5%)	3 (18.8%)	
Grade I	2 (11.8%)	5 (31.3%)	0.576
Grade II	9 (52.9%)	7 (43.8%)	
Grade III	2 (11.8%)	1 (6.3%)	
Xerostomia:			
Grade I	2 (11.8%)	1 (6.3%)	0.466
Grade II	7 (41.2%)	10 (62.5%)	
Grade III	8 (47.1%)	5 (31.2%)	
Salivary gland changes:			
Grade 0	6 (35.3%)	4 (25%)	
Grade I	7 (41.2%)	10 (62.5%)	0.457
Grade II	4 (23.5%)	2 (12.5%)	
Dysgeusia & taste alteration:			
Grade I	4 (23.5%)	2 (12.5%)	0.703
Grade II	6 (35.3%)	6 (37.5%)	
Grade III	7 (41.2%)	8 (50%)	
Voice changes & dysarthria:			
Grade 0	7 (41.2%)	8 (50%)	
Grade I	2 (11.8%)	4 (25%)	0.471
Grade II	7 (41.2%)	4 (25%)	
Grade III	1 (5.9%)	0 (0%)	

4.3.1.3. Acute toxicities and XRT interruption for 30 patients who received concurrent PF regimen according to the XRT technique

Analysis of the subgroup of patients who received concurrent PF regimen**,** HART-SEQ-IMRT patients also showed higher grades of erythema than patients who were enrolled in the SIB-IMRT arm (p=0.038) (Table 18).

Table 18: Comparison of acute toxicities for 30 patients treated with PF Regimen according to the XRT technique

Toxicity	XRT technique		p-value
	HART-SEQ-IMRT NO = 24 NO (%)	SIB-IMRT NO = 6 NO (%)	
XRT interruption			
No	16 (66.7%)	5 (83.3%)	0.426
Yes	8 (33.3%)	1 (16.7)	
fatigue:			
Grade 0	8 (33.3%)	4 (66.7%)	
Grade I	9 (37.5%)	1 (16.7%)	0.503
Grade II	6 (25%)	1 (16.7%)	
Grade III	1 (4.2%)	0 (0%)	
Weight loss:			
Grade 0	11 (45.8%)	5(83.3%)	0.228
Grade I	5 (20.8%)	0 (0%)	
Grade II	8 (33.3%)	1 (16.7%)	
Dysphagia:			
Grade I	0 (0%)	1 (16.7%)	0.109
Grade II	11 (45.8%)	3 (50%)	
Grade III	13 (54.2%)	2 (33.3%)	
Erythema:			
Grade II	15 (62.5%)	1 (16.7%)	0.038
Grade III	9 (37.5%)	5 (83.3%)	
Mucositis:			
Grade I	0 (0%)	1 (16.7%)	0.117
Grade II	12 (50%)	3 (50%)	
Grade III	12 (50%)	2 (33.3%)	
Pain:			
Grade 0	3 (12.5%)	1 (16.7%)	
Grade I	3 (12.5%)	2 (33.3%)	0.553
Grade II	15 (62.5%)	2 (33.3%)	
Grade III	3 (12.5%)	1 (16.7%)	
Xerostomia:			
Grade I	2 (8.3%)	0 (0%)	0.749
Grade II	10 (41.7%)	3 (50%)	
Grade III	12 (50%)	3 (50%)	
Salivary gland changes:			
Grade 0	7 (29.2%)	1 (16.7%)	0.434
Grade I	9 (37.5%)	4 (66.7%)	
Grade II	8 (33.3%)	1 (16.7%)	
Dysgeusia & taste alteration:			
Grade I	4 (16.7%)	1 (16.7%)	0.482
Grade II	10 (41.7%)	1 (16.7%)	
Grade III	10 (41.7%)	4 (66.7%)	
Voice changes & dysarthria:			
Grade 0	7 (29.2%)	4 (66.7%)	
Grade I	4 (16.7%)	1 (16.7%)	0.339
Grade II	11 (45.8%)	1 (16.7%)	
Grade III	2 (8.3%)	0 (0%)	

4.3.1.4. Acute toxicities and XRT interruption for 14 patients who received neoadjuvant TPF regimen according to the XRT technique

Analysis of the subgroup of patients who received neoadjuvant TPF regimen revealed no statistically significant differences between the two XRT techniques, except for XRT interruption, where all patients (100%) enrolled in the HART-SEQ-IMRT arm had XRT course interruption compared to 10 % of patients in the SIB-IMRT arm (p=0.001) (Table 19).

Table 19: Comparison of acute toxicities for 14 patients treated with TPF regimen according to the XRT technique

Toxicity	XRT technique		p-value
	HART-SEQ-IMRT NO = 4 NO (%)	SIB-IMRT NO =10 NO (%)	
XRT interruption			
No	0 (0%)	9 (9%)	0.001
yes	4 (100%)	1 (10%)	
fatigue:			
Grade 0	0 (0%)	4 (40%)	
Grade I	3 (75%)	5 (50%)	0.186
Grade II	1 (25%)	0 (0%)	
Grade III	0 (0%)	1 (10%)	
Weight loss:			
Grade 0	1 (25%)	8 (80%)	0.140
Grade I	2 (50%)	1 (10%)	
Grade II	1 (25%)	1 (10%)	
Dysphagia:			
Grade I	0 (0%)	2 (20%)	0.141
Grade II	1 (25%)	6 (60%)	
Grade III	3 (75%)	2 (20%)	
Erythema:			
Grade I	0 (0%)	2 (20%)	0.533
Grade II	3 (75%)	7 (70%)	
Grade III	1 (25%)	1 (10%)	
Mucositis:			
Grade I	1 (25%)	1 (10%)	0.307
Grade II	1 (25%)	7 (70%)	
Grade III	2 (50%)	2 (20%)	
Pain:			
Grade 0	1 (25%)	2 (20%)	0.462
Grade I	0 (0%)	3 (30%)	
Grade II	3 (75%)	5 (50%)	
Xerostomia:			
Grade I	0 (0%)	1 (10%)	0.147
Grade II	1(25%)	7 (70%)	
Grade III	3 (75%)	2 (20%)	
Salivary gland changes:			
Grade 0	1 (25%)	3 (30%)	0.769
Grade I	2 (50%)	6 (60%)	
Grade II	1 (25%)	1 (10%)	
Dysgeusia & taste alteration:			
Grade I	1 (25%)	1 (10%)	0.207
Grade II	0 (0%)	5 (50%)	
Grade III	3 (75%)	4 (4%)	
Voice changes & dysarthria:			
Grade 0	0 (0%)	4 (40%)	0.061
Grade I	0 (0%)	3 (30%)	
Grade II	4 (100%)	3 (30%)	

4.3.2. Late morbidities 6 months after XRT

Late morbidity 6 months after XRT among 41 surviving patients was evaluated (Table 20). Eleven (26.8%) patients had grade 0 dysphagia, 15 (36.6%) grade I, 14 (34.2%) grade II, and only 1 (2.4%) patient had grade III. Twelve (29.3%) patients were still using PEG for nutritional support, while 29 (70.7%) were free from PEG by 6 months after therapy.

Twenty-four (58.5%) patients had grade 0 pain, 13 (31.7%) grade I, 3 (7.3%) grade II, and only one (2.4%) had grade III pain. Eight (19.5%) patients had grade 0 xerostomia, 13 (31.7%) grade I, 20 (48.8%) grade II, and no (0%) patient had grade III.

Nine (22%) patients had grade 0 dysgeusia and taste alteration, 20 (48.8%) grade I, 12 (29.3%) grade II, and no (0%) patient had grade III. Twenty-seven (65.9% had grade 0 voice changes and dysarthria, 6 (14.6%) grade I, 7 (17.1%) grade II, and only one (2.4%) had grade III.

Nineteen (46.3%) patients had grade 0 skin changes, 20 (48.8%) grade I, 2 (4.9%) grade II, and no (0%) patient had grade III. Seventeen (41.5%) patients had grade 0 lymphedema, 21 (51.2%) grade I, 3 (6.8%) grade II, and no (0%) patient had grade III. Thirty-nine (95.1%) patients had grade 0 mandibular ORN and only 2 (4.9%) with oral cavity tumors complained of mandibular ORN of grade 1. Thirty-five (85.4%) hade grade 0 trismus, 3 (7.3%) grade I, 2 (4.9%) grade II, and only one (2.4%) patient had grade III trismus. No patient (0%) had myelitis and also no (0%) patient complained of brachial plexopathy.

4.3.2.1. Late morbidities 6 months after XRT according to the XRT technique

Late toxicity 6 months after XRT among 41 surviving patients was compared between the two XRT techniques. There were no statistical differences between the HART-SEQ-IMRT arm and the SIB-IMRT arm (Table 21).

4.3.2.2. Late morbidities 6 months after XRT for patients with GTV ≤ 100 cm^3according to the XRT technique

On the other hand, we compared the late morbidity 6 months after XRT between the two XRT techniques in a subgroup of surviving patients with GTV ≤ 100 cm^3 (31 patients). Also, no statistically significant differences could be recorded between the HART-SEQ-IMRT arm and the SIB-IMRT arm (Table 22).

Table 20: Distribution of late morbidities 6 months after XRT among 41 surviving patients

Toxicity 6 months	**NO = 41** **NO (%)**
Dysphagia:	
Grade 0	11 (26.8%)
Grade I	15 (36.6%)
Grade II	14 (34.1%)
Grade III	1 (2.4%)
PEG:	
Yes	12 (29.3%)
No	29 (70.7%)
Pain:	
Grade 0	24 (58.5%)
Grade I	13 (31.7%)
Grade II	3 (7.3%)
Grade III	1 (2.4%)
Xerostomia:	
Grade 0	8 (19.5%)
Grade I	13 (31.7%)
Grade II	20 (48.8%)
Grade III	0 (0%)
Dysgeusia & taste alteration:	
Grade 0	9 (22%)
Grade I	20 (48.8%)
Grade II	12 (29.3%)
Grade III	0 (0%)
Voice changes & dysarthria:	
Grade 0	27 (65.9%)
Grade I	6 (14.6%)
Grade II	7 (17.1%)
Grade III	1 (2.4%)
Skin changes:	
Grade 0	19 (46.3%)
Grade I	20 (48.8%)
Grade II	2 (4.9)
Grade III	0 (0%)
Lymphedema:	
Grade 0	17 (41.5%)
Grade I	21 (51.2%)
Grade II	3 (6.8%)
Grade III	0 (0%)
Osteoradionecrosis:	
Grade 0	39 (95.1%)
Grade I	2 (4.9%)
Trismus:	
Grade 0	35 (85.4%)
Grade I	3 (7.3%)
Grade II	2 (4.9%)
Grade III	1 (2.4%)
Myelities:	
Grade 0	41 (100%)
Brachial plexopathy:	
Grade 0	41 (100%)

Table 21: Comparison of late morbidities 6 months after XRT among 41 surviving patients according to the XRT technique

Toxicity 6 months	**XRT technique**		**p-value**
	HART-SEQ-IMRT N= 26 NO (%)	**SIB-IMRT NO = 15 NO (%)**	
Dysphagia:			
Grade 0	5 (19.2%)	6 (40%)	0.312
Grade I	9 (34.6%)	6 (40%)	
Grade II	11 (42.3%)	3 (20%)	
Grade III	1 (3.8%)	0 (0%)	
PEG:			
Yes	9 (34.6%)	3 (20%)	0.266
No	17 (65.4%)	12 (80%)	
Pain:			
Grade 0	14 (53.8%)	10 (66.7%)	0.386
Grade I	10 (38.5%)	3 (20%)	
Grade II	1 (3.8%)	2 (13.3%)	
Grade III	1 (3.8%)	0 (0%)	
Xerostomia:			
Grade 0	4 (15.4%)	4 (26.7%)	0.602
Grade I	8 (30.8%)	5 (33.3%)	
Grade II	14 (53.8%)	6 (40%)	
Grade III	0 (0%)	0 (0%)	
Dysgeusia & taste alteration:			
Grade 0	7 (26.9%)	2 (13.3%)	0.481
Grade I	11 (42.3%)	9 (60%)	
Grade II	8 (30.8%)	4 (26.7%)	
Grade III	0 (0%)	0 (0%)	
Voice changes & dysarthria:			
Grade 0	14 (53.8%)	13 (86.7%)	0.102
Grade I	4 (15.4%)	2 (13.3%)	
Grade II	7 (26.9%)	0 (0%)	
Grade III	1 (3.8%)	0 (0%)	
Skin changes:			
Grade 0	10 (38.5%)	9 (60%)	0.289
Grade I	14 (53.8%)	6 (40%)	
Grade II	2 (7.7%)	0 (0%)	
Grade III	0 (0%)	0 (0%)	
Lymphedema:			
Grade 0	10 (38.5%)	7 (46.7%)	0.876
Grade I	14 (53.8%)	7 (46.7%)	
Grade II	2 (7.7%)	1 (6.7%)	
Grade III	0 (0%)	0 (0%)	
Osteoradionecrosis:			
Grade 0	24 (92.3%)	15 (100%)	0.271
Grade I	2 (7.7%)	0 (0%)	
Trismus:			
Grade 0	21 (80.8%)	14 (93.3%)	0.589
Grade I	2 (7.7%)	1 (6.7%)	
Grade II	2 (7.7%)	0 (0%)	
Grade III	1 (3.8%)	0 (0%)	

Table 22: Comparison of late morbidities 6 months after XRT among 31 surviving patients with GTV ≤ 100 cm^3 patients according to the technique

Toxicity 6 months	**XRT technique**		**p-value**
	HART-SEQ-IMRT NO = 16 NO (%)	**SIB-IMRT NO = 15 NO (%)**	
Dysphagia:			
Grade 0	5 (31.3%)	6 (40%)	0.870
Grade I	7 (43.8%)	6 (40%)	
Grade II	4 (25%)	3 (20%)	
PEG:			
Yes	1 (6.3%)	3 (20%)	0.275
No	15 (93.8%)	12 (80%)	
Pain:			
Grade 0	9 (56.3%)	10 (66.7%)	0.163
Grade I	7 (43.8%)	3 (20%)	
Grade II	0 (0%)	2 (13.3%)	
Xerostomia:			
Grade 0	3 (18.8%)	4 (26.7%)	0.801
Grade I	7 (43.8%)	5 (33.3%)	
Grade II	6 (37.5%)	6 (40%)	
Grade III	0 (0%)	0 (0%)	
Dysgeusia & taste alteration:			
Grade 0	4 (25%)	2 (13.3%)	0.707
Grade I	8 (50%)	9 (60%)	
Grade II	4 (25%)	4 (26.7%)	
Voice changes & dysarthria:			
Grade 0	9 (56.3%)	13 (86.7%)	0.179
Grade I	3 (18.8%)	2 (13.3%)	
Grade II	3 (18.8%)	0 (0%)	
Grade III	1 (6.3%)	0 (0%)	
Skin changes:			
Grade 0	6 (37.5%)	9 (60%)	0.338
Grade I	9 (56.3%)	6 (40%)	
Grade II	1 (6.3%)	0 (0%)	
Lymphedema:			
Grade 0	8 (50%)	7 (46.7%)	0.983
Grade I	7 (43.8%)	7 (46.7%)	
Grade II	1 (6.3%)	1 (6.7%)	
Osteoradionecrosis:			
Grade 0	14 (87.5%)	15 (100%)	0.484
Grade I	2 (12.5%)	0 (0%)	
Trismus:			
Grade 0	13 (81.3%)	14 (93.3%)	0.512
Grade I	2 (12.5%)	1 (6.7%)	
Grade II	1 (6.3%)	0 (0%)	

4.3.3. Late morbidities 9 months after XRT

Late morbidity 9 months after XRT among 30 surviving patients was evaluated (Table 23). Ten (33.3%) patients had grade 0 dysphagia, 14 (46.7%) grade I, 5 (16.7%) grade II, and only 1 (3.3%) patient had grade III. Six (20 %) patients were still using PEG for nutritional support, while 24 (80%) were free from PEG by 9 months after therapy.

Twenty-two (73.3%) patients had grade 0 pain, 6 (20%) grade I, 1 (3.3%) grade II, and one (3.3%) had grade III pain. Seven (23.3%) patients had grade 0 xerostomia, 13 (43.3%) grade I, 10 (33.3%) grade II, and no (0%) patient had grade III. Ten (33.3%) patients had grade 0 dysgeusia and taste alteration, 16 (53.3%) grade I, 4 (13.3%) grade II, and no (0%) patient had grade III. Twenty (66.7%) had grade 0 voice changes and dysarthria, 6 (20%) grade I, 3 (10%) grade II, and only one (3.3%) had grade III.

Fourteen (46.7%) patients had grade 0 skin changes, 15 (50%) grade I, 1 (3.3%) grade II, and no (0%) patient had grade III. Twelve (40%) patients had grade 0 lymphedema, 16 (53.3%) grade I, 2 (6.7%) grade II, and no (0%) patient had grade III. Twenty-nine (96.7%) patients had grade 0 mandibular ORN and only one (3.3%) patient with oral cavity tumors complained of mandibular ORN of grade 1. Twenty-six (86.7%) hade grade 0 trismus, 0 (0%) grade I, 3 (10%) grade II, and only one (3.3%) patient had grade III trismus.

4.3.3.1. Late morbidities 9 months after XRT according to the XRT arm

Late morbidities 9 months after XRT among 30 surviving patients were compared between the two XRT arms. There were no statistically significant differences between the HART-SEQ-IMRT arm (16 patients) and the SIB-IMRT arm (14 patients) (Table 24).

4.3.2.2. Late morbidities 9 months after XRT for patients with GTV ≤ 100 cm^3according to the XRT arm

Furthermore, we compared the late morbidity 9 months after XRT between the two XRT arms in subgroup of surviving patients with GTV ≤ 100 cm^3. Also, no statistical differences could be recorded between HART-SEQ-IMRT arm (9 patients) and SIB-IMRT arm (14 patients) (Table 25).

Table 23: Distribution of late morbidities 9 months after XRT among 30 surviving patients

Toxicity 9 months	**NO = 30** **NO (%)**
Dysphagia:	
Grade 0	10 (33.3%)
Grade I	14 (46.7%)
Grade II	5 (16.7%)
Grade III	1 (3.3%)
PEG:	
Yes	6 (20%)
No	24 (80%)
Pain:	
Grade 0	22 (73.3%)
Grade I	6 (20%)
Grade II	1 (3.3%)
Grade III	1(3.3%)
Xerostomia:	
Grade 0	7 (23.3%)
Grade I	13 (43.3%)
Grade II	10 (33.3%)
Grade III	0 (0%)
Dysgeusia & taste alteration:	
Grade 0	10 (33.3%)
Grade I	16 (53.3%)
Grade II	4 (13.3%)
Grade III	0 (0%)
Voice changes & dysarthria:	
Grade 0	20 (66.7%)
Grade I	6 (20%)
Grade II	3 (10%)
Grade III	1 (3.3%)
Skin changes:	
Grade 0	14 (46.7 %)
Grade I	15 (50%)
Grade II	1 (3.3%)
Grade III	0 (0%)
Lymphedema:	
Grade 0	12 (40%)
Grade I	16 (53.3%)
Grade II	2 (6.7%)
Grade III	0 (0%)
Osteoradionecrosis:	
Grade 0	29 (96.7%)
Grade I	1 (3.3%)
Trismus:	
Grade 0	26 (86.7%)
Grade I	0 (0%)
Grade II	3 (10%)
Grade III	1 (3.3%)
Myelities:	
Grade 0	41 (100%)
Brachial plexopathy:	
Grade 0	41 (100%)

Table 24: Comparison of late morbidities 9 months after XRT among 30 surviving patients according to the XRT technique

Toxicity 9 months	**XRT technique**		**p-value**
	HART-SEQ-IMRT NO = 16 NO (%)	**SIB-IMRT NO = 14 NO (%)**	
Dysphagia:			
Grade 0	3 (18.8)	7 (50%)	
Grade I	8 (50%)	6 (42.9%)	0.206
Grade II	4 (25%)	1 (7.1%)	
Grade III	1 (6.3%)	0 (0%)	
PEG:			
Yes	5 (31.2%)	1 (7.1%)	0.116
No	11 (68.8 %)	13 (92.9%)	
Pain:			
Grade 0	11 (68.8%)	11 (78.6%)	
Grade I	4 (25%)	2 (14.3%)	0.467
Grade II	1 (6.3%)	0 (0%)	
Grade III	0 (0%)	1 (7.1%)	
Xerostomia:			
Grade 0	2 (12.5%)	5 (35.7%)	
Grade I	7 (43.8%)	6 (42.9%)	0.241
Grade II	7 (43.8%)	3 (21.4%)	
Grade III	0 (0%)	0 (0%)	
Dysgeusia & taste alteration:			
Grade 0	7 (43.8%)	3 (21.4%)	
Grade I	7 (43.8%)	9 (64.3%)	0.422
Grade II	2 (12.5%)	2 (14.3%)	
Grade III	0 (0%)	0 (0%)	
Voice changes & dysarthria:			
Grade 0	8 (47.1%)	12 (85.7%)	
Grade I	4 (23.5%)	2 (14.3%)	0.101
Grade II	4 (23.5%)	0 (0%)	
Grade III	1 (5.9%)	0 (0%)	
Skin changes:			
Grade 0	6 (37.5%)	8 (57.1%)	
Grade I	9 (56.3%)	6 (42.9%)	0.415
Grade II	1 (6.3%)	0 (0%)	
Grade III	0 (0%)	0 (0%)	
Lymphedema:			
Grade 0	5 (31.2%)	7 (50%)	
Grade I	11 (68.8)	5 (35.7%)	0.107
Grade II	0 (0%)	2 (14.3%)	
Grade III	0 (0%)	0 (0%)	
Osteoradionecrosis:			
Grade 0	15 (93.8%)	14 (100%)	0.341
Grade II	1 (6.3%)	0 (0%)	
Trismus:			
Grade 0	13 (81.3%)	13 (92.9%)	
Grade I	0 (0%)	0 (0%)	0.547
Grade II	2 (12.5%)	1 (7.1%)	
Grade III	1 (6.3%)	0 (0%)	

Table 25: Comparison of late morbidities 9 months after XRT among 23 surviving patients with GTV ≤ 100 cm^3 according to the XRT technique

Toxicity 9 months	**XRT technique**		**p-value**
	HART-SEQ-IMRT NO = 9 NO (%)	**SIB-IMRT NO = 14 NO (%)**	
Dysphagia:			
Grade 0	3 (33.3%)	7 (50%)	0.520
Grade I	4 (44.4%)	6 (42.9%)	
Grade II	2 (22.2%)	1 (7.1%)	
PEG:			
Yes	1 (11.1%)	1 (7.1%)	0.640
No	8 (88.9%)	13 (92.9%)	
Pain:			
Grade 0	7 (77.8%)	11 (78.6%)	0.656
Grade I	2 (22.2%)	2 (14.3%)	
Grade II	0 (0%)	0 (0%)	
Grade III	0 (0%)	1 (7.1%)	
Xerostomia:			
Grade 0	2 (22.2%)	5 (35.7%)	0.773
Grade I	5 (55.6%)	6 (42.9%)	
Grade II	2 (22.2%)	3 (21.4%)	
Dysgeusia & taste alteration:			
Grade 0	4 (44.4%)	3 (21.4%)	0.315
Grade I	5 (55.6%)	9 (64.3%)	
Grade II	0 (0%)	2 (14.3%)	
Voice changes & dysarthria:			
Grade 0	4 (44.4%)	12 (85.7%)	0.102
Grade I	2 (22.2%)	2 (14.3%)	
Grade II	2 (22.2%)	0 (0%)	
Grade III	1 (11.1%)	0 (0%)	
Skin changes:			
Grade 0	3 (33.3%)	8 (57.1%)	0.265
Grade I	6 (77.7%)	6 (42.9%)	
Grade II	0 (0%)	0 (0%)	
Lymphedema:			
Grade 0	4 (44.4%)	7 (50%)	0.403
Grade I	5 (55.6%)	5 (35.7%)	
Grade II	0 (0%)	2 (14.3%)	
Osteoradionecrosis:			
Grade 0	8 (88.9%)	14 (100%)	0.391
Grade II	1 (11.1%)	0 (0%)	
Trismus:			
Grade 0	8 (88.9%)	13 (92.9%)	1.0
Grade I	0 (0%)	0 (0%)	
Grade II	1 (11.1%)	1 (7.1%)	

4.4. Dosimetric distribution in relation to clinical outcome

4.4.1. Treatment interruption of more than 3 days

We found that that there were statistically significant differences between the patients who had XRT course interruptions of ≤ 3 days, patients with interruptions of XRT course > 3 days, and patients who had no interruptions, as regards the volume of GTV, CTVA $_{(low\text{-}risk)}$ $D_{difference}$, PTVB $_{(high\text{-}risk)}$ $D_{95\ \%}$, and PTVC $_{(gross\ tumor)}$ volume (Table 26).

Table 26: Treatment interruption of 3 days according to different dosimetric parameters

Parameter	Treatment interruption of more than 3 days			p-value[1)]
	No interruption NO=30 Mean ± SD	Interruption ≤ 3 days NO=4 Mean ± SD	Interruption > 3 days NO=10 Mean ± SD	
GTV Volume	50.62 ± 41.61	119.7 ± 49.67	94.51 ± 39.01	0.001
CTVA$_{(low\text{-}risk)}$ $D_{difference}$	4.56 ± 2.89	6.68 ± 0.88	7.81 ± 4.16	0.047
PTVB$_{(high\text{-}risk)}$ $D_{95\ \%}$	59.55 ± 3.54	61.06 ± 5.07	57.34 ± 0.62	0.023
PTVC$_{(gross\ tumor)}$ Volume	264.55 ± 136.92	455.6 ± 115.38	423.97 ± 233.32	0.013

Volume is prescribed in cm^3 and doses are prescribed in Gy
[1)] Kruskal-Wallis-test

4.4.2. Treatment interruption of more than one week

Also, a statistically significant difference could be recorded between patients who had XRT course interruptions of ≤one week, patients with interruptions of XRT course >one week, and patients who had no interruptions, as regards the volume of GTV, CTVA $_{(low\text{-}risk)}$ $D_{difference}$, and PTVC $_{(gross\ tumor)}$ volume (Table 27).

Table 27: Treatment interruption of one week according to different dosimetric parameters

Parameter	Treatment interruption of more than one week			p-value[1)]
	No interruption NO =30 Mean ± SD	Interruption < 1 week NO =10 Mean ± SD	Interruption ≥ 1 week NO =4 Mean ± SD	
GTV Volume	50.62 ± 41.61	99.64 ± 37.09	106.88 ± 58.82	0.002
CTVA $_{(low\text{-}risk)}$ $D_{difference}$	4.56 ± 2.89	7.43 ± 3.81	7.63 ± 3.22	0.046
PTVC $_{(gross\ tumor)}$				
Volume	264.55 ± 136.92	376.0 ± 123.54	575.53 ± 306.39	0.011
D_{mean}	71.69 ± 1.17	72.48 ± 0.89	71.89 ± 0.99	0.035

Volume is prescribed in cm^3 and doses are prescribed in Gy
[1)] Kruskal-Wallis-test

4.4.3. Mucositis

We observed that there were statistically significant differences between different grades of mucositis as regard the volume of PTVC $_{(gross\ tumor)}$, and oral cavity outside PTVs D_{mean} (Table 28).

Table 28: Grades of mucositis according to different dosimetric parameters

Parameter	Mucositis			p-value[1)]
	GradeI NO = 3 Mean ± SD	Grade II NO = 23 Mean ± SD	Grade III NO =18 Mean ± SD	
PTVC $_{(gross\ tumor)}$ Volume	324.47 ± 141.57	256.11 ± 184.13	396.37 ± 146.02	0.007
Oral cavity D_{mean}	40.58 ± 7.87	45.33 ± 11.52	52.93 ± 9.21	0.049

Volume is prescribed in cm^3 and Doses are prescribed in Gy
[1)] Kruskal-Wallis-test

4.4.4. Dysphagia

Significant differences could be observed between different grades of dysphagia regarding volume of GTV, CTVA $_{(low\text{-}risk)}$ $D_{difference}$, D_{mean}, $D_{50\%}$, PTVA $_{(low\text{-}risk)}$ $D_{difference}$, D_{mean}, $D_{50\%}$, $D_{2\%}$, D_{max}, CTVB $_{(high\text{-}risk)}$ D_{mean}, $D_{50\%}$, PTVB $_{(high\text{-}risk)}$, $D_{50\%}$, $D_{2\%}$, D_{max} , CTVC $_{(gross\ tumor)}$ D_{mean}, $D_{50\%}$,, and PTVC $_{(gross\ tumor)}$ volume, D_{mean}, and $D_{2\%}$ (Table 29).

