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How Safe Are Reduced Doses per Fraction in Target Volumes of 2nd to 4th Order in the Simultaneous Integrated Boost Irradiation Technique in Head and Neck Carcinoma Patients?

A. Buchali[1*], C. Schroeder[1,2], C. Boerrnert[1], I. Maekelburg[1], W. Huhnt[1], A. Franzen[3]

[1]Department of Radiooncology, Ruppiner Kliniken GmbH, Neuruppin, Germany
[2]Justus Liebig University, Giessen, Germany
[3]Department of Otolaryngology, Ruppiner Kliniken GmbH, Neuruppin, Germany
Email: [*]a.buchali@ruppiner-kliniken.de

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Abstract

Aim: The simultaneous irradiation of target volumes of different total dose levels using intensity modulated radiotherapy leads to reduced doses per fraction and longer treatment times in target volumes of 2nd to 4th order. Does the thereby caused reduced biological effectiveness induce an increased recurrence risk? The current work deals with the problem of recurrences of patients with head and neck carcinomas treated either with an intensitiy (IMRT) or with a volumetric modulated (VMAT) irradiation technique. Methods: From October 2002 to September 2014, 699 patients with carcinomas of the head and neck were irradiated using IMRT or VMAT. The median follow up of the patients was 21.9 months (2 to 145 months). Primary tumor regions (1st order target volume) of 565 patients were treated with doses per fraction of 2 Gy. Accordingly, further 133 target volumes of the primary tumor received reduced doses per fraction. In 1 patient, the lymphatic drainage was treated solely without irradiation of the primary region. For the lympatic drainage, 854 1st order target volumes were treated with a dose per fraction of 2 Gy. Reduced doses per fraction were applied to further 1780 target volumes. Results: 54 of 699 patients developed a recurrence in the primary tumor region after radio-(chemo) therapy, 4 patients developed a recurrence of the primary tumor and a unilateral recurrence of the lymphatic drainage, 2 patients a recurrence of the primary tumor and a bilateral lymph node recurrence. 18 patients showed an isolated unilateral recurrence and additionally 2 patients a bilateral recurrence of the

[*]Corresponding author.

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lymphatic drainage. 619 patients stayed recurrence free. In primary tumor regions, receiving a dose per fraction of 2 Gy 55 patients (9.7%) developed a recurrence, whereas in target volumes receiving a reduced dose per fraction 5 patients (3.8%) developed a recurrence ($p < 0.001$). In lympatic drainage target volumes receiving a dose per fraction of 2 Gy, 25 target volumes (2.9%) developed a recurrence, whereas in target volumes receiving a reduced dose per fraction, 5 patients (0.3%) developed a recurrence ($p = 0.001$). Conclusion: The recurrence risk in target volumes of 2nd to 4th order was not increased due to reduced doses per fraction deposited by means of a simultaneous integrated boost technique. Therefore, the simultaneous irradiation of target volumes with different dose levels is safely applicable within one treatment plan.

Keywords

Head and Neck Carcinoma, Simultaneous Integrated Boost Technique, Dose Painting, Dose per Fraction, Recurrence Risk

1. Introduction

Irradiating patients with head and neck carcinomas, it is necessary to treat target volumes with different total doses, depending on the presence of macroscopic or microscopic tumor manifestations. Using a conventional 3D-dimensional radiation technique, usually, a new treatment plan with a reduced target volume is calculated after reaching a certain dose level. Thereby, all target volumes are irradiated with the same single dose.

The intensity modulated (IMRT) as well as the volumetric modulated arc radiotherapy (VMAT) allows to treat several dose levels in one treatment plan. As a consequence, different target volumes are irradiated with different doses per fraction. Therefore, the biological efficacy varies compared to a conventional fractionated radiotherapy due to reduced doses per fraction and increased treatment times. This is discussed controversially, especially in fast growing tumors, like squamous cell carcinomas.

With the introduction of the IMRT in October 2002, all patients with head and neck carcinomas got simultaneous integrated boost irradiation techniques. Since June 2011, the VMAT was additionally introduced as an alternative treatment technique for patients with head and neck carcinomas, but without changing the treatment strategy. Preventing late side effects, the dose per fraction was limited to 2 Gy for the target volume with the highest total dose (1st order target volume). Target volumes of 2nd to 4th order received lower doses per fraction, respectively.

