Moderately Hypofractionated Intensity Modulated Radiotherapy (IMRT) With a Simultaneous Integrated Boost for Locally Advanced Head and Cancer – Do Modern Techniques Held Their Promise?

Jörn Wichmann (wichmann.joern@mh-hannover.de)
Hannover Medical School: Medizinische Hochschule Hannover https://orcid.org/0000-0001-5575-8933
Martin Durisin
Medizinische Hochschule Hannover
Robert Michael Hermann
Medizinische Hochschule Hannover
Roland Merten
Medizinische Hochschule Hannover
Hans Christiansen
Medizinische Hochschule Hannover

Research

Keywords: head and neck cancer, radiotherapy, IMRT, hypofractionation, toxicity

Posted Date: February 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-205189/v1

Abstract

Purpose

Intensity-modulated-radiotherapy (IMRT) is still a standard of care for radiotherapy in locally advanced head and neck cancer (LA-HNSCC). Simultaneous-integrated-boost (SIB) and moderately hypofractionation offer an opportunity of individual dose painting and reduction of overall treatment time. We present retrospective data on toxicity and local-regional-control of a patient cohort with LA-HNSCC treated with an IMRT-SIB-concept in comparison to normofractionated 3D-conformal radiotherapy (3D-RT) after a long-term follow-up.

Methods

Between 2012 and 2014, n=67 patients with HNSCC (stages III/IV without distant metastases) were treated with IMRT-SIB either definitive (single/total doses: 2.2/66Gy, 2.08/62.4Gy, 1.8/54Gy in 30 fractions) or in the postoperative setting (2.08/62.4Gy, 1.92/57.6Gy, 1.8/54Gy). These patients' clinical course was matched (for gender, primary, and treatment concept) as part of a matched-pair-analysis with patients treated before mid-2012 with normofractionated 3D-CRT (definitive: 2Gy/50Gy followed by a sequential boost up to 70Gy; postoperative: 2Gy/60-64Gy). Chemotherapy/immunotherapy was given concomitantly in both groups in the definitive situation (postoperative dependent on risk factors). Primary endpoints were acute and late toxicity; secondary endpoint was loco-regional-control (LRC).

Results

67 patients treated with IMRT-SIB (n = 20 definitive, n = 47 adjuvant) were matched with 67 patients treated with 3D-RT. There were minor imbalances between the groups concerning non-matching-variables like extracapsular extension (ECE) and chemotherapy in IMRT-SIB.

Significantly less toxicity was found in favor of IMRT-SIB concerning dysphagia, radiation dermatitis, xerostomia, fibrosis, and lymphoedema. After a median follow-up of 63 months, median LRC was not reached (IMRT-SIB) vs. 69.5m (3D-RT) (p=0.63).

Conclusion

This moderately hypofractionated IMRT-SIB-concept showed to be feasible with less toxicity compared to conventional 3D-RT in this long-term follow-up observation.

Introduction

In locally advanced head and neck cancer (LA-HNSCC), radiotherapy (RT) is an essential element in curative treatment strategies, either in the definitive (in case of inoperability or to avoid mutilating surgery in oropharyngeal cancers) or in the postoperative-adjuvant situation [1]. Thereby, concomitant – usually Cisplatin-based – chemotherapy improves the prognosis in the definitive [2], as well as in the

postoperative-adjuvant situation, in particular in case of extracapsular spread of nodes (ECE) and/or microscopically involved resection margins [3].

Moderately hypofractionated RT becomes more common in clinical practice. It is already the standard of care in postoperative-adjuvant RT of breast cancer after breast-conserving surgery [4] and is a guideline-based alternative in RT for prostate cancer [5, 6]. Similarly, it has also already been used in HNSCC [7].

Nowadays, intensity modulated radiotherapy (IMRT) is used as the standard of care in RT for HNSCC to lower the risk of high-grade chronic toxicity [8]. The implementation of IMRT also offers the possibility of simultaneous integrated boost (SIB) radiation for individual dose painting and – using moderately hypofractionated concepts – for reduction of overall treatment time [9].

Here, we present a cohort of patients with locally advanced HNSCC in the curative setting treated with RT or radiochemotherapy (RCT), either definitive or postoperative-adjuvant, using an at our institution implemented moderately hypofractionated IMRT-SIB concept. Data on toxicity and loco-regional-control are reported and compared to a historical cohort of patients treated with normofractionated 3D-conformal radiotherapy (3D-RT) before the IMRT-era using a matched-pair analysis.