Table 29: Grades of dysphagia according to different dosimetric parameters

Parameter	Dysphagia			p-value[1)]
	Grade I NO = 3 Mean ± SD	Grade II NO = 21 Mean ± SD	Grade III NO = 20 Mean ± SD	
GTV volume	48.47 ± 34.71	35.72 ± 19.81	102.35 ± 46.56	<0.001
CTVA $_{(low\text{-}risk)}$**:**				
D_{mean}	63.43 ± 0.49	59.90 ± 4.77	62.05 ± 3.98	0.019
$D_{difference}$	2.63 ± 0.49	5.34 ± 3.4	6.67 ± 3.29	0.032
$D_{50\ \%}$	62.56 ± 0.51	59.43 ± 5.21	61.71 ± 4.26	0.014
PTVA $_{(low\text{-}risk)}$**:**				
D_{mean}	61.41 ± 0.24	58.1 ± 4.49	60.27 ± 3.72	0.017
$D_{difference}$	0.61 ± 0.24	3.83 ± 3.01	4.89 ± 3.21	0.021
$D_{50\ \%}$	61.32 ± 0.36	57.91 ± 4.67	59.88 ± 3.6	0.016
D_{max}	70.8 ± 0.78	70.46 ± 5.51	72.72 ± 3.57	0.018
$D_{2\ \%}$	66.76 ± 0.79	65.08 ± 5.67	67.49 ± 4.73	0.016
CTVB $_{(high\text{-}risk)}$**:**				
D_{mean}	63.43 ± 0.49	66.49 ± 2.92	67.66 ± 3.18	0.003
$D_{50\ \%}$	62.55 ± 0.51	66.45 ± 3.77	67.78 ± 3.87	0.003
PTVB $_{(high\text{-}risk)}$**:**				
D_{mean}	61.41 ± 0.24	64.53 ± 2.95	65.59 ± 3.41	0.004
$D_{50\ \%}$	61.32 ± 0.36	64.33 ± 3.22	65.45 ± 3.88	0.011
D_{max}	72.68 ± 0.9	74.15 ± 2.11	75.16 ± 1.95	0.045
$D_{2\ \%}$	66.06 ± 0.91	70.79 ± 2.74	72.41 ± 2.64	0.002
CTVC $_{(gross\ tumor)}$**:**				
D_{mean}	71.16 ± 0.17	72.24 ± 0.89	72.70 ± 0.76	0.016
$D_{50\ \%}$	71.19 ± 0.17	72.33 ± 0.90	72.77 ± 0.76	0.013
PTVC $_{(gross\ tumor)}$**:**				
Volume	268.53 ± 185.12	211.51 ± 89.64	437.56 ± 175.71	0.000
D_{mean}	70.4 ± 0.0	71.65 ± 1.16	72.23 ± 0.98	0.021
$D_{2\ \%}$	73.83 ± 0.76	47.17 ± 0.88	74.87 ± 0.91	0.02

Volume is prescribed in cm^3 and doses are prescribed in Gy
[1)] Kruskal-Wallis-test

4.4.5. Taste alteration and dysgeusia

Also, we recorded a statistical trend between different grades of taste alteration and dysgeusia as regard the oral cavity outside PTVs $D_{50\%}$ (Table 30).

Table 30: Grades of taste alteration and dysgeusia according to different dosimetric parameters

Parameter	Taste alteration & dysgeusia			p-value[1)]
	Grade I NO = 7 Mean ± SD	Grade II NO = 16 Mean ± SD	Grade III NO = 21 Mean ± SD	
Oral cavity $D_{50\ \%}$ [1)]	36.95 ± 14.41	51.42 ± 11.36	49.75 ± 10.89	0.058

Dose is prescribed in Gy
[1)] Kruskal-Wallis-test

4.4.6. Xerostomia

We found statistically significant differences between different grades of xerostomia as regard the CTVA (low-risk) D_{mean}, $D_{50\%}$, PTVA (low-risk) D_{mean}, $D_{50\%}$, $D_{2\%}$, D_{max}, , $D_{98\%}$, $D_{95\%}$, PTVB (high-risk), $D_{95\%}$, $D_{98\%}$, D_{min} , PTVC (gross tumor) volume, ipsilateral parotid D_{mean} , $D_{50\%}$, and contralateral parotid D_{mean}, $D_{50\%}$ (Table 31).

Table 31: Grades of xerostomia according to different dosimetric parameters

Parameter	Xerostomia			p-value[1)]
	Grade I NO = 3 Mean ± SD	Grade II NO = 21 Mean ± SD	Grade III NO = 20 Mean ± SD	
CTVA (low-risk)**:**				
D_{mean}	57.85 ± 1.95	59.14 ± 4.52	62.72 ± 4.03	0.025
$D_{50\ \%}$	57.06 ± 1.35	58.63 ± 4.86	62.35 ± 4.46	0.03
PTVA (low-risk)**:**				
D_{mean}	55.53 ± 0.94	57.46 ± 4.22	60.85 ± 3.79	0.015
$D_{50\ \%}$	54.8 ± 0.61	57.42 ± 4.42	60.48 ± 3.86	0.015
D_{min}	39.39 ± 3.19	40.02 ± 9.01	47.25 ± 4.75	0.002
$D_{98\%}$	48.74 ± 1.69	51.36 ± 3.67	54.46 ± 3.38	0.009
$D_{2\ \%}$	66.02 ± 7.29	63.66 ± 4.77	68.01 ± 4.89	0.027
$D_{95\ \%}$	49.72 ± 1.63	52.83 ± 3.77	55.54 ± 3.38	0.018
PTVB (high-risk)**:**				
D_{min}	41.9 ± 14.57	38.42 ± 9.78	49.05 ± 9.7	0.002
$D_{98\%}$	54.07 ± 5.42	56.21 ± 2.83	59.4 ± 3.89	0.003
$D_{95\%}$	56.79 ± 2.64	58.19 ± 2.41	60.52 ± 3.89	0.027
PTVC (gross tumor)**:**				
Volume	184.77 ± 44.84	261.97 ± 113.61	397.15 ± 210.34	0.018
Ipsilateral Parotid:				
D_{mean}	39.97 ± 13.46	49.07 ± 9.64	57.88 ± 8.15	0.003
$D_{50\ \%}$	41.89 ± 17.63	51.30 ± 11.83	59.88 ± 8.72	0.011
Contralateral Parotid:				
D_{mean}	23.95 ± 1.46	29.56 ± 10.25	52.77 ± 9.51	0.000
$D_{50\ \%}$	19.13 ± 0.71	25.26 ± 13.53	53.96 ± 12.05	<0.001

Volume is prescribed in cm^3 and doses are prescribed in Gy
[1)] Kruskal-Wallis-test

4.4.7. Erythema

We recorded statistically significant differences between different grades of erythema as regards the PTVA $_{(low\text{-}risk)}$ $D_{difference,}$ CTVB $_{(high\text{-}risk)}$ $D_{mean,}$ $D_{50\%}$, PTVB $_{(high\text{-}risk),}$ D_{mean}, $D_{difference}$ D_{max} , and PTVC $_{(gross\ tumor)}$ volume, D_{max} (Table32).

Table 32: Grades of erythema according to different Dosimetric parameters

Parameter	Erythema			p-value[1)]
	Grade I NO = 3 Mean ± SD	Grade II NO = 30 Mean ± SD	Grade III NO = 11 Mean ± SD	
PTVA $_{(low\text{-}risk)}$**:**				
$D_{difference}$	0.61 ± 0.24	3.83 ± 3.01	4.89 ± 3.21	0.05
CTVB $_{(high\text{-}risk)}$**:**				
D_{mean}	63.43 ± 0.49	66.49 ± 2.92	67.66 ± 3.18	0.046
$D_{difference}$	2.63 ± 0.49	5.54 ± 2.22	6.23 ± 2.07	0.024
PTVB $_{(high\text{-}risk)}$**:**				
D_{mean}	61.41 ± 0.24	64.53 ± 2.95	65.59 ± 3.41	0.048
$D_{difference}$	0.61 ± 0.24	3.57 ± 1.96	4.16 ± 1.66	0.027
D_{max}	70.8 ± 0.78	74.65 ± 2.11	75.18 ± 0.8	0.028
PTVC $_{(gross\ tumor)}$**:**				
Volume	296.27 ± 160.91	285.28 ± 181.38	413.76 ± 143.89	0.04
D_{max}	74.63 ± 0.1	76.09 ± 1.11	76.44 ± 0.69	0.03

Volume is prescribed in cm^3 and doses are prescribed in Gy

[1)] Kruskal-Wallis-test

4.4.8. Predictors of XRT interruption and grade III toxicities

As mentioned before, we performed univariate analyses for all patients, disease, and treatment characteristics, in addition to different dosimetric parameters for different target volumes and OARs, in relation to XRT interruption and grade III toxicities. After selecting those variables from univariate analyses with $p \leq 0.025$, we conducted univariate logistic regressions for these variables and included such variables that showed statistical significance into the multivariate logistic regression. Furthermore, other factors that might contribute to XRT interruption and grade III toxicities (gender, age, KPS, primary tumor site, T stage, N stage, XRT arm, and systemic therapy received) were included in multivariate regression. Regarding grade III erythema, only XRT technique, HART-SEQ-IMRT in reference to SIB-IMRT with marginally significant (p= 0.055). Furthermore for grade III dysphagia, we found that the XRT technique, HART-SEQ-IMRT in reference to SIB-IMRT (p= 0.035), volume of GTV (p=0.004), and CTVB$_{(high\text{-}risk)}$ D_{mean} (p=0.052) were significant predictors. PTVA$_{(low\text{-}risk)}$,$D_{2\%}$ (p=0.012), and oral cavity subtracted from PTVs D_{mean} (p=0.006) were the only predictor of grade III mucositis. Contralateral parotid D_{mean} ($p<0.001$) was a significant predictor of grade III xerostomia (Table 33). After stepwise feature selection in multivariate logistic analysis for XRT interruption, only primary tumor site with oral cavity in reference to other tumor sites (p =0.029), volume of GTV (p=0.002), and PTVA$_{(low\text{-}risk)}$ $D_{difference}$ (p=0.012) proved to be predictors (Table 33).

Table 33: Predictors of XRT interruption and grade III toxicities (results of logistic regression analysis)

Toxicity\Variable		B	SE	Wald	OR	95% CI	p-value
Erythema grade III							
Univariate analysis							
XRT arm	HART-SEQ-IMRT with reference to SIB-IMRT	-2.120	1,106	3.678	1.20	(0.01 -1.05)	0.055
$PTVC_{(gross\ tumor)}$ volume	Continuous variable	0.004	0.002	3.647	1.004	(1.0-1.01)	0.056
Multivariate analysis							
XRT arm	HART-SEQ-IMRT with reference to SIB-IMRT	-2.120	1,106	3.678	1.20	(0.01 -1.05)	0.055
Dysphagia grade III							
Univariate analysis							
XRT arm	HART-SEQ-IMRT with reference to SIB-IMRT	1.386	0.692	4.011	4.000	(1.03-15.53)	0.045
GTV volume	Continuous variable	0.051	0.014	12.59	1.052	(1.02-1.08)	<0.001
$CTVA_{(low\text{-}risk)}$ D_{mean}	Continuous variable	0.214	0.082	6.855	1.239	(1.05-1.45)	0.009
$CTVA_{(low\text{-}risk)}$ $D_{50\%}$	Continuous variable	0.198	0.077	6.572	1.219	(1.05-1.42)	0.010
$PTVA_{(low\text{-}risk)}$ D_{mean}	Continuous variable	0.228	0.086	7.079	1.256	(1.06-1.49)	0.008
$PTVA_{(low\text{-}risk)}$ D_{max}	Continuous variable	0.195	0.084	5.413	1.216	(1.03-1.43)	0.020
$PTVA_{(low\text{-}risk)}$ $D_{98\%}$	Continuous variable	0.179	0.087	4.182	1.196	(1.01-1.42)	0.041
$PTVA_{(low\text{-}risk)}$ $D_{2\%}$	Continuous variable	0.170	0.067	6.373	1.185	(1.04-1.35)	0.012
$PTVA_{(low\text{-}risk)}$ $D_{95\%}$	Continuous variable	0.197	0.089	4.867	1.218	(1.02-1.45)	0.027
$PTVA_{(low\text{-}risk)}$ $D_{50\%}$	Continuous variable	0.231	0.087	7.002	1.260	(1.06-1.49)	0.008
$CTVB_{(high\text{-}risk)}$ D_{mean}	Continuous variable	0.413	0.144	8.250	1.512	(1.14-2.0)	0.004
$CTVB_{(high\text{-}risk)}$ $D_{50\%}$	Continuous variable	0.270	0.097	7.774	1.310	(1.1-1.58)	0.005
$PTVB_{(high\text{-}risk)}$ D_{mean}	Continuous variable	0.406	0.149	7.383	1.500	(1.12-2.01)	0.007
$PTVB_{(high\text{-}risk)}$ D_{max}	Continuous variable	0.314	0.169	3.448	1.369	(0.98-1.9)	0.063
$PTVB_{(high\text{-}risk)}$ D_{min}	Continuous variable	0.056	0.031	3.210	1.058	(0.99-1.13)	0.073
$PTVB_{(high\text{-}risk)}$ $D_{2\%}$	Continuous variable	0.278	0.120	5.361	1.321	(1.04-1.67)	0.021
$PTVB_{(high\text{-}risk)}$ $D_{95\%}$	Continuous variable	0.366	0.157	5.457	1.442	(1.06-1.96)	0.019
$PTVB_{(high\text{-}risk)}$ $D_{50\%}$	Continuous variable	0.379	0.133	8.109	1.461	(1.13-1.89)	0.004
$CTVC_{(gross\ tumor)}$ $D_{50\%}$	Continuous variable	0.792	0.380	4.346	2.209	(1.05-4.65)	0.037
$CTVC_{(gross\ tumor)}$ D_{mean}	Continuous variable	0.824	0.384	4.616	2.280	(1.07-4.84)	0.032
$PTVC_{(gross\ tumor)}$ D_{mean}	Continuous variable	0.627	0.298	4.438	1.872	(1.05-3.35)	0.035
$PTVC_{(gross\ tumor)}$ volume	Continuous variable	0.012	0.003	12.31	1.012	(1.01-1.02)	<0.001
$PTVC_{(gross\ tumor)}$ D_{max}	Continuous variable	0.778	0.339	5.253	2.177	(1.12-4.24)	0.022
$PTVC_{(gross\ tumor)}$ $D_{2\%}$	Continuous variable	0.972	0.396	6.021	2.644	(1.22-5.75)	0.014
Multivariate analysis							
XRT arm	HART-SEQ-IMRT with reference to SIB-IMRT	-4.381	2.293	4.438	0.008	(0.0-0.714)	0.035
GTV volume	Continuous variable	0.072	0.025	8.279	1.074	(1.02-1.13)	0.004
$CTVB_{(high\text{-}risk)}$ D_{mean}	Continuous variable	0.629	0.478	3.762	2.525	(0.99-6.44)	0.052

(Continued)

Table 33: Predictors of XRT interruption and grade III toxicities (results of logistic regression analysis) (Continued)

Toxicity\Variable		B	SE	Wald	OR	95% CI	p-value
Mucositis grade III							
Univariate analysis							
$PTVA_{(low\text{-}risk)}$ $D_{2\%}$	Continuous variable	0.113	0.963	3.199	1.119	(0.98-1.27)	0.074
$CTVC_{(gross\ tumor)}$ $D_{50\%}$	Continuous variable	0.635	0.374	2.878	1.887	(0.91-3.93)	0.090
$CTVC_{(gross\ tumor)}$ D_{mean}	Continuous variable	0.663	0.378	3.076	1.887	(0.93-4.07)	0.079
$PTVC_{(gross\ tumor)}$ D_{mean}	Continuous variable	0.514	0.296	3.007	1.671	(0.94-2.99)	0.083
$PTVC_{(gross\ tumor)}$ volume	Continuous variable	0.005	0.002	5.221	1.005	(1.0-1.01)	0.022
Whole Oral cavity D_{mean}	Continuous variable	0.055	0.028	3.883	1.056	(1.0-1.2)	0.049
Oral cavity Sub $D_{50\%}$	Continuous variable	0.068	0.031	4.722	1.070	(1.01-1.14)	0.030
Oral cavity Sub D_{mean}	Continuous variable	0.081	0.035	5.246	1.084	(1.01-1.16)	0.022
Multivariate analysis							
$PTVA_{(low\text{-}risk)}$ $D_{2\%}$	Continuous variable	0.198	0.079	6.296	1.219	(1.04-1.42)	0.012
Oral cavity Sub D_{mean}	Continuous variable	0.115	0.042	7.674	1.122	(1.03-1.22)	0.006
Xerostomia grade III							
Univariate analysis							
$CTVA_{(low\text{-}risk)}$ D_{mean}	Continuous variable	0.212	0.081	6.770	1.236	(1.05-1.45)	0.009
$CTVA_{(low\text{-}risk)}$ $D_{50\%}$	Continuous variable	0.192	0.076	6.288	1.211	(1.04-1.41)	0.012
$PTVA_{(low\text{-}risk)}$ D_{mean}	Continuous variable	0.230	0.086	7.160	1.259	(1.06-1.49)	0.007
$PTVA_{(low\text{-}risk)}$ D_{min}	Continuous variable	0.208	0.077	7.260	1.231	(1.06-1.43)	0.007
$PTVA_{(low\text{-}risk)}$ $D_{98\%}$	Continuous variable	0.270	0.097	7.772	1.310	(1.08-1.58)	0.005
$PTVA_{(low\text{-}risk)}$ $D_{2\%}$	Continuous variable	0.162	0.066	5.939	1.176	(1.03-1.34)	0.015
$PTVA_{(low\text{-}risk)}$ $D_{95\%}$	Continuous variable	0.240	0.094	6.538	1.271	(1.06-1.53)	0.011
$CTVB_{(high\text{-}risk)}$ D_{mean}	Continuous variable	0.210	0.113	3.435	1.234	(0.99-1.54)	0.064
$CTVB_{(high\text{-}risk)}$ $D_{50\%}$	Continuous variable	0.154	0.086	3.201	1.167	(0.99-1.38)	0.074
$PTVB_{(high\text{-}risk)}$ D_{mean}	Continuous variable	0.227	0.115	3.906	1.255	(1.0-1.57)	0.048
$PTVB_{(high\text{-}risk)}$ D_{min}	Continuous variable	0.108	0.040	7.327	1.114	(1.03-1.2)	0.007
$PTVB_{(high\text{-}risk)}$ $D_{98\%}$	Continuous variable	0.327	0.136	5.745	1.387	(1.06-1.81)	0.017
$PTVB_{(high\text{-}risk)}$ $D_{95\%}$	Continuous variable	0.403	0.186	4.717	1.497	(1.04-2.15)	0.030
$CTVC_{(gross\ tumor)}$ $D_{50\%}$	Continuous variable	0.638	0.367	3.020	1.892	(0.92-3.88)	0.082
$PTVC_{(gross\ tumor)}$ volume	Continuous variable	0.006	0.002	6.411	1.006	(1.0-1.01)	0.011
Ipsilateral parotid $D_{50\%}$	Continuous variable	0.090	0.036	6.158	1.094	(1.02-1.17)	0.013
Ipsilateral parotid D_{mean}	Continuous variable	0.119	0.042	8.076	1.127	(1.04-1.12)	0.004
Contralateral parotid $D_{50\%}$	Continuous variable	0.118	0.029	16.55	1.125	(1.06-1.19)	<0.001
Contralateral parotid D_{mean}	Continuous variable	0.157	0.039	16.22	1.171	(1.08-1.126)	<0.001
Multivariate analysis							
Contralateral parotid D_{mean}	Continuous variable	0.156	0.039	15.89	1.169	(1.08-1.13)	<0.001

(Continued)

Table 33: Predictors of XRT interruption and grade III toxicities (results of logistic regression analysis) (Continued)

Toxicity\Variable		B	SE	Wald	OR	95% CI	p-value
XRT Interruption							
Univariate analysis							
XRT arm	HART-SEQ-IMRT reference to SIB-IMRT	1.685	0.847	3.834	5.250	(0.99 -27.6)	0.05
Primary tumor site	Oral cavity in reference to other sites	0.288	0.771	0.139	1.333	(0.29 -6.04)	0.709
GTV volume	Continuous variable	0.026	0.009	8.617	1.026	(1.01-1.04)	0.003
$CTVA_{(low\text{-}risk)}$ $D_{difference}$	Continuous variable	0.286	0.114	6.621	1.331	(1.06-1.67)	0.012
$PTVA_{(low\text{-}risk)}$ $D_{difference}$	Continuous variable	0.302	0.128	5.562	1.352	(1.05-1.74)	0.018
$PTVC_{(gross\ tumor)}$ volume	Continuous variable	0.006	0.002	6.930	1.006	(1.0-1.01)	0.008
$PTVC_{(gross\ tumor)}$ D_{mean}	Continuous variable	0.630	0.337	3.493	1.877	(0.97-3.63)	0.062
$PTVC_{(gross\ tumor)}$ $D_{2\%}$	Continuous variable	0.753	0.407	3.427	2.123	(0.96-4.71)	0.064
Multivariate analysis							
Primary tumor site	Oral cavity with reference to other sites	-3.528	1563	5.996	0.029	(0.001 -0.63)	0.029
GTV volume	Continuous variable	0.055	0.018	9.377	1.057	(1.02-1.095)	0.002
$PTVA_{(low\text{-}risk)}$ $D_{difference}$	Continuous variable	0.828	0.325	6.336	2.266	(1.2-4.28)	0.012

Volume is prescribed in cm^3 and doses are prescribed in Gy

4.5. Treatment Outcome

4.5.1. Response Rate

Three months after completion of XRT, patients were evaluated for response. Out of 44 patients, 32 (72.7%) patients had CR, 7 (15.9%) PR, 2 (4.6%) SD, and 3 (6.8%) patients had PD. The overall residual rate at 3 months was 27.3% (12 patients). All residual tumors (100%) were inside $CTVC_{(gross\ tumor)}$ (Table 34).

4.5.1.1. Response rate according to the XRT arm (all patients)

There was no statistically significant difference between the two XRT techniques regarding response. Twenty-one (75%) patients had CR in the HART-SEQ-IMRT arm, 4 (14.3%) PR, 1 (3.6%) SD, and 2 (7.1%) PD, in comparison to 11 (68.8%), 3 (18.8%), 1 (6.2%), and 1 (6.2%), respectively, in the SIB-IMRT arm (p=0.949). The overall residual rate among HART-SEQ-IMRT patients was 25% (7 patients), compared to 31.3% (5 patients) for SIB-IMRT patients (p=0.654) (Table 35).

Table 34: Treatment outcome for the 44 patients enrolled in the study

Treatment outcome	**NO (%)**
Objective Response:	
CR	32 (72.7%)
PR	7 (15.9%)
SD	2 (4.5%)
PD	3 (6.8%)
Residual disease:	
No	32 (75%)
yes	12 (27.3 %)
Site of residual in 12 patients	
CTVA (low-risk)	0 (0%)
CTVB (high-risk)	0 (0%)
CTVC (gross tumor)	12 (100%)
Out of field	0 (0%)
Early Death within 3 months:	
No	41 (93.2)
Yes	3 (6.8%)
Pattern of Failure:	
No failure	25 (56.8%)
Local failure	5 (11.4%)
Regional failure	4 (9.1%)
Both local and regional failure	5 (11.4%)
Distant failure	2 (4.5%)
Local, regional, and distant failure	3 (6.8%)
Locoregional failure:	
No	27 (61.4%)
yes	17 (38.6%)
Site of Locoregional Failure in 17 patients:	
CTVA (low-risk)	0 (0%)
CTVB (high-risk)	1 (5.8%)
CTVC (gross tumor)	12 (70.6%)
CTVC (gross tumor) + CTVB (high-risk)	4 (23.6%)
Out of field	0 (0%)
Distant failure:	
No	39 (88.6%)
yes	5 (11.4%)
Site of metastases in 5 patients:	
Lung	1 (20%)
Mediastinum	1 (20%)
Lung and mediastinum	2 (40%)
Skin	1 (20%)
Death:	
No	36 (81.8)
yes	8 (18.2%)
Cause of death in 8 patients:	
Tumor progression	3 (37.5%)
Metastases	3 (37.5%)
Treatment toxicity	0 (0%)
Others	2 (25%)

Table 35: Treatment outcome for 44 patients according to the XRT technique

Treatment outcome	XRT Technique		p-value
	HART-SEQ-IMRT NO = 28 NO (%)	SIB-IMRT NO = 16 NO (%)	
Objective Response:			
CR	21 (75%)	11 (68.8%)	0.949
PR	4 (14.3%)	3 (18.8%)	
SD	1 (3.6%)	1 (6.3%)	
PD	2 (7.1%)	1 (6.3%)	
Residual disease:			
No	21 (75%)	11 (68.8%)	0.654
Yes	7 (25%)	5 (31.3%)	
Early Death within 3 months:			
No	26 (92.9%)	15 (93.8%)	0.910
Yes	2 (7.1%)	1 (6.3%)	
Locoregional failure:			
No	18 (64.3%)	9 (56.3%)	0.598
yes	10 (35.7%)	7 (43.8%)	
Pattern of Failure:			
No failure	17 (60.7%)	8 (50%)	0.219
Local failure	2 (7.1%)	3 (18.8%)	
Regional failure	1 (3.6%)	3 (18.8%)	
Both local and regional failure	5 (17.9%)	0 (0%)	
Distant failure	1 (3.6%)	1 (6.3%)	
Local, regional, and distant failure	2 (7.1%)	1 (6.3%)	
Distant failure:			
No	25 (89.3%)	14 (87.5%)	0.858
yes	3 (10.7%)	2 (12.5%)	
Death:			
No	22 (78.6%)	14 (87.5%)	0.460
Yes	6 (21.4%)	2 (12.5%)	

4.5.1.2. Response rate for patients with GTV ≤ 100 cm^3according to the XRT technique

Further analysis of 33 patients with GTV ≤ 100 cm^3 revealed more residual cases in the SIB-IMRT arm than in the HART-SEQ-IMRT arm; however this difference could not reach any statistical significance. Fifteen (88.2%) patients in the HART-SEQ-IMRT arm had CR, 1 (5.9%) PR, 0 (0%) SD, and 1 (5.9%) had PD, in comparison to 11 (68.8%), 3 (18.8%), 1 (6.2%), and 1 (6.2%), respectively, in the SIB-IMRT arm (p=0.460).

The overall residual rate among 17 HART-SEQ-IMRT patients with GTV ≤ 100 cm^3 was 11.8% (2 patients), compared to 31.3% (5 patients) among SIB-IMRT patients (p=0.171) (Table 36).

Table 36: Treatment outcome for 33 patients with GTV ≤ 100 cm^3 according to the XRT technique

Treatment outcome	**XRT Technique**		**p-value**
	HART-SEQ-IMRT NO =17 NO (%)	**SIB-MRT NO =16 NO (%)**	
Objective Response:			
CR	15 (88.2%)	11 (68.8%)	
PR	1 (5.9%)	3 (18.8%)	0.460
SD	0 (0%)	1 (6.3%)	
PD	1 (5.9%)	1 (6.3%)	
Residual disease:			
No	15 (88.2%)	11 (68.8%)	0.171
Yes	2 (11.8%)	5 (31.3%)	
Early Death within 3 montths:			
No	16 (94.1%)	15 (93.8%)	0.965
Yes	1 (5.9%)	1 (6.3%)	
Locoregional failure:			
No	13 (76.5%)	9 (56.3%)	0.218
yes	4 (23.5%)	7 (43.8%)	
Pattern of Failure:			
No failure	12 (70.6%)	8 (50%)	
Local failure	1 (5.9%)	3 (18.8%)	
Regional failure	0 (0%)	3 (18.8%)	0.238
Both local and regional failure	2 (11.8%)	0 (0%)	
Distant failure	1 (5.9%)	1 (6.3%)	
Local, regional, and distant failure	1 (5.9%)	1 (6.3%)	
Distant failure:			
No	15 (88.2%)	14 (87.5%)	0.948
yes	2 (11.8%)	2 (12.5%)	
Death:			
No	15 (88.2%)	14 (87.5%)	0.948
yes	2 (11.8%)	2 (12.5%)	

4.5.1.3. Response rate according to the systemic therapy received (all patients)

The TPF group had a higher rate of residual tumors; nevertheless, we reported no statistical difference between the PF group and TPF group as regards response rates. Among the PF group, 24 (80%) patients had CR, 5 (16.7%) PR, 0 (0%) SD, and only 1 (3.3%) had PD, in comparison to 8 (57.1%), 2 (14.3%), 2 (14.3%), and 2 (14.3%), respectively, amongst the TPF group (0.083). The overall residual rate amongst PF patients was 20% (6 patients), compared to 42.9% (6 patients) for SIB-IMRT patients (p=0.113) (Table 37).

4.5.1.3.1. Response rate for PF patients according to the XRT technique

Analysis of subgroup of patients who received the PF regimen showed that there was no statistically significant difference between the two XRT techniques regarding response. Nineteen (79.2%) patients had CR in the HART-SEQ-IMRT arm, 4 (16.7%) PR, 0 (0%) SD, and 1 (4.1%)

had PD, in comparison to 5 (83.3%), 1 (16.7%), 0 (0%), and 0 (0%), respectively, in the SIB-IMRT arm (p=0.878). Residual rate among HART-SEQ-IMRT patients was 20.8% (5 patients), compared to 16.7% (1 patient) for SIB-IMRT patients (p=0.819) (Table 38).

4.5.1.3.2. Response rate for TPF patients according to the XRT technique

An analysis of a subgroup of patients who received the TPF regimen, also showed that there was no statistically significant difference between the two XRT techniques regarding response. Two (50%) patients had CR in the HART-SEQ-IMRT arm, 0 (0%) PR, 1 (25%) SD, and 1 (25%) had PD, in comparison to 6 (60%), 2 (20%), 1 (10%), and 1 (10%), respectively, in the SIB-IMRT arm (p=0.626). Residual rate among HART-SEQ-IMRT patients was 50 % (2 patients), compared to 40% (4 patients) for SIB-IMRT patients (p=0.733) (Table 39).