The frequency of recurrences has been analysed to survey the impact of the reduced biological efficacy following the radiation schedule of target volumes of 2nd or 4th order due to lower doses per fraction and increased treatment times. Finally, it is used as an indicator to estimate the harmlessness of a simultaneous irradiation of different target volumes with varying dose levels.

2. Material and Methods

From October 2002 to September 2014, 699 patients (130 female, 569 male) with head-neck squamous cell carcinomas were treated using IMRT or VMAT. The mean age at the start of the treatment was 58.2 (30.5 - 84.2) years. The median follow-up of the patients was 21.9 months (2 to 145 months). The patient characteristics are shown in **Table 1**.

The treatment plan of each patient contains from one up to five target volumes, one target volume for the primary tumor and a maximum of 4 target volumes for the lymphatic drainage. The irradiation of the lymph node area was divided in a caudal and a cranial part. The caudal part included Level IIB, Level III, the cranial Levels V and VI, as well as Level I or IIA, if indicated. The caudal part consisted of the caudal Levels V and VI in addition of the supraclavicular node area. A typical example of a treatment plan is demonstrated in **Figure 1**. 20 patients received a unilateral treatment of the lymphatic drainage and in 15 patients, the primary tumor region was treated without and lyphatic dranage. Eventually, an exclusive irradiation of the cranial part of the neck node area was delivered in additionally 29 patients. The number of target volumes per patient is shown in **Figure 2** and the number of lymphatic drainage volumes is shown in **Figure 3**.

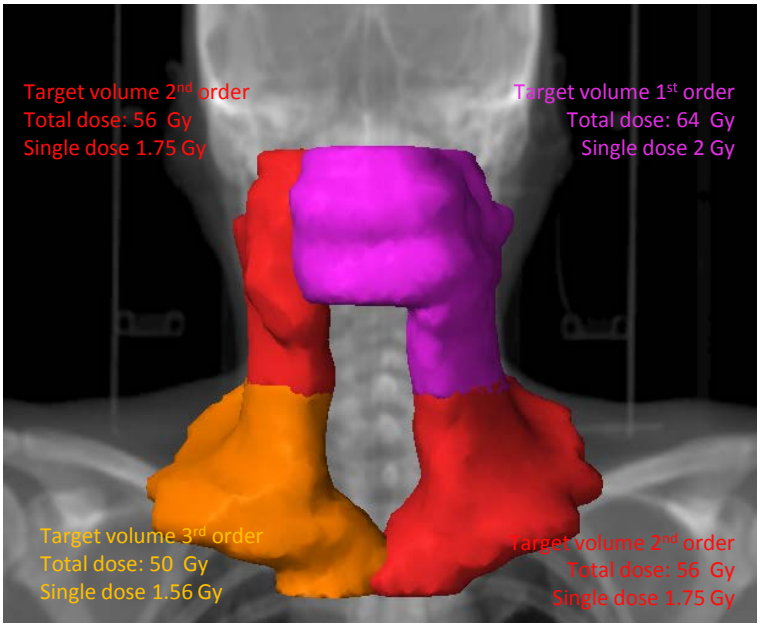

Figure 1. Treatment plan of a patient. Diagnosis: Carcinoma of the oropharynx pT4. pN2c: right: 3/15 no extracapsular spread; left: 7/17 extracapsular spread. Resection: Resection of the primary: R1, bilateral neck dissection. Radiochemotherapy: Target volume 1: 64 Gy: primary tumor extension and, cranial left neck node area, PTV: purple. Target volume 2: 56 Gy: cranial right neck node area, and caudal left neck node area, PTV: red. Target volume 3: 50 Gy: caudal right neck node area, PTV: orange.

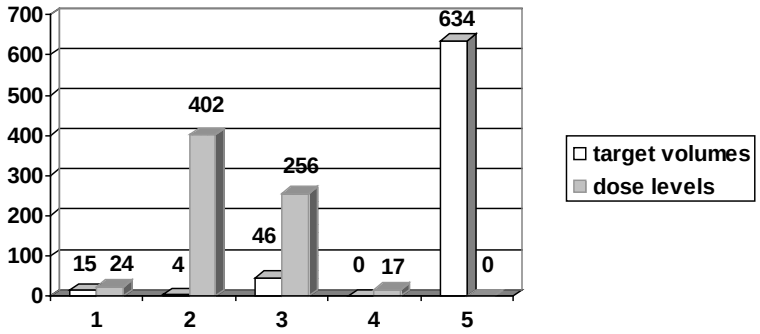

Figure 2. Number of targets volumes and dose levels per patient (n = 699).