Patients And Methods

From 2012 to 2014, the analyzed 67 patients with locally advanced (stage III / IV without distant metastases; mostly squamous cell carcinomas) cancers were treated at our department with RT in curative intent with the following moderately hypofractionated IMRT-SIB concepts. For definitive RCT we used a slightly modified fractionation as proposed by RTOG 0022: 66 Gy (daily dose 2.2 Gy) for gross tumor volumes, 62.4 Gy (2.08 Gy) for elective cervical nodes considered to be at exceptionally high risk for subclinical disease, and 54 Gy (1.8 Gy) for elective cervical nodes. In case of postoperative-adjuvant treatment, 62.4 Gy (daily dose 2.08 Gy) for the primary tumor region and cervical regions with involved nodes with ECE, 57.6 Gy (1.92 Gy) for cervical regions with involved nodes without ECE, and 54 Gy (1.8 Gy) for elective cervical nodes were given. All patients were immobilized with a thermoplastic mask, including the head and the neck and shoulder regions. A planning CT scan with a minimum slice thickness of 3mm was obtained in all patients. On each CT slice, the gross tumor volumes (GTV) were delineated by the treating physician, as well as the areas at especially high risk of potential microscopic disease and other potentially affected regions including lymph nodes (CTV). The margins to compensate for set up variability and organ motions were mostly 5mm. Furthermore, organs at risk (OAR) like the parotids, spinal cord, brachial plexus, and brainstem were drawn. All calculations were done with Monaco (Electa) by experienced physicists. A phantom measurement with the PTW OCTAVIUS® (4D) Phantom (PTW Freiburg GmbH – Germany) and the corresponding PTW VeriSoft ® in the latest available version was performed to verify each plan. Planning objectives like dose prescriptions and normal tissue constraints had to be realized according to ICRU-83 [10] and to QUANTEC-data (spinal cord Dmax < 45 Gy, brachial plexus Dmax < 54 Gy, contralateral parotid gland Dmean < 23 Gy) [11]. To reach these

objectives/constraints, the PTV coverage was modified if necessary. For RT, linear accelerators with 6MV photon energy were used.

For comparison, another cohort was additionally analyzed using a matched-pair analysis. The 67 patients of this cohort were treated before the IMRT-era at our institution from 2008 to 2012 with normofractionated 3D-RT as follows: Primary and involved as well as elective cervical nodes up to a dose of 50 Gy followed by a sequential boost to the primary and involved nodes (or regions with ECE in case of adjuvant therapy) to a total dose of 70 (definitive) or 60 to 64 Gy (postoperative-adjuvant). Planning was done by multi-field 3D conformal forward planning using 6, 10, and 15MV photon beams and a “shrinking field approach”. Dose prescriptions had to be realized according to ICRU-50. To avoid long-term toxicity, the supraclavicular lymph nodes were mostly spared at 46 to 54 Gy and the spinal cord at 45 Gy.

In both cohorts, concomitant chemotherapy was given regularly in the definitive situation, in the postoperative-adjuvant setting in case of ECE or microscopically involved resection margins.

All patients were clinically assessed weekly during RT and three months after that by experienced staff to evaluate and grade acute toxicity (oral mucositis, dysphagia, radiation dermatitis, and nadir of hemoglobin levels, white blood cell count, and platelet count) according to CTCAE v4.03 [12]. Afterward, patients were asked to show up for yearly follow-up visits to score late toxicities according to LENT/SOMA (xerostomia, taste alteration, fibrosis, lymphedema, hoarseness, fistula, necrosis of mandible, and trismus) [13] in order to generate a long-term follow-up observation, since late toxicity partly occurs some years later.

Statistics

For this retrospective matched-pair analysis, about 200 consecutive patients who received and completed 3D-RT in curative intent for HNSCC between 01.2008 and 05.2012 were screened as controls. Furthermore, 67 consecutive patients who received hypofractionated IMRT-SIB between 06.2012 and 04.2014 were documented. To select 3D patients as controls, three variables had to match between both groups: gender, site of the primary tumor, and treatment concept (definitive vs. postoperative). Retrospectively demographical, histopathological, clinical, and toxicity data were collected from the charts. Staging was done according to the 7th version of the TNM-manual.