Table 37: Treatment outcome for 44 patients according to the systemic therapy received

Treatment outcome	**Systemic Therapy**		**p-value**
	PF NO =30 NO (%)	**TPF NO =14 NO (%)**	
Objective Response:			
CR	24 (80%)	8 (57.1%)	
PR	5 (16.7%)	2 (14.3%)	0.083
SD	0 (0%)	2 (14.3%)	
PD	1 (3.3%)	2 (14.3%)	
Residual disease:			
No	24 (80%)	8(57.1%)	0.113
yes	6 (20%)	6 (42.9%)	
Early Death within 3 montths:			
No	29 (96.7%)	12 (85.7%)	0.179
yes	1 (3.3%)	2 (14.3%)	
Locoregional failure:			
No	22 (73.3%)	5 (35.7%)	0.017
yes	8 (26.7%)	9 (64.3%)	
Pattern of Failure:			
No failure	20 (66.7%)	5(35.7%)	
Local failure	1 (3.3%)	4 (28.6%)	
Regional failure	1 (3.3%9	3 (21.4%)	0.024
Both local and regional failure	3 (10%)	2 (14.3%)	
Distant failure	2 (6.7%)	0 (0%)	
Local, regional, and distant failure	3 (10%)	0 (0%)	
Distant failure:			
No	25 (83.3%)	14 (100%)	0.105
yes	5 (16.7%)	0 (0%)	
Death:			
No	25 (83.3%)	11 (78.6%)	0.703
yes	5 (16.7%)	3 (21.4%)	

Table 38: Treatment outcome for 30 patients who received PF regimen according to the XRT technique

Treatment outcome	**XRT Technique**		**p-value**
	HART-SEQ-IMRT NO = 24 NO (%)	**SIB-IMRT NO = 6 NO (%)**	
Objective Response:			
CR	19 (79.2%)	5 (83.3%)	
PR	4 (16.7%)	1 (16.7%)	0.878
SD	0 (0%)	0 (0%)	
PD	1 (4.2%)	0 (0%)	
Residual disease:			
No	19 (79.2%)	5 (83.3%)	0.819
yes	5 (20.8%)	1 (16.7%)	
Early Death within 3 montths:			
No	23 (95.8%)	6 (60%)	1.0
yes	1 (4.2%)	0 (0%)	
Locoregional failure:			
No	17 (70.8%)	5 (83.3%)	0.536
yes	7 (29.2%)	1 (16.7%)	
Pattern of Failure:			
No failure	16 (66.7%)	4 (66.7%)	
Local failure	1 (4.2%)	0 (0%)	
Regional failure	1 (4.2%)	0 (0%)	0.745
Both local and regional failure	3 (12.5%)	0 (0%)	
Distant failure	1 (4.2%)	1 (16.7%)	
Local, regional, and distant failure	2 (8.3%)	1 (16.7%)	
Distant failure:			
No	21 (87.5%)	4 (66.7%)	0.221
yes	3 (12.5%)	2 (33.3%)	
Death:			
No	20 (83.3%)	5 (83.3%)	1.0
yes	4 (16.7%)	1 (16.7%)	

Table 39: Treatment outcome for 14 patients who received TPF regimen according to XRT technique

Treatment outcome	**XRT Technique**		**p-value**
	HART-SEQ-IMRT NO = 4 NO (%)	**SIB-IMRT NO = 10 NO (%)**	
Objective Response:			
CR	2 (50%)	6 (60%)	
PR	0 (0%)	2 (20%)	0.626
SD	1 (25%)	1 (10%)	
PD	1 (25%)	1 (10%)	
Residual disease:			
No	2 (50%)	6 (60%)	0.733
yes	2 (50%)	4 (40%)	
Early Death within 3 montths:			
No	3 (75%)	9 (90%)	0.469
yes	1 (25%)	1 (10%)	
Locoregional failure:			
No	1 (25%)	4 (40%)	0.597
yes	3 (75%)	6 (60%)	
Pattern of Failure:			
No failure	1 (25%)	4 (40%)	
Local failure	1 (25%)	3 (30%)	0.093
Regional failure	0 (0%)	3 (30%)	
Both local and regional failure	2 (50%)	0 (0%)	
Death:			
No	2 (50%)	9 (90%)	0.099
yes	2 (50%)	1 (10%)	

4.5.2. Treatment failure

After a median follow-up time of 11.75 months (95% CI 9.83 – 13.67), 25 (56.8%) patients were progression free, 5 (11.4%) patients had local failure, 4 (9.1%) had regional failure, 5 (11.4%) had both local and regional failure, 2 (4.5%) had distant failure, and 3 (6.8%) had local, regional and distant failure (Table 34). There was no statistical difference regarding site of failure between the HART-SEQ-IMRT technique and the SIB-IMRT technique (p=0.219) (Table 35). Also after analysis of subgroup of patients with GTV ≤ 100 cm3, there was no statistical difference regarding site of failure between the techniques (p= 0.238) (Table 36).

The pattern of failure was significantly different according to systemic therapy received. Twenty out of 30 (66.7%) patients in PF group had disease control, one (3.3%) had local failure, 1 (3.3%) regional failure, 3 (10%) both local and regional failure, 2 (6.7%) distant failure, and 3 (10%) had local, regional, and distant failure, in comparison to 5 (35.7%), 4 (28.6%), 3 (21.4%), 2 (14.3%), 0 (0%), and 0 (0%) patients in TPF group (p=0.024) (Table 37). Further analysis of the subgroup of patients who received PF regimen, showed no statistically significant differences regarding site of failure between the HART-SEQ-IMRT arm and the SIB-IMRT arm (p= 0.745) (Table 38). Also, after analysis of the subgroup of patients who received TPF regimen, there was also no statistical difference regarding site of failure between the HART-SEQ-IMRT arm and the SIB-IMRT arm (p= 0.093) (Table 39).

The median follow-up for PFS is 13.25 months (95%-CI: 11.86 – 14.64). Median survival-time for PFS was not reached. The one-year PFS for the 44 patients was 58.8% (Fig. 9). PFS for HART-SEQ-IMRT patients (one-year survival 60.3%) was not different compared to SIB-IMRT patients (one-year survival 56.3%) (p=0.640) (Fig. 10). Also, PFS for HART-SEQ-IMRT patients with GTV ≤ 100 cm^3 (one-year survival 70.1%) was not different compared to SIB-IMRT patients (one-year survival 56.3%) (p=0.318) (Fig.11).

According to systemic therapy received, PFS for PF patients (one-year PFS 69.7%) was different compared to TPF patients (one-year PFS 35.7%) (p=0.031) (Fig.12). Regarding analysis of subgroup of patients who received PF regimen, PFS for HART-SEQ-IMRT patients (one-year PFS 66.2%) was not different in comparison to SIB-IMRT patients (one-year PFS 83.3 %) (p=0.774) (Fig.13). For the subgroup of patients who received neoadjuvant TPF regimen, PFS for HART-SEQ-IMRT patients (one-year PFS 25%) was not different in comparison to SIB-IMRT patients (one-year PFS 40%) (p=0.540 (Fig. 14).

After the previously described selection process, multivariate Cox's regression analysis resulted in interruption of XRT as a predictor of disease progression (p=0.038). PFS for patients with no interruption of XRT course (one-year 69.8%) was better compared to patients with XRT interruption (one-year 37.5%) (p=0.028) (Fig.15).

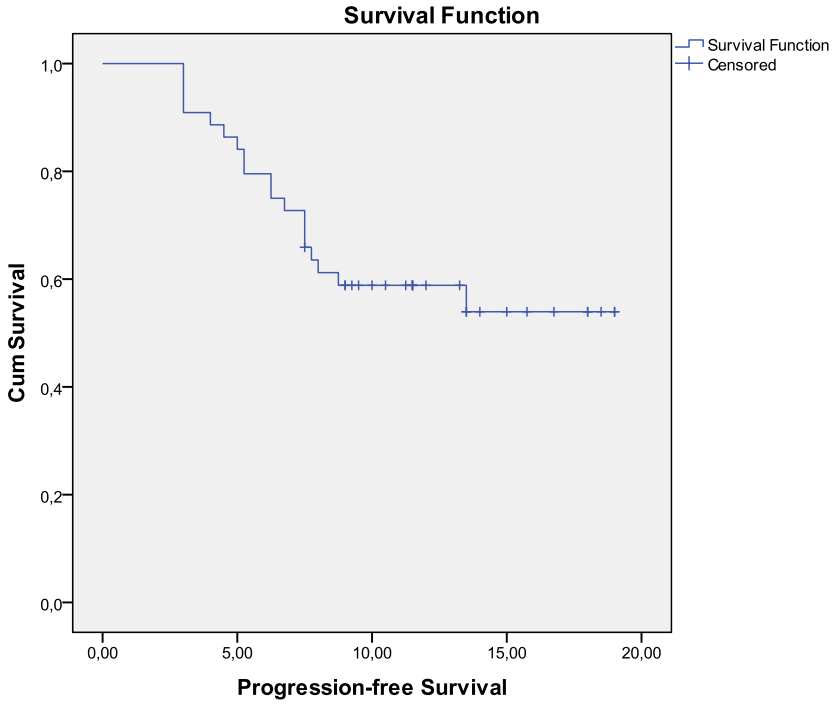


Fig. 9: Kaplan-Meier estimate of PFS for 44 patients treated with IMRT

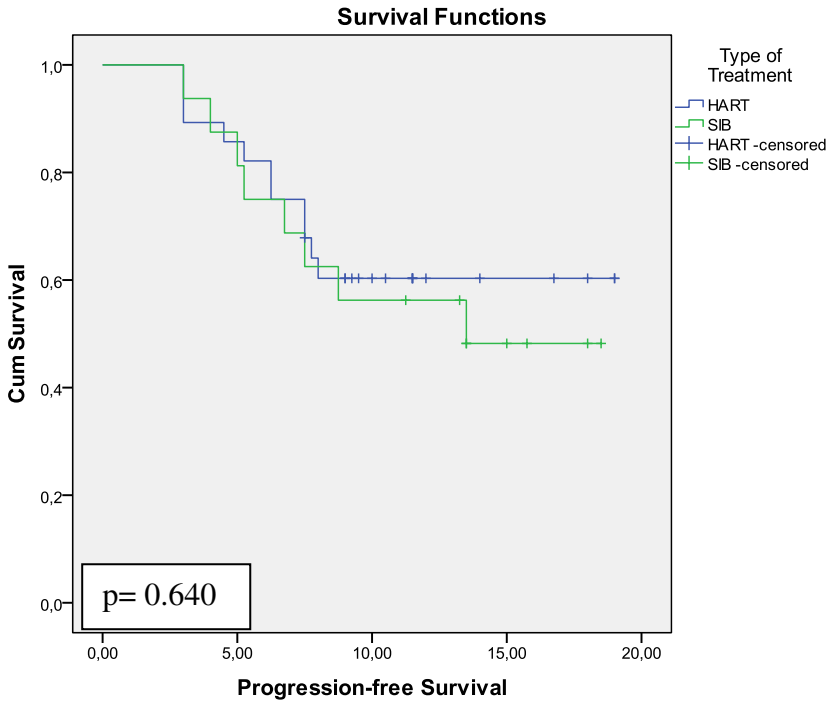


Fig.10: Kaplan-Meier estimate of PFS for 44 patients according to the XRT technique used in the study

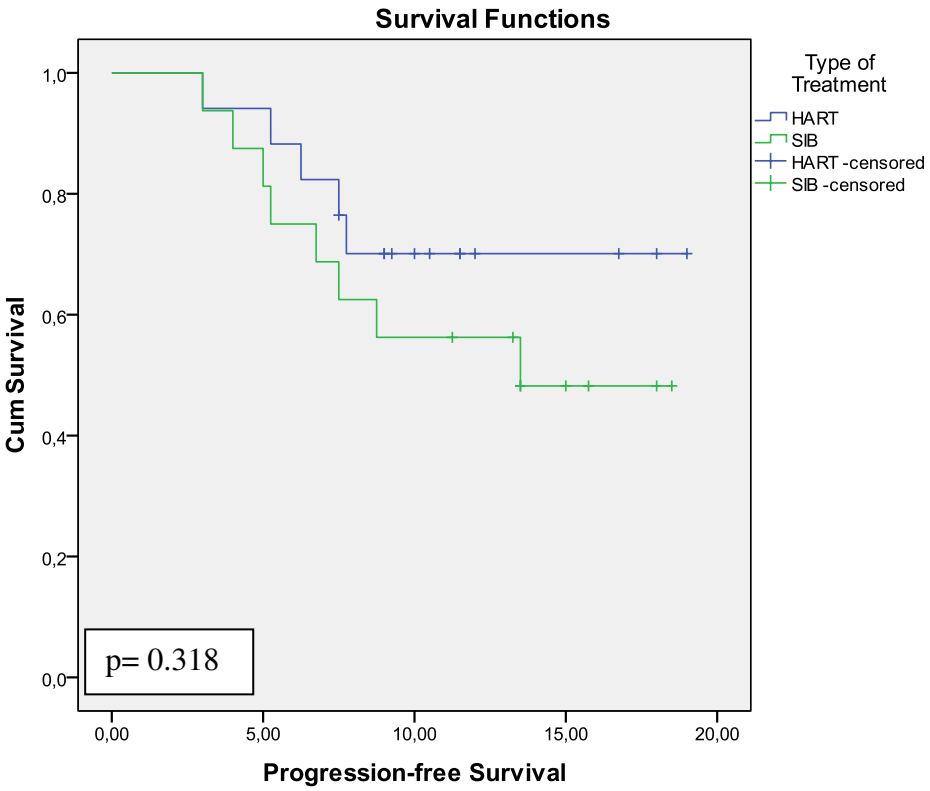


Fig.11: Kaplan-Meier estimate of PFS for 33 patients with GTV ≤ 100 cm^3 according to the XRT technique used in the study

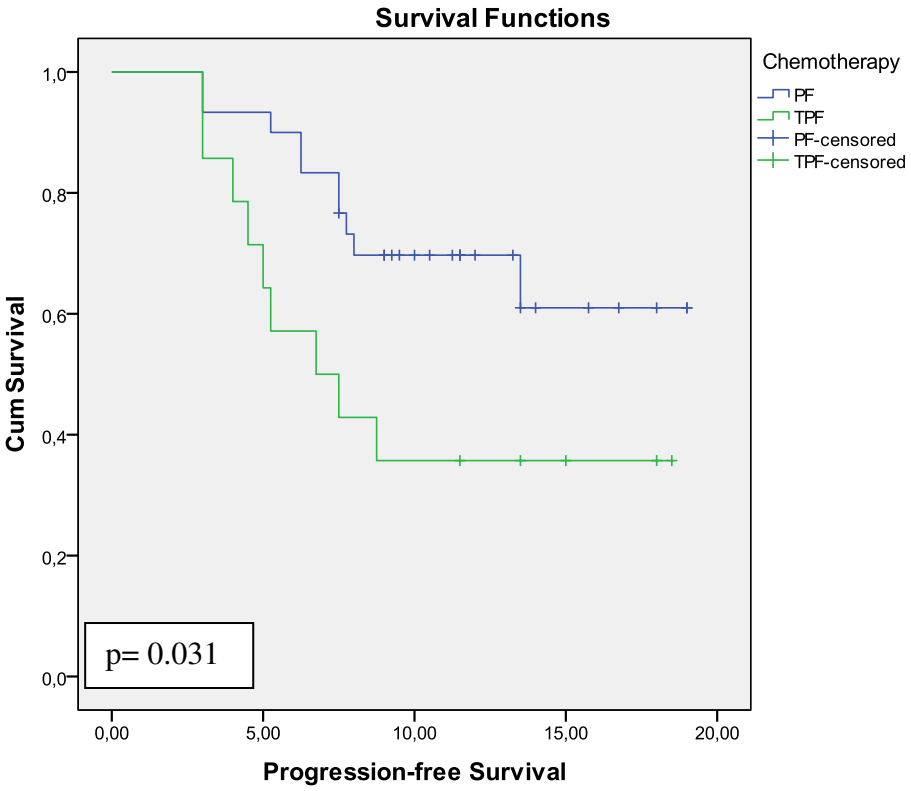


Fig.12: Kaplan-Meier estimate of PFS for 44 patients according to the systemic therapy used in the study

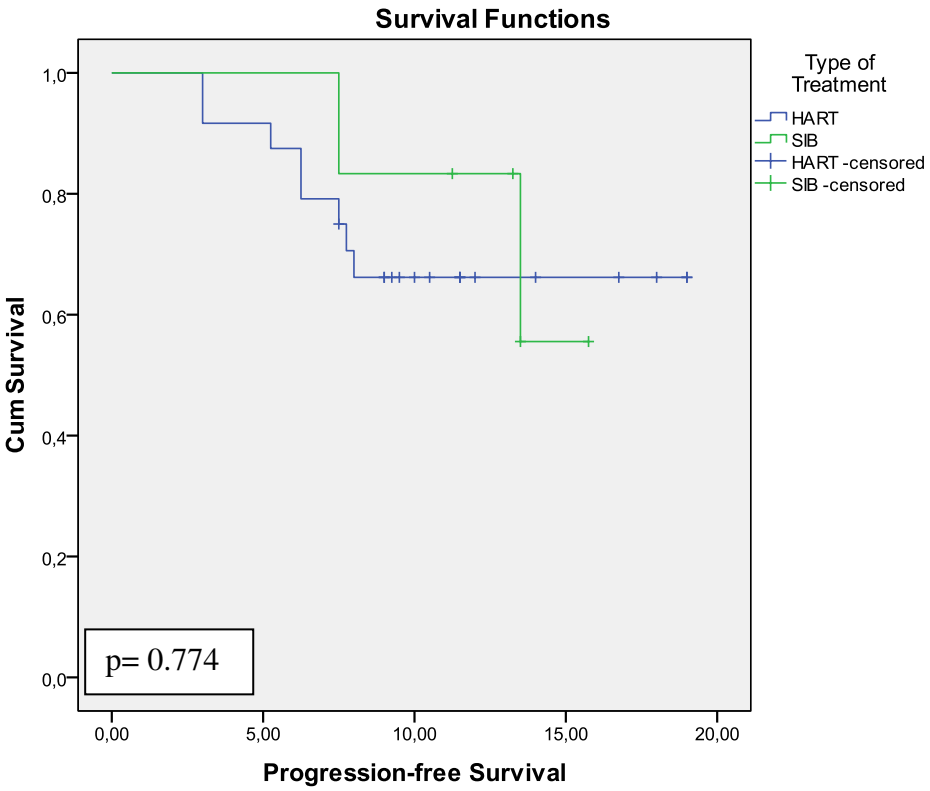


Fig.13: Kaplan-Meier estimate of PFS for 30 patients who received PF regimen according to the XRT technique used in the study

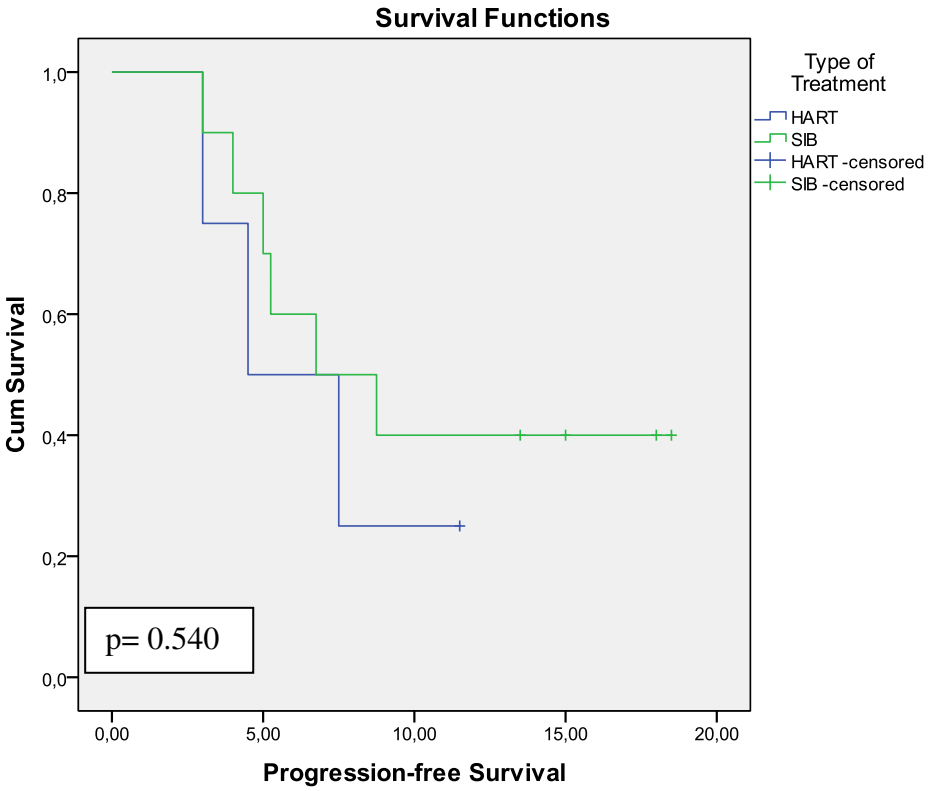


Fig.14: Kaplan-Meier estimate of PFS for 14 patients who received TPF regimen according to the XRT technique used in the study

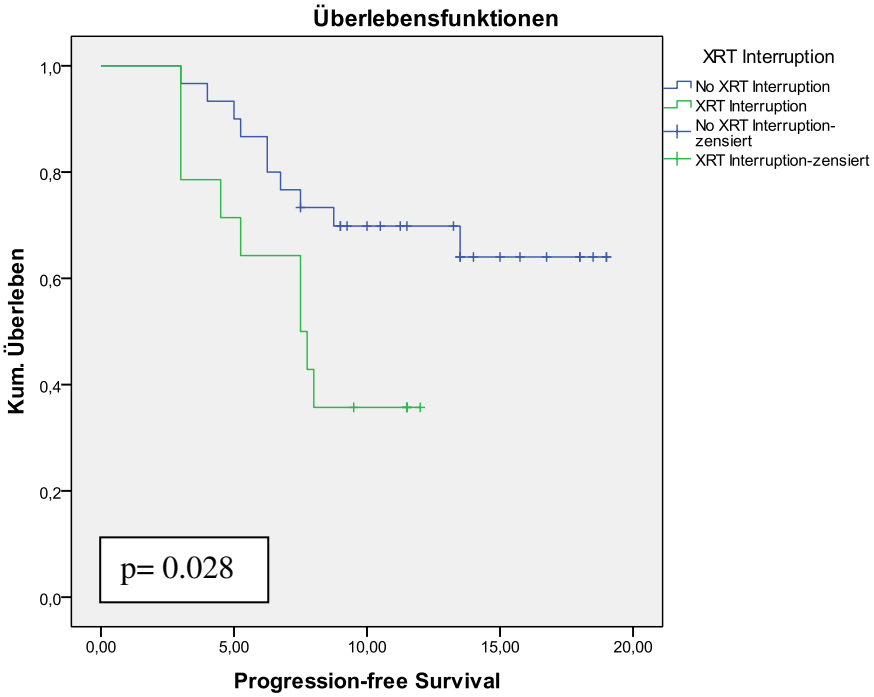


Fig.15: Kaplan-Meier estimate of PFS for 44 patients according to the XRT course interruption

4.5.3. Locoregional failure (LRF)

Loco-regional control was achieved in 27/44 patients (61.4%). Seventeen of 44 (38.6%) patients had LRF; tumor persistence in 5 patients, and tumor recurrence in 12 patients. The site of locoregional recurrence was in 12 (70.6%) patients in CTVC $_{(\text{gross tumor})}$, in one patient in CTVB $_{(\text{high-risk})}$, and in 4 (23.6%) patients in both CTVC $_{(\text{gross tumor})}$ + CTVB $_{(\text{high-risk})}$. No patient developed recurrence in CTVA $_{(\text{low-risk})}$ or out of XRT field recurrence (Table 34). There was no statistically significant difference between the two XRT techniques regarding rate of LRF. Ten of 28 (35.7%) patients in the HART-SEQ-IMRT arm had LRF in comparison to 7 of 16 (43.8%) patients in the SIB-IMRT arm (p=0.598) (Table 35). For the subgroup of patients with GTV ≤ 100 cm3, there was also no statistically significant difference between the two XRT arms regarding LRF (p=0.218) (Table 36).

Most of the patients who received the TPF regimen experienced LRF. Nine out of 14 (64.3%) patients in the TPF group had LRF, compared to 8 out of 30 (26.7%) patients in the PF group (p=0.017) (Table 37). Further analysis of the subgroup of patients who received PF regimen revealed no statistically significant differences regarding LRF rate between the HART-SEQ-IMRT arm and the SIB-IMRT arm (p= 0.536) (Table 38). After analysis of the subgroup of patients who received the TPF regimen, there was also no statistically significant difference regarding site of failure between the HART-SEQ-IMRT arm and the SIB-IMRT arm (p= 0.597) (Table 39).

Through further univariate analysis, we found that male patients experienced more LRF than female patients, where all 17 cases with LRF were males (100%) and no female patient had LRF (p=0.036). Also, we reported a difference between patients with LRF and patient without as regard primary site of tumor. We found that LRF was more pronounced in patients with larynx and\or hypopharynx tumors than in patients with oral cavity or oropharynx tumors. (p=0.05). Patients who had to interrupt their XRT course experienced LRF more than patients who did not, 9 out of 14 patients with XRT course interruption suffered from LRF, compared to 8 out of 30 patients with no XRT course interruption had LRF (p=0.017) (Table 40).

Analysis of LRF according to dosimetric parameters revealed differences between plans of patients who experienced LRF and plans of patients who did not experience LRF especially for CTVB\PTV $_{(high\text{-}risk)}$. CTVB $_{(high\text{-}risk)}$ $D_{50\ \%}$ was higher (67.47 ± 3.78 Gy) for patients without LRF, compared to 65.08 ± 3.51 Gy for patients with LRF (p=0.047), PTV $_{(high\text{-}risk)}$ D_{min} was 46.56 ± 9.83 Gy, compared to 39.09 ± 11.67 Gy, respectively, (p=0.039), PTV $_{(high\text{-}risk)}$ $D_{98\ \%}$ was 58.73 ± 3.67 Gy, compared to 55.74 ± 3.63 Gy, respectively, (p=0.006), PTV $_{(high\text{-}risk)}$ $D_{95\ \%}$ was 60.01 ± 3.55 Gy, compared to 57.91 ± 2.78 Gy, respectively, (p=0.022), and PTV $_{(high\text{-}risk)}$ $V_{95\ \%}$ was 98.2 ± 2.03%, compared to 95.96 ± 4.36 %, respectively, (p=0.016) (Table 40).

Table 40: Univariate analysis of locoregional failure for 44 patients

Variable	No locoregional failure NO = 27 NO (%)*	locoregional failure NO = 17 NO (%)*	p-value
Gender:			
Male	21 (77.8%)	17 (100%)	0.036
Female	6 (22.2%)	0 (0%)	
Primary site:			
Oropharynx	14 (51.9%)	2 (11.8%)	
Hypopharynx	3 (11.1%)	5 (29.4%)	0.050
Oral cavity	5 (18.5%)	6 (35.3%)	
Larynx	5 (18.5%)	4 (23.5%)	
Systemic therapy:			
Concurrent PF regimen	22 (81.5%)	8 (47.1%)	0.017
Neoadjuvant TPF + cetuximab concurrent with XRT	5 (18.5%)	9 (52.9%)	
XRT interruption:			
No	22 (81.5%)	8 (47.1%)	0.017
Yes	5 (18.5%)	9 (52.9%)	
CTVB $_{(high\text{-}risk)}$**:**			0.047
$D_{50\ \%}$	67.47 ± 3.78	65.08 ± 3.51	
PTVB $_{(high\text{-}risk)}$**:**			
D_{min}	46.56 ± 9.83	39.09 ± 11.67	0.039
$D_{98\ \%}$	58.73 ± 3.67	55.74 ± 3.63	0.006
$D_{95\ \%}$	60.01 ± 3.55	57.91 ± 2.78	0.022
$V_{95\%}$ (%)	98.2 ± 2.03	95.96 ± 4.36	0.016

Volume is prescribed in cm^3 and doses are prescribed in Gy.
***** Except as otherwise stated.

Using univariate Cox's regression analysis, we found that systemic therapy received, (neoadjuvant TPF with reference to concurrent PF) (p=0.015), XRT interruption (p=0.023), and $PTVB_{(intermediate\text{-}risk)}$ $D_{98\%}$ (p=0.022) were predictors of LRF. Other clinical factors that did not show statistical significance in univariate Cox's regression analysis but might contribute to LRF (gender, age, KPS, primary tumor site, histology, T stage, N stage, XRT arm) were included in multivariate regression analysis. After multivariate analysis with stepwise selection, only systemic therapy received (p=0.014), and XRT interruption (p=0.02) continued to show prediction of LRF (Table 41).

Table 41: Predictors for locoregional failure (results of Cox regression analysis)

Variable		B	SE	HR	95% CI	p-value
Univariate analysis						
Systemic therapy	Neoadjuvant TPF with reference to concurrent PF	-1.184	0.488	5.872	(0.11-0.79)	0.015
XRT interruption	Yes with reference to no	-1.108	0.488	5.160	(0.13-0.86)	0.023
$PTVB_{(high\text{-}risk)}$ $D_{98\%}$	Continuous variable	-0.150	0.066	5.243	(0.75-0.97)	0.022
Multivariate analysis						
Systemic therapy	Neoadjuvant TPF with reference to concurrent PF	-1.209	0.490	6.804	(0.11-0.78)	0.014
XRT interruption	Yes with reference to no	-1.134	0.489	5.37	(0.12- .84)	0.02

The median follow-up for LRFS is 12 months (95%-CI: 10.32 – 13.69). Median survival for LRFS was not reached. The one-year LRFS for the 44 patients was 61 % (Fig. 16). LRFS for HART-SEQ-IMRT patients (one-year LRFS 63.9%) was not different compared to SIB-IMRT patients (one-year LRFS 56.3%) (p=0.638) (Fig.17). Furthermore, LRFS for HART-SEQ-IMRT patients with GTV $\leq$ 100 cm^3 (one-year LRFS 76%) was not different compared to SIB-IMRT patients (one-year LRFS 56.3%) (p=0.241) (Fig.18).

Regarding systemic therapy, LRFS for PF patients (one-year LRFS 73%) was statistically better compared to TPF patients (one-year LRFS 35.7%) (p=0.009) (Fig.19). After analysis of subgroup of patients who received the PF regimen, LRFS for HART-SEQ-IMRT patients (one-year LRFS 70.4%) was not different in comparison to SIB-IMRT patients (one-year LRFS 83.3%) (p=0.520) (Fig.20). For the subgroup of patients who received the TPF regimen, LRFS for HART-SEQ-IMRT patients (one-year LRFS 25%) was not different compared to SIB-IMRT patients (one-year LRFS 40%) (p=0.540) (Fig. 21).