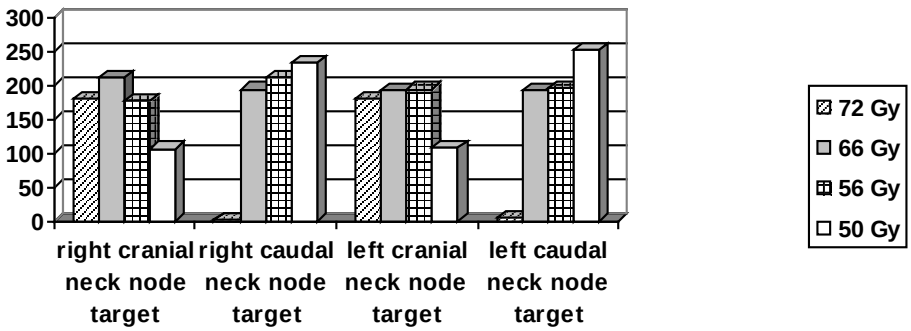

Figure 3. Number of the volumes of the neck node areas per dose level. The cranial part included Level IIB, Level III, the cranial Levels V and VI, as well as Level I or IIA if indicated. The caudal part included caudal Levels V and VI and the supraclavicular node area.

Table 1. Characteristics of patients (n = 699).

Primary tumor localisation	Oropharynx	260
	Floor of the mouth	100
	Larynx	106
	Hypopharynx	93
	Tongue	46
	CuP	38
	Nasopharynx	24
	Paranasal sinus	17
	Salivary gland	15
T stage	Tx (CuP)	38
	T1	83
	T2	220
	T3	175
	T4	183
N stage	N0	149
	N1	71
	N2a	27
	N2b	211
	N2c	207
	N3	34
UICC stage	Stage I	22
	Stage II	61
	Stage III	98
	Stage IV	518
Resection status	Definitive treatment	185
	R2 resection	75
	R1 resection	130
	R0 resection	309
Chemotherapy	Without chemotherapy	
	No indication	133
	Contraindication	113
	Simultaneous chemotherapy	453

The treatment was accomplished by means of four groups of total dose levels. Within the first group a dose of 72 Gy was disposed to macroscopic tumor volumes, either for a definitive treatment of the primary tumor, the tumor bed after R2-resection, or for an identifiable tumor mass within the treatment planning CT (n = 230 target volumes). In case of macroscopic lymph node metastases, lymph nodes received total doses of 72 Gy as well (n = 365 target volumes). A total dose of 66 Gy was applied for patients of the second group characterized by tar-

get volumes of microscopic tumor sites, *i.e.* to treat the primary tumor bed after R1-resection (n = 218 target volumes), the postoperative lymphatic drainage in case of extracapsular infiltration, or 1st level of clinical non involved lymph node areas within a definitive treatment course (n = 786 target volumes). Accordingly reduced total doses were exhibited to the primary tumor bed after R0-resection. In those cases (n = 208 target volumes) as well as for a postoperative treatment of the neck node area (if there was no extracapsular spread, or if the second lymphatic drainage was not involved, n = 784), a total dose of 56 Gy was irradiated. Finally, total doses of 50 Gy were applied to the naso-, oro- and hypopharynx in patients with a CUP syndrome (n = 42 target volumes) or to the lymph node level in a pN0 situation (n = 699 target volumes). The number of dose levels per patient is also shown in **Figure 2**.

Clinical target volumes (CTV) and planning target volumens (PTV) were obtained by surrounding gross tumor volumens (GTV) and CTV's, respectively, each with a margin of 6 mm in all directions. Treatment plans were calculated to a single dose of 2 Gy for the target volume with the highest total dose according to the criteria of the ICRU. The target volumes of 2nd to 4th order were also calculated according the homogeneity criteria of the ICRU, excluding a margin of 5 mm to the PTV of higher order, to achieve the dose criteria in the PTV's of higher order.

Descriptive statistics were performed using MS Excel (Microsoft Corp. Redmond WA). For further analysis using Chi Square and Man & Whitney U-test, SPSS for Windows (SPSS Inc., Chicago IL) was used.

3. Results

After radio-(chemo-) therapy 54 of 699 patients developed a recurrence in the primary tumor region, 4 patients developed a recurrence of the primary tumor and a unilateral recurrence of the lymphatic drainage, 2 patients a recurrence of the primary tumor and a bilateral lymph node recurrence. 18 patients showed an isolated unilateral recurrence and additionally 2 patients a bilateral recurrence of the lymphatic drainage without a recurrence of the primary tumor region. 619 patients stayed recurrence free.