After data collection, for comparison between the patients’ characteristics in both cohorts the McNemar-Test for binary characteristics or Cohens Kappa for characteristics with more levels were used. Loco-regional-control (LRC) was analyzed using the Kaplan-Meier-method [14]. Differences in toxicity were tested for statistical significance with the Wilcoxon signed-rank test. We used SPSS Version 26 to do the statistical analyses. Significance was defined as $p < 0.05$.

Results

Overall, in each group 67 patients were analyzed (20 definitive, 47 postoperative in each cohort). Median follow-up for all patients was 63 months. The essential patients' characteristics are summarized in Table 1. They were sufficiently balanced between the groups. However, there were significantly more patients with ECE (27% vs. 8%) and with concomitant chemotherapy (70% vs. 49%) treated in the IMRT-SIB cohort, as well as six vs. three patients were suffering from cN2c disease.

Acute and chronic toxicity are shown in table 2. There were no significant differences in acute oral mucositis incidences, although there were slightly more patients with at least grade 3 mucositis with 3D-RT (48% vs. 40%). However, a statistically significant difference was documented with lower toxicity in the IMRT-SIB group for overall dysphagia ($p = 0.044$) and radiation dermatitis ($p = 0.002$).

Concerning late toxicity xerostomia, fibrosis and edema were significantly lower in the IMRT-SIB group. 9% in IMRT-SIB vs. nearly 60% were suffering from xerostomia grade 2/3, 7.5% had fibrosis grade 1/2 vs. about 34%, and edema grade 2/3 were documented in 11.9% vs. 44.8%.

3-year LRC was 77% (SIB-IMRT) vs. 78% (3D-RT). Median LRC was not reached (SIB-IMRT) vs. 69.5m (log rank 0.23, $p = 0.63$).

Discussion

With the advent of IMRT in RT for HNSCC as a standard of care, diverse individual concepts have been implemented in different radiotherapy departments. Thereby, the application of a SIB and moderately hypofractionation are often applied to ensure individual dose painting and reduction of overall treatment time, which is crucial in RT for HNSCC [15].

To our knowledge, there is only little prospectively randomized evidence to evaluate the efficacy of IMRT in comparison to 3D-RT in RT of HNSCC. One study (PASPORT) randomized n = 94 patients between IMRT and 3D-RT (with parallel opposed lateral fields) [16]. This study was focused on avoiding xerostomia. At 12 and 24 months, xerostomia at least grade 2 was significantly less prevalent after IMRT. Other late toxicities and loco-regional-control, or overall survival did not differ between both groups. Comparable results were obtained in a small randomized trial (n = 60 patients) from India [17].

In nasopharyngeal cancer, this advanced technique has demonstrated a higher oncological efficacy in n = 616 patients compared to outdated 2D planning techniques: OS and progression-free survival were significantly improved. At the same time, high-grade chronic toxicity was reduced [18].

The recently published GORTEC 2004-01 randomized phase III trial showed again that the IMRT technique can even reach a dose escalation with markedly decreased late xerostomia, but without a significant improvement of local tumor control [31]. The authors used a slightly different irradiation concept with a sequential moderate hypofractionated boost to 75 Gy overall dose (25Gy/10F boost dose) in a total of 35 fractions. The frequency of grade ≥ 2 xerostomia was around 2/3 lower after 1 und 3 years in the IMRT group.

At last, Gupta et al. showed repeatedly in a prospective randomized trial with a very long follow-up and enough power and sample size that the moderate hypofractionation with 66 Gy in 30 fraction and IMRT technique leads to a meaningful reduction in severe xerostomia and fibrosis with comparable locoregional control and overall survivial in the 3D control group [32].

Other observational studies support the assessment of lower acute and chronic toxicity by IMRT in RT for HNSCC in comparison to 3D planning. In this context, Jirkovska et al. demonstrated that acute toxicity and xerostomia were significantly reduced in HNSCC treated by IMRT [19]. Modesto et al. showed similar data, especially for severe late toxicities like xerostomia, dysphagia, or feeding-tube dependency [20]. Our data confirm these findings showing lower toxicity in the IMRT-SIB group for dysphagia, dermatitis, xerostomia, fibrosis, and edema.