LRFS for patients with no interruption of XRT (one-year LRFS 73%) was statistically better compared to patients with interruption of XRT (one-year LRFS 35.7%) (p=0.015) (Fig. 22).

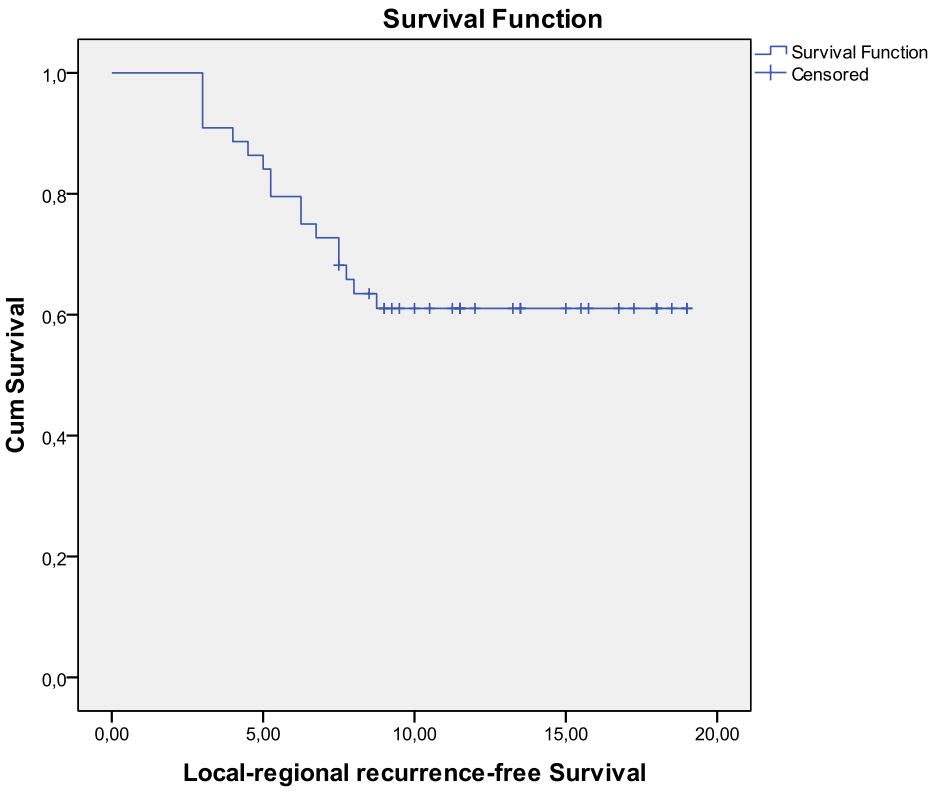


Fig. 16: Kaplan-Meier estimate of LRFS for 44 patients treated with IMRT

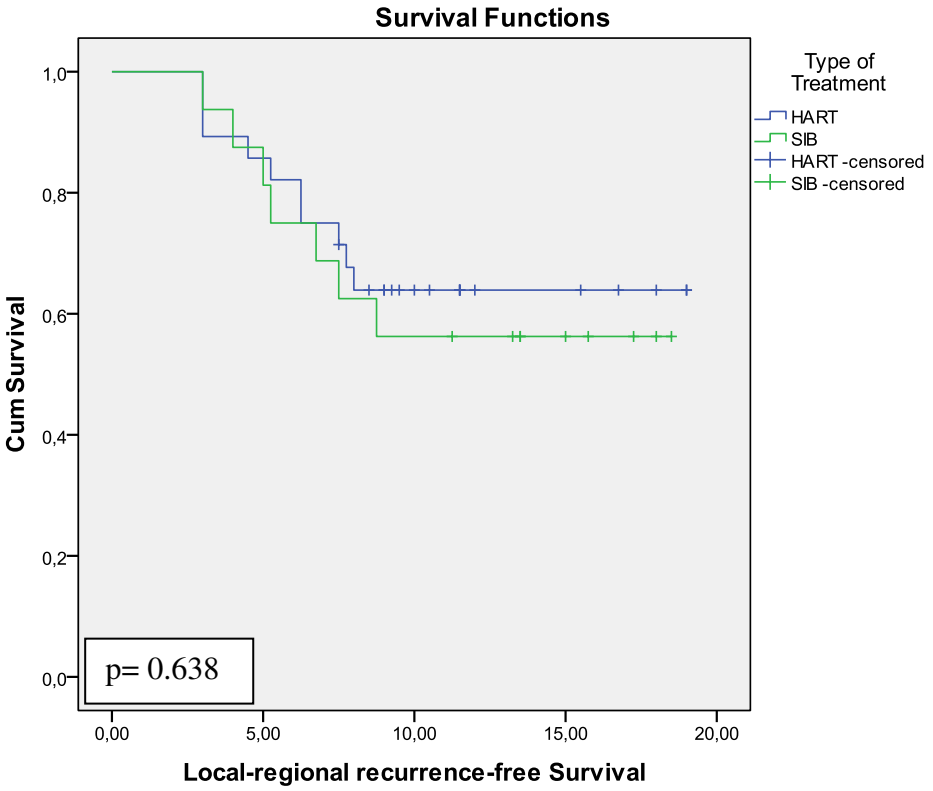


Fig.17: Kaplan-Meier estimate of LRFS for 44 patients according to the XRT technique used in the study

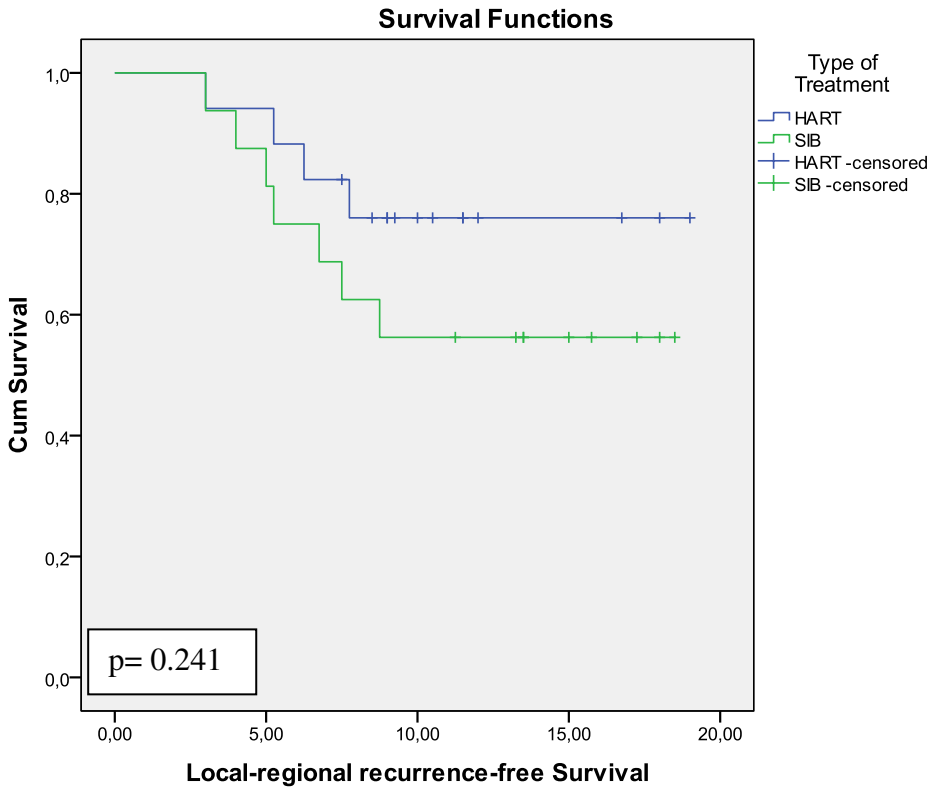


Fig.18: Kaplan-Meier estimate of LRFS for 33 patients with GTV ≤ 100 cm^3 according to the XRT technique used in the study

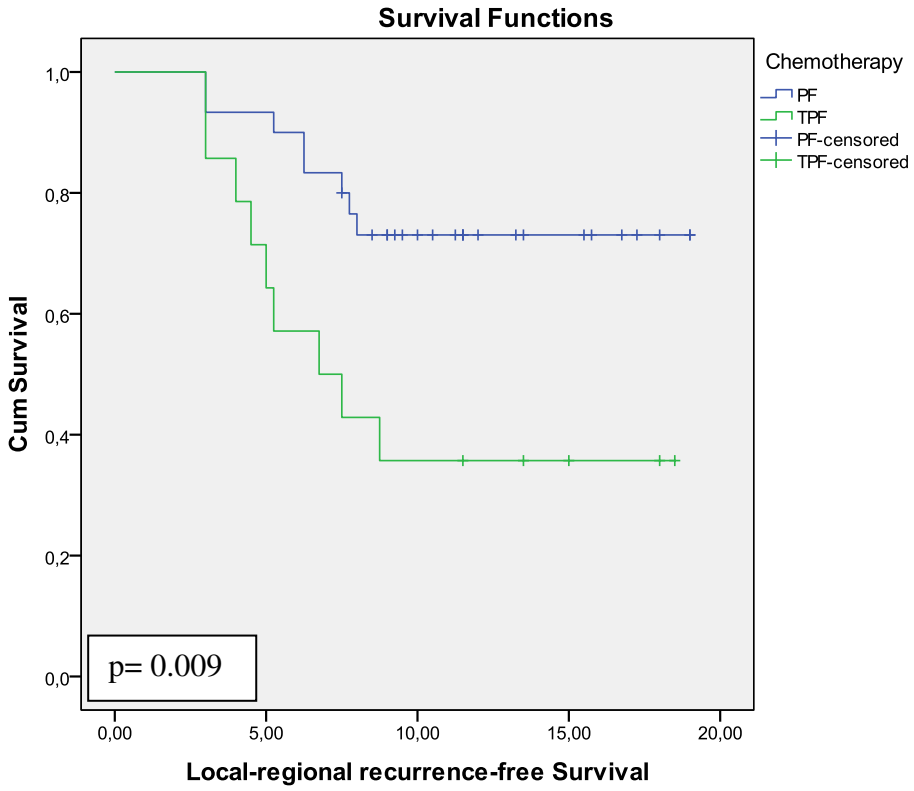


Fig.19: Kaplan-Meier estimate of LRFS for 44 patients according to the systemic therapy used in the study

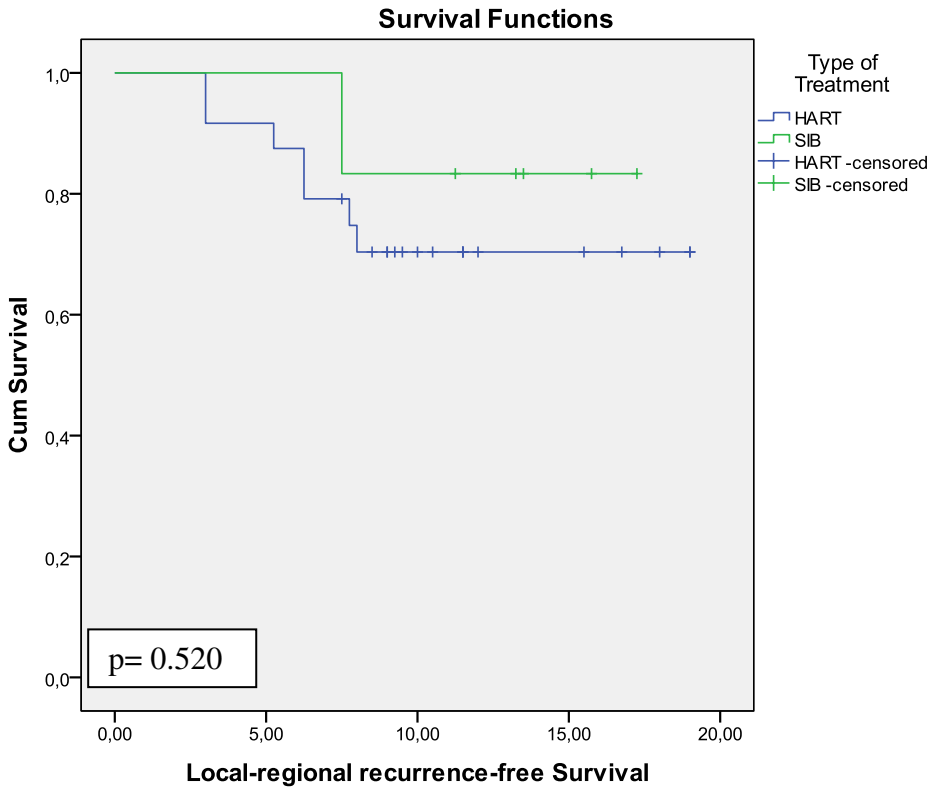


Fig.20: Kaplan-Meier estimate of LRFS for 30 patients who received PF regimen according to the XRT technique used in the study

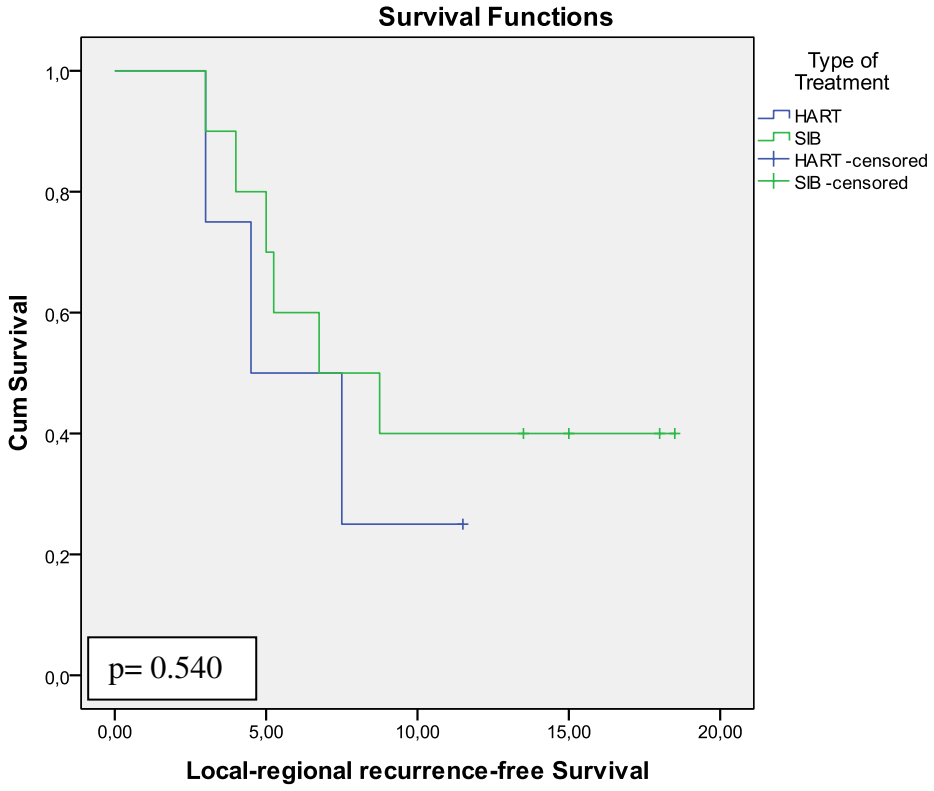


Fig.21: Kaplan-Meier estimate of LRFS for 14 patients who received TPF regimen according to the XRT technique used in the study

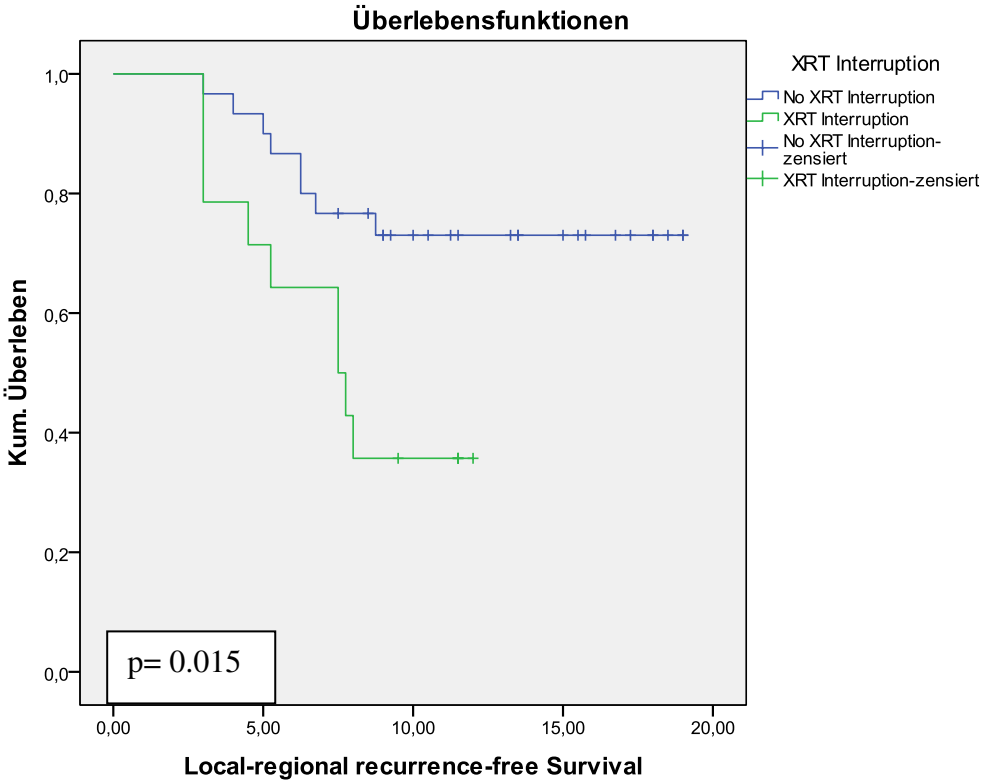


Fig.22: Kaplan-Meier estimate of LRFS for 44 patients received according to the XRT interruption

4.5.4. Distant failure

Distant disease control was achieved in 39/44 patients (88.6%). Five of 44 (11.4%) patients experienced distant failure. The Site of distant metastases was lung in 1 (20%) patient, mediastinal lymph nodes in one (20%) patient, both lung and mediastinal lymph nodes in 2 (40%) patients and in skin in one (20%) patient (Table 34). There was no statistically significant difference between the two XRT techniques regarding distant failure. Three of 28 (10.7%) patients in the HART-SEQ-IMRT arm had distant failure in comparison to 2 of 16 (12.5%) patients in the SIB-IMRT arm (p=0.858) (Table 35). For the subgroup of patients with GTV ≤ 100 cm^3, there was also no statistically significant difference between the two XRT arms regarding LRF (p=0.948) (Table 36).

None of the14 patients who received the TPF regimen experienced distant failure, compared to 5 out of 30 patients (16.7%) who received the PF regimen experienced distant failure, however this difference could not reach any statistical significance (p=0.105) (Table 37). Further analysis of the subgroup of patients who received the PF regimen showed no statistically significant

difference regarding LRF rate between the HART-SEQ-IMRT arm and the SIB-IMRT arm (p=0.221) (Table 38).

The median follow-up for DMFS is 12 months (95% CI 10.65 – 13.35). The median survival time for DMFS was not reached. The one-year DMFS for the 44 patients was 89.7% (Fig.23). DMFS for HART-SEQ-IMRT patients (one-year DMFS 87%) was not different compared to SIB-IMRT patients (one-year DMFS 93.3%) (p=0.865) (Fig.24). Additionally, DMFS for HART-SEQ-IMRT patients with GTV $\leq$ 100 cm^3 (one-year DMFS 87.8%) was not different compared to SIB-IMRT patients (one-year DMFS 93.3%) (p=0.850) (Fig.25).

According to the systemic therapy received, DMFS for PF patients (one-year DMFS 85.3%) was not different compared to TPF patients (The one-year DMFS 100%) (p=0.108) (Fig.26). Regarding analysis of the subgroup of patients who received the PF regimen, DMFS for HART-SEQ-IMRT patients (one-year DMFS 85.4%) was not different in comparison to SIB-IMRT patients (one-year DMFS 83.3%) (p=0.405) (Fig. 27).

No correlation between XRT interruption and distant metastases (p=0.058) was found. Nevertheless, DMFS for patients with no interruption of XRT (one-year DMFS 96.7%) was different in comparison to patients with interruption of XRT (one-year DMFS 70.7%) (p=0.032) (Fig.28).

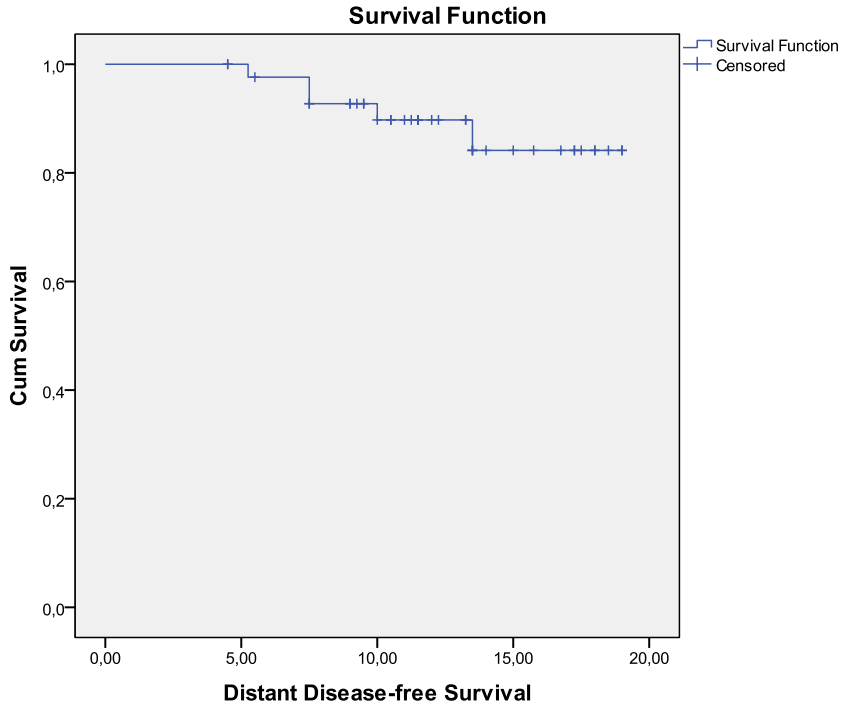


Fig. 23: Kaplan-Meier estimate of DMFS for 44 patients treated with IMRT

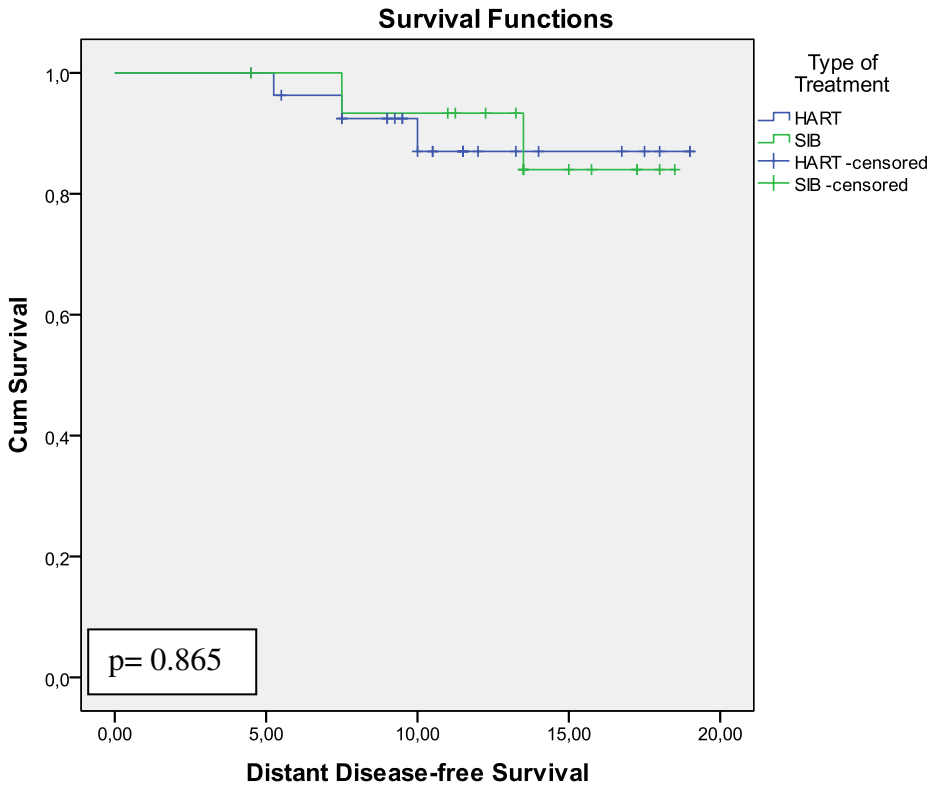


Fig.24: Kaplan-Meier estimate of DMFS for 44 patients according to the XRT technique used in the study

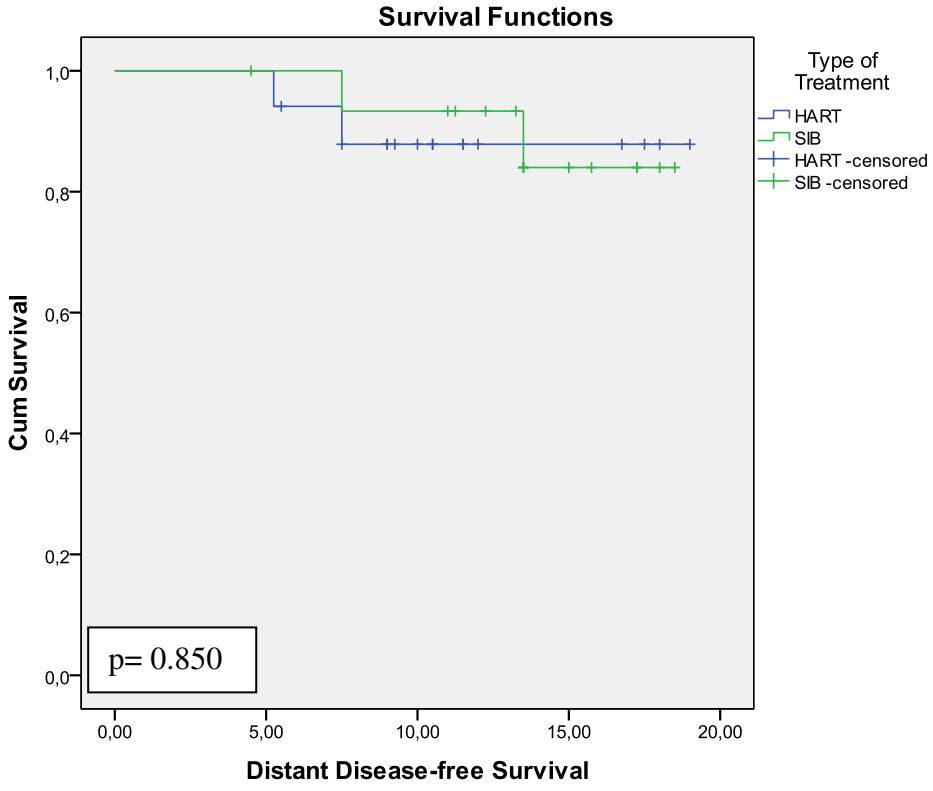


Fig.25: Kaplan-Meier estimate of DMFS for 33 patients with GTV $\leq$ 100 cm^3 according to the XRT technique used in the study

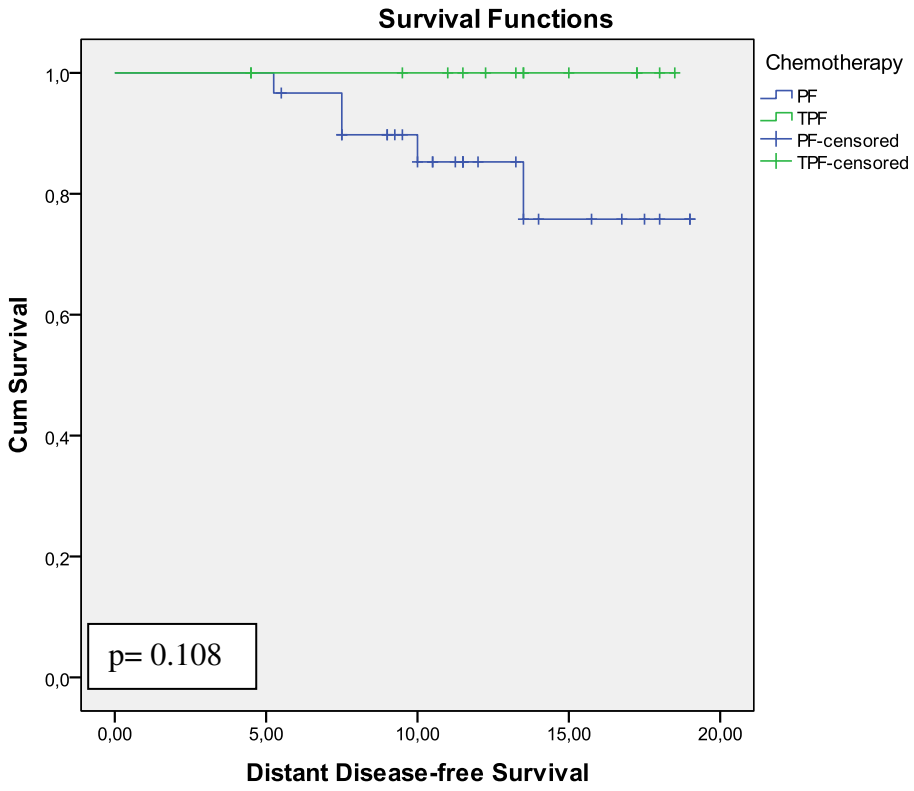


Fig. 26: Kaplan-Meier estimate of DMFS for 44 patients according to the systemic therapy used in the study

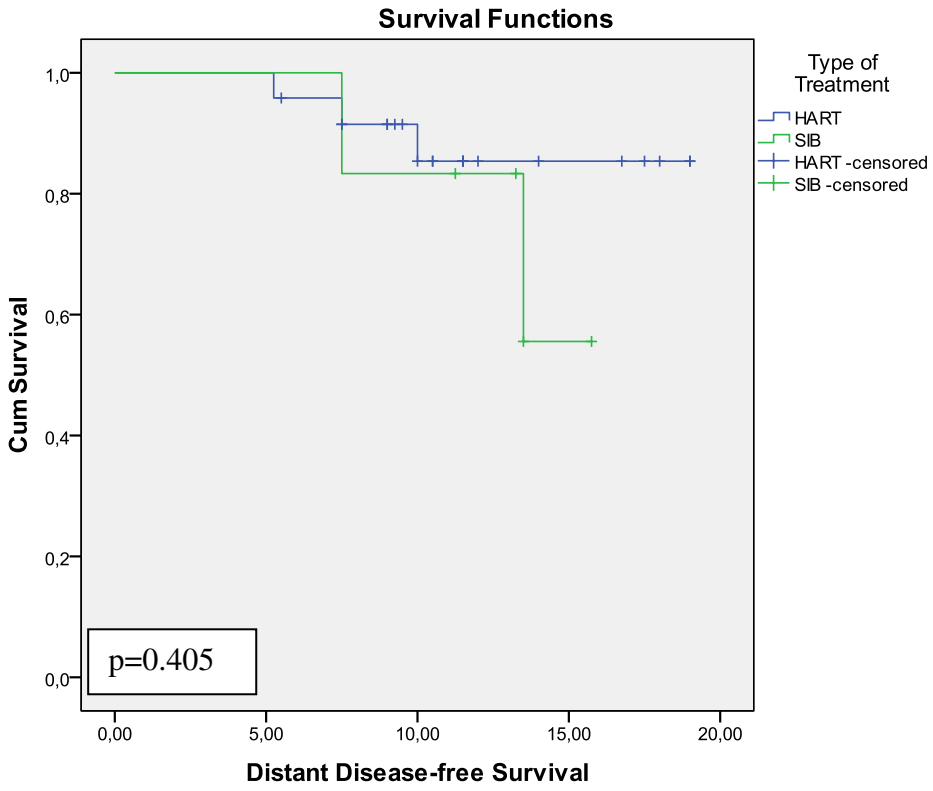


Fig.27: Kaplan-Meier estimate of DMFS for 30 patients who received PF regimen according to the XRT technique used in the study

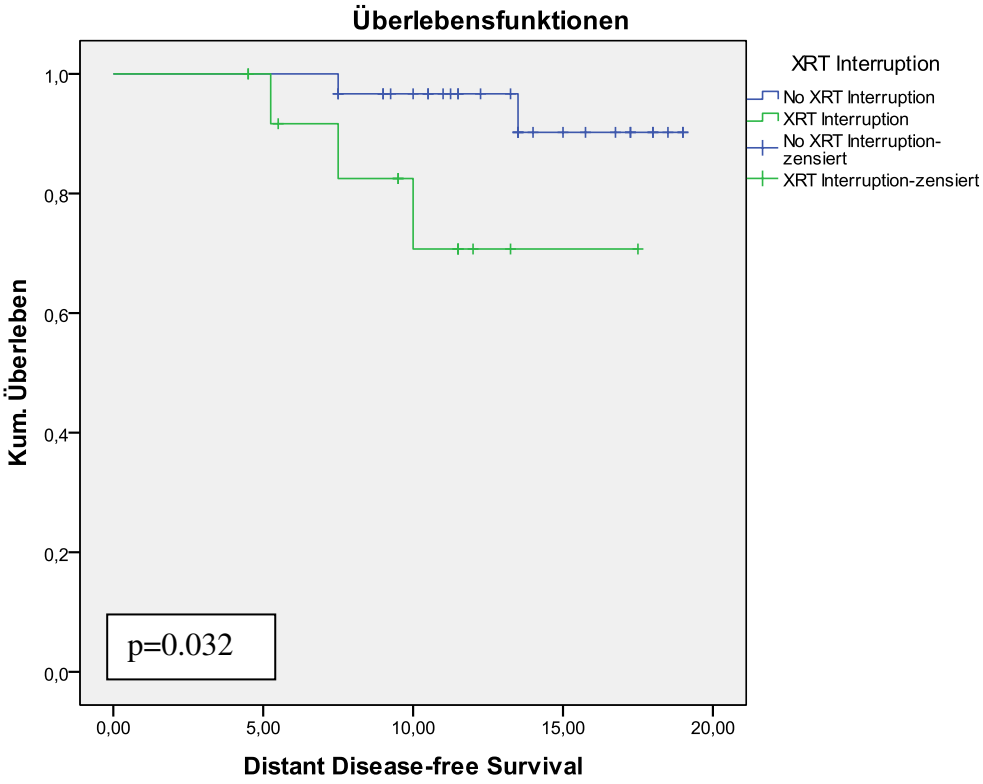


Fig. 28: Kaplan-Meier estimate of DMFS for 44 patients according to XRT interruption

4.5.5. Overall Survival

Eight of 44 (18.2%) patients at the last analysis (December 2010) were dead. Three of them (2 in HART-SEQ-IMRT, and one in SIB-IMRT) died within 3 months of XRT. The cause of death was tumor progression in 3 (37.5%) patients, metastases in 3 (37.5%) patients, and other non-tumor related causes in 2 (25%) patients (Table 34). One patient developed acute respiratory distress syndrome, and the other had gastrointestinal bleeding. No patient died because of treatment toxicity (Table 34).

There was no statistically significant difference between the two XRT arms regarding death or early death within 3 months after XRT. Six of 28 (21.4%) patients in the HART-SEQ-IMRT arm died in comparison to 2 of 16 (12.5%) patients in the SIB-IMRT arm (p=0.46) (Table 35). For subgroup of patients with GTV ≤ 100 cm3, there was also no statistically significant difference between the two XRT arms regarding death (p=0.948) (Table 36).

Three of 14 (21.4%) patients received the TPF regimen died, compared to 5 out 30 patients (16.7%) who received the PF regimen (p=0.703) (Table 37). Further analysis of the subgroup of patients who received the PF regimen revealed no statistically significant difference regarding death rate between the HART-SEQ-IMRT arm and the SIB-IMRT arm (p=1.0) (Table 38).

Analysis of the subgroup of patients who received the TPF regimen showed no statistically significant difference regarding death rate between the HART-SEQ-IMRT arm and the SIB-IMRT arm (p= 0.099) (Table 39).

The median follow-up for OS is 13.25 months (95% CI 11.6 – 14.89). Median survival time for OS was not reached. The one-year OS for the 44 patients was 80.6% (Fig.29).

OS for HART-SEQ-IMRT patients (one-year OS 75.3%) was not different compared to SIB-IMRT patients (one-year OS 87.5%) (p=0.411) (Fig.30). Also, OS for HART-SEQ-IMRT patients with GTV ≤ 100 cm^3 (one-year OS 87.8%) was not different compared to SIB-IMRT patients (one-year OS 87.5%) (p=0.949) (Fig. 31).

According to systemic therapy, OS for PF patients (one-year OS81.3%) was not different in comparison to TPF patients (one-year OS 78.6%) (p=0.758) (Fig.32). For the subgroup of patients who received the PF regimen, OS for HART-SEQ-IMRT patients (one-year OS 80%) was not different in comparison to SIB-IMRT patients (one-year OS 83.3%) (p=0.901) (Fig. 33). Analysis of the subgroup of patients who received the TPF regimen showed that the OS for HART-SEQ-IMRT patients (one-year OS 50%) was not different in comparison to SIB-IMRT patients (one-year OS 90%) (p=0.117) (Fig. 34).

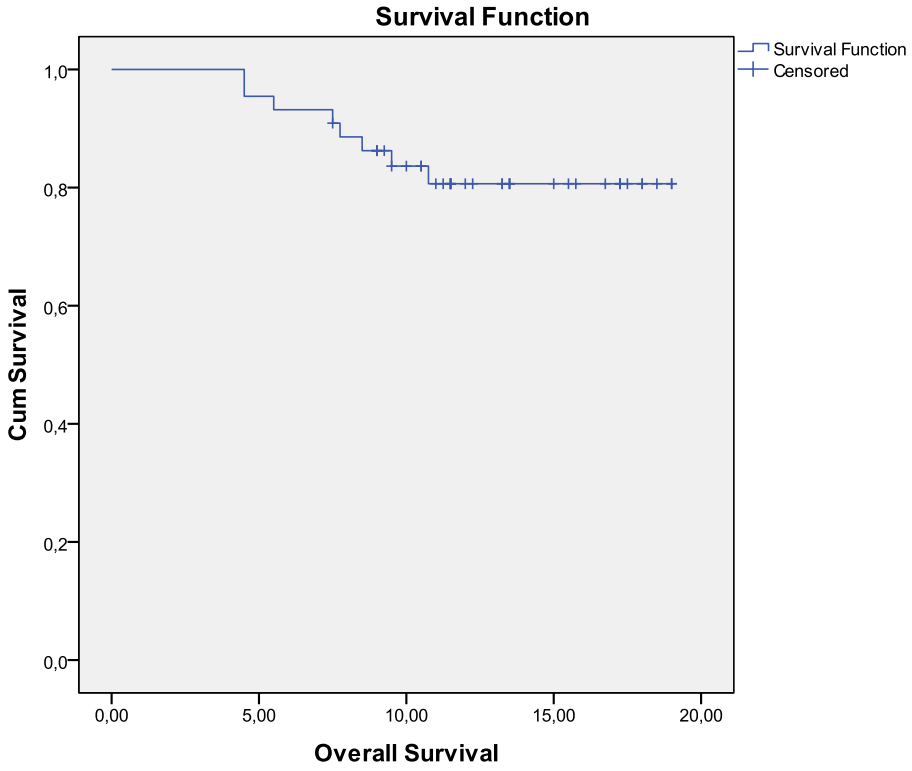


Fig. 29: Kaplan-Meier estimate of OS for 44 patients treated with IMRT

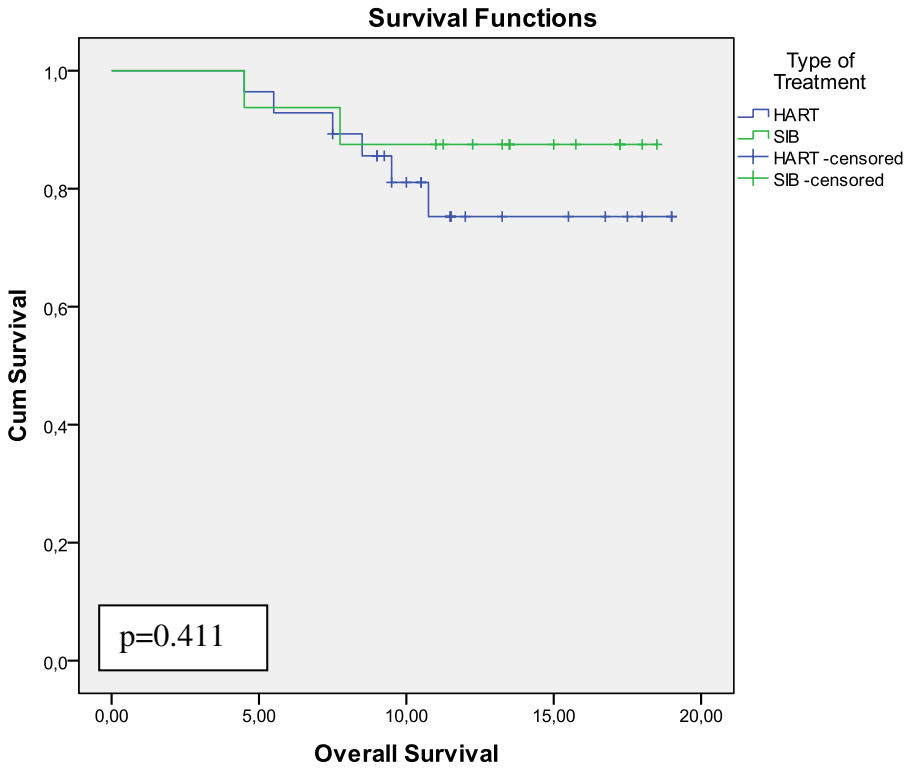


Fig. 30: Kaplan-Meier estimate of OS for 44 patients according to the XRT technique used in the study

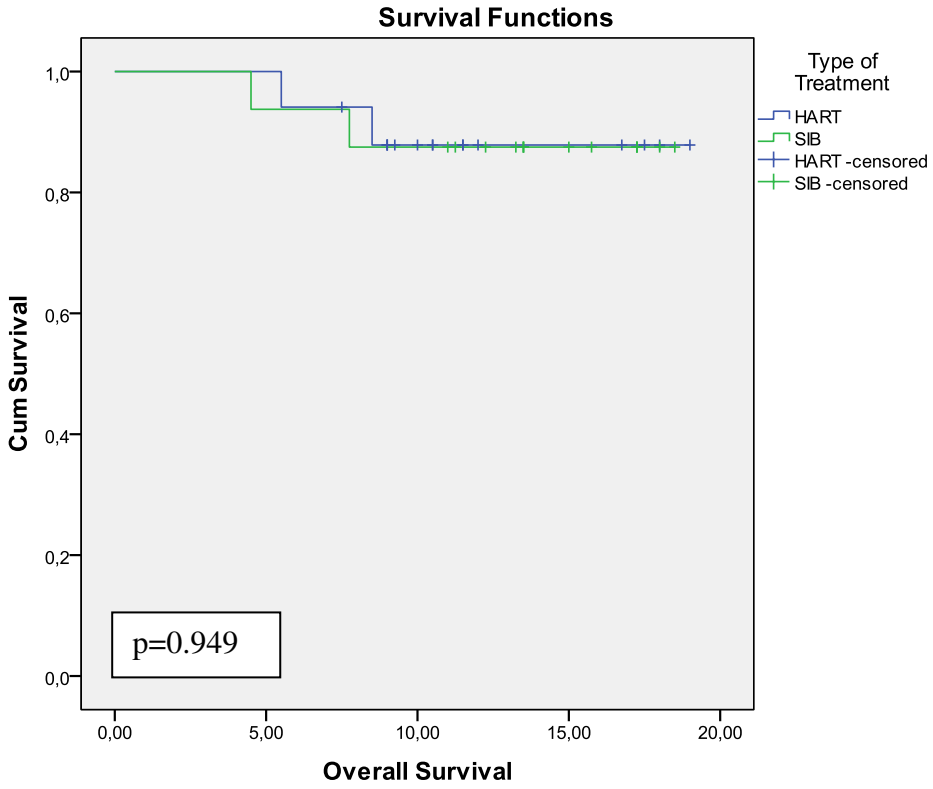


Fig. 31: Kaplan-Meier estimate of OS for 33 patients with GTV $\leq$ 100 cm^3 according to the XRT technique used in the study

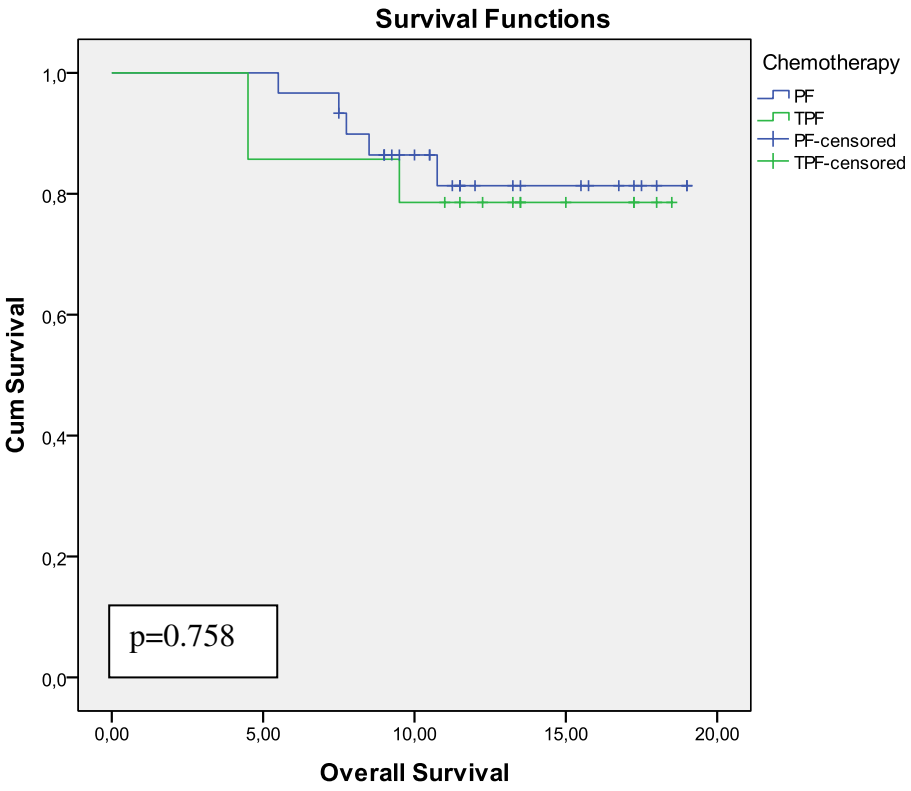


Fig. 32: Kaplan-Meier estimate of OS for 44 patients according to the systemic therapy used in the study

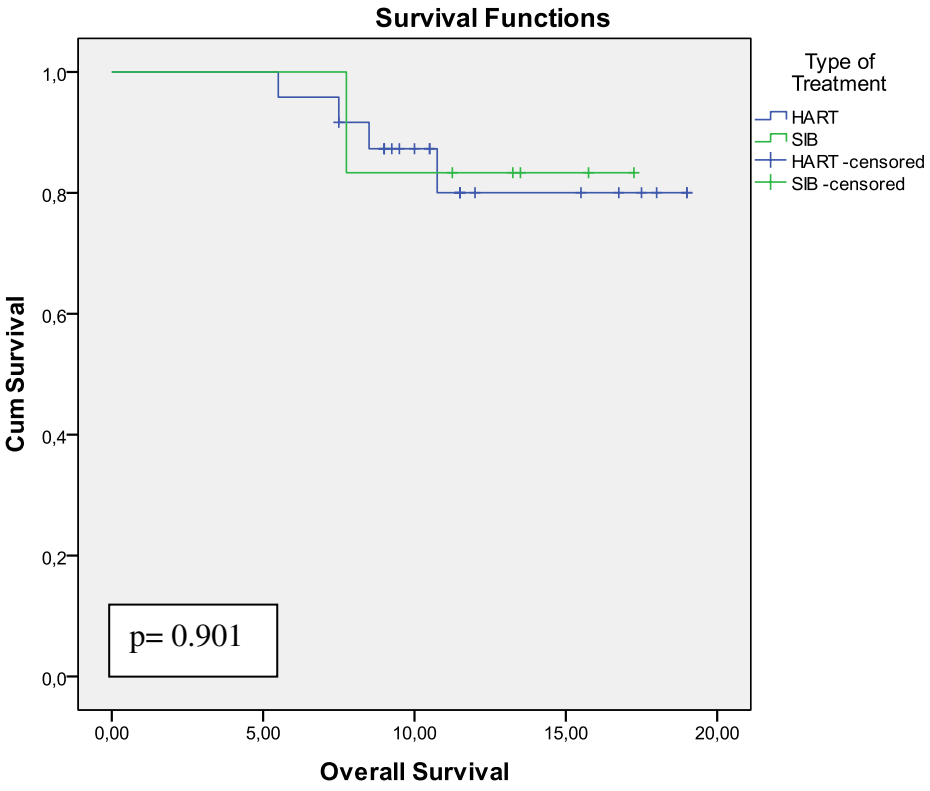


Fig. 33: Kaplan-Meier estimate of OS for 30 patients who received the PF regimen according to the XRT technique used in the study

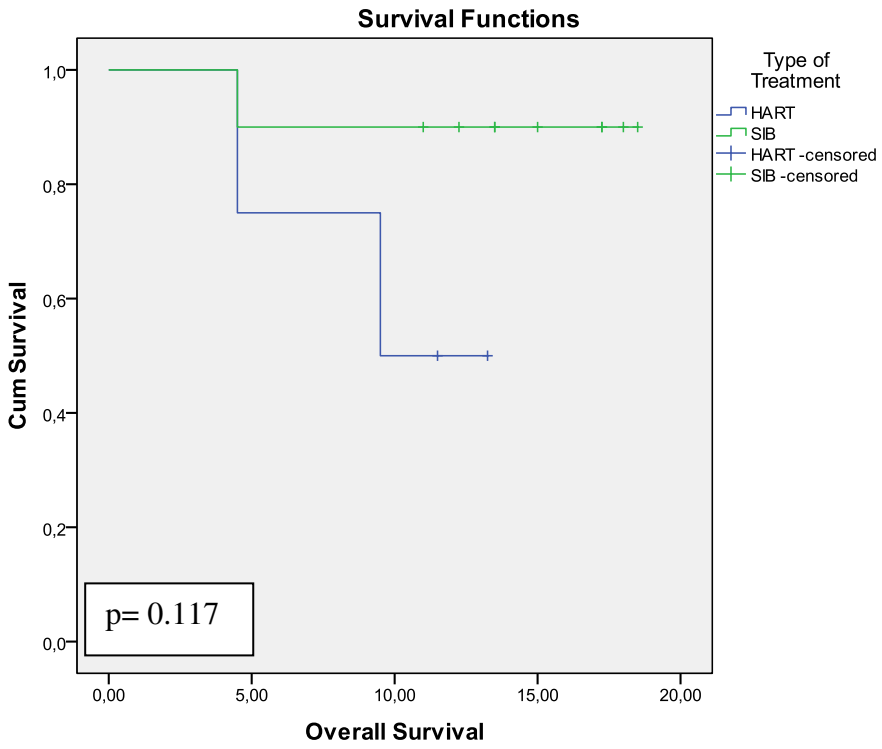


Fig. 34: Kaplan-Meier estimate of OS for 14 patients who received the TPF regimen according to the XRT technique used in the study

After multivariate Cox's regression analysis with stepwise selection, we found that interruption of XRT (p=0.013), LRF (p=0.016), and volume of GTV (p=0.035) were predictors for increased risk of death. OS for patients with no interruption of XRT (one-year OS 93.2%) was better in comparison to patients with interruption of XRT (one-year OS 54.4%) (p=0.003) (Fig.35). OS for patients who did not develop LRF (one-year OS 96.2%) was better than patients who developed LRF (one-year OS 57%) (p=0.002) (Fig.36).

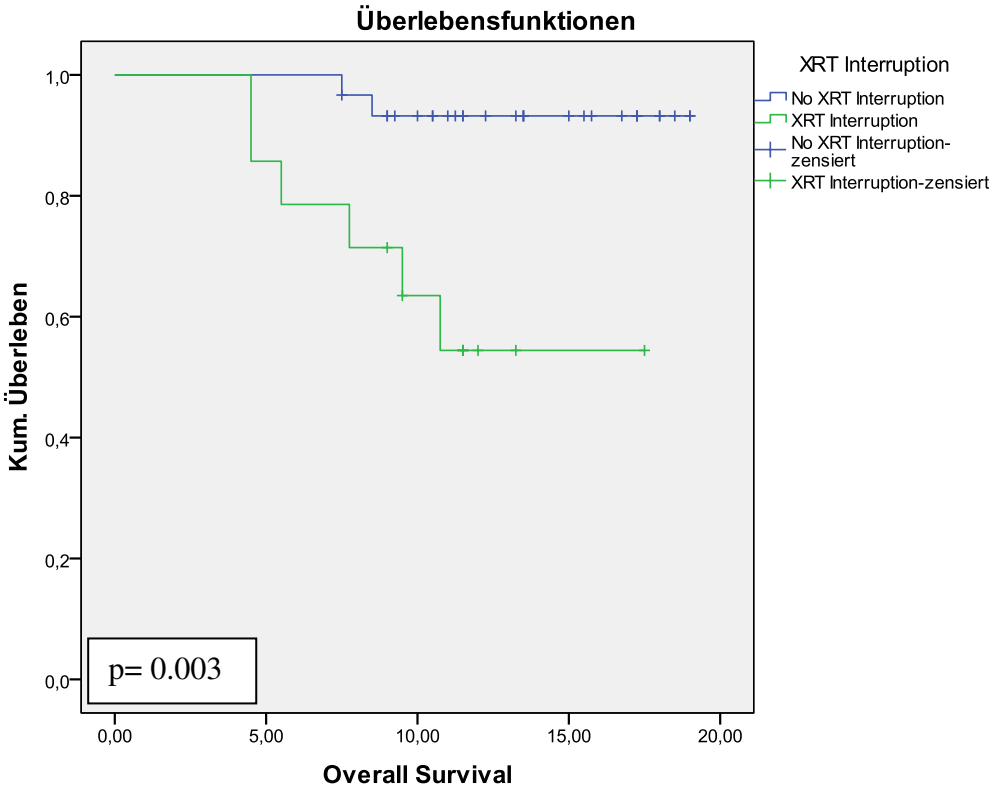


Fig.35: Kaplan-Meier estimate of OS for 44 patients according to XRT interruption

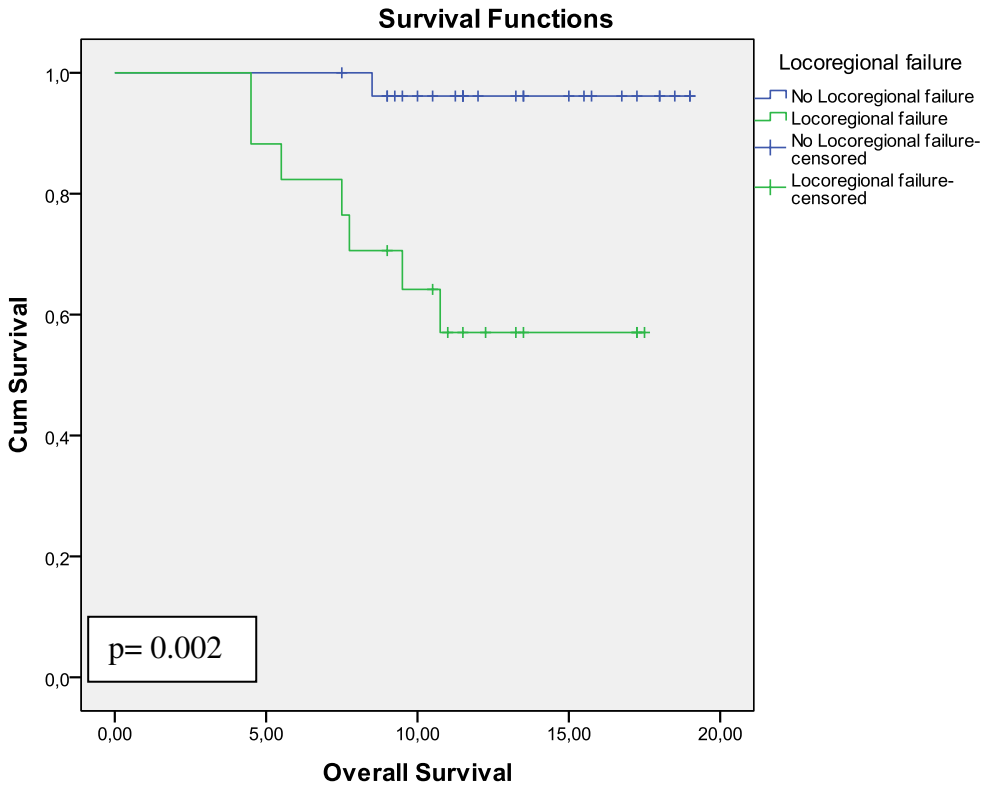
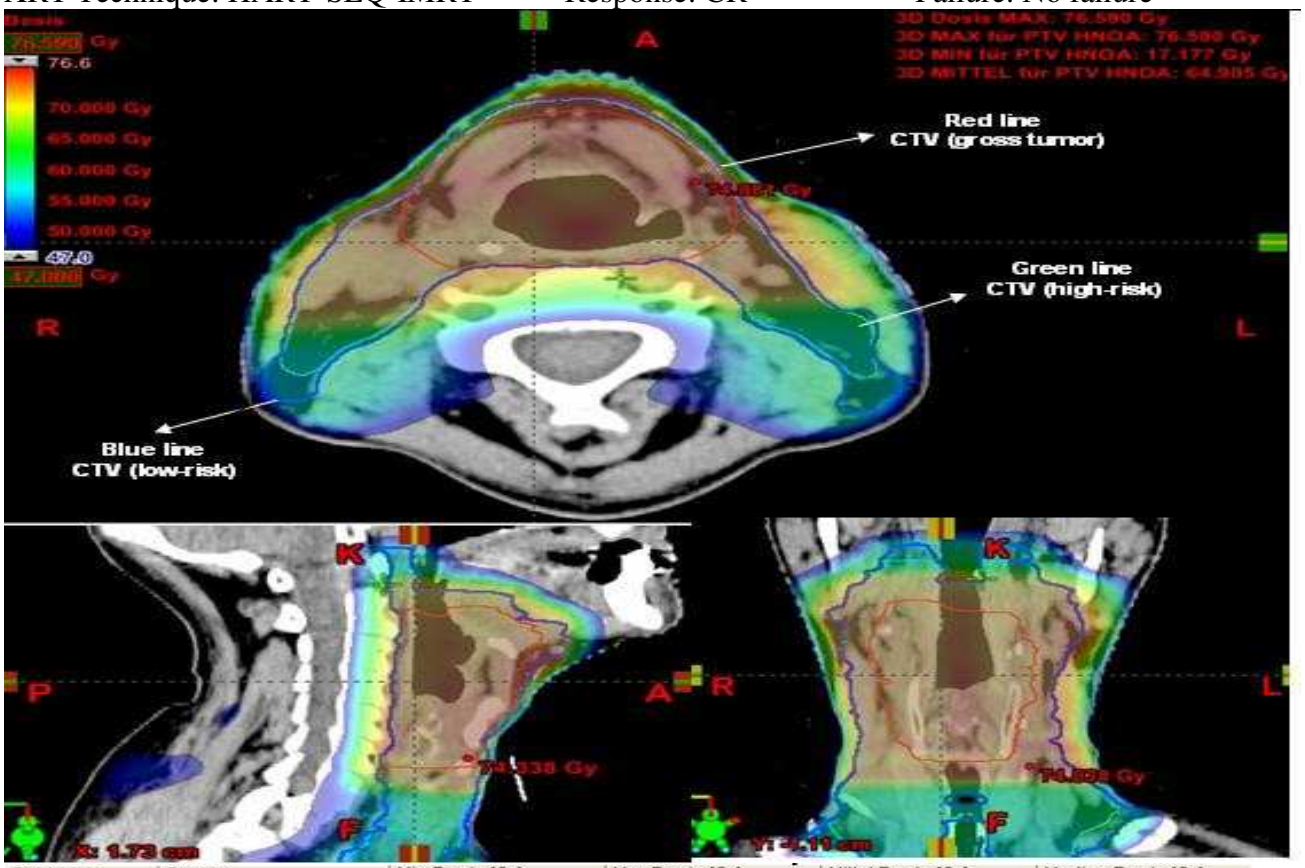


Fig.36: Kaplan-Meier estimate of OS for 44 patients received according to locoregional failure

5. Case Presentation

Case No 1

Male patient, 64years old, laryngeal HNSCC, cT4 cN2c cM0
Therapy: 3 cycles TPF followed by XRT combined with cetuximab
XRT Technique: HART-SEQ-IMRT Response: CR Failure: No failure



DVH-Linie	Struktur	Min Dosis [Gy]	Max Dosis [Gy]	Mittel Dosis [Gy]	Median Dosis [Gy]
	BODY				
	Brain stem	1.585	36.597	7.425	3.550
	CTV HNOA	48.298	76.590	66.570	70.907
	CTV HNOB	53.111	76.590	68.702	72.058
	CTV HNOC	67.755	75.365	73.032	73.008
	GTV prech	69.814	74.947	73.056	73.056
	Lips	4.557	27.193	14.292	14.081
	PTV HNOA	17.177	76.590	64.905	64.325
	PTV HNOB	17.423	76.590	67.111	70.418
	PTV HNOC	65.537	76.027	72.756	72.812
	Parotide left	12.073	72.969	50.338	53.741
	Parotide right	4.663	72.329	46.564	50.718
	Spinal cord	4.293	42.722	33.763	35.995
	Oral cavity	8.452	68.908	30.331	25.759

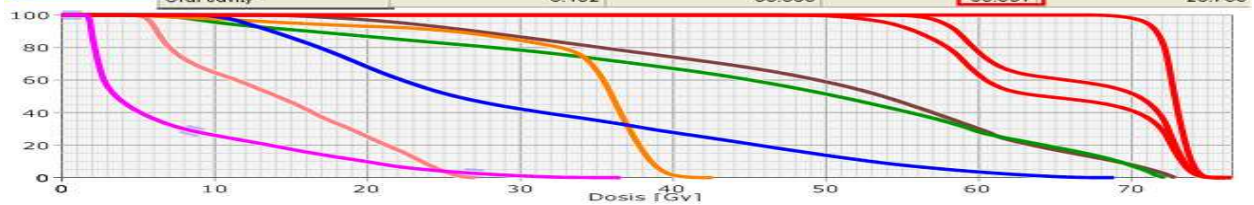
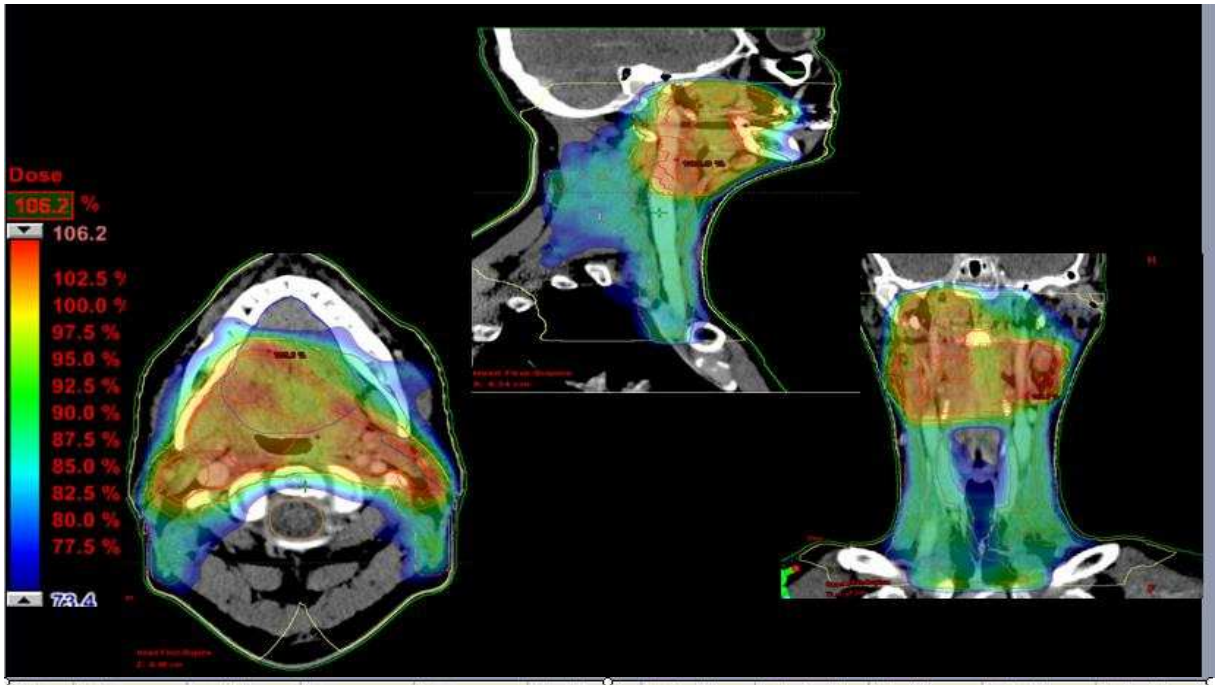


Fig. 37: SEQ-IMRT plan for first phase treatment using 9 coplanar fields with 6-MV x-rays: First plan included PTVA (low-risk), PTVB (high-risk), and PTVC (gross tumor),: 30 Gy (2 Gy\fraction) + 19.6 Gy (2x1.4 Gy\fraction) to a total dose of 49.6 Gy, followed by second plan included PTVB (high-risk), and PTVC (gross tumor): 9.8 Gy (2x1.4 Gy\fraction) to a total dose of 59.4 Gy, followed by third plan included PTVC (gross tumor): 19.8 Gy (2x1.4 Gy\fraction) to a total dose of 72 Gy. (a) Dose colour wash analysis displayed in axial, coronal, and sagittal images. (b) Absolute and relative DVH from the summation plan showed dose received by target volumes and different OARs (No attempt of parotid gland sparing because of N2c and tumor crossing midline).

Case No 2

Male patient, 47 years old, base of tongue HNSCC, cT3 cN2c cM0
Therapy: 3 cycles TPF followed by combined XRT and cetuximab
XRT Technique: SIB-IMRT
Response: CR
Failure: No failure

a



b

DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
	LK prechemo	Approved	HNOA-IMRT	C1						
	LK postchemoth	Approved	HNOA-IMRT	C1						
	z-ptv	Approved	HNOA-IMRT	C1						
	BODY	Approved	HNOA-IMRT	C1						
	brain stem	Approved	HNOA-IMRT	C1	19.1	100.0	100.0	4.079	50.599	27.253
	CTV HNOA	Approved	HNOA-IMRT	C1						
	CTV HNOB	Approved	HNOA-IMRT	C1						
	GTV preCTx	Approved	HNOA-IMRT	C1						
	Lips	Approved	HNOA-IMRT	C1	9.1	100.0	100.0	12.848	52.069	31.32
	Oral cavity	Approved	HNOA-IMRT	C1	105.1	100.0	100.0	24.236	74.547	63.56
	PTV HNOA	Approved	HNOA-IMRT	C1	819.3	100.0	100.0	48.156	71.700	61.152
	PTV HNOB	Approved	HNOA-IMRT	C1	482.0	100.0	100.0	59.092	74.747	70.40
	Parotide left	Approved	HNOA-IMRT	C1	25.9	100.0	99.9	26.086	74.130	57.61
	Parotide right	Approved	HNOA-IMRT	C1	22.0	100.0	100.0	30.050	72.578	58.810
	Spinal cord	Approved	HNOA-IMRT	C1	59.4	100.0	100.0	8.594	45.123	35.150

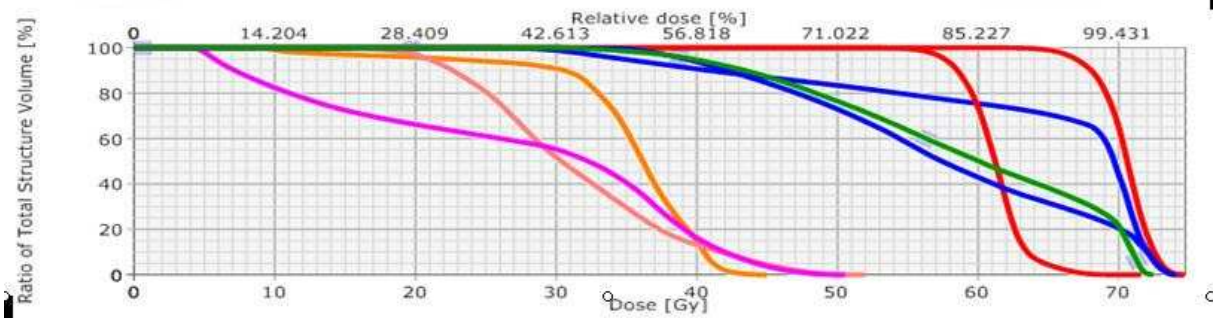
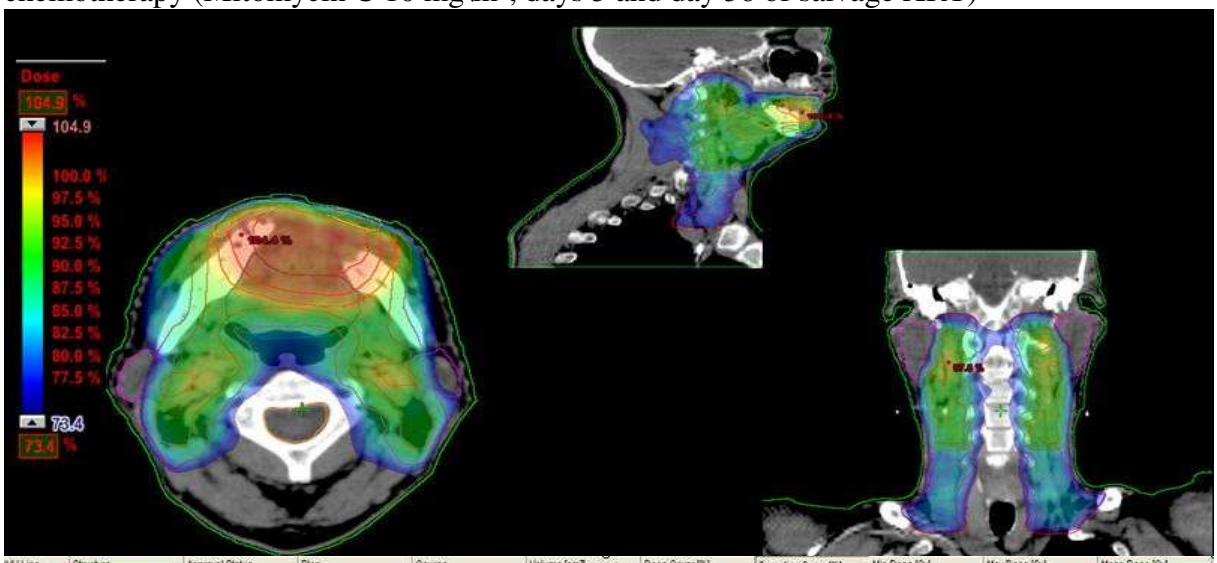


Fig. 38: SIB-IMRT plan using 9 coplanar fields with 6-MV x-rays delivered a total dose of 70.4 Gy to the PTVC (gross tumor) at 2.2 Gy /fraction, and 60.8 Gy for prophylaxis to PTVA (high risk) at 1.9 Gy/fraction over 32 fractions: (a) Dose colour wash analysis displayed in axial, coronal, and sagittal images. (b) Absolute and relative DVH showed dose received by target volumes and different OARs (No attempt of parotid gland sparing because of N2c).

Case No 3

Male patient, 54 years old, oral cavity HNSCC, cT4 cN2c cM0
Therapy: 3 cycles of TPF followed by combined XRT and cetuximab
XRT Technique: SIB-IMRT
Response: PR
1st failure: Regional failure in ipsilateral left- sided neck lymph nodes (level IIA)
Time to failure: 5 months
Salvage therapy: Left sided lymph node neck dissection
2nd failure: Regional failure in ipsilateral left-sided neck lymph nodes (level IIA, III)
Time to failure: 13 months
Salvage therapy: Hyperfractionated XRT (2x 1.2 Gy to total dose of 66 Gy) combined with chemotherapy (Mitomycin C 10 mg\m^2, days 5 and day 36 of salvage XRT)

a



b

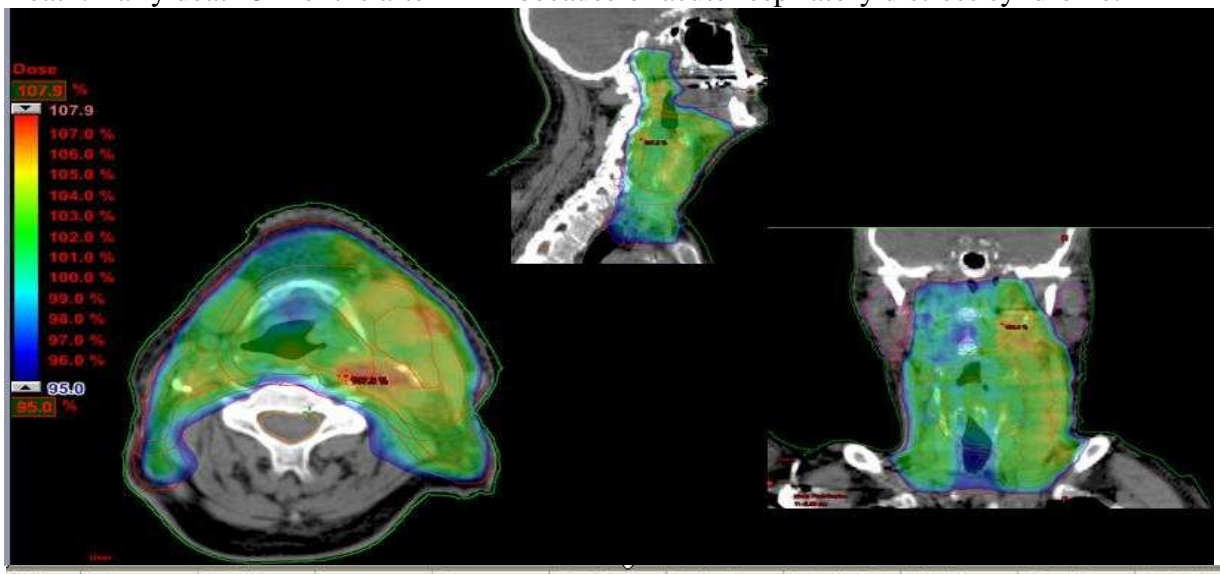
VH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
	Parotide left	Approved	HNO_SIB70,4GY	C1	19.9	100.0	99.9	10.015	68.402	40.195
	GTV	Approved	HNO_SIB70,4GY	C1						
	Oral cavity	Approved	HNO_SIB70,4GY	C1	66.7	100.0	100.0	27.421	72.859	55.928
	PTV HNOA	Approved	HNO_SIB70,4GY	C1	208.8	100.0	100.0	45.373	63.053	55.932
	PTV HNOB	Approved	HNO_SIB70,4GY	C1	344.0	100.0	100.0	43.888	71.340	63.043
	PTV HNOC	Approved	HNO_SIB70,4GY	C1	79.8	100.0	100.0	56.986	73.822	70.418
	Parotide right	Approved	HNO_SIB70,4GY	C1	19.0	100.0	100.0	12.940	68.170	34.437
	Spinal cord	Approved	HNO_SIB70,4GY	C1	34.8	100.0	99.9	4.428	47.348	39.073
	LK prech	Approved	HNO_SIB70,4GY	C1						
	z-ptv	Approved	HNO_SIB70,4GY	C1						
	CTV HNOC	Approved	HNO_SIB70,4GY	C1						
	Lips	Approved	HNO_SIB70,4GY	C1	8.8	100.0	100.1	22.034	72.068	54.974
	Brain stem	Approved	HNO_SIB70,4GY	C1	10.5	100.0	99.6	5.348	50.203	30.550
	Body	Approved	HNO_SIB70,4GY	C1						
	CTV HNOA	Approved	HNO_SIB70,4GY	C1						
	CTV HNOB	Approved	HNO_SIB70,4GY	C1						

Fig 39: SIB-IMRT plan using 9 coplanar fields with 6-MV x-rays delivered a total dose of 70.4 Gy to the PTVC (gross tumor) at 2.2 Gy /fraction, 60.8 Gy for prophylaxis to PTVB (-high risk) at 1.9 Gy/fraction, and 54.4 Gy for prophylaxis to PTVA (low- risk) at 1.7 Gy/fraction over 32 fractions: (a) Dose colour wash analysis displayed in axial, coronal, and sagittal images. (b) Absolute and relative DVH showed dose received by target volumes and different OARs (No attempt of parotid gland sparing because of N2c and tumor crossing midline).

Case No 4

Male patient, 74 years old, hypopharyngeal HNSCC, cT4 cN2b cM0.
Therapy: 3 cycles TPF followed by XRT combined with cetuximab.
XRT Technique: HART-SEQ-IMRT
Response: PR
Death: Early death 3 months after XRT because of acute respiratory distress syndrome.

a



b

DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover [%]	Sampling Cover [%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
	z-ptv	Approved	PlanA+B+C=72Gy	C1						
	CTV HN0C	Approved	PlanA+B+C=72Gy	C1						
	GTV	Approved	PlanA+B+C=72Gy	C1						
	Lips	Approved	PlanA+B+C=72Gy	C1	5.1	100.0	100.1	8.278	36.373	26.120
	Oral cavity	Approved	PlanA+B+C=72Gy	C1	77.9	100.0	100.0	27.068	71.361	43.216
	PTV HN0A	Approved	PlanA+B+C=72Gy	C1	1016.6	100.0	100.0	31.159	77.280	68.809
	CTV HN0B	Approved	PlanA+B+C=72Gy	C1						
	PTV HN0C	Approved	PlanA+B+C=72Gy	C1	463.1	100.0	100.0	62.133	77.280	73.292
	Parotide right	Approved	PlanA+B+C=72Gy	C1	28.4	100.0	100.1	8.959	59.653	24.910
	Spinal cord	Approved	PlanA+B+C=72Gy	C1	38.8	100.0	100.1	9.849	50.037	39.370
	PTV HN0B	Approved	PlanA+B+C=72Gy	C1	976.9	100.0	100.0	31.159	77.280	69.116
	Parotide left	Approved	PlanA+B+C=72Gy	C1	22.3	100.0	100.0	17.538	73.974	49.014
	LK	Approved	PlanA+B+C=72Gy	C1						
	Brain stem	Approved	PlanA+B+C=72Gy	C1	10.6	100.0	99.9	13.881	53.335	35.173
	Body	Approved	PlanA+B+C=72Gy	C1						
	CTV HN0A	Approved	PlanA+B+C=72Gy	C1						

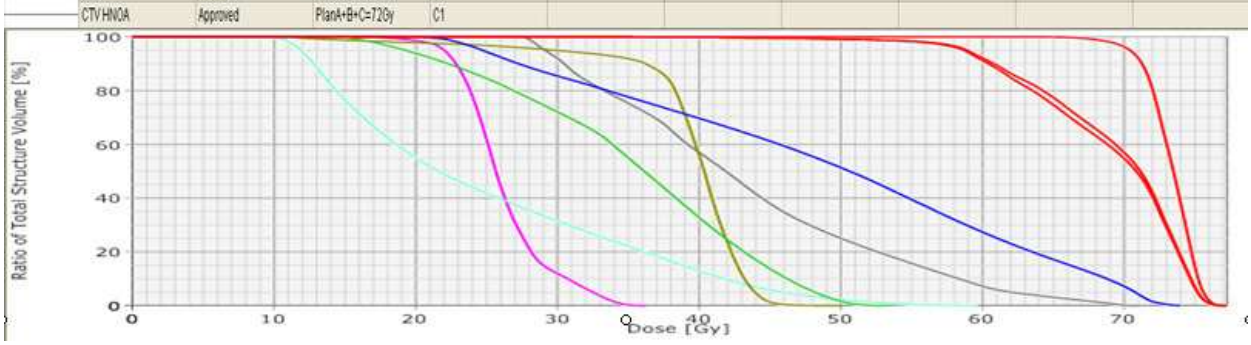
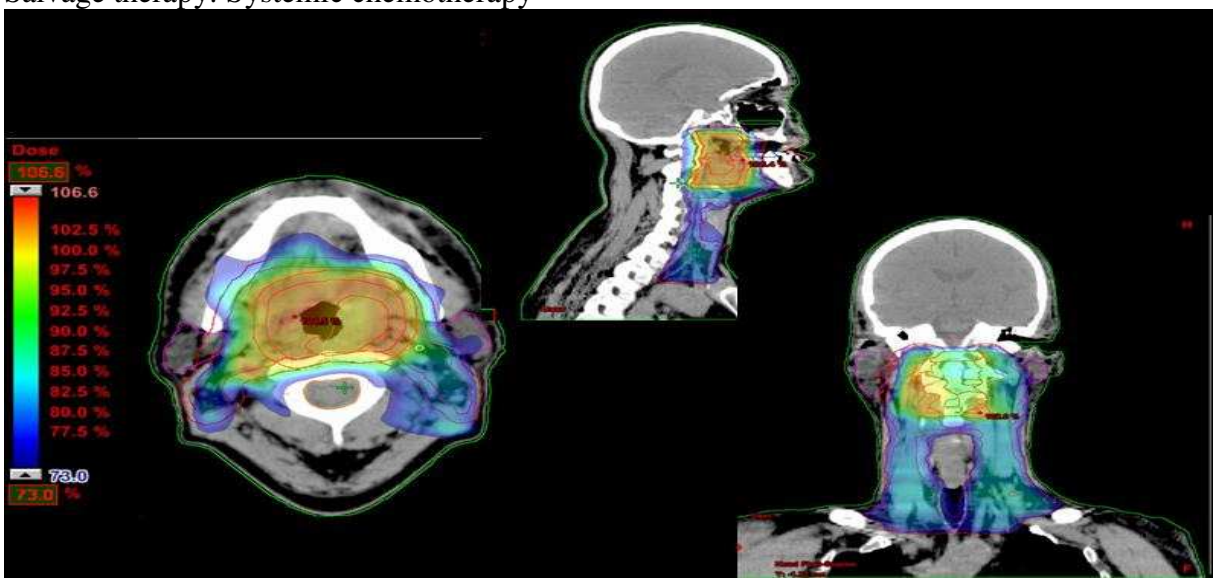


Fig. 40: SEQ-IMRT plan for first phase treatment using 9 coplanar fields with 6-MV x-rays: First plan included PTVA $_{(low\text{-}risk)}$, PTVB $_{(high\text{-}risk)}$, and PTVC $_{(gross\ tumor)}$,: 30 Gy (2 Gy\fraction) + 19.6 Gy (2x1.4 Gy\fraction) to a total dose of 49.6 Gy, followed by second plan included PTVB $_{(high\text{-}risk)}$, and PTVC $_{(gross\ tumor)}$: 9.8 Gy (2x1.4 Gy\fraction) to a total dose of 59.4 Gy, followed by third plan included PTVC $_{(gross\ tumor)}$: 19.8 Gy (2x1.4 Gy\fraction) to a total dose of 72 Gy. (a) Dose colour wash analysis displayed in axial, coronal, and sagittal images. (b) Absolute and relative DVH from the summation plan showed dose received by target volumes and different OARs (contralateral right parotid gland received D_{mean} 24.9 Gy).

Case No 5

Male patient, 59 years old, HNSCC of oropharynx, cT2 cN2b cM0
Therapy: Combined chemoradiotherapy with PF regimen
XRT Technique: SIB-IMRT
Response: PR
Failure: Distant metastases to lung and mediastinal lymph nodes
Time to failure: 13.5 months
Salvage therapy: Systemic chemotherapy

a



b

DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover [%]	Sampling Cover [%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
	PTV HNOB	Approved	HNO_SIB70,4GY	C1	195.6	100.0	100.0	58.948	75.039	70.41
	GTV	Approved	HNO_SIB70,4GY	C1						
	Oral cavity	Approved	HNO_SIB70,4GY	C1	55.6	100.0	100.0	28.858	74.381	56.700
	Parotide right	Approved	HNO_SIB70,4GY	C1	31.8	100.0	100.0	7.848	62.705	20.059
	CTV HNOA	Approved	HNO_SIB70,4GY	C1						
	Parotide left	Approved	HNO_SIB70,4GY	C1	31.9	100.0	99.9	16.623	69.791	43.465
	CTV HNOB	Approved	HNO_SIB70,4GY	C1						
	Lips	Approved	HNO_SIB70,4GY	C1	7.5	100.0	100.0	15.937	43.147	31.088
	PTV HNOA	Approved	HNO_SIB70,4GY	C1	848.1	100.0	100.0	20.920	73.313	57.165
	Spinal cord	Approved	HNO_SIB70,4GY	C1	48.4	100.0	99.8	7.773	49.844	38.613
	LN	Approved	HNO_SIB70,4GY	C1						
	z-plv	Approved	HNO_SIB70,4GY	C1						
	Body	Approved	HNO_SIB70,4GY	C1						
	Brain stem	Approved	HNO_SIB70,4GY	C1	5.8	100.0	100.1	15.847	55.993	35.234

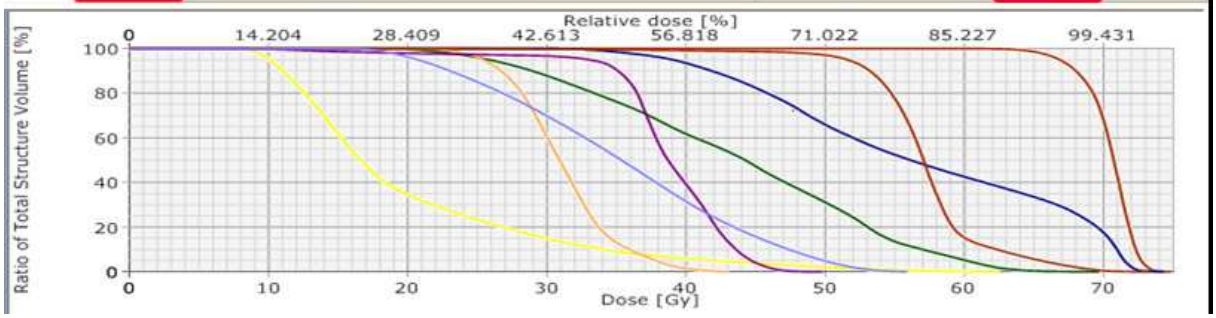


Fig. 41: SIB-IMRT plan using 9 coplanar fields with 6-MV x-rays delivered a total dose of 70.4 Gy to the PTVC $_{(\text{gross tumor})}$ at 2.2 Gy /fraction, and 54.4 Gy for prophylaxis to PTVA $_{(\text{low-risk})}$ at 1.7 Gy/fraction over 32 fractions: (a) Dose colour wash analysis displayed in axial, coronal, and sagittal images. (b) Absolute and relative DVH showed dose received by target volumes and different OARs (contralateral right parotid gland received D_{mean} 20.06 Gy).

6. Discussion

Reduced toxicity from IMRT may permit dose escalation and\or OTT acceleration, along with concurrent systemic therapies, both of which might improve disease outcome in LAHNSCC. Since 2005, we have adopted HART-SEQ-IMRT using hybrid fractionation concurrent with CTH as a standard of care for patients with stage IV HNSCC. With the demonstration of benefit from SIB-IMRT schedules (Mohan et al., 2000, Dogan et al., 2003), our investigation has focused on the use of the SIB-IMRT technique and on testing its feasibility especially in the context of CTH and\or targeted therapy.

SIB-IMRT was not considered appropriate for patients with large tumors, or tumors involving neurologic structures. Such patients are likely to be at higher risk of late morbidity (Orlandi et al., 2010; Lauve et al., 2004). On this basis, our first steps with SIB-IMRT have generally been restricted to patients with GTV volumes smaller than or equal to 100 cm^3 and tumors not involving neurologic structures.

An appraisal for 44 patients with stage IV HNSCCs (hypopharynx, oropharynx, larynx, and oral cavity) was done in this study (Table 6). Twenty-eight patients were enrolled in the HART-SEQ-IMRT arm and 16 patients in the SIB-IMRT arm. There were no significant variabilities in patients and disease characteristics among the two cohorts; however a significant discrepancy existed regarding the volume of GTV and the systemic therapy received (Table 7).

Patients enrolled in the HART-SEQ-IMRT arm had significantly larger GTV than patients in the SIB-IMRT arm (mean volume 82.49 ± SD 50.8 cm^3 vs 39.54 ± SD 25.23 $cm^{3,}$ respectively, p= 0.003). For more consistent analyses, we had to conduct a further dosimetric\clinical outcome comparison between the two XRT arms for subgroup of patients with GTV ≤ 100 cm^3. Also the systemic therapy received was not consistent across the patients. More patients in the SIB-IMRT arm received neoadjuvant TPF regimen while more patients in the HART-SEQ-IMRT arm received concurrent PF regimen (p=0.001). To be more pertinent, a further clinical outcome analysis and comparison between the two XRT techniques was done for 2 subgroups of patients (PF group and TPF group).

6.1. Dosimetric analysis

6.1.1. Target volumes

By analyzing the dosimetric distribution for each target\dose level for both techniques, we found that both techniques provided the requisite coverage for the target volumes and acceptable

sparing of the ORAs, however the sequential field plans resulted in higher absorbed doses to all target volumes (table 8, 9, and 10).

The difference between the prescribed dose for each target volume and the mean absorbed dose was significantly high in HART-SEQ-IMRT plans, for example, the $D_{difference}$ for the low risk nodal target volume (CTV 49.6 Gy) reached 8.25 ± 3.57 Gy, 6.92 ± 1.72 Gy for the low\high nodal target volume (CTV59.4 Gy), and it was 4.88 ± 1.12 Gy for high nodal target volume (CTV66.4 Gy). Mohan et al. (2000) in their phantom based study found that in the second phase of the two-phase sequential IMRT plan the nodes received a dose that is 8 Gy higher than in the SIB plan.

In our study, this higher dose delivered by sequential field plans subsequently resulted in acceptable high levels of D_{mean}, $D_{50\ \%}$, and $D_{95\ \%}$, and satisfactory levels of D_{min}, $D_{near\text{-}min}$, and $V_{95\%}$ for each target volume. However it was at the expense of D_{max} and $D_{near\text{-}max}$ which were high reaching to D_{max} of 71.4 ± 3.98 Gy and $D_{near\text{-}max}$ of 64.29 ± 3.96 Gy for PTV 49.6 Gy, D_{max} of 75.31 ± 1.4 Gy and $D_{near\text{-}max}$ of 72.23 ± 1.56 Gy for PTV 59.4 Gy, D_{max} of 76.11 ± 0.78 Gy and $D_{near\text{-}max}$ of 74.11 ± 0.59 Gy for PTV 66.4Gy, D_{max} of 76.57 ± 0.83 Gy and $D_{near\text{-}max}$ of 75.02 ± 0.58 Gy for PTV 72 Gy (Table 8).

SIB-IMRT is delivered using one plan; therefore the control over the spatial dose distribution is more precise. For low risk nodal target volume (CTV 54.4 Gy), the difference between the prescribed dose and the mean absorbed dose was only 2.37 ± 1.41 Gy, and reaching to 3.24 ± 0.74Gy Gy for the low\high nodal target volume (CTV 60.8 Gy). Correspondingly, acceptable levels of D_{mean}, D_{max}, $D_{\ near\text{-}max}$, $D_{95\ \%}$, $D_{50\ \%}$, and $V_{95\%}$ for each target volume could be achieved. However, low levels of D_{min} and $D_{near\text{-}min}$ were observed, for low risk nodal target volume (PTV 54.4 Gy), the D_{min} was 39.97 ± 10.47 Gy and the $D_{near\text{-}\ min}$ was 50.72 ± 1.12 Gy; for low\high nodal target volume (PTV 60.8Gy), the D_{min} was 38.43 ± 10.08 and the $D_{near\text{-}min}$ was 55.77 ± 2.55 Gy; and for gross tumor volume (PTV 70.4 Gy), the D_{min} was 55.68 ± 7.25 Gy, and the $D_{near\ minimum}$ was 65.35 ± 0.69 Gy (Table 9)

In this study, the dose distributions produced by the HART- SEQ-IMRT technique were compared to those produced by the SIB-IMRT technique. In principle, our main goal was not to make a direct dosimetric comparison between the SEQ-IMRT and the SIB-IMRT techniques, but rather to conduct a dosimetric⁄clinical outcome analysis with comparison between the study arms (HART-SEQ-IMRT and SIB-IMRT). Thus, we did not need to conduct any direct plan comparison for any patient. Also, concerning this point, we have to mention that the expected

benefit due to SIB-IMRT with respect to SEQ-IMRT already proved in multiple previous studies to be a higher conformality (Mohan et al., 2000; Dogan et al., 2003). Since the purpose of conducting this study was to compare between the two study arms in terms of dosimetric distribution and their relations to clinical outcome, homogeneity indices achievable with the two strategies were beyond our aim and were ignored.

There were no statistically significant differences between the two XRT arms as regard prescribed doses to different target volumes. The total dose was delivered over 30 days for HAR-SEQ-IMRT patients, and 32 days for SIB-IMRT patients (Table 11).

Many dosimetric target volumes parameters were clearly higher with the HART-SEQ-IMRT technique than with the SIB-IMRT technique (Table 11). For example, using HART-SEQ-IMRT technique, higher D_{mean} for PTVA $_{(low\text{-}risk)}$ was received (59.82 ± 4.62 Gy) compared to 57.20 ± 3.02 Gy for SIB-IMRT plans (p=0.023), and the $D_{50\%}$ was 59.43 ± 4.86 Gy vs. 57.23 ± 2.96 Gy, respectively, (p=0.045). Regarding PTVB $_{(high\text{-}risk)}$**,** the D_{mean} for HART-SEQ-IMRT plans was 65.99 ± 2.89 Gy compared to 61.96 ± 1.13 Gy for SIB-IMRT plans (p<0.001), and the $D_{50\%}$ was 65.69 ± 3.51 Gy compared to 62.00 ± 1.12 Gy, respectively, (p=0.001). For PTVC$_{(gross\ tumor)}$**,** the D_{mean} for HART-SEQ-IMRT plans was 72.65 ± 0.39 Gy compared to 70.406 ± 0.01 Gy for SIB-IMRT plans (p<0.001), and the $D_{50\%}$ was 72.85 ± 0.38 Gy compared to 70.70 ± 0.18 Gy , respectively, (p<0.001).

HART-SEQ-IMRT plans resulted in higher absorbed dose to PTVA$_{(low\text{-}risk)}$ above prescribed dose of 5.32 ± 2.77 Gy compared to 0.98 ± 0.76 Gy increase in the mean absorbed dose for SIB-IMRT plans (p<0.001), and for PTVB $_{(high\text{-}risk)}$ 4.59 ± 1.41 Gy, compared to 1.36 ± 0.86 Gy, respectively, (p<0.001) (Table 11).

As expected, HART-SEQ-IMRT resulted in better volume covered by 95% isodose level ($V_{95\%}$) for PTVA $_{(low\text{-}risk)}$ of 98.48 ± 1.55 %, compared to 96.73 ± 2.47 % for SIB-IMRT (p=0.017), for PTVB $_{(high\text{-}risk)}$ 98.36 ± 1.48 % compared to 95.38 ± 4.72 %, respectively, p=0.012), and for PTVC$_{(gross\ tumor)}$ 98.70 ± 1.15 % compared to 94.52 ± 1.44%, respectively, (P=<0.001). Moreover for PTVC$_{(gross\ tumor)}$, HART-SEQ-IMRT plans resulted in higher values compared to SIB-IMRT plans regarding D_{min} (p=0.038), $D_{near\text{-}min}$(p<0.001), D_{max} (p<0.001), $D_{near\text{-}max}$ (p<0.001), and $D_{95\%}$ (p<0.001) (Table 11).

After analysis of patients with GTV ≤ 100 cm^3, HART-SEQ-IMRT plans continued to show higher dosimetric target volumes parameters than SIB-IMRT plans especially for CTV\PTV$_{(high\text{-}risk)}$ and CTV\PTVC$_{(gross\ tumor)}$ (Table 13).

Our results could be comparable to those obtained by Fogliata et al. (2003), who compared standard SEQ-IMRT, pure SIB-IMRT, and a modified SIB (SEQ/SIB), where the actual SIB follows a first phase of conventional fractionation to the elective volume. In their study, the target coverage for both PTVI (tumor bed and areas at high risk) and PTVII–PTVI (tissues at risk for sub-clinical or microscopic disease) presented differences using different fractionation schemes. For example the mean dose to PTVI was higher ($p<0.02$) for the SEQ/SIB regime of about 3% (2 Gy) with respect to the SIB scheme, while the SEQ was in between the two. The minimum significant dose was kept, with SIB, to a level of about 80% of the prescribed dose, while for the other two schemes it was increased by 5–7%. The D_{min} for PTVI was 69.2 ± 4.8 Gy for SEQ arm, 64 ± 6.8 Gy for pure SIB arm, 68.4 ± 5.6 Gy for SEQ/SIB arm ($p<0.002$). The same tendency was noted for the $V_{95\%}$ parameter, where the lower value for the SIB was highly significant, $V_{95\%}$ was 91.2 ± 3.9% for SEQ arm, 88.8 ± 5.9 % for pure SIB arm, 93.8 ± 3.1 % for SEQ/SIB arm ($p<0.002$).

Similarly, Dogan et al. (2003) in their planning comparison study for 5 HNC cases found that the sequential field technique resulted in higher mean absorbed doses to target volumes than SIB-IMRT. In their study, the mean dose to PTV1 (tissues at risk for sub-clinical or microscopic disease) was 62.5 ± 2.2 Gy for sequential conventional XRT- IMRT boost, 64.6 ± 2.6 Gy for SEQ-IMRT, and 62.6 ± 2.6 Gy for SIB-IMRT. Chen et al. (2005) reported also approximately similar higher doses for SEQ-IMRT in comparison to SIB-IMRT in their study on 14 NPC patients. The mean dose to CTV1 (GTV with 5-10-mm margin of adjacent tissues) was 101.7 ± 2.4% and 102.3 ± 3.1% of the prescribed dose for SIB-IMRT and SEQ-IMRT, respectively. The mean CTV2 dose (ipsilateral or contralateral elective nodal regions at risk of harboring microscopic tumor) was 109.8 ± 4.7% of the prescribed dose for SIB-IMRT and 112.6 ± 6.0% of the prescribed dose for SEQ-IMRT.

6.1.2. Organs at risk

In the present study, after maintaining PTV prescription for each target volume, all patients met constraints for cord and brain stem. By virtue of advanced locoregional stage, high percentage of N2c patients and large tumors crossing the midline, the contralateral parotid constraint was met only in 19 patients (43.2%). But we have to take into consideration that this was accomplished by reducing the PTV-parotid overlap. Furthermore, because of the high percentage of patients with oral cavity and oropharynx tumors, only 10 patients (22.7%) could meet the oral cavity constraints (Table 10). Both techniques were able to keep the doses to OARs within acceptable tolerance limits. There were no statistical differences regarding the dose received by

OARs, except for brain stem maximal received dose, which was higher for SIB-IMRT plans (p=0.045) (Table 12). An analysis of the subgroup of patients with GTV ≤ 100 cm^3 revealed no statistically significant differences between the two XRT techniques, however, the higher maximum dose received by the brain stem achieved with SIB-IMRT in comparison to HART-SEQ-IMRT was kept and magnified (52.4 ± 5.57 Gy vs. 43.54 ± 10.09Gy, respectively, p = 0.007) (Table 13). The only explanation for this finding that is in patients enrolled in the SIB-IMRT arm the boost volume (CTV\PTV $_{(gross\ tumor)}$) might be relatively nearer to brain stem.

A higher dose to the brain stem resulting from SIB-IMRT was previously recorded by Chen et al. (2005), who found that the maximal dose to the brain stem was significantly higher using the SIB technique (52.84 ± 551 Gy) than SEQ-IMRT (48.34 ± 3.88 Gy) (p=0.0001). However, they could report lower doses to OARs (parotid glands and ear apparatus) using SIB-IMRT. Also, Dogan et al. (2003) found that the mean brainstem dose was ≈18% lower using SEQ-IMRT (12.6 ± 6.3 Gy) compared to SEQ-conventional XRT- IMRT boost (15.4 ± 5.8 Gy), and SIB-IMRT (15 ± 7.6 Gy); on the other hand, they could not find similar results regarding the brain stem D_{max} which was ≈7% lower using SIB-IMRT as compared to SEQ-IMRT. In agreement with the findings of Chen et al. (2005), Dogan et al. (2003) reported lower doses to OARs (parotid glands and spinal cord).

6.2. Acute toxicity

Concurrent chemoradiotherapy is standard treatment for LAHNSCC. Whether short induction CTH provides survival gains additionally to chemoradiotherapy is an open question. According to RTOG 95-01 adjuvant chemoradiation study, the frequency of acute grade III toxicities reached 77% in patients received chemoradiation versus 34% in those patients who received XRT alone (p < 0.0001) (Cooper et al.,2004).

The use of IMRT for head and neck cancer can reduce the parotid volume treated with high doses and result in an improved salivary status (Chao et al. 2001; Eisbruch et al. 1999, 2001; Wu et al. 2000). Phase III trials have demonstrated lower rates of patient-reported toxicities with IMRT when compared to 3DRT techniques in the treatment of oropharyngeal cancer (Nutting et al., 2009) and NPC (Pow et al., 2006; Kam et al., 2007).

In addition to the role of IMRT in reducing patient's reported toxicities during and after treatment, patient's follow-up and supportive therapy during XRT especially when combined with CTH and/or targeted therapy has significant importance. During therapy, all our patients were hospitalized and strongly supported, and all of them required PEG.

For the whole patient cohort, it was obvious that IMRT, despite stage IV disease and concurrent systemic therapy, could keep the acute toxicities lower than historical controls. No grade IV toxicities could be reported. The XRT course could be completed without interruption in 68.2% of patients, while it was interrupted for ≤ 3 days in 4 (9.1%) patients and for > 3 days in 10 (22.7%) patients, of whom only 4 (9.1%) patients needed interruption for > one week. The cause of interruption was mainly because of pain resulting from severe mucositis.

During XRT, 4.5% of patients had grade III fatigue, 45.5% grade III dysphagia, 25% grade III erythema, 40.9% grade III mucositis, 9.1% grade III pain, 45.5% grade III xerostomia. 47.7% grade III dysgeusia and taste alteration, and only 4.5% grade III voice changes. No patient was complaining of grade III weight loss or grade III salivary gland changes.

Both IMRT and good nutritional support during XRT may be attributed to absence of grade III weight loss. Also, subtraction of PTVs from the skin by 3 mm resulted in lower grades of erythema (Table 15).

Our prescribed scheme for SIB resulted in typically higher fractional doses to the boost volume (2.2 Gy/fraction), which is obviously a higher dose per fraction than that given by the HART-SEQ-IMRT scheme (1.4 Gy/fraction). This suggests that normal tissues embedded within or adjacent to the target regions might also receive a higher dose per fraction and therefore, the normal tissues may be at greater risk.

As expected, higher grades of toxicities among HART-SEQ-IMRT patients owing to larger GTV were recorded. Patients who were enrolled in HART-SEQ-IMRT arm were complaining of higher grades of weight loss, dysphagia, erythema, mucositis, pain, xerostomia, salivary gland changes, and voice changes than patients who were enrolled in SIB-IMRT arm (Table 16). However, only the differences in weight loss (p=0.045), dysphagia (p=0.019), and erythema (p=0.011) grades could reach a statistical significance. Also, patients who were enrolled in the HART-SEQ-IMRT arm were exposed to more interruption of XRT than patients in the SIB-IMRT arm (42.9% vs. 12.5%, respectively, p=0.038).

Acute toxicities are not only related to the dose per fraction, but also to the total radiation therapy dose, and the OTT. We have to take into consideration that despite the fact that the dose per fraction was smaller for the HART-SEQ-IMRT scheme, the cumulative total dose received by the two fractions per day after 3 weeks from beginning of XRT was higher (2.8 Gy) than with the SIB-IMRT scheme. Also, as we reported before, the HART-SEQ-IMRT plans resulted in higher doses delivered to target volumes, which may be reflected by normal tissues embedded

within or adjacent to the target regions. Higher cumulative total dose together with higher doses to nodal target volumes could explain the higher grades of toxicities and higher incidence of XRT interruption among patients enrolled in the HART-SEQ-IMRT arm.

By comparing 17 patients with GTV≤ 100 cm^3 who were enrolled in the HART-SEQ-IMRT arm to 16 SIB-IMRT patients, the differences in XRT interruption and acute toxicity outcome between the two arms were reduced (Table 17). We observed only higher grades of erythema in patients enrolled in the HART-SEQ-IMRT arm than in patients enrolled in the SIB-IMRT arm (P=0.037). Furthermore, an analysis of 30 patients who received concurrent PF regimen revealed that HART-SEQ-IMRT patients suffered only higher grades of erythema than patients who were enrolled in the SIB-IMRT arm (P=0.038) (Table 18). In an analysis of 14 patients who received neoadjuvant TPF regimen and cetuximab concurrent with XRT revealed that all patients (100%) enrolled in HART-SEQ-IMRT were subjected to XRT interruption compared to only 10 % of patients in the SIB-IMRT arm (P=0.001) (Table 19). Regarding this point, we have to mention that the relative number of patients in these subgroups was small.

In comparison to other trials that used IMRT concurrent with CTH in LAHNSCC, our results seem to be excellent. Nuyts et al. (2009) treated 90 LAHNSCC patients with HART according to a hybrid fractionation schedule consisting of 20 fractions of 2 Gy (once daily) followed by 20 fractions of 1.6 Gy (twice daily) to a total dose of 72 Gy. Concomitant cisplatin 100 mg/m^2 was administered at the start of weeks 1 and 4. They reported grade III dysphagia (82.2%), grade III mucositis (74.5%), and grade III dermatitis (30.0%), Grades II–III xerostomia (92.2%) and grade III pain (28.9%). In the present study, we reported in patients enrolled in the HART-SEQ-IMRT arm less acute toxicities, grade II xerostomia (39.3%), grade III xerostomia (53.6 %), grade III mucositis (50%), grade III dermatitis (35.7%), grade III dysphagia (57.1 %), and grade III pain (10.7%). However, in the study conducted by Nuyts et al. (2009), XRT was delivered using IMRT in only 14 patients.

Studer et al. (2006) in a trial on 115 HNC patients tested SIB-IMRT, in which dose per fraction escalated to GTV (2 to 60–70 Gy, 2.2 to 66–68.2 Gy, or 2.11 to 69.6 Gy) was used. They reported the following early toxicities: grade III xerostomia (10 %), grade III mucositis (15 %), grade III dermatitis (5 %), and grade III dysphagia (20 %). No radiation toxicity related treatment interruption occurred in their trial. In our SIB-IMRT arm, in which dose per fraction escalated to CTV $_{(gross\ tumor)}$ (2.2 to 70.4 Gy) was used, we observed more or less similar acceptable acute toxicities; grade III xerostomia (31.2 %), grade III mucositis (25%), grade III

dermatitis (6.3 %), and grade III dysphagia (25 %). However, we observed XRT interruption in 12.5% of SIB-IMRT arm patients.

de Arruda et al. (2006) reviewed the Memorial Sloan-Kettering Cancer Center's experience in using IMRT for the treatment of 50 patients with oropharyngeal cancer. Concurrent CTH was used in 43 patients (86%). Patients were treated using three different IMRT approaches: 76% SIB-IMRT, 18% concomitant boost with IMRT in both am and pm deliveries, and 6% concomitant boost with IMRT only in pm delivery. The average prescription dose to the gross tumor PTV was 70 Gy, while the average dose delivered to the subclinical volume was 59.4 Gy in the SIB-IMRT group and 54 Gy in the concomitant boost group. The worst acute mucositis experienced was grade 2 in 54%, and grade 3 in 38% of patients.

Schwartz et al. (2007) retrospectively analyzed 49 patients with HNSCC who were treated with SIB-IMRT technique. The dose per fraction was escalated to 2.5 Gy for a total of 60 Gy in 25 fractions to the GTV and 50 Gy in 25 fractions to the CTV. Twenty-nine patients were administered concomitant CTH. Grade 3 acute toxicities included 55% mucositis, 20% odynophagia, and 8% skin. There were no grade IV toxicities. Also, Seung et al. (2008) tested SIB-IMRT in 69 patients with nasopharyngeal and oropharyngeal cancer. Forty-five patients (65%) received concurrent CTH. The dose per fraction for GTV was escalated to 2.12 Gy for a total of 70 Gy. The most common acute toxicities were dermatitis (32 grade II, 5 grade III), mucositis (33 grade II, 28 grade III), and xerostomia (29 grade II, 40 grade III).

Table 42: Results from selected series regarding grade III acute toxicities in HNSCC patients treated with SIB-IMRT

Author	No	CTH	Stage	Dose prescription	Mucositis	Erythema	Dysphagia
Studer et al. (2006)	115	78%	III\IV	5 × 2.2 Gy/week to 66–68.2 Gy	15%	5%	20%
Schwartz et al. (2007)	49	59%	III\IV	5 × 2.5 Gy/week to 60 Gy	55%	8%	20%
Lee et al. (2007)	31	100%	III\IV	5 × 2.12 Gy/week to 70-72Gy 5 × 2.2 Gy/week to 66Gy	22.6%	3.2%	12.9%
Chakraborty et al. (2009)	28	0%	I-IVA	5 × 2.18 Gy/week to 72Gy 5 × 2.2 Gy/week to 66Gy	42.9%	14.3%	10.7%
Present study	16	100%	IV	5 × 2.2 Gy/week to 70.4Gy	25%	6.3%	25%

6.3. Late morbidity

Our SIB schedule nominal physical dose to $PTV_{(gross\ tumor)}$ was 70.4 Gy which radiobiologically higher and equivalent to 73.92 Gy, and HART schedule nominal physical dose to $PTV_{(gross\ tumor)}$ was 72 Gy which is radiobiologically lower and equivalent to 65.61 Gy, assuming α/β of 10 Gy for late reacting tissue (Table 5).

In our study, of 41 surviving patients 6 months after XRT we also noted excellent results regarding late morbidity (Table 21). The maximal late toxicities were: Grade II dysphagia (34.1%), grade III dysphagia (2.4%), grade II pain (7.3%), grade III (2.4%) pain, grade II xerostomia (48.8%), grade II dysgeusia and taste alteration (29.3%), grade III voice changes (2.4%), grade II skin changes (4.9%), grade II lymphedema (6.8%), and grade I mandibular ORN (4.9%). Grade I trismus presented in 7.3% of patients, grade II in 4.9%, while grade III presented in only one (2.4%) patient.

Our excellent results continued also after 9 months from XRT among 30 surviving patients, we observed improved dysphagia, xerostomia, and taste alteration with time (Table 23). The maximal late toxicities reported after 9 months were: Grade II dysphagia (16.7%), grade III dysphagia (3.3%), grade II pain (3.3%), grade III pain (3.3%), grade II xerostomia (33.3%), grade II dysgeusia and taste alteration (13.3%), grade III voice changes (3.3%), grade II skin changes (3.3%), grade II lymphedema (6.7%), and grade I mandibular ORN (3.3%). Grade II trismus was noted in 10%, while grade III presented in only one (3.3%) patient, in whom surgical interference for trismus was required. Regarding PEG dependence, twelve (29.3%) patients were still using PEG for nutritional support at 6 months, and only six (20 %) patients continued to use PEG at 9 months. No patient complained of brachial plexopathy or myelopathy. An analysis of late toxicities after 6 and 9 months from XRT among the whole group of surviving patients and subgroups with GTV $\leq 100 cm^3$, HART-SEQ-IMRT and SIB-IMRT techniques showed no statistically significant differences between them (Tables 21,22,24,25).

Recently, Montejo et al. (2010), analysed 43 consecutive patients with advanced HNSCC who received SIB-IMRT (dose escalated to GTV 2.25 to 67.5 Gy in 30 days) with concurrent cisplatin or cetuximab. In patients with sufficient follow-up, 82% were PEG feeding free by 6 months after therapy; 13% remained on PEG at 1 year. Grade II xerostomia was noted in 12 (27.9%) of patients, grade III soft-tissue fibrosis, esophageal stricture, ORN, and trismus occurred in 3 patients (6.9%), 5 patients (11.6%), 1 patient (2.3%), and 3 patients (6.9%), respectively. In our study, late toxicities 9 months after XRT among SIB-IMRT patients were

similarly good; PEG dependence was recorded in one patient (7.1%), grade II dysphagia in one patient (7.1%), grade II xerostomia in 3 patients (21.4%), grade II dysgeusia and taste alteration in 2 patients (14.3%), grade II-III skin changes (0%), grade II lymphedema in 2 patients (14.3%), grade II trismus in 1 patient (7.1%), and no patient had mandibular ORN.

Our results are also better than those reported by Studer and associates (2006), who reported two grade IV late morbidity (dysphagia, laryngeal fibrosis) patients following SIB schedule with 2.2 Gy per fraction. de Arruda et al. (2006) reported at least 9 months of follow-up for their patients, grade 2 xerostomia in 33%, and cervical esophageal stricture in 6% of patients. In a group of patients evaluated by Schwartz et al. (2007) two patients (4% of the total) required a permanent PEG, and ORN occurred in one patient (2% of the total).

Table 43: Results from selected series regarding worst late morbidities in HNSCC patients treated with SIB-IMRT

Author	**Follow-up**	**Worst late morbidities**
Studer et al. (2006)	One year after XRT	Dysphagia grade III (1.8%) Xerostomia grade III (1.8%) Dysphagia grade IV (0.9%) ORN grade III (0.9%) Laryngeal fibrosis grade IV (0.9%)
Schwartz et al. (2007)	3 -53 months after XRT	Dysphagia grade III 4% ORN 2% grade III 2%
Lee et al. (2007)	One year after XRT	Xerostomia grade II (3.2%) Dysphagia grade III (19.4%) Laryngeal oedema grade IV (6.5%) PEG dependency (19.4%)
Present study	9 months after XRT	Dysphagia grade II (7.1%) PEG dependency (7.1%) Xerostomia grade II (21.4%) Dysgeusia grade II (14.3%) Trismus grade II (7.1%)

6.4. Disease control

We escalated dose per fraction to $PTV_{(gross\ tumor)}$ in our SIB schedule to 2.2 Gy to a total dose of 70.4 Gy in 32 fractions, which is radiobiologically more and equivalent to 71.57 Gy, assuming α/β of 10 Gy to tumor tissue. On the other hand, our HART schedule escalated the dose to $PTV_{(gross\ tumor)}$, using 2 Gy per fraction in the first 3 weeks followed by HART (1.4 Gy\fraction twice daily) for the last 3 weeks, to a total dose of 72 Gy, which is radiobiologically equivalent to 69.9 Gy, assuming α/β of 10 Gy to tumor tissue (Table 5).

Regarding the response of tumor to treatment, we had good results (Table 34). Three months after XRT, CR rate for the 44 patients was 72.7% and the overall residual rate was 27.3%. All residual diseases after XRT were in CTVC\PTV$_{(gross\ tumor)}$, in which $V_{95\%}$ was 98.70 ± 1.15% with HART-SEQ-IMRT plans, and 94.52 ± 1.44% with SIB-IMRT plans. The underlying cause may be the presence of radioresistance in some of the tumor cell clones.

As mentioned before, HART-SEQ-IMRT resulted in higher doses to target volumes especially to nodal target volumes than SIB-IMRT. Nevertheless, higher doses were not translated into better tumor response and control rates. There was no statistically significant difference between the HART-SEQ-IMRT arm and the SIB-IMRT arm regarding CR rate (75% vs. 68.8%, respectively, P=0.949) (Table 35). Also, no statistically significant differences could be recorded between the two XRT techniques in an analysis of subgroups of patients (patients with GTV $\leq$100cm^3, PF group, and TPF group) (Tables 36, 38, and 39).

Our results can be compared to results published by Montejo et al. (2010) and Morganti et al. (2010). Montejo et al. (2010) reported CR of 74.4% after SIB-IMRT combined with concurrent cisplatin or cetuximab in 43 patients with LAHNSCC. Also, Morganti et al. (2010) investigated 36 LAHNSCC patients who received 3 courses of induction CTH (PF or TPF), followed by concurrent CTH (weekly cisplatin 30 mg/m^2) plus SIB-IMRT (dose per fraction escalated to 2.25 to a total of 67.5 Gy). In their trial, after chemoradiation, the CR rate was 63.8%.

In the present study, after a median follow-up time of 11.75 months, 56.8% of patients were progression free. Several recent studies have demonstrated excellent LRC rates with IMRT in HNSCC (Chao et al., 2003; Lee et al., 2002; Chao et al., 2004; Dawson et al., 2000). Our result for LRC rate of 61.4% is considered lower than those reported by other IMRT series for HNC. For instance, Chao et al. (2003) reported the Washington University experience in 126 HNSCC treated with IMRT, 17 of them developed LRF, showing a 2-year actuarial LRC rate of 85%. In 2004, Chao et al. reported a 4-year LRC rate of 87% for 74 patients with SCC of oropharynx who were treated with IMRT, 17 of them received CTH combined with XRT. However, the cohort of patients in Chao et al. (2004) had only oropharynx cancer which is thought to have a better prognosis, and also they included patients with stages I-IV. Eisbruch et al. (2004) also reported excellent treatment outcomes with IMRT in HNC; at a median follow-up of 32 months, 21 patients (16%) had LRF, showing 3-year actuarial LRFS rates for definitive IMRT of 81%. Earlier, Dawson et al. (2000) reported after median follow-up of 27 months, 12 LRF cases out of 58 HNSCC treated with IMRT, showing a 2-year actuarial LCR of 79%.

The site of LRF was mainly in $CTVC_{(gross\ tumor)}$, one patient developed failure marginal to $CTVC_{(gross\ tumor)}$ and it was inside $CTVB_{(high\text{-}risk)}$. And 4 patients developed failure inside both $CTV_{(gross\ tumor)}$+$CTVB_{(high\text{-}risk)}$. Median time to LRF was 12 ± 0.86 months. Consistent with previous studies, the sites of LRF in our study were mostly (16\17 patients) in-field of gross disease failures (Table 34) indicating that our guidelines for target volume definition and delineation in these patients were adequate. For example, of 12 LRF cases reported by Dawson et al. (2000), 10 patients (80%) relapsed in-field (in areas of previous gross tumor in 9 patients), and 2 patients developed marginal recurrences in the side of the neck at highest risk). Also, in the study reported by Chao et al. (2003), of 17 LRF cases, 9 (53%) were inside CTV1 (gross tumor and the region adjacent to the gross tumor). One failure (6%) was marginal to CTV1 but inside CTV2 (prophylactically treated neck). One failure (6%) occurred outside CTV1 but inside CTV2. Another failure was marginal to CTV2. Of the 17 failures, 5 (28%) were found outside of the IMRT field and in the lower neck.

In our study, distant disease control was 88.6%, and the disease metastasized mostly to lung and mediastinum, only one patient had skin metastases (Table 34). This recorded rate of distant metastases is more or less concordant with that results published by Studer et al. (2008) who reported distant metastases rate of 7% (28 out of 399 HNC patients treated with definitive or postoperative IMRT). Chao et al. (2004) reported distant metastasis in 6 patients out of 74 (8%) oropharyngeal cancer patients treated with definitive or postoperative IMRT. Similarly, by analysing results of 20 laryngeal and 11 hypopharyngeal carcinoma patients underwent IMRT with concurrent platinum-based CTH , Lee et al. (2007) found that the most common site of distant failure involved the lung, with a 92% 2-year freedom from distant metastasis rate. Our recorded rate of distant metastases is better than this reported by Totan et al. (2010), who recorded an overall incidence of distant metastases of 27.84% among 176 HNSCC patients treated with definitive XRT. They reported that 80% of the metastases were detected within two years after XRT.

In the present study, at the time of analysis (December 2010), 8⁄44 (18.2%) patients were dead; 75% of them died due to tumor related causes. A remarkable early death of 3 patients within 3 months after XRT was recorded (Table 34). There were no statistically significant differences between the HART-SEQ-IMRT arm and the SIB-IMRT arm regarding LRC (64.3% vs. 56.3%, respectively, P=0.598), and distant disease control rates (89.3% vs. 87.5%, respectively, p=0.858). Furthermore, no statistical significant differences could be recorded between the two

XRT techniques in an analysis of subgroups of patients (patients with GTV ≤100cm^3, PF group, and TPF group) (Tables 36,37,39).

For the 44 patients, one-year PFS, LRFS, DMFS, and OS were; 58.8%, 61 %, 89.7 %, and 80.6%, respectively. No statistically significant differences were found between the HART-SEQ-IMRT arm and the SIB-IMRT arm regarding one-year PFS (60.3% vs. 56.3%, respectively), LRFS (63.9% vs. 56.3%, respectively), DMFS (87% vs. 93.3%, respectively), or OS (75.3% vs. 87.5%, respectively). Also, no statistically significant differences could be recorded in one-year PFS, LRFS, DMFS, and OS between the two XRT techniques in an analysis of subgroups of patients (patients with GTV ≤100cm^3, PF group, and TPF group).

In comparison to other trials that investigated IMRT in LAHNSCC, we observed more or less similar OS and DMFS rates, and lower PFS and LRFS rates. Studer and associates (2006) reported 2-year LRFS, RPFS, and DMFS of 77%, 87%, and 78%, respectively.

de Arruda et al. (2006) also reported higher survival rates than our results; the 2-year estimates of LRFS, RPFS, DMFS, and OS were 98%, 88%, 84%, and 98%, respectively. Schwartz et al. (2007) with a median follow-up of 25 months reported LCR of 83%, and OS of 80%. Seung et al. (2008) with a median duration of follow-up of 18 months, reported a 2-year LCR, regional control rate, distant control, and OS rates of 98%, 100%, 98%, and 90%, respectively. One explanation for our lower survival and control rates is that in our study we are dealing with stage IV disease only, which in turn might have worse prognosis, whereas in most of these trials, the authors investigated cohorts of patients with both stage III and IV disease.

In our study, we examined a small cohort of patients (14 patients) who received neoadjuvant TPF followed by XRT concurrent with cetuximab. After randomized clinical trial EORTC-24971 conducted by Posner et al. (2007), and TAX324 trial conducted by Vermorken et al. (2007), TPF regimen as induction CTH regimen was adopted as of choice for LAHNSCC. And on the basis of the encouraging results from a randomized phase III trial initiated by Bonner et al. (2006, and 2010), and reported 5-year OS of 45.6% in the cetuximab-plus-XRT group compared to 36.4% in the XRT-alone group. Several clinical trials are running to investigate combination of XRT with cetuximab or other targeted agent.

As expected, the pattern of progression of the PF group was obviously different from that of the TPF group and. The PF group experienced less local and regional failure rates and more distant failure rates in comparison to the TPF group. No patient in the TPF group had distant metastases; however a high percentage of patients had local and regional failure (Table 37).

TPF patients experienced worse PFS and LRFS than PF patients: one-year PFS (35.7% vs. 69.7%, respectively), LRFS (35.7% vs. 73%, respectively), DMFS (100% vs. 85.3%, respectively), and OS (78.6 % vs. 81.3%, respectively). A further analysis of subgroups of patients (patients with GTV ≤ 100 cm3, TPF patients, and PF patients), showed that the differences in PFS, LRFS, DMFS, and OS between the HART-SEQ-IMRT arm and the SIB-IMRT arm were not statistically significant.

In our study, the fact that a remarkably poor one- year LRFS of 25% for patients who received TPF regimen followed by cetuximab + HART-SEQ-IMRT, and one-year LRFS of 40% for patients received TPF regimen followed by cetuximab + SIB-IMRT, were observed should not be ignored.

Our results contradict the findings reported by Paccagnella et al. (2010), who published better results for TPF induction CTH before concomitant PF chemoradiotherapy in their phase II/III trial in 101 patients with LAHNSCC. Comparing concomitant PF chemoradiotherapy to TPF plus chemoradiotherapy, the CR rate, median survival, and 1-year OS were: 21% vs. 50%, respectively, 33.3 months vs. 39.6 months, respectively, and 78% vs. 86% respectively. Furthermore, Morganti et al. (2010) reported 2-year LCR, PFS, and OS of 88.7%, 74.5% and 60.9%, respectively in 36 HNSCC patients treated with induction TPF and concomitant PF chemoradiotherapy. Recently, Lorch et al. (2011) published the 6 year median follow up results of a TAX 324 trial. They reported very encouraging results for patients received neoadjuvant TPF; the median survival was 70.6 months, the estimated 5-year OS was 52% and PFS was 38.1 months. Our results are considered also inferior to those reported by Bonner et al. (2010) who recorded encouraging results for adding cetuximab to XRT as regards OS in patients with LAHNSCC.

It is clear that our results regarding for patients who received TPF followed by cetuximab + IMRT are similar to the results reported in earlier phase II and III studies conducted by Paccagnella et al. (1994), Domenge et al. (2000) and Zorat et al. (2004). In these trials, induction CTH followed by only local therapy (XRT alone or XRT +surgery) was investigated. According to these trials, induction CTH resulted in lower rates of distant metastases but at the expense of significant high rates of LRF due to absence of systemic CTH concurrent with XRT. However in our study we used cetuximab concurrent with XRT, which suggests that combination of cetuximab alone with XRT after TPF did not add much benefit to XRT as regards LRC. More aggressive combination of chemotherapeutic agents with targeted therapy during XRT is warranted and must be demanded for patients with LAHNSCC.

6.5. Patients, disease, and treatment characteristics together with dosimetric distribution obtained from DVH in relation to clinical outcome

The aim of our study was not to investigate the impact of IMRT on the swallowing function or salivary gland function; nevertheless, we tried to find correlation between different dosimetric parameters and the clinical outcome.

All patient, disease, and treatment characteristics together with dosimetric parameters obtained from DVH for each CTV\PTV and for different OARs in relation to XRT interruption and acute toxicities were analysed.

A multivariate analysis revealed that only primary tumor site (oral cavity with reference to other tumor sites) (p=0.029), volume of GTV (p=0.002), and $PTVA_{(low\text{-}risk)}$ $D_{difference}$ (p=0.012) proved to be predictors for XRT interruption (Table 33). Data in literature concerning predictors for XRT interruption in HNC patients are sparse.

We confirmed that the XRT technique (HART-SEQ-IMRT with reference to SIB-IMRT) (p= 0.035), volume of GTV (p=0.004), and $CTVB_{(high\text{-}risk)}$ D_{mean} (p=0.052) were significant predictors for grade III dysphagia. According to studies conducted by Eisbruch et al. (2004), Feng et al. (2007), Jensen et al. (2007), and Caglar et al. (2008), the dose to the larynx and pharyngeal musculature may be associated with a risk of dysphagia. In our study, delineation of the larynx and of various pharyngeal structures as well as dose constraints for these structures was not warranted. However, dose constraints for swallowing structures when uninvolved should be further considered in the future.

$PTVA_{(low\text{-}risk)}$ $D_{2\%}$ (p=0.012), and oral cavity subtracted from PTVs D_{mean} (p=0.006) were the only predictor for grade III mucositis. Contralateral parotid Dmean (p<0.001) was a significant predictor for grade III xerostomia (Table 33). Strigari et al. (2010) also confirmed through multivariate analysis that the total parotid gland mean dose (p = 0.00066) and pretreatment stimulated salivary flow (p= 0.00420) are independent factors for predicting xerostomia.

Similarly, we investigated all patients, disease, and treatment characteristics together with dosimetric parameters obtained from DVH for each CTV\PTV and for OAR, in relation to LRF. We found that male patients experienced more LRF than female patients (p=0.036). LRF was observed more frequently in patients with larynx and/or hypopharynx tumors than in patients with oral cavity or oropharynx tumors (p=0.05) and in patients who experienced XRT interruption than patients who did not (p=0.017). Patients who received the TPF regimen experienced more LRF than patients in the PF group (p=0.017). Also, dosimetric factors

($CTVB_{(high\text{-}risk)}D_{50\%}$, $PTV_{(high\text{-}risk)}$ D_{min}, $D_{98\ \%}$, $D_{95\ \%}$, and $V_{95\ \%}$) could differentiate between the patients who had LRF and patients who did not (Table 40). However, a multivariate analysis showed that only the systemic therapy received (TPF with reference to PF, p=0.014), and XRT interruption (p=0.02) continued to show prediction for LRF (Table 41).

We should like to emphasize the results of Bese et al. (2007) who reported a 10% to 12% loss in local control was associated with treatment breaks of approximately 1 week in patients with HNSCC who were treated with conventional XRT. McCloskey et al. (2009) also proved that duration of radiation treatment and baseline haemoglobin levels were significant predictors of local control. LRF occurred in 6 of 13 patients (46%) with XRT interruptions (>1 week) versus 9 of 65 patients (14%) completing the XRT without interruption (p= 0.0148).

Furthermore, we investigated the effect of XRT interruption on different survival endpoints investigated in the study. We found that interruption of XRT was a predictor for disease progression (p=0.038). We found a low one-year PFS rate for patients with interruption of XRT in comparison to those with no XRT interruption (35.7% vs. 69.8%, respectively). The one-year LRFS for patients with no interruption of XRT was 73% vs. 35.7% for patients with XRT interruption. There was no correlation between XRT interruption and distant metastases (p=0.058). Nevertheless, the one-year DMFS for patients with no interruption of XRT was 96.7% compared to 70.7% for patients with XRT interruption.

In the present study, we found that interruption of XRT (p=0.013), LRF (p=0.016), and volume of GTV (p=0.035) were predictors for increased risk of death. The one-year OS for patients with no interruption of XRT was 93.2% vs. 54.4% for patients with interruption of XRT. The one-year OS for patients who did not have LRF was 96.2% vs. 57% for patients who had LRF. Similarly, Rades et al. (2008) found that improved OS was associated with no XRT interruptions (p=0.021), and improved local control was significantly associated with no XRT interruptions (p=0.15).

Contrary to results reported by Lee et al. (1993), Mancuso et al. (1999), and Doweck et al. (2002), and Chao et al. (2004), who found that The GTV and nodal GTV are the most important factors predictive of therapeutic outcome, we could not find any correlation between GTV and LRF, or disease progression. However and as mentioned before, a correlation was found between GTV and increased risk of death was found (p=0.035).

Although some studies have reported that there is an association between tumor characteristics and disease outcome in patients with HNSCC, we could not find any correlation between any

tumor characteristics (T stage, N stage, histological differentiation, primary tumor site) and disease outcome. Gupta et al. (2009) reported in multivariate analysis of tumor and treatment characteristics data in patients with HNSCC that stage grouping, primary site, and intensity of treatment were significant predictors of LRC and DFS. Also Kreppel et al. (2010) recorded in their univariate analysis a significant impact of T stage ($p=0.009$), N stage ($p<0.001$), and tumor stage ($p<0.001$) on OS of patients with oral cavity cancers. A multivariate analysis of local control by Mendenhall et al. (2003) revealed that T stage ($p <0.0001$) significantly influenced this end point. Recently, daly et al. (2010) recorded in patients with HNSCC of oropharynx treated with IMRT, that T stage (T4 vs. T1-T3) was predictive of poorer LRC ($p = 0.001$), OS ($p = 0.001$), and PFS ($p < 0.001$) rates. Earlier, Sanguineti et al. (1999) could prove that N stage ($p= 0.010$) was an independent predictors of LRC in patients with HNC.

As mentioned before, pitfalls of this study include its non-randomised nature, small number of patients, and heterogeneities between the two study arms. All of these factors can explain our findings as regards lack of association between patients\disease characteristics and disease outcome.

7. Summary & Conclusion

Purpose: This study was conducted to compare differences in dosimetric and clinical endpoints among patients with stage IV head and neck squamous cell carcinoma (HNSCC) treated by HART-SEQ-IMRT and SIB-IMRT.

Patients and methods: 44 patients with stage IV HNSCC were prospectively enrolled (16 SIB-IMRT arm and 28 HART-SEQ-IMRT arm). Thirty patients received cisplatin+ 5 Fu weekly with XRT, while 14 received 3 cycles of docetaxel+ Cisplatin+ 5 Fu followed by cetuximab concurrent with XRT. Two- three clinical target volume were defined; CTVC $_{(\text{gross tumor})}$, CTVB $_{(\text{high-risk})}$ and CTVA $_{(\text{low-risk})}$. Dose volume histogram (DVHs) dose metrics comparison between the two techniques was done using ICRU Report 83. Acute and late toxicities using NCI-CTC v.3, tumor response and control rates were compared.

Results: After analysis of DVHs, HART-SEQ-IMRT plans resulted in higher levels of D_{mean}, $D_{50\%}$, $D_{95\%}$, $D_{max,}$ $D_{near\text{-}max,}$ D_{min}, $D_{near\text{-}min}$, $D_{difference,}$ and $V_{95\%}$ especially for CTVPTV$_{(\text{high-risk})}$ and CTVPTVC$_{(\text{gross tumor})}$ in comparison to SIB-IMRT. Irrespective of GTV, HART-SEQ-IMRT patients had more XRT interruption than patients in the SIB-IMRT arm (p=0.038), higher grades of weight loss (p=0.045), dysphagia (p=0.019) and erythema (p=0.011). An analysis of patients with GTV≤ 100 cm^3 revealed that HART-SEQ-IMRT patients had only higher grades of erythema than patients in the SIB-IMRT arm (p=0.037). There was no statistical significant difference between the two XRT techniques regarding response, the overall residual rate among HART-SEQ-IMRT patients was 25% vs. 31.3% among SIB-IMRT patients (p=0.654). After a median follow-up time of 11.75 months, LRC was achieved in 27/44 patients (61.4%), and distant disease control in 39/44 patients (88.6%). Eight of 44 (18.2%) patients at the last analysis (December 2010) were dead. 10⁄28 (35.7%) patients in the HART-SEQ-IMRT had LRF compared to 7\16 (43.8%) in the SIB-IMRT arm (p=0.598). For the 44 patients, 1-year PFS, LRFS, DMFS, and OS were: 58.8%, 61 %, 89.7 %, and 80.6%, respectively. No statistically significant differences were found between the HART-SEQ-IMRT arm and the SIB-IMRT arm regarding 1-year PFS (60.3% vs. 56.3%, respectively), 1-year LRFS (63.9% vs. 56.3%, respectively), 1-year DMFS (87% vs. 93.3 % %, respectively), or 1-year OS (75.3% vs. 87.5%, respectively). Analysis of subgroups of patients (patients with GTV ≤ 100 cm^3, TPF patients, and PF patients), showed that the differences in 1-year PFS, 1-year LRFS, 1-year DMFS, and 1-year OS between the HART-SEQ-IMRT arm and the SIB-IMRT arm were not statistically significant. After multivariate Cox's regression analysis, we could not find any correlation

between the XRT technique and different outcome endpoints (toxicities, survival, and control rates) except for dysphagia and erythema, in which the HART-SEQ-IMRT technique was predictor for grade III dysphagia and erythema. Regarding systemic therapy, patients who received neoadjuvant TPF followed by cetuximab concurrent with XRT experienced worse PFS and LRFS than patients who received XRT concurrent with PF; 1-year PFS (35.7% vs. 69.7%, respectively), and 1-year LRFS (35.7% vs. 73%, respectively). Patients who experienced an XRT interruption had worse PFS and LRFS, DMFS, and OS than patients who did not; 1-year PFS (35.7% vs. 69.7%, respectively), 1-year LRFS (35.7% vs. 73%, respectively), 1-year DMFS (70.7% vs. 96.7% %, respectively), and 1-year OS (54.4% vs. 93.2%, respectively). Tumors of oral cavity, volume of GTV, and $PTVA_{(low\text{-}risk)}D_{difference}$ proved to be predictors for XRT interruption. HART-SEQ-IMRT, volume of GTV, and $CTVB_{(high\text{-}risk)}$ mean dose were significant predictors for grade III dysphagia. HART-SEQ-IMRT was predictor for grade III erythema. $PTVA_{(low\text{-}risk)}$ $D_{2\%}$, and oral cavity mean dose were predictor for grade III mucositis. Contralateral parotid mean dose correlated with xerostomia.

Conclusion: HART-SEQ-IMRT resulted in higher doses to target volumes especially to nodal target volumes than SIB-IMRT. Nevertheless, higher doses were not translated into better tumor response and control rates. HART-SEQ-IMRT technique with reference to SIB-IMRT was predictor for grade III dysphagia and erythema. Preliminary survival data revealed no differences between HART-SEQ-IMRT technique and SIB-IMRT technique. SIB-IMRT implementation is logistically easier; furthermore, it provides satisfactory results comparable to HART-SEQ-IMRT. This study suggests that SIB- IMRT could be a routine treatment in a subset of patients with LAHNSCC (with GTV $\leq$ 100 cm^3, and tumors not involving neurologic structures); however, SIB-IMRT should be further investigated in the context of larger tumors in order to find the maximal volume of GTV that can be treated using SIB-IMRT without devastating morbidity. LRF remains the most difficult challenge in treatment of LAHNSCC. Neoadjuvant TPF therapy followed by cetuximab concurrent with XRT, and XRT interruption correlated with LRF. Cetuximab alone concurrent with XRT did not add much benefit as regards LRC. More effective systemic agent combination should be explored. Even in the context of IMRT, dose escalation and acceleration of OTT in LAHNSCC patients is associated with XRT interruption. In our study, XRT interruption was associated with worse survival rates. Future studies with introduction of molecular functional imaging could add further improvement in the definition of different target tumor volumes and OARs.

8. Zusammenfassung

Ziel: Vergleich der intensitätsmodulierter hyperfraktionierter akzelerierter Strahlentherapie mit sequentieller Feld (HART-SEQ-IMRT) Technik mit Intensitätsmodulierter akzelerierter Strahlentherapie mit simultan integriertem Boost (SIB-IMRT) Technik zur Behandlung neu diagnostizierter, unbehandelter lokal fortgeschrittenen Plattenepithelialkarzinom der Kopf-Halsregion (LAHNSCC) bezüglich Dosisverteilung, Toxizität, Tumorkontrolle und Überleben.

Patienten und Methode: Es werden insgesamt 44 Patienten mit einem LAHNSCC prospektiv evaluiert, von denen 28 mit HART-SEQ-IMRT Technik und 16 mit SIB-IMRT Technik behandelt werden. Die Dosen für die Risiko-Organe und für die Targetvolumen wurden von den Dosis-Volumen-Histogrammen (DVH) entnommen. Die Akut- und Spättoxizitat wurden bewertet. Das Überleben und die lokoregionale Kontrolle wurden ermittelt.

Ergebnisse: Für HART-SEQ-IMRT Pläne wird eine höhere D_{mean}, $D_{50\%}$, $D_{95\%}$, D_{max}, $D_{near\text{-}max}$, D_{min}, $D_{near\text{-}min}$, $D_{difference}$, und $V_{95\%}$ besonders für CTV\PTV $_{(high\text{-}risk)}$ und CTV\PTVC $_{(gross\ Tumor)}$ im Vergleich zu SIB-IMRT- erreicht. Unabhängig von Tumorvolumen haben mehr Patienten im HART-SEQ-IMRT Arm die Strahlentherapie unterbrochen als Patienten im SIB-IMRT Arm ($p = 0,038$). Bei Patienten im HART-SEQ-IMRT Arm wurde eine höhere Gewichtsabnahme ($p = 0,045$), mehr Dysphagie Beschwerden ($p = 0,019$) und ein stärkeres Erythem ($p = 0,011$) beobachtet. Patienten mit einen Tumorvolumen $\leq 100cm^3$ hatten ein signifikant verstärktes Erythem im Bestrahlungsfeld in der HART-SEQ-IMRT-Gruppe im Vergleich zur SIB-IMRT-Gruppe ($p=0,037$). Es gab keinen statistisch signifikanten Unterschied zwischen den zwei Techniken im Bezug auf die Remission. Nach einem medianen Follow-up von 11,75 Monaten hatten 10 \ 28 (35,7%) der HART-SEQ-IMRT- Patienten ein lokoregionäres Rezidiv (LRF) im Vergleich zu 7\16 (43,8%) im SIB-IMRT-Arm ($p = 0,598$). Nach derselben Nachbeoabachtungszeit hatten 25 (56,8%) Patienten keine Progression, 5 (11,4%) ein lokales Rezidiv, 4 (9,1%) ein regionales Rezidiv und 5 (11,4%) sowohl ein lokales wie auch regionales Rezidiv. Außerdem hatten 2 Patienten Fernmetastasen ohne ein lokoregionäres Therapieversagen (4,5%) und 3 (6,8%) hatten lokoregionale Rezidive und Fernmetastasen. Lokalregionärrezidive traten bei 17 Patienten auf, entsprechend einer lokoregionäre Tumorkontrollrate von 61,4% und Fernmetastasen traten bei 5/44 Patienten (11,4%) auf. Acht von 44 Patienten (18,2%) sind zum Zeitpunkt der letzten Analyse (Dezember 2010) verstorben. Für alle 44 Patienten betrug das 1-Jahresprogressionsfreie Überleben (PFS), das lokoregionärrezidivfreie Überleben (LRFS), das Metastasenfreie Überleben (DMFS) und das Gesamtüberleben (OS) 58,8%, 61%, 89,7%, und 80,6%. Es gab keine statistisch signifikanten Unterschiede zwischen HART-SEQ-IMRT Arm und SIB-IMRT Arm im 1-Jahres-PFS (60,3% vs. 56,3%), 1-Jahres-LRFS (63,9% vs. 56,3%), 1-Jahre- DMFS (87% vs. 93,3%%), oder 1-Jahres-OS (75,3% vs. 87,5%). Die weitere

Analyse der Untergruppen von Patienten (Patienten mit GTV ≤ 100 cm^3, TPF Patienten und PF Patienten), zeigten keine statistisch signifikanten Unterschiede im 1-Jahres-PFS, 1- Jahres-LRFS, 1-Jahres- DMFS und 1-Jahres- OS zwischen den beiden Therapiearmen. Das PFS und das LRFS waren ebenfalls besser nach der Cisplatin-5FU-haltigen Radio-Chemotherapie (PF-Gruppe) im Vergleich zur Induktionschemotherapie mit Docetaxel-Cisplatin-5FU- gefolgt von Strahlentherapie und simultanem Cetuximab (TPF-Gruppe). Es ergaben sich folgende Überlebensraten: 1-Jahres-PFS (PF:69,7% vs. TPF:35,7%), 1-Jahres-LRFS (PF:73% vs. TPF:35,7%). Patienten mit Strahlentherapiepausen hatten schlechtere PFS (35,7% vs. 69,7%), LRFS (35,7% vs. 73%), DMFS (70,7% vs. 96,7%%) und OS (54,4% vs. 93,2%) im Vergleich zu den Patienten, die die Strahlentherapie ohne Unterbrechung erhalten haben. Primären Tumoren der Mundhöhle, GTV-Volumina, und $PTVA_{(low\text{-}risk)}$ $-D_{difference}$ waren die Hauptursachen für eine Strahlentherapieunterbrechung. HART-SEQ-IMRT, GTV-Volumina und $CTVB_{(high\text{-}risk)}$ D_{mean} waren signifikante Ursachen für die Entwickelung einer Grad III Dysphagie. HART-SEQ-IMRT war eine signifikante Ursache für die Entwickelung einer Grad III Erythem. $PTVA_{(low\text{-}risk)}$ $D_{near\text{-}max}$, und der Mundhöhle D_{mean} waren signifikante Ursachen für die Entwickelung einer Grad III Mukositis. Die Kontralaterale Parotis D_{mean} korrelierte mit Grade III Xerostomie. Die neoadjuvante TPF-Therapie gefolgt von Cetuximab in Kombination mit der Strahlentherapie, wie auch Strahlentherapieunterbrechung korreliert signifikant mit der Lokoregionären Rezidivrate.

Schlussfolgerungen: Die HART-SEQ-IMRT Technik konnte trotz höhere Targetvolumendosen am Primärtumor + befallenen Lymphknoten im Vergleich zu SIB-IMRT Technik keine signifikante Verbesserung der Tumorresponse und lokalen Kontrolle erzielen. Es konnte eine Korrelation zwischen der Strahlentherapietechnik (HART-SEQ-IMRT) und der Stärke des Erythems sowie der Dysphagie beobachtet werden. Keine Korrelation konnte hingegen zwischen der Technik und weiteren Toxizitäten, dem Überleben und den Kontrollraten gefunden werden. Die Durchführung der SIB-IMRT ist ökonomischer und führte zu vergleichbaren Ergebnissen wie HART-SEQ-IMRT. Diese Studie zeigt, dass die SIB-IMRT zur Routine Behandlung von Patienten mit LAHNSCC mit Tumorvolumen ≤ 100 cm^3 ohne Beteiligung neurologischer Strukturen geeignet ist. Für größere Tumorvolumina muss die Wertigkeit der SIB-IMRT Technik im Rahmen weiterer klinischer Studien geprüft werden. Das Lokoregionäre Rezidiv bleibt die größte Herausforderung beim lokal fortgeschrittenen Kopf-Hals Tumor. Auch bei Anwendung unterschiedlicher modernster IMRT Verfahren sind toxizitäten-bedingte Therapieunterbrechungen- allerdings im geringeren Ausmaß als mit der 3D-konformalen Strahlentherapie- nicht komplett zu vermeiden. Zukünftige Studien unter Einleitung Z.B. molekularer Funktionsbildgebung, ist eine weitere Verbesserung in der Differenzierung von Tumorvolumen und Risikostrukturen vorzubehalten.

9. References

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Eigenständigkeitserklärung

„Ich, Dalia Abdel-Moaty Ahmad Khalil, erkläre, dass ich die vorgelegte Dissertation mit dem Thema: [Accelerated intensity modulated radiotherapy using simultaneous integrated boost (SIB-IMRT) versus intensity modulated hyperfractionated accelerated radiotherapy using sequential field (HART-SEQ-IMRT) for primary treatment in patients with locally advanced head and neck squamous cell carcinoma], selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die unzulässige Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

Datum
20.02.2011

Unterschrift

List of Publications

Parts of this study were already presented;

Poster Presentation:

- Simultaneous integrated boost intensity modulated radiotherapy (SIB-IMRT) technique versus hyperfractionated accelerated radiotherapy using sequential field IMRT (HART-SEQ-IMRT) technique for primary treatment of stage IV squamous cell carcinoma of the head and neck: Preliminary survival results. Dalia Ahmad Khalil, Peter Wust, Dirk Böhmer, Reinhold Graf, Ulrich Jahn, Klaus-Dieter Wernecke, Volker Budach. Poster presented as E-Poster at the 17. DEGRO-Kongress, June 02-05, 2011, Wiesbaden, Germany.
- Predictors of loco-regional failure in patients with stage IV Head and neck squamous cell carcinoma treated with intensity modulated radiotherapy. Dalia Ahmad_Khalil, Peter Wust, Dirk Böhmer, Reinhold Graf, Ulrich Jahn, Klaus-Dieter Wernecke, Volker Budach. Poster presented as E-Poster at the 17. DEGRO-Kongress, June 02-05, 2011, Wiesbaden, Germany.
- Accelerated intensity modulated radiotherapy using simultaneous integrated boost (SIB-IMRT) versus hyperfractionated accelerated radiotherapy using sequential field IMRT (HART-SEQ-IMRT) for primary treatment of patients with stage IV squamous cell carcinoma of the head and neck. Dalia Ahmad_Khalil, Peter Wust, Dirk Böhmer, Reinhold Graf, Ulrich Jahn, Klaus-Dieter Wernecke, Volker Budach. Poster presented as E-Poster at the 17. DEGRO-Kongress, June 02-05, 2011, Wiesbaden, Germany.

Talk Presentation:

- Impact of Radiotherapy interruption on survival of patients with stage IV squamous cell carcinoma of the head and neck treated by intensity modulated radiotherapy (IMRT). Dalia Ahmad_Khalil, Peter Wust, Dirk Böhmer, Reinhold Graf, Ulrich Jahn, Klaus-Dieter Wernecke, Volker Budach. Oral Presentation at the 17. DEGRO-Kongress, June 02-05, 2011, Wiesbaden, Germany.

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gruenden in der elektronischen Version meiner Arbeit nicht veroeffentlicht.