In primary tumor regions receiving a dose per fraction of 2 Gy, 55 patients (9.7%) developed a recurrence. Within this patient group, 10 of 134 patients developed a recurrence after treatment with a total dose 56 Gy (R0 resection), 17 of 201 after 66 Gy (R1 resection), and 28 of 203 after 72 Gy (definitive treatment). In the group of patients with target volumes receiving a reduced dose per fraction, 5 patients (3.8%) developed a recurrence ($p < 0.001$). Three of them were treated within the primary tumor region with a total dose of 56 Gy after R0 resection, whereat according treatment plans contained higher total doses of 66 Gy addressed to the lymphatic drainage. Thereby, a dose per fraction of 1.7 Gy resulted for the primary tumor region. The remaining two recurrences occurred after 66 Gy (R1 resection) for treatment plans with total doses of 72 Gy aimed to macroscopic lymph node metastases. A single dose of 1.83 Gy followed for the primary tumor bed.

Within 698 primary tumor regions, 565 PTV's were treated with a dose per fraction of 2 Gy (1st order PTV's). Accordingly, reduced doses per fraction were delivered to the remaining 133 PTV's. In primary tumor PTV's receiving a dose per fraction of 2 Gy, 55 patients (9.7%) developed a recurrence, whereas in PTV's receiving reduced doses per fraction, 5 patients (3.8%) developed a recurrence ($p < 0.001$) (**Table 2**).

Irradiating the lympatic drainage, all together 854 PTV's were treated with a dose per fraction of 2 Gy (1st order PTV's) and 1780 PTV's received reduced doses per fraction. For both groups the recurrence rate was low (**Table 3**). First order PTV's developed a recurrence in 25 cases (2.9 %). The number of recurrences was 17 of 365 after 72 Gy, 4 of 291 after 66 Gy, and 4 of 198 after 56 Gy, respectively. Target volumes treated with a reduced dose per fraction developed recurrences only in 5 cases ($p = 0.001$). Four of them occurred after a dose of 56 Gy in treatment plans with total doses of 66 Gy leading single doses of 1.7 Gy. The remaining recurrence appeared after 50 Gy in a treatment plan with a total dose of 66 Gy, which resulted in a dose per fraction of 1.52 Gy.

The recurrence risk was not increased in 2nd to 4th order target volumes, neither for the primary tumor region nor for the lymphatic drainage.

4. Discussion

The total rates of locoregional recurrences inside the treated PTV's amounts to 11.4%. These results are in good agreement with other studies of varying follow up periods, showing recurrence rates from 5.6% to 31% as a result of a definitive radiation therapy [1]-[7] and between 7% and 10% after a postoperative radiation therapy [1]-[3].

Table 2. Recurrence rate of primary tumor bed related to the single dose (n = 699).

Total dose[*1] treatment plan	Total dose[*2]	Single dose primary tumor	n[*3]	Number of recurrences	Recurrence rate	p-Value
72 Gy	50 Gy (4th order)	1.39 Gy	11	0	0.00%	
66 Gy	50 Gy (3rd order)	1.52 Gy	23	0	0.00%	
72 Gy	56 Gy (3rd order)	1.56 Gy	8	0	0.00%	
66 Gy	56 Gy (2nd order)	1.70 Gy	66	3	4.50%	
56 Gy	50 Gy (2nd order)	1.79 Gy	8	0	0.00%	
72 Gy	66 Gy (2nd order)	1.83 Gy	17	2	11.80%	
72 Gy	72 Gy (1st order)	2.00 Gy	230	28	12.20%	
66 Gy	66 Gy (1st order)	2.00 Gy	201	17	8.50%	
56 Gy	56 Gy (1st order)	2.00 Gy	134	10	7.50%	
Total	(2nd, 3rd, 4th order)	<2.00 Gy	133	5	3.80%	p < 0.001
	(1st order)	2.00 Gy	565	55	9.70%	

[*1]The total dose of the whole treatment plan is calculated for a single dose of 2 Gy for the target volume, needing the highest total dose; [*2]The indications leading to the total dose of the primary are: 50 Gy: CuP: Naso-, Oro-, Hypopharynx; 56 Gy: R0 resection; 66 Gy: R1 resection; 72 Gy: R2 resection or definitive treatment; [*3]In 1 patient only lymph nodes without primary tumor have been treated.