Other retrospective studies also showed an advantage for IMRT concerning prognosis in LRC [21] or even OS [22]. In contrast, in our patients LRC was equal between both groups. However, OS differed to the disadvantage of IMRT-SIB. This finding is most likely explained by more aggressive tumors in IMRT-SIB, as more patients had ECE and had to receive concomitant chemotherapy. Furthermore, despite the matched pair analysis, other biases due to the study's retrospective nature might play a role. However, such a finding is not totally in conflict with the literature. A recent meta-analysis on IMRT versus 3D-CRT in RT for HNSCC confirmed the superiority of IMRT in terms of toxicity (mainly xerostomia) but did not find improved oncological outcomes. The authors concluded that a positive impact of IMRT on tumor control and survival mains to be proven [8].

As concomitant chemotherapy in RT for locally advanced HNSCC is crucial for prognosis in the definitive and specific postoperative-adjuvant situations, RT approaches have to be designed so that the dose-fractionation concepts do not compromise the use of concurrent systemic therapy and vice versa. Therefore, we chose a chemotherapy protocol with weekly low dose cisplatin (40 mg/m² BSA up to at least cumulative ≥ 200 mg/² BSA, see above) as a continuous radiosensitizer and decided against a higher hypofractionated RT schedule > 2.2 Gy in the volume. Such a low dose weekly cisplatin application is an established regimen [23] besides likewise often used high dose application - for example 100 mg/m² BSA twice or thrice during radiotherapy [3]. A cumulative cisplatin dose of approximately 200 mg/m^2 BSA, independent of the schedule, might be sufficient to yield a beneficial antitumor effect [24]. However, prospective studies in adequately sized phase III trials on this subject are still pending [25]. We saw good tolerance and feasibility of our approach with moderately hypofractionation without compromising one part of the combined treatment. Other studies actually show that higher hypofractionation (with single doses in SIB volumes up to 2.25 or 2.4 Gy) combined with chemotherapy seems to be possible [26, 27].

IMRT-SIB RT concepts will further be modified according to human papillomavirus (HPV) status in locally advanced HNSCC. On the one hand, HPV positive tumors have a better prognosis and are possible candidates for dose reduction, which is the subject of several ongoing clinical trials [28]. On the other hand, other studies examine the feasibility of dose-escalated hypofractionated chemoradiation in HPV-

negative cancer [29]. Unfortunately, in our retrospective patient cohorts, HPV-status was not available for most of the tumors.

In summary, the presented moderately hypofractionated IMRT-SIB-concept showed to be feasible with an acceptable loco-regional-control and less toxicity compared to conventional 3D-CRT. IMRT is the standard of care in RT for locally advanced HNSCC. The optimal dose-/fractionation concept concerning moderate hypofractionation still has to be defined.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the local ethics committee (number 1795-2013) and all patients declared their written informed consent. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

No funding was granted.

Authors' contributions

JW collected, analyzed and interpreted the patient data, RMH and HC were major contributor in writing the manuscript. MD and RM gave important notes due to their clinical expertise. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank Loukia Spineli for her assistance with the analysis plan at the earlier stages of the study.

References

1. Marur S, Forastiere AA (2016) Head and Neck Squamous Cell Carcinoma: Update on Epidemiology, Diagnosis, and Treatment. Mayo Clin Proc 91:386-396
2. Pignon JP, le Maître A, Maillard E et al (2009) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomized trials and 17.346 patients. Radiother Oncol 92:4-14
3. Bernier J, Cooper JS, Pajak TF et al (2005) Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 27:843-850
4. Interdisziplinäre S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.3 – Februar 2020 AWMF-Registernummer: 032-045OL. https://www.leitlinienprogramm-onkologie.de/index.php?id=67&type=0. Accessed 30 August 2020
5. Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms. Version 5.1 – Mai 2019 AWMF-Registernummer: 043/022OL. https://www.leitlinienprogramm-onkologie.de/index.php?id=58&type=0. Accessed 30 August 2020
6. Vassis S, Nöldeke B, Christiansen H et al (2020) Moderately HRT vs. CRT for localized prostate cancer using image-guided VMAT with SIB: evaluation of acute and late toxicities. Strahlenther Onkol 196:598-607
7. Franzese C, Fogliata A, Franceschini D et al (2020) Impact of hypofractionated schemes in radiotherapy for locally advanced head and neck cancer patients. Laryngoscope 130:E163-170
8. Felice F, Pranno N, Papi P et al (2020) Xerostomia and Clinical Outcomes in Definitive Intensity Modulated Radiotherapy (IMRT) Versus Three-dimensional Conformal Radiotherapy (3D-CRT) for Head and Neck Squamous Cell Carcinoma: A Meta-analysis. Vivo 34:623-629
9. Orlandi E, Palazzi M, Pignoli E et al (2010) Radiobiological basis and clinical results of the simultaneous integrated boost (SIB) in intensity modulated radiotherapy (IMRT) for head and neck cancer: A review. Crit Rev Oncol Hematol 73:111-125
10. ICRU (2010) Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). Journal of the ICRU 10: Report 83. https:// doi:10.1093/jicru/ndq002
11. Bentzen SM, Constine LS, Deasy JO et al (2010) Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys 76(3 Suppl):S3-S9
12. NCI Common Terminology Criteria for Adverse Events (CTCAE) https://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed 30 August 2020
13. (1995) LENT SOMA tables. Radiother Oncol 35:17-60
14. Kaplan E, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 58:457-481
15. Dahlke S, Steinmann D, Christiansen H et al (2017) Impact of Time Factors on Outcome in Patients with Head and Neck Cancer Treated with Definitive Radio(Chemo)Therapy. In Vivo 31:949-955

16. Nutting CM, Morden JP, Harrington KJ et al (2011) Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 12:127–136
17. Ghosh-Laskar S, Yathiraj PH, Dutta D et al (2016) Prospective randomized controlled trial to compare 3-dimensional conformal radiotherapy to intensity-modulated radiotherapy in head and neck squamous cell carcinoma: Long-term results. Head Neck 38 Suppl 1:E1481-1487
18. Peng G, Wang T, Yang K et al (2012) A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiother Oncol 104:286–293
19. Jirkovska M, Novak T, Malinova B et al (2019) Three-dimensional conformal radiotherapy versus intensity modulated radiotherapy with simultaneous integrated boost in the treatment of locally advanced head and neck carcinoma. Neoplasma 66:830-838
20. Modesto A, Laprie A, Vieillevigne L et al (2015) Intensity-modulated radiotherapy for laryngeal and hypopharyngeal cancer: minimization of late dysphagia without jeopardizing tumor control. Strahlenther Onkol 191:225-233
21. Mok G, Gauthier I, Jiang H et al (2015) Outcomes of intensity-modulated radiotherapy versus conventional radiotherapy for hypopharyngeal cancer. Head Neck 37:655-661
22. Kılıç S, Kılıç SS, Hsueh WD et al (2018) Radiotherapy modality as a predictor of survival in hypopharyngeal cancer. Head Neck 40:2441-2448
23. Weykamp F, Seidensaal K, Rieken S et al (2020) Age-dependent hemato- and nephrotoxicity in patients with head and neck cancer receiving chemoradiotherapy with weekly cisplatin. Strahlenther Onkol 196:515-521
24. Ang KK (2004) Concurrent radiation chemotherapy for locally advanced head and neck carcinoma: are we addressing burning subjects? J Clin Oncol 22:4657-4659
25. Szturz P, Wouters K, Kiyota N et al (2017) Weekly Low-Dose Versus Three-Weekly High-Dose Cisplatin for Concurrent Chemoradiation in Locoregionally Advanced Non-Nasopharyngeal Head and Neck Cancer: A Systematic Review and Meta-Analysis of Aggregate Data. Oncologist 22:1056-1066
26. Guerrero Urbano T, Clark CH, Hansen VN et al (2007) A phase I study of dose-escalated chemoradiation with accelerated intensity modulated radiotherapy in locally advanced head and neck cancer. Radiother Oncol 85:36-41
27. Schwartz M, Vuong T, Ballivy O et al (2007) Accelerated radiotherapy with simultaneous integrated boost fractionation and intensity-modulated radiotherapy for advanced head and neck cancer. Otolaryngol Head Neck Surg 136:549-555
28. Patel RR, Ludmir EB, Augustyn A et al (2020) De-intensification of therapy in human papillomavirus associated oropharyngeal cancer: A systematic review of prospective trials. Oral Oncol 103:104608.
29. Meade S, Gaunt P, Hartley A et al (2018) Feasibility of Dose-escalated Hypofractionated Chemoradiation in Human Papilloma Virus-negative or Smoking-associated Oropharyngeal Cancer. Clin Oncol (R Coll Radiol) 30:366-374

30. Landis J, Koch G (1977) The Measurement of Observer Agreement for Categorical Data. Biometrics 33:159-174
31. Tao Y, Auperin A, Blanchard P et al (2020) Concurrent cisplatin and dose escalation with intensity-modulated radiotherapy (IMRT) versus conventional radiotherapy for locally advanced head and neck squamous cell carcinomas (HNSCC): GORTEC 2004-01 randomized phase III trial. Radiother Oncol 150:18-25
32. Gupta T, Sinha S, Ghosh-Laskar, S et al (2020) Intensity-modulated radiation therapy versus three-dimensional conformal radiotherapy in head and neck squamous cell carcinoma: long-term and mature outcomes of a prospective randomized trial. Radiat Oncol 15: 218

Tables

Table 1

Patients and Tumor Characteristics

Variable	Indicator	3D-RT	IMRT-SIB	McNemar or Cohens Kappa** (p-Value)
Gender	male	53 (79%)	53 (79%)	p = 1.000
	female	14 (21%)	14 (21%)	
Tumor subsite	Oral cavity	24 (36%)	24 (36%)	1.000
	Oropharynx	16 (24%)	16 (24%)	(p < 0.005)
	Hypopharynx	6 (9%)	6 (9%)	
	Larynx	8 (12%)	8 (12%)	
	Great glands	5 (8%)	5 (8%)	
	CUP	8 (12%)	8 (12%)	
Treatment concept	Definitive	20 (30%)	20 (30%)	p = 1.000
	Adjuvant	47 (70%)	47 (70%)	
Age	< 65	47 (70%)	48 (72%)	
	> 65	20 (30%)	19 (28%)	
Histology	SCC	62 (93%)	59 (88%)	0.423
	Other	5 (7%)	8 (12%)	(p < 0.005)
Grade	G1	0 (0%)	2 (3%)	
	G2	39 (58%)	35 (52%)	-0.058
	G3	27 (40%)	26 (39%)	(p = 0,619)***
	G4	0 (0%)	1 (2%)	
	GX	1 (2%)	3 (5%)	
UICC stage	III	16 (24%)	15 (22%)	0.579
	IVA	47 (70%)	46 (69%)	(p < 0.005)
	IVB	4 (6%)	4 (6%)	
T stage	cT1	1	0	
	cT2	0	0	
	cT3	4	6	

	cT4/4a	13	14	
	cT4b	2	0	
	pT1	13	7	
	pT2	10	14	
	pT3	5	9	
	pT4/4a	11	8	
	pT4b	0	0	
N stage	cN0	5	8	
	cN1	1	0	
	cN2a	0	1	
	cN2b	5	4	
	cN2c	3	6	
	cN3	1	1	
	pN0	9	11	
	pN1	13	7	
	pN2a	5	5	
	pN2b	15	16	
	pN2c	6	5	
	pN3	2	3	
Resection Status	R0	34 (51%)	39 (58%)	0.614
	R1	6 (9%)	4 (6%)	(p < 0.005)
	R2	0 (0%)	1 (2%)	
	RX	5 (8%)	3 (5%)	
Treatment for relapse†	Yes	12 (18%)	6 (9%)	p = 0.210
	No	55 (82%)	61 (91%)	
ECE	Yes	5 (8%)	18 (27%)	p = 0.001*
	No	47 (70%)	29 (43%)	
	Not examined	15 (22%)	20 (30%)	
Chemotherapy	Yes	33 (49%)	47 (70%)	p = 0.007*
	No	34 (51%)	20 (30%)	

* Statistically significant difference between the groups

** *Cohens Kappa* < 0.00 poor agreement, 0.00 – 0.20 slight, 0.21 – 0.40 fair, 0.41 – 0.60 moderate, 0.61 – 0.80 substantial, 0.81 – 1.00 almost perfect according to (30)

*** Negative *Cohens Kappa* cannot be interpreted, there for there is no statistical significance

† The current treatment was due to a relaps.

Table 2

Acute and late toxicity according to CTCAE and LENT-SOMA classification, worst observed during the follow-up

Acute toxicity		IMRT-group	Control-group	Statistics*	
Mucositis	Grade 0	1 (1.5%)	0	Z-value (Wilcoxon)	-0.688
	Grade I	6 (9.0%)	7 (10.4%)	p-value	0.492
	Grade II	33 (49.3%)	28 (41.8%)	n	67
	Grade III	27 (40.3%)	32 (47.8%)	r	0.08
	Grade IV	0	0	comment	non-significant
	median	2	2		
Dermatitis	Grade 0	1 (1.5%)	0	Z-value (Wilcoxon)	-3.024
	Grade I	49 (73.1%)	40 (59.7%)	p-value	0.002
	Grade II	17 (25.4%)	22 (32.8%)	n	67
	Grade III	0	5 (7.5%)	r	0.37
	Grade IV	0	0	comment	significant,
	median	1	1		medium effect
Dysphagia	Grade 0	9 (13.4%)	1 (1.5%)	Z-value (Wilcoxon)	-2.014
	Grade I	9 (13.4%)	6 (9.0%)	p-value	0.044
	Grade II	20 (29.9%)	28 (41.8%)	n	66
	Grade III	28 (41.8%)	32 (47.8%)	r	0.25
	Grade IV	0	0	comment	significant,
	median	2	2		medium effect
Late toxicity		IMRT-group	Control-group	Statistics	
Xerostomia	Grade 0	3 (4.5)	4 (6.0%)	Z-value (Wilcoxon)	-4.029
	Grade I	43 (64.2%)	10 (14.9%)	p-value	0.000
	Grade II	6 (9.0%)	32 (47.8%)	n	45
	Grade III	0	8 (11.9%)	r	0.60
	Grade IV	0	0	comment	significant,
	median	1	2		large effect
Fibrosis	Grade 0	47 (70.1%)	31 (46.3%)	Z-value (Wilcoxon)	-3.554

	Grade I	5 (7.5%)	18 (26.9%)	p-value	0.000
	Grade II	0	5 (7.5%)	n	45
	Grade III	0	0	r	0.53
	Grade IV	0	0	comment	significant,
	median	0	0		large effect
Hoarseness	Grade 0	34 (50.7%)	38 (56.7%)	Z-value (Wilcoxon)	-0.220
	Grade I	15 (22.4%)	9 (13.4%)	p-value	0.826
	Grade II	0	6 (9.0%)	n	44
	Grade III	1 (1.5%)	1 (1.5%)	r	0.03
	Grade IV	0	0	comment	non-significant
	median	0	0		
Taste alteration	Grade 0	20 (29.9%)	22 (32.8%)	Z-value (Wilcoxon)	-1.136
	Grade I	28 (41.8%)	20 (29.9%)	p-value	0.256
	Grade II	4 (6.0%)	12 (17.9%)	n	45
	Grade III	0	0	r	0.17
	Grade IV	0	0	comment	non-significant
	median	1	1		
Edema	Grade 0	28 (41.8%)	14 (20.9%)	Z-value (Wilcoxon)	-3.749
	Grade I	16 (23.9%)	10 (14.9%)	p-value	0.000
	Grade II	7 (10.4%)	29 (43.3%)	n	45
	Grade III	1 (1.5%)	1 (1.5%)	r	0.56
	Grade IV	0		comment	significant,
	median	0	2		large effect
Trismus	Grade 0	51 (76.1%)	49 (73.1%)	Z-value (Wilcoxon)	-1.134
	Grade I	0	3 (4.5%)	p-value	0.257
	Grade II	1 (1.5%)	2 (3.0%)	n	45
	Grade III	0	0	r	0.17
	Grade IV	0	0	comment	non-significant
	median	0	0		

Necrosis	Grade 0	50 (74.6%)	49 (73.1%)	Z-value (Wilcoxon)	-1.687
	Grade I	0	1 (1.5%)	p-value	0.092
	Grade II	1 (1.5%)	1 (1.5%)	n	45
	Grade III	1 (1.5%)	1 (1.5%)	r	0.25
	Grade IV	0	2 (3.0%)	comment	non-significant
	median	0	0		
Fistula	Grade 0	51 (76.1%)	53 (79.1%)	Z-value (Wilcoxon)	-0.447
	Grade I	0	0	p-value	0.655
	Grade II	0	0	n	45
	Grade III	0	1 (1.5%)	r	0.07
	Grade IV	1 (1.5%)	0	comment	non-significant
	median	0	0		

* Reported statistics: Z-value – test statistic of the Wilcoxon signed-rank test; p-value – significance < 0.05; n – number of pairs, which have both reported adverse events; r – effect size, calculated by $r = \frac{z}{\sqrt{N}}$; comment: r < 0.3 small effect, r between 0.3 and 0.5 medium effect, r > 0.5 large effect according to Cohen