Table 3. Recurrence rate of lymph node levels related to the single dose.

Total dose[*1] treatment plan	Total dose[*2] lymph node level	Single dose lymph node level	n[*3]	Number of recurrences	Recurrence rate	p-Value
72 Gy	50 Gy (4th order)	1.39 Gy	43	0	0.00%	
66 Gy	50 Gy (3rd order)	1.52 Gy	332	1	0.30%	
72 Gy	56 Gy (3rd order)	1.56 Gy	141	0	0.00%	
66 Gy	56 Gy (2nd order)	1.70 Gy	445	4	0.90%	
56 Gy	50 Gy (2nd order)	1.79 Gy	324	0	0.00%	
72 Gy	66 Gy (2nd order)	1.83 Gy	495	0	0.00%	
72 Gy	72 Gy (1st order)	2.00 Gy	365	17	4.70%	
66 Gy	66 Gy (1st order)	2.00 Gy	291	4	1.40%	
56 Gy	56 Gy (1st order)	2.00 Gy	198	4	2.00%	
Total		<2.00 Gy	1780	5	0.30%	p = 0.001
		2.00 Gy	854	25	2.90%	

[*1]The total dose of the whole treatment plan is calculated for a single dose of 2 Gy for the target volume, needing the highest total dose; [*2]The indications leading to the total dose of the lymph node level are: 50 Gy: pN0; 56 Gy: pN+ and no extracapsular spread or 2nd noninvolved level; 64 Gy: pN+ and extracapsular spread or 1st noninvolved level; 72 Gy: cN+; [*3]In 15 patients the primary was treated without lymphatic drainage, in 20 patients only unilateral lymphatic drainage and in 29 patients only the cranial part of lymphatic drainage has been treated.

The distribution of stages reveals that some departments show a more favourable risk profile of patients [2]. Our data again match previous studies according to locoregional control rates after definitive therapy of 56% to 95% after 2 to 5 years [1] [3] [6] [8]-[15] and after postoperative therapy of 85% after 3 years [3] [16].

However, no data could be found concerning the problem addressed in the current work: the question, whether a lower biological efficacy, which is caused by lower doses per fraction and increased corresponding treatment times, leads to a higher rate of recurrences for simultaneous irradiated PTV's of 2nd to 4th order? The current study shows, that among all in-field recurrences only 3 recurrences emerged within the primary tumor region and further 3 within the lymphatic drainage after a treatment by means of reduced single doses. They count

for 8.3% of the in-field recurrences of the primary tumor region and for 15.8% of the in-field recurrences of the lymphatic drainage, respectively. Most in-field recurrences have been developed in our investigation after irradiation of macroscopic tumor mass with doses per fraction of 2 Gy. In agreement with these results, Collan *et al.* also located all of the observed recurrences inside target volumes, which were irradiated receiving high total doses and consecutively high doses per fraction [1].

Several groups emphasize risk factors for locoregional recurrence. They include the volume of the tumor and lymph node metastases, the perinodal infiltration, the number of lymph nodes involved and the resection rim, forming different risk groups [17]-[19]. Patients with these risk factors were treated more rigidly in our department concerning total radiation dose and/or simultaneous chemotherapy. Appropriate PTV's received highest total doses with doses per fraction of 2 Gy, respectively.

PTV's of lower risk for recurrencies (e.g. pN+ without perinodal infiltration, pN0) were irradiated with lower doses per fraction and total doses, since, especially for the low dose elective target volumes (pN0 situation) a very low recurrence rate is expected. Nevertheless, there are known cases, for which the indication of a radiation therapy of a pN0 situation seems to be questionable [20]-[24].

Further factors are known to influence the recurrence rate. Among tumors of the same kind there is a broad variability of intrinsic radiation sensitivity [25]. Further, the quality of target volume determination within the radiation planning process is crucial [26]-[30]. The limitation of total radiation treatment time of macroscopic tumor regions seems to have a high relevance to the recurrence rate, too [31].

5. Conclusion

According to the shown results, recurrence rates of primary tumors as well as of lymphatic drainages are not increased after treating them in a risk adapted concept as target volumes of 2nd to 4th order with decreased doses per fraction and consequently increased treatment time.

Conflict of Interest

The authors state that there are no conflicts of interest.

Statement

The accompanying manuscript does not include studies on humans or animals.